Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline

Derek LeRoith,[1] Geert Jan Biessels,[2] Susan S. Braithwaite,[3,4] Felipe F. Casanueva,[5] Boris Draznin,[6] Jeffrey B. Halter,[7,8] Irl B. Hirsch,[9] Marie E. McDonnell,[10] Mark E. Molitch,[11] M. Hassan Murad,[12] and Alan J. Sinclair[13]

[1]Icahn School of Medicine at Mount Sinai, New York, New York 10029; [2]University Medical Center Utrecht, 3584 CX Utrecht, Netherlands; [3]Presence Saint Francis Hospital, Evanston, Illinois 60202; [4]Presence Saint Joseph Hospital, Chicago, Illinois 60657; [5]Complejo Hospitalario Universitario de Santiago, CIBER de Fisiopatologia Obesidad y Nutricion, Instituto Salud Carlos III, 15782 Santiago de Compostela, Spain; [6]University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado 80045; [7]University of Michigan, Ann Arbor, Michigan 48109; [8]National University of Singapore, Singapore 119077, Singapore; [9]University of Washington Medical Center–Roosevelt, Seattle, Washington 98105; [10]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115; [11]Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611; [12]Division of Preventive Medicine, Mayo Clinic, Rochester, Minnesota 55905; and [13]King's College, London SE1 9NH, United Kingdom

ORCiD numbers: 0000-0002-7920-8474 (D. LeRoith).

***Cosponsoring Associations:** European Society of Endocrinology, The Gerontological Society of America, and The Obesity Society.

Objective: The objective is to formulate clinical practice guidelines for the treatment of diabetes in older adults.

Conclusions: Diabetes, particularly type 2, is becoming more prevalent in the general population, especially in individuals over the age of 65 years. The underlying pathophysiology of the disease in these patients is exacerbated by the direct effects of aging on metabolic regulation. Similarly, aging effects interact with diabetes to accelerate the progression of many common diabetes complications. Each section in this guideline covers all aspects of the etiology and available evidence, primarily from controlled trials, on therapeutic options and outcomes in this population. The goal is to give guidance to practicing health care providers that will benefit patients with diabetes (both type 1 and type 2), paying particular attention to avoiding unnecessary and/or harmful adverse effects. (***J Clin Endocrinol Metab*** **104: 1520–1574, 2019)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 25 January 2019. Accepted 25 January 2019.
First Published Online 23 March 2019

Abbreviations: ACE, angiotensin-converting enzyme; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADA, American Diabetes Association; ADL, activity of daily living; ARB, angiotensin receptor blocker; BP, blood pressure; CGM, continuous glucose monitoring; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GLP-1, glucagon-like-peptide 1; GFR, glomerular filtration rate; HR, hazard ratio; IADL, instrumental ADL; LDL-C, low-density lipoprotein cholesterol; LTCF, long-term care facility; MACE, major adverse cardiovascular event; MCI, mild cognitive impairment; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized control trial; RR, relative risk; SGLT2, sodium-glucose cotransporter 2; SBP, systolic blood pressure; SDM, shared decision-making; SPRINT, Systolic Blood Pressure Intervention Trial; SU, sulfonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study; VEGF, vascular endothelial growth factor.

List of Recommendations

Role of the endocrinologist and diabetes care specialist

1.1 In patients aged 65 years and older with newly diagnosed diabetes, we advise that an endocrinologist or diabetes care specialist should work with the primary care provider, a multidisciplinary team, and the patient in the development of individualized diabetes treatment goals. (Ungraded Good Practice Statement)

1.2 In patients aged 65 years and older with diabetes, an endocrinologist or diabetes care specialist should be primarily responsible for diabetes care if the patient has type 1 diabetes, or requires complex hyperglycemia treatment to achieve treatment goals, or has recurrent severe hypoglycemia, or has multiple diabetes complications. (Ungraded Good Practice Statement)

Screening for diabetes and prediabetes, and diabetes prevention

2.1 In patients aged 65 years and older without known diabetes, we recommend fasting plasma glucose and/or HbA1c screening to diagnose diabetes or prediabetes. (1|⊕⊕⊕⊕)
Technical remark: The measurement of HbA1c may be inaccurate in some people in this age group because of comorbidities that can affect the lifespan of red blood cells in the circulation. Although the optimal screening frequency for patients whose initial screening test is normal remains unclear, the writing committee advocates repeat screening every 2 years thereafter. As with any health screening, the decision about diabetes and prediabetes screening for an individual patient depends on whether some action will be taken as a result and the likelihood of benefit. For example, such screening may not be appropriate for an older patient with end-stage cancer or organ system failure. In these situations, shared decision-making with the patient is recommended.

2.2 In patients aged 65 years and older without known diabetes who meet the criteria for prediabetes by fasting plasma glucose or HbA1c, we suggest obtaining a 2-hour glucose post–oral glucose tolerance test measurement. (2|⊕⊕⊕O)
Technical remark: This recommendation is most applicable to high-risk patients with any of the following characteristics: overweight or obese, first-degree relative with diabetes, high-risk race/ethnicity (*e.g.*, African American, Latino, Native American, Asian American, Pacific Islander), history of cardiovascular disease, hypertension (≥140/90 mm Hg or on therapy for hypertension), high-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L), sleep apnea, or physical inactivity. Shared decision-making is advised for performing this procedure in frail older people or in those for whom it may be overly burdensome. Standard dietary preparation for an oral glucose tolerance test is advised.

2.3 In patients aged 65 years and older who have prediabetes, we recommend a lifestyle program similar to the Diabetes Prevention Program to delay progression to diabetes. (1|⊕⊕⊕⊕)
Technical remark: Metformin is not recommended for diabetes prevention at this time, as it is not approved by the Food and Drug Administration for this indication. As of 2018, a Diabetes Prevention Program–like lifestyle intervention is a covered benefit for Medicare beneficiaries in the United States who meet the criteria for prediabetes.

Assessment of older patients with diabetes

3.1 In patients aged 65 years and older with diabetes, we advise assessing the patient's overall health (see Table 2) and personal values prior to the determination of treatment goals and strategies (see Table 3). (Ungraded Good Practice Statement)

3.2 In patients aged 65 years and older with diabetes, we suggest that periodic cognitive screening should be performed to identify undiagnosed cognitive impairment. (2|⊕⊕OO)
Technical remark: Use of validated self-administered tests is an efficient and cost-effective way to implement screening (see text). Alternative screening test options, such as the Mini-Mental State Examination or Montreal Cognitive Assessment, are widely used. An initial screening should be performed at the time of diagnosis or when a patient enters a care program. Screening should be repeated every 2 to 3 years after a normal screening test result for patients without cognitive complaints or repeated 1 year after a borderline normal test result. Always evaluate cognitive complaints and assess cognition in patients with complaints.

3.3 In patients aged 65 years and older with diabetes and a diagnosis of cognitive impairment (*i.e.*, mild cognitive impairment or dementia), we suggest that medication regimens should be simplified (see recommendation 3.1) and glycemic targets tailored (*i.e.*, be more lenient; see recommendation 4.1) to

improve compliance and prevent treatment-related complications. (2|⊕⊕OO)

Technical remark: Medical and nonmedical treatment and care for cognitive symptoms in people with diabetes and cognitive impairment are no different from those in people without diabetes and cognitive impairment. Depending on the situation and preferences of the patient, a primary caregiver can be involved in decision-making and management of medication.

Treatment of hyperglycemia

Setting glycemic targets and goals

4.1 In patients aged 65 years and older with diabetes, we recommend that outpatient diabetes regimens be designed specifically to minimize hypoglycemia. (1|⊕⊕⊕O)

Technical remark: Although evidence for specific targets is lacking, glycemic targets should be tailored to overall health and management strategies (*e.g.*, whether a medication that can cause hypoglycemia is used) (see Table 3).

Assessing glycemia in older adults with diabetes

4.2 In patients aged 65 years and older with diabetes who are treated with insulin, we recommend frequent fingerstick glucose monitoring and/or continuous glucose monitoring (to assess glycemia) in addition to HbA1c. (1|⊕⊕OO)

Lifestyle interventions for older adults with diabetes

Lifestyle modifications

4.3 In patients aged 65 years and older with diabetes who are ambulatory, we recommend lifestyle modification as the first-line treatment of hyperglycemia. (1|⊕⊕⊕⊕)

Nutrition

4.4 In patients aged 65 years and older with diabetes, we recommend assessing nutritional status to detect and manage malnutrition. (1|⊕⊕⊕⊕)

Technical remark: Nutritional status can be assessed using validated tools such as the Mini Nutritional Assessment and Short Nutritional Assessment Questionnaire.

4.5 In patients aged 65 years and older with diabetes and frailty, we suggest the use of diets rich in protein and energy to prevent malnutrition and weight loss. (2|⊕⊕OO)

4.6 In patients aged 65 years and older with diabetes who cannot achieve glycemic targets with lifestyle modification, we suggest avoiding the use of restrictive diets and instead limiting consumption of simple sugars if patients are at risk for malnutrition. (2|⊕OOO)

Technical remark: Patients' glycemic responses to changes in diet should be monitored closely. This recommendation applies to both older adults living in the community and those in nursing homes.

Drug therapy for hyperglycemia

Glycemic management of diabetes in older adults with diabetes

4.7 In patients aged 65 years and older with diabetes, we recommend metformin as the initial oral medication chosen for glycemic management in addition to lifestyle management. (1|⊕⊕⊕O)

Technical remark: This recommendation should not be implemented in patients who have significantly impaired kidney function (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or have a gastrointestinal intolerance.

4.8 In patients aged 65 years and older with diabetes who have not achieved glycemic targets with metformin and lifestyle, we recommend that other oral or injectable agents and/or insulin should be added to metformin. (1|⊕⊕⊕⊕)

Technical remark: To reduce the risk of hypoglycemia, avoid using sulfonylureas and glinides, and use insulin sparingly. Glycemic treatment regimens should be kept as simple as possible.

Treating complications of diabetes

Management of hypertension in older adults with diabetes

5.1 In patients aged 65 to 85 years with diabetes, we recommend a target blood pressure of 140/90 mm Hg to decrease the risk of cardiovascular disease outcomes, stroke, and progressive chronic kidney disease. (1|⊕⊕⊕O)

Technical remark: Patients in certain high-risk groups could be considered for lower blood pressure targets (130/80 mm Hg), such as those with previous stroke or progressing chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or albuminuria). If lower blood pressure targets are selected, careful

monitoring of such patients is needed to avoid orthostatic hypotension. Patients with high disease complexity (group 3, poor health, Table 3) could be considered for higher blood pressure targets (145 to 160/90 mm Hg). Choosing a blood pressure target involves shared decision-making between the clinician and patient, with full discussion of the benefits and risks of each target.

5.2 In patients aged 65 years and older with diabetes and hypertension, we recommend that an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be the first-line therapy. (1|⊕⊕⊕O)
Technical remark: If one class is not tolerated, the other should be substituted.

Management of hyperlipidemia in older adults with diabetes

5.3 In patients aged 65 years and older with diabetes, we recommend an annual lipid profile. (1|⊕⊕OO)

5.4 In patients aged 65 years and older with diabetes, we recommend statin therapy and the use of an annual lipid profile to achieve the recommended levels for reducing absolute cardiovascular disease events and all-cause mortality. (1|⊕⊕⊕⊕)
Technical remark: The Writing Committee did not rigorously evaluate the evidence for specific low-density lipoprotein cholesterol targets in this population, so we refrained from endorsing specific low-density lipoprotein cholesterol targets in this guideline. For patients aged 80 years old and older or with short life expectancy, we advocate that low-density lipoprotein cholesterol goal levels should not be so strict.

5.5 In patients aged 65 years and older with diabetes, we suggest that if statin therapy is inadequate for reaching the low-density lipoprotein cholesterol reduction goal, either because of side effects or because the low-density lipoprotein cholesterol target is elusive, then alternative or additional approaches (such as including ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors) should be initiated. (2|⊕OOO)

5.6 In patients aged 65 years and older with diabetes and fasting triglycerides >500 mg/dL, we recommend the use of fish oil and/or fenofibrate to reduce the risk of pancreatitis. (1|⊕⊕OO)

Management of congestive heart failure in older adults with diabetes

5.7 In patients aged 65 years and older who have diabetes and congestive heart failure, we advise treatment in accordance with published clinical practice guidelines on congestive heart failure. (Ungraded Good Practice Statement)

5.8 In patients aged 65 years and older who have diabetes and congestive heart failure, the following oral hypoglycemic agents should be prescribed with caution to prevent worsening of heart failure: glinides, rosiglitazone, pioglitazone, and dipeptidyl peptidase-4 inhibitors. (Ungraded Good Practice Statement)

Management of atherosclerosis in older adults with diabetes

5.9 In patients aged 65 years and older with diabetes and a history of atherosclerotic cardiovascular disease, we recommend low-dosage aspirin (75 to 162 mg/d) for secondary prevention of cardiovascular disease after careful assessment of bleeding risk and collaborative decision-making with the patient, family, and other caregivers. (1|⊕⊕OO)

Eye complications in older adults with diabetes

5.10 In patients aged 65 years and older with diabetes, we recommend annual comprehensive eye examinations to detect retinal disease (1|⊕⊕⊕⊕).
Technical remark: Screening and treatment should be conducted by an ophthalmologist or optometrist in line with present-day standards.

Neuropathy, falls, and lower extremity problems in older adults with diabetes

5.11 In patients aged 65 years and older with diabetes and advanced chronic sensorimotor distal polyneuropathy, we suggest treatment regimens that minimize fall risk, such as the minimized use of sedative drugs or drugs that promote orthostatic hypotension and/or hypoglycemia. (2|⊕OOO)

5.12 In patients aged 65 years and older with diabetes and peripheral neuropathy with balance and gait problems, we suggest referral to physical therapy or a fall management program to reduce the risk of fractures and fracture-related complications. (2|⊕OOO)

5.13 In patients aged 65 years and older with diabetes and peripheral neuropathy and/or peripheral vascular disease, we suggest referral to a podiatrist, orthopedist, or vascular specialist for preventive care to reduce the risk of foot ulceration and/or lower extremity amputation. (2|⊕⊕OO)

Chronic kidney disease in older adults with diabetes

5.14 In patients aged 65 years and older with diabetes who are not on dialysis, we recommend annual screening for chronic kidney disease with an estimated glomerular filtration rate and urine albumin-to-creatinine ratio. (1|⊕⊕⊕⊕)

5.15 In patients aged 65 years and older with diabetes who are in group 3 (poor health, see Table 3) of the framework and have a previous albumin-to-creatinine ratio of <30 mg/g, we suggest against additional annual albumin-to-creatinine ratio measurements. (2|⊕⊕OO)

5.16 In patients aged 65 years and older with diabetes and decreased estimated glomerular filtration rate, we recommend limiting the use or dosage of many classes of diabetes medications to minimize the side effects and complications associated with chronic kidney disease. (1|⊕⊕OO)
Technical remark: Specific use/dosing guidance on each class of diabetes medication is provided in Table 7.

Special settings and populations

Management of diabetes away from home—in hospitals and long-term care facilities—and transitions of care

6.1 In patients aged 65 years and over with diabetes in hospitals or nursing homes, we recommend establishing clear targets for glycemia at 100 to 140 mg/dL (5.55 to 7.77 mmol/L) fasting and 140 to 180 mg/dL (7.77 to 10 mmol/L) postprandial while avoiding hypoglycemia. (1|⊕⊕OO)
Technical remark: An explicit discharge plan should be developed to reestablish long-term glycemic treatment targets and glucose-lowering medications as the patient transitions to posthospital care.

6.2 In patients aged 65 years and older with diabetes and a terminal illness or severe comorbidities, we recommend simplifying diabetes management strategies. (1|⊕OOO)

6.3 In patients aged 65 years and older without diagnosed diabetes, we suggest routine screening for HbA1c during admission to the hospital to ensure detection and treatment where needed (see the technical remark in recommendation 2.1). (2|⊕⊕OO)

Introduction

Scope of guideline

In recognition of the broad nature of the topic, the Writing Committee has identified topics deemed to have the greatest impact on the overall health and quality of life of older individuals (defined here as age 65 years or older) with diabetes. The Writing Committee has chosen to use the American Diabetes Association (ADA) definitions for diabetes and prediabetes (see section 2 on "Screening for Diabetes and Prediabetes, and Diabetes Prevention"). We discuss pathophysiology and epidemiology unique to older adults, evidenced-based treatment strategies, such as lifestyle management and drug therapy, and the identification and management of common comorbidities and diabetes-related complications, such as hypertension, hyperlipidemia, congestive heart failure (CHF), retinopathy, neuropathy, and chronic kidney disease (CKD). We also discuss special settings and type 1 diabetes (T1D). Some topics, such as a detailed discussion on the use of devices and technology, are identified as being important for the care of patients with diabetes but are beyond the scope of the guideline. Furthermore, we emphasize the heterogeneity of the older adult population with diabetes and provide guidance for individualization of treatment plans by creating a conceptual framework that suggests three categories of overall health (see "Assessment of Older Patients With Diabetes"). This framework is discussed in detail in section 3 and referenced in specific recommendations wherever relevant. Lastly, members of the Writing Committee sought to incorporate the patient's voice into this guideline by developing and administering a brief survey in collaboration with patient advocacy organizations/community organizers who helped us identify individuals with diabetes for participation. The results of this survey are reported in a designated section in Appendix B.

Epidemiology

Among older adults with diabetes, >90% have type 2 diabetes (T2D), and in one study, this value was 96% (1). T2D is an age-related disease with a prevalence of 33% in the US population aged 65 years or older, and nearly 50% of older people meet the criteria for prediabetes (2). The incidence of newly diagnosed diabetes is highest among those aged 65 to 79 years. The reported duration of T2D among older people is illustrated in Fig. 1 (3). Although nearly half of those with diabetes aged 60 to 69 years report having had the disease for >10 years, ~20% of individuals over the age 80 years report a duration of <5 years. However, the duration of T2D may be underestimated unless individuals are screened regularly. The prevalence of diabetes in the United States is projected to increase dramatically during the next 3 decades; as the population ages, the numbers of higher-risk minority groups increase, and people with diabetes live longer because of decreasing rates of cardiovascular

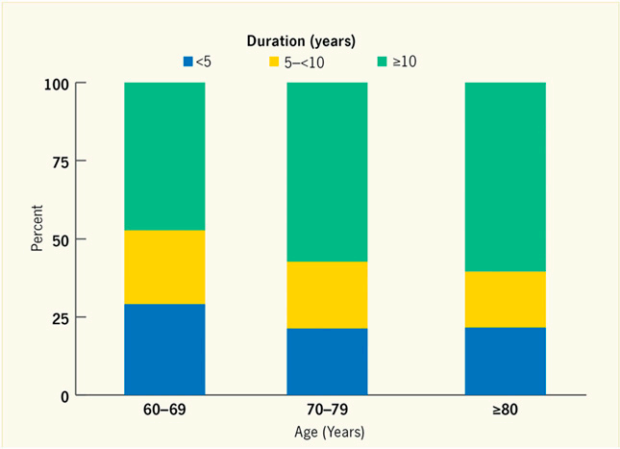

Figure 1. Duration of diabetes among adults aged ≥60 y, by age, United States, 2009–2010 (3). [Reproduced from Laiteerapong N, Huang ES. Chapter 16: Diabetes in older adults. In Cowie CC, Casagrande SS, Menke A, *et al.*, eds. Diabetes in America, 3rd ed. Bethesda, MD: National Institutes of Health, NIH Pub No. 17-1468, 2017; pp 16-1 to 16-26.]

deaths (4). Moreover, older adults are susceptible to all of the usual complications of diabetes [reviewed in Refs. (3) and (5)]. The prevalence rates of end-stage renal disease, loss of vision, myocardial infarction, stroke, peripheral vascular disease, and peripheral neuropathy are increased by the presence of diabetes, as illustrated in Fig. 2 for cardiovascular diseases (CVDs) and in Fig. 3 for microvascular complications (3).

The dramatic effect of age on the incidence of major diabetes complications is illustrated in Fig. 4 (6). As summarized in Halter *et al.* (7), ~50% of individuals over age 65 years with diabetes have diabetic nephropathy, which manifests as albuminuria, impaired glomerular

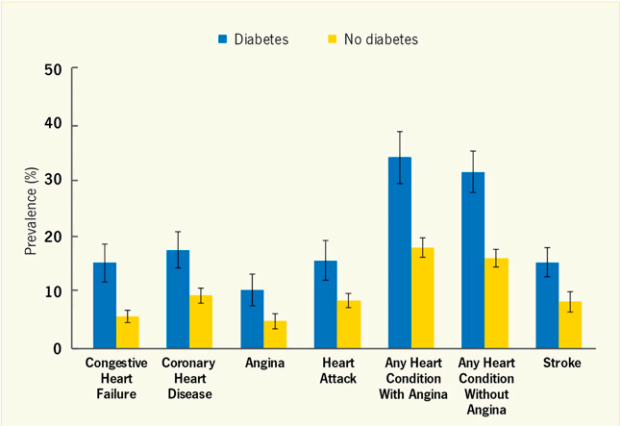

Figure 2. Cardiovascular complications among adults age ≥65 y, by diabetes status, United States, 2007–2010. Data are self-reported. Error bards represent 95% CIs. [Reproduced from Laiteerapong N, Huang ES. Chapter 16: Diabetes in older adults. In Cowie CC, Casagrande SS, Menke A, *et al.*, eds. Diabetes in America, 3rd ed. Bethesda, MD: National Institutes of Health, NIH Pub No. 17-1468, 2017; pp 16-1 to 16-26.]

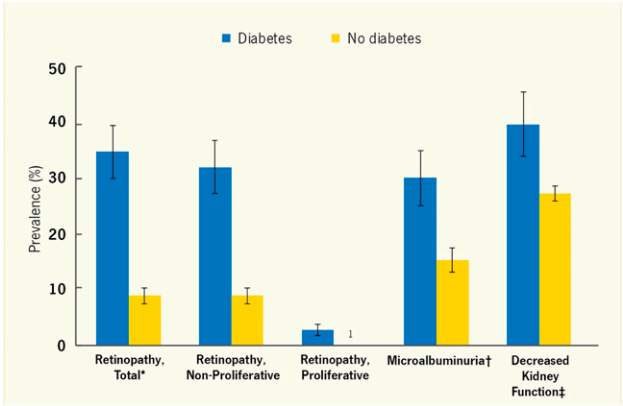

Figure 3. Microvascular complications among adults age ≥65 y, by diabetes status, United States, 2005–2010. Diabetes status is self-reported. Error bars represent 95% CIs. *Retinopathy detected by nonmydriatic digital fundus photography. Based on 2005–2008 data. †Microalbuminuria defined as an albumin-to-creatinine ratio of 30 to 300 mg/g. Based on 2007–2010 data. ‡Decreased kidney function based on eGFR <60 mL/min/1.73 m^2 determined using the CKD-EPI equation and serum creatinine. [1]Estimate is too unreliable to present; one case (or no cases) or relative SE >50%. [Reproduced from Laiteerapong N, Huang ES. Chapter 16: Diabetes in older adults. In Cowie CC, Casagrande SS, Menke A, *et al.*, eds. Diabetes in America, 3rd ed. Bethesda, MD: National Institutes of Health, NIH Pub No. 17-1468, 2017; pp 16-1 to 16-26.]

filtration rate (GFR), or both. Diabetic kidney disease accounts for nearly half of all cases of end-stage renal disease in the United States, and the rate is highest among those aged ≥75 years. The risk for lower extremity amputation is 10-fold greater in older people with diabetes than in those without diabetes.

Pathophysiology of hyperglycemia

A detailed discussion of the pathophysiology of T2D and its relationship to aging is beyond the scope of this report. As summarized recently (8), T2D occurs in the

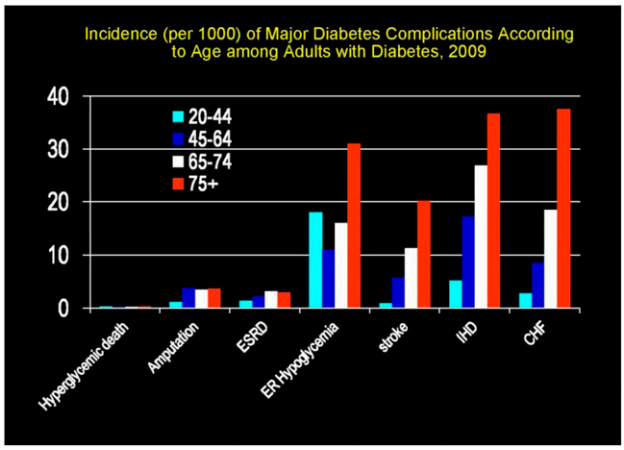

Figure 4. Incidence (per 1000) of major diabetes complications according to age among adults with diabetes, 2009 (6). ER, emergency room; ESRD, end-stage renal disease; IHD, ischemic heart disease. [Reproduced from the National Diabetes Surveillance System at http://www.cdc.gov/diabetes]

older population as a result of a complex interaction among genetic, lifestyle, and aging influences [see Fig. 5 (9)]. This complexity means that there is substantial heterogeneity in the pathophysiology, clinical features, and rate of progression of the disease among older people. A recent review summarizes the effects of aging on glucose tolerance and insulin secretion (8). Notably, consistent declines in β cell function and insulin secretion are hallmarks of aging in rodents and humans (10–18). These impairments limit the response to lifestyle-induced insulin resistance, resulting in progression to prediabetes and T2D. Glucose toxicity from chronic exposure to hyperglycemia can worsen insulin resistance and further impair pancreatic β cell function (19). Thus, hyperglycemia in diabetes may drive further worsening of age-related impairments of both β cell function and proliferation. Lipotoxicity from exposure to products of fat cell lipolysis may also contribute to this vicious cycle (20), as do visceral obesity and intramyocellular fat. The heterogeneity of T2D likely reflects the varying contributions of multiple factors to the development of hyperglycemia in a given individual or family. Understanding these factors for an individual patient may provide a basis for the selection of glucose-lowering interventions (8).

Systematic Review and Meta-Analyses

The Writing Committee commissioned two systematic reviews to support this guideline. Both reviews focused on individuals aged 65 years and older. Although the target population of this guideline is individuals with diabetes, concerns about not identifying sufficient evidence necessitated that the two systematic reviews summarize evidence on individuals with and without diabetes (presented separately).

The first review attempted to answer the following question: In older individuals, does treatment with antihypertensive pharmacologic therapy lead to improvement in patient-important outcomes? The review identified 19 randomized trials. Antihypertensive therapy was associated with a reduction in all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and CKD. Older patients with diabetes treated with antihypertensive therapy had lower risk of CKD without a significant reduction in other outcomes; however, there was no significant difference in estimates of beneficial effects between those with and without diabetes.

The second review attempted to answer the following question: In older individuals, does treatment with lipid-lowering pharmacologic therapy lead to improvement in patient-important outcomes? The review identified 23 randomized trials. For primary prevention, statins reduced the risk of coronary artery disease and myocardial infarction, but not all-cause or cardiovascular mortality or stroke. These effects were imprecise in patients with diabetes, but there was no significant interaction between diabetes status and the intervention effect. For secondary prevention, statins reduced all-cause mortality, cardiovascular mortality, coronary artery disease, myocardial infarction, and revascularization. Intensive (vs less intensive) statin therapy reduced the risk of coronary artery disease and heart failure.

In both of the systematic reviews, the quality of evidence, or certainty in the estimates, was high for most outcomes when evaluated in all older patients. When the evaluation was restricted to those with diabetes, the estimates of beneficial effects were generally similar to those observed in all older patients, but the CIs were relatively wide, indicating imprecision. Accordingly, the corresponding quality of evidence was considered to be moderate for older patients with diabetes. There was also no significant difference in estimates (interaction) between those with and without diabetes, suggesting that extrapolation of data from the older population at large to older individuals with diabetes is reasonable.

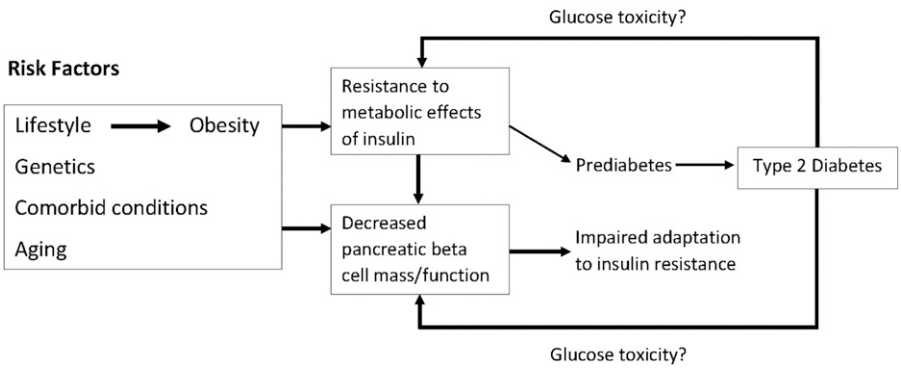

Figure 5. Model for age-related hyperglycemia (9). [Adapted with permission from Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab 2003;284:E7–E12.]

1. Role of the Endocrinologist and Diabetes Care Specialist

1.1 In patients aged 65 years and older with newly diagnosed diabetes, we advise that an endocrinologist or diabetes care specialist should work with the primary care provider, a multidisciplinary team, and the patient in the development of individualized diabetes treatment goals. (Ungraded Good Practice Statement)

1.2 In patients aged 65 years and older with diabetes, an endocrinologist or diabetes care specialist should be primarily responsible for diabetes care if the patient has T1D, or requires complex hyperglycemia treatment to achieve treatment goals, or has recurrent severe hypoglycemia, or has multiple diabetes complications. (Ungraded Good Practice Statement)

Evidence

Given the heterogeneity of the population of older adults with diabetes, the role of the endocrinologist or the diabetes care specialist in the care of an individual patient may vary considerably during the course of the disease. Decision-making about this role requires active participation and good lines of communication among the endocrinologist or diabetes care specialist, the primary care physician, and the patient. Because of the high burden of diabetes and its complications on overall health status (21, 22), many older patients benefit from care by an interdisciplinary team. The endocrinologist or diabetes care specialist functions as the leader of the diabetes care team, which includes a nurse educator, dietician, and others (*e.g.*, pharmacist, psychologist, social worker). The endocrinologist or diabetes care specialist may also serve the medical community by providing up-to-date training in the care of older patients with diabetes. Possible roles of the endocrinologist or diabetes care specialist include the following.

No role. Diabetes care is provided by the patient's primary care team, which has received up-to-date training in the care of older patients with diabetes. An endocrinologist or diabetes care specialist may not be needed for patients whose hyperglycemia and CVD prevention treatment goals are easily achieved with lifestyle alone or with simple oral agent therapy (one or two medications). Application of the Chronic Disease Model can facilitate diabetes quality care in the primary care setting (23).

Consultant-only collaborative care. Overall diabetes care is provided by the patient's primary care team. The endocrinologist or diabetes care specialist assists in assessing the patient's diabetes status and related complications and setting treatment goals with recommendations for specific interventions. Consultation may occur at the time of original diabetes diagnosis or when there is a change in the patient's diabetes status (*e.g.*, treatment goals no longer being achieved, recurrent hypoglycemia, development of one or more diabetes complications). Consultation may involve only a member (not all) of the diabetes care team (*e.g.*, nurse educator or dietician). The endocrinologist or diabetes care specialist may be asked to initiate insulin therapy for a patient and then send the patient back to the primary care provider once stable, or they may consult to assist with glycemic management when a patient is hospitalized.

Overall diabetes management. For selected patients, the endocrinologist or diabetes care specialist and the diabetes care team are primarily responsible for diabetes care and collaborate with providers who manage the patient's other health problems and comorbidities. This situation may occur by default if the patient has no primary care provider or if the patient is already under the care of the endocrinologist or diabetes care specialist for long-standing T1D or other endocrine conditions. Specific indications for the endocrinologist or diabetes care specialist to assume control of overall diabetes management for an older patient include complex hyperglycemia treatment (use of three or more glucose-lowering agents; the addition of insulin, especially multiple types or injections), recurrent severe hypoglycemia, multiple diabetes complications, and a long history of diabetes.

2. Screening for Diabetes and Prediabetes, and Diabetes Prevention

2.1 In patients aged 65 years and older without known diabetes, we recommend fasting plasma glucose and/or HbA1c screening to diagnose diabetes or prediabetes. (1l⊕⊕⊕⊕)

Technical remark: The measurement of HbA1c may be inaccurate in some people in this age group because of comorbidities that can affect the lifespan of red blood cells in the circulation. Although the optimal screening frequency for patients whose initial screening test is normal remains unclear, the writing committee advocates repeat screening every 2 years thereafter. As with any health screening, the decision about diabetes and prediabetes screening for an individual patient depends on whether some action will be taken as a result and the likelihood of benefit. For example, such screening may not be appropriate for an older patient with end-stage cancer or organ system failure. In these

situations, shared decision-making with the patient is recommended.

2.2 In patients aged 65 years and older without known diabetes who meet the criteria for prediabetes by fasting plasma glucose or HbA1c, we suggest obtaining a 2-hour glucose post–oral glucose tolerance test measurement. (2|⊕⊕⊕O)
Technical remark: This recommendation is most applicable to high-risk patients with any of the following characteristics: overweight or obese, first-degree relative with diabetes, high-risk race/ethnicity (*e.g.*, African American, Latino, Native American, Asian American, Pacific Islander), history of CVD, hypertension (≥140/90 mm Hg or on therapy for hypertension), high-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L), sleep apnea, or physical inactivity. Shared decision-making is advised for performing this procedure in frail older people or in those for whom it may be overly burdensome. Standard dietary preparation for an oral glucose tolerance test is advised.

2.3 In patients aged 65 years and older who have prediabetes, we recommend a lifestyle program similar to the Diabetes Prevention Program to delay progression to diabetes. (1|⊕⊕⊕⊕)
Technical remark: Metformin is not recommended for diabetes prevention at this time, as it is not approved by the Food and Drug Administration for this indication. As of 2018, a Diabetes Prevention Program–like lifestyle intervention is a covered benefit for Medicare beneficiaries in the United States who meet the criteria for prediabetes.

Evidence

The ADA defines diabetes and prediabetes based on glucose measures (24). Importantly, individuals with prediabetes are at increased risk for progression to diabetes and development of CVDs; Table 1 (24) lists the ADA criteria for prediabetes and diabetes. The fasting plasma glucose and HbA1c categories allow easy identification of both diabetes and prediabetes. However, many people over the age of 60 years affected with diabetes and prediabetes are not diagnosed unless an oral glucose tolerance test is performed (2). Importantly, individuals with prediabetes are at increased risk for progression to diabetes and development of CVDs. Population screening demonstrates a high rate of detection of newly diagnosed diabetes. Additionally, modeling such studies suggests that early detection and treatment of diabetes can reduce long-term complications (25). Furthermore, diabetes and prediabetes criteria predict risk for subsequent diabetes and CVD similarly in both older and younger people. The prevalence of disorders of sleep increases with age, and such disorders have been associated with the development or exacerbation of diabetes and risks of cardiovascular events. Therefore, assessment for sleep disorders and their treatment should be considered in older patients at risk for and with diabetes (26).

Progression from prediabetes to diabetes can be slowed substantially (27–30). Evidence supporting this observation includes recent meta-analyses involving

Table 1. ADA Criteria for Prediabetes and Diabetes

Prediabetes[a]	Diabetes[b]
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) = IFG OR 2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) = IGT OR A1C 5.7%–6.4% (39–47 mmol/mol)[d]	FPG ≥126 mg/dL (7.0 mmol/L) OR 2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT[c] OR A1C ≥6.5% (48 mmol/mol)[d] OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL (11.1 mmol/L).

[Data from American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019; 42:S13–s28].

Abbreviations: FPG, fasting PG; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

[a]For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

[b]In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

[c]The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

[d]The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay.

nearly 50,000 subjects (31, 32). In people over the age of 60 years in the Diabetes Prevention Program, lifestyle intervention to reduce body weight and increase physical activity reduced the rate of progression to diabetes by 71% during 4 years (estimated number needed to treat to prevent one person progressing to diabetes, 5.6). The reduced rate of progression to diabetes was maintained during 15 years of follow-up, although the lifestyle intervention was much less intense during the last 10 years (28, 29). Notably, the impact of this intervention is cost-effective (27). Additionally, metformin was less effective in people over the age of 60 years (estimated number needed to treat, 39.2) in the Diabetes Prevention Program, and the meta-analyses suggest that drug treatment tends to have transitory effects on diabetes prevention.

3. Assessment of Older Patients With Diabetes

Overall health framework

3.1 In patients aged 65 years and older with diabetes, we advise assessing the patient's overall health (see Table 2) and personal values prior to the determination of treatment goals and strategies (see Table 3). (Ungraded Good Practice Statement)

Evidence

The treatment strategies and goals developed for older adults depend on overall patient health, including medical complexity and functional status. Table 2 (33, 34) provides a guide for the comprehensive assessment of the older adult, including the general medical assessment and diabetes-focused evaluations. Functional status refers to a person's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being (35). Both aging and diabetes are independent risk factors for impaired functional status, and the interaction of these two factors is highly complex and unique for each patient. For this reason, recent diabetes guidelines have generally concluded that care of the aging patient with diabetes requires an individualized, rather than purely algorithmic, approach (36–38). However, there is no standard tool recommended for the assessment and documentation of how effectively older adults function in their lives. Functional status is most often documented using subsets of specific activities that are necessary for living independently. They include activities of daily living (ADLs), that is, bathing, dressing, eating, toileting, and transferring, as well as instrumental ADLs (IADLs), that is, preparing meals, shopping, managing money, using the telephone, and managing medications (Table 2) (34). In patients with diabetes, deficits in IADLs identified during routine evaluation should trigger a more in-depth evaluation of the patient, including a detailed assessment of hypoglycemia and hyperglycemia, microvascular and macrovascular complications, and cognition, as discussed in depth in this guideline.

Table 2. Clinical Care of Older People

General Health Assessment[a]	General Health Tests[b]	Diabetes-Specific Health[c]
Functional status (ADLs/IADLs[d])	ECG	Retinopathy
Depression	Lipid panel	Nephropathy
Cognition	Bone mineral density	Neuropathy
Fall risk	AAA ultrasound	Medical nutrition therapy
Weight (kg)/height $(m)^2$ = BMI	Diabetes screening (for nondiabetic persons)	Diabetes management
Blood pressure		Diabetes self-management training
Tobacco use		
Alcohol use		
Medication review		
Cancer screening		
Hearing		
Comorbid conditions		
Visual acuity		
Frailty/physical performance		

Abbreviations: AAA, abdominal aortic aneurysm; ADL, activity of daily living; BMI, body mass index; IADL, instrumental activity of daily living.

[a] All items are required services to qualify for Medicare coverage of annual wellness examinations for people in the United States >65 y of age, except for frailty/physical performance (33). These are generally conducted by primary care providers.

[b] All items are services covered by Medicare for people in the United State >65 y of age as part of annual wellness examinations at intervals varying from annually to once per lifetime (33).

[c] All items are services covered by Medicare for people in the United States >65 y of age as part of standard diabetes care (33). These are covered annually except for diabetes management visits, which are covered as recommended by the diabetes care team.

[d] Functional status is based on assessment of independence or dependency (having difficulty and receiving assistance) of five ADLs (bathing, dressing, eating, toileting, and transferring) and five IADLs (preparing meals, shopping, managing money, using the telephone, and managing medications) (34).

Table 3. Conceptual Framework for Considering Overall Health and Patient Values in Determining Clinical Targets in Adults Aged 65 y and Older

Overall Health Category		Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Patient characteristics		No comorbidities **or** 1-2 non-diabetes chronic illnesses* **and** No ADL€ impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses* **and/or** Any one of the following: mild cognitive impairment or early dementia; ≥2 IADL impairments	Any **one** of the following: End-stage medical condition(s)**; Moderate to severe dementia; ≥2 ADL impairments; Residence in a long-term nursing facility
		Reasonable glucose target ranges and HbA1c by group		
		Shared decision-making: individualized goal may be lower or higher		
Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)	No	Fasting: 90-130 mg/dL Bedtime: 90-150 mg/dL <7.5%	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL <8%	Fasting: 100-180 mg/dL Bedtime: 110-200 mg/dL <8.5%¥
	Yes£	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL ≥7.0 and <7.5%	Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL ≥7.5 and <8.0%	Fasting: 100-180 mg/dL Bedtime: 150-250 mg/dL ≥8.0 and <8.5%¥

Note: While glucose targets are highlighted for each group in this framework, overall health categories can also be considered for other treatment goals such as blood pressure and dyslipidemia. See Appendix A on "How to use the conceptual framework."

* Coexisting chronic illnesses may include osteoarthritis, hypertension, chronic kidney disease stages 1-3, or stroke, among others.

**One or more chronic illnesses with limited treatments and reduced life expectancy. These include metastatic cancer, oxygen-dependent lung disease, end-stage kidney disease requiring dialysis, and advanced heart failure.

£ As long as achievable without clinically significant hypoglycemia; otherwise, higher glucose targets may be appropriate. Note also that the lower HbA1c boundary was included as data suggesting increased hypoglycemia and mortality risk at lower HbA1c levels are strongest in the setting of insulin use. However, the lower boundary should not reduce vigilance for detailed hypoglycemia assessment.

¥ HbA1c of 8.5% correlates with an average glucose level of approximately 200 mg/dL. Higher targets than this may result in glycosuria, dehydration, hyperglycemic crisis and poor wound healing.

€ ADLs include bathing, dressing, eating, toileting, and transferring, and IADLs include preparing meals, shopping, managing money, using the telephone, and managing medications.

Includes data from Cigolle CT, Kabeto MU, Lee PG, Blaum CS. Clinical complexity and mortality in middle-aged and older adults with diabetes. J Gerontol A Biol Sci Med Sci 2012; 67(12):1313-1320 (39); and from Kirkman MS, Jones Briscoe V, Clark N, et al. Diabetes in older adults. Diabetes Care 2012; 35(12): 2650-2664 (40).

Abbreviations: IADL, instrumental activity of daily living; ADL, activity of daily living; SU, sulfonylurea.

Overall health in older adults has been described in terms of frameworks or categories that guide the clinician to consider multiple factors when assessing the health of an adult over the age of 65 years. One such framework was developed by Blaum *et al.* (35) and was incorporated into the 2012 ADA consensus report on the care of older adults with diabetes. The Blaum framework suggests considering chronic diseases (fewer than three vs three or more), cognitive or visual impairment (none, mild, moderate to severe), and IADL dependencies (none vs two or more) to define functional status. This framework was used to identify three classes of patients corresponding to increasing levels of mortality risk and was thus validated as a tool for determining the likelihood of benefit of a treatment strategy based on life expectancy (39). Using this evidence, the Blaum categories and the 2012 ADA consensus report as guides, we developed a conceptual framework for overall health that categorizes patients into good health (group 1), intermediate health (group 2), and poor health (group 3) groups [Table 3 (39, 40) and "Setting glycemic targets and goals" under section 4 on "Treatment of Hyperglycemia"].

Frailty

Frailty can be defined as a state of increased vulnerability to physical or psychological stressors because of decreased physiological reserves in multiple organ systems that cause a limited capacity to maintain homeostasis. Moreover, it represents a predisability condition that can be responsive to intervention (41).

Screening for geriatric syndromes, including frailty, should be part of a stepped-care approach in older people with diabetes, particularly in primary and community care settings. Where there is evidence of moderate to severe physical or cognitive impairment or functional loss, referral to geriatricians or other skilled clinicians for a comprehensive assessment is needed. The importance of detecting frailty lies in the opportunity to consider targeted interventions that reduce functional decline and risk of disability.

Any report of a change in mobility, presence of falls, noticeable decrease in IADLs after recent discharge from a hospital, or presence of continuing fatigue should prompt the clinician to screen for functional loss and/or frailty [Table 4 (42–45)]. An initial screen for physical impairment can be obtained by using the following commonly employed measures in geriatric practice (46) [Table 5 (47–51)].

Screening for sarcopenia

Sarcopenia is an age-related loss of muscle mass that has now been linked to progressive loss of muscle strength and reduced physical performance (52). Sarcopenia is accelerated in the presence of diabetes. Clinicians can refer patients with possible sarcopenia for a dual-energy X-ray absorptiometry scan, but this procedure is expensive and may not be convenient. Bioelectrical impedance analysis is an alternative method for the assessment of lean muscle mass and may be considered in place of dual-energy X-ray absorptiometry scanning. Alternatively, a rapid screening test for sarcopenia in a clinical setting can be obtained using a simple five-question instrument called the Sarc-F, which looks at fall history, ability to lift objects, and difficulties with mobility. This scale has been validated extensively and has been shown to be highly predictive of future disability and hospitalization (53).

Table 4. Tools to Detect Frailty

Assessment Tool	Comments
Fried score	Well-established physical frailty tool based on data from the Cardiovascular Health Study; often seen as a reference frame for studies of frailty in community-dwelling older adults; requires two procedures/measures (gait speed and grip strength) and answers to three questions (relating to weight loss, level of exhaustion, and amount of physical activity); can identify "prefrail" individuals (42).
Clinical Frailty Scale (Note: A larger 70-item assessment tool called the Frailty Index is also available.)	Based on data from the Canadian Study of Health and Aging; seven-point scale; predictive of future events including mortality; easy to employ in routine clinical practice (43).
FRAIL score	Well-validated in multiple population groups; sensitivity and specificity similar to that of the Fried scale. Comprises only five questions (no procedures) covering fatigue, climbing stairs, walking, number of illnesses, and weight loss (44).

[Reproduced with permission from Sinclair AJ, Abdelhafiz A, Dunning T, Izquierdo M, Rodriguez Manas L, Bourdel-Marchasson I, Morley JE, Munshi M, Woo J, Vellas B. An international position statement on the management of frailty in diabetes mellitus: summary of recommendations 2017. J Frailty Aging 2018;7:10–20.] (45)

Table 5. Commonly Employed Measures to Screen for Physical Impairment

Measure	Comments
Timed "get-up and go" test	Most adults can complete this test. Good correlation with gait speed, Barthel Index, and measures of balance (47, 48).
4-m Gait speed	Robust, clinically friendly measure. Easy to perform. Can be used to measure functional status in older adults and to predict future health and well-being. Population norms available (49, 50).
Grip strength	Requires a dynamometer for objective measurement; normative ranges in older people available. Predictive of increased future functional limitations and disability, increased fracture risk, and increased all-cause mortality (51).

Cognitive impairment in older adults with diabetes

In the general population, the prevalence of dementia increases from 1% to 2% at ages 60 to 64 years to 6% to 9% at ages 75 to 79 years to well above 35% in those who are 90 years and older (54). The population burden of cognitive impairment in older individuals is even larger if predementia stages of cognitive dysfunction, such as mild cognitive impairment (MCI), are also considered.

Epidemiological studies have found clear associations between diabetes and dementia risk (55). A meta-analysis including over 1 million individuals presented a pooled overall relative risk (RR) for dementia in people with diabetes of 1.73 (95% CI, 1.65 to 1.82) compared to people without diabetes (56). This increased risk was present in both Alzheimer's disease (RR, 1.56; 95% CI, 1.41 to 1.73) and vascular dementia (RR, 2.27; 95% CI, 1.94 to 2.66) (56); notably, however, Alzheimer's disease generally was not diagnosed with biomarker support in these epidemiological studies. Neuropathological studies indicate that diabetes is primarily associated with an increase in the burden of vascular pathologies rather than plaques and tangles, the neuropathological hallmarks of Alzheimer's disease (57). Moreover, diabetes is associated with an increased risk of MCI (RR, 1.21; 95% CI, 1.02 to 1.45) (58) and an increased rate of conversion from MCI to dementia (OR, 1.65; 95% CI, 1.12 to 2.43) (59). Of note, these numbers primarily apply to patients with T2D because data on older individuals with T1D are still scarce.

With the aging of the population and trends in diabetes prevalence, the combination of cognitive impairment and diabetes is likely to become more common, having implications for diabetes care. Clearly, cognitive impairment in patients with diabetes is associated with poorer diabetes self-management and glycemic control (60, 61), an increased frequency of hospital admissions and occurrence of severe hypoglycemic episodes (62, 63), and an increased occurrence of major cardiovascular events and death (64). Early identification of individuals with cognitive impairment may avoid some of these poor outcomes (65–67). Of note, the relationship between some of these "outcomes" and cognitive impairment may be bidirectional: there are clear indications that CVD, but also occurrence of hypoglycemic episodes (68), increase the risk of developing cognitive impairment in older patients with diabetes.

Detection and diagnosis

3.2 In patients aged 65 years and older with diabetes, we suggest that periodic cognitive screening should be performed to identify undiagnosed cognitive impairment. (2|⊕⊕OO)

Technical remark: Use of validated self-administered tests is an efficient and cost-effective way to implement screening (see text). Alternative screening test options, such as the Mini-Mental State Examination or Montreal Cognitive Assessment, are widely used. An initial screening should be performed at the time of diagnosis or when a patient enters a care program. Screening should be repeated every 2 to 3 years after a normal screening test result for patients without cognitive complaints or repeated 1 year after a borderline normal test result. Always evaluate cognitive complaints and assess cognition in patients with complaints.

Evidence

In the general population, screening for cognitive impairment and dementia is currently not recommended because of insufficient evidence on the balance of benefits and harms of screening (69). This ratio may be different in people with diabetes because the harm of unrecognized cognitive impairment (*e.g.*, risks related to diabetes treatment) might be larger than that in people without diabetes. The benefit of screening is that this harm might be at least partially avoided (67). Therefore, an active approach to the detection of cognitive impairment (*i.e.*, screening) has been advocated for older adults with diabetes (65, 67). However, the evidence base upon which screening procedures can be operationalized (*i.e.*, which target groups, type of test, frequency of testing) is limited. With regard to the target group, the chance of encountering cognitive impairment should be sufficiently high to warrant screening. At this stage, we therefore suggest that screening should be limited to those over the age of 65 years; in younger patients, actively responding to cognitive complaints should be sufficient.

The purpose of screening is to identify marked clinically relevant stages of cognitive impairment (*i.e.*, MCI or dementia) likely to interfere with diabetes management. A positive screening test should be complemented by an appropriate diagnostic evaluation, starting with history taking, to formally diagnose or rule out these conditions. With regard to the choice of screening test, brief widely used tests such as the Mini-Mental State Examination or Montreal Cognitive Assessment may be suitable, although administering these tests still requires ~10 minutes, and currently no strong evidence supports the choice of one particular test over another (70, 71). Notably, self-administered cognitive screening tools are becoming available and might offer an efficient alternative (72), greatly facilitating widespread implementation.

With regard to the timing and frequency of screening, performing an initial assessment at the time of diabetes diagnosis or when a patient enters a care program would be appropriate. Screening could then be repeated annually, or even less frequently, depending on the perceived risk. In patients without cognitive complaints, screening should be repeated 2 to 3 years after an initial normal screening test result or 1 year after a borderline normal test result. Cognitive complaints should always be evaluated.

Thus far, no evidence supports a benefit of intensive glycemic treatment to preserve cognitive function in patients with diabetes (68). However, further trials are underway, and cognition is increasingly considered an (secondary) outcome measure in drug trials in diabetes.

Management and treatment

3.3 In patients aged 65 years and older with diabetes and a diagnosis of cognitive impairment (*i.e.*, MCI or dementia), we suggest that medication regimens should be simplified (see recommendation 3.1) and glycemic targets tailored (*i.e.*, be more lenient; see recommendation 4.1) to improve compliance and prevent treatment-related complications. (2|⊕⊕OO)

Technical remark: Medical and nonmedical treatment and care for cognitive symptoms in people with diabetes and cognitive impairment is no different from those in people without diabetes and cognitive impairment. Depending on the situation and preferences of the patient, a primary caregiver can be involved in decision-making and management of medication.

Evidence

No randomized controlled trials (RCTs) have shown that simplified glucose-lowering treatment regimens improve adherence in patients with diabetes and cognitive impairment or that tailored glycemic targets reduce the risk of treatment-related adverse events, particularly hypoglycemic episodes. However, patients with impaired cognition are known to have lower adherence and an increased risk of adverse events (60, 61, 63). Furthermore, more stringent control increases the risk of hypoglycemia (see "Balancing risks and benefits of lower glycemic targets" under section 4 on "Treatment of Hyperglycemia"). Therefore, the assumption that simplifying treatments and tailoring targets improve compliance and prevent treatment-related complications in patients with impaired cognition is reasonable. HbA1c levels <8.0% (64 mmol/mol) have been proposed for mild-to-moderate cognitive impairment, and those below 8.5% (69 mmol/mol) for moderate to severe cognitive impairment (66).

With regard to patient care and management in those with cognitive impairment, regular review of the patient's ability to self-manage diabetes and the need for appropriate support is essential. Providing support for caregivers and involving them in all aspects of care are also important.

4. Treatment of Hyperglycemia

Setting glycemic targets and goals

4.1 In patients aged 65 years and older with diabetes, we recommend that outpatient diabetes regimens be designed specifically to minimize hypoglycemia. (1|⊕⊕⊕O)

Technical remark: Although evidence for specific targets is lacking, glycemic targets should be tailored to overall health and management strategies (*e.g.*, whether a medication that can cause hypoglycemia is used) (see Table 3).

Evidence

Hypoglycemia has both acute and chronic negative effects on individuals with diabetes in both outpatient and inpatient settings, although this section pertains to outpatient practice only (see "Special Settings and Populations" for evidence relevant to inpatient care). In the adult population aged 65 years and older, hypoglycemia appears to increase the risk of traumatic falls (73–75) and has a bidirectional relationship with cognitive dysfunction (see "Cognitive impairment in older adults with diabetes" under section 3 on "Assessment of Older Patients with Diabetes"). Hypoglycemia has also been associated with morbidity and mortality in *post hoc* analyses of data from large clinical trials that included older adults. In one study that analyzed data from the

Action in Diabetes and Vascular Disease: Preterax and Dimicron Modified Release Controlled Evaluation (ADVANCE) trial, 231 patients had at least one severe hypoglycemic episode. Of these patients, most (65%) had been randomized to the intensive control arm of the trial (goal HbA1c <6.5%). The authors reported that severe hypoglycemia was associated with an approximate doubling of the adjusted risks of major macrovascular and microvascular events, death from a cardiovascular cause and death from any cause ($P < 0.001$). Severe hypoglycemia was also associated with other conditions such as respiratory and gastrointestinal conditions (76).

Although avoidance of hypoglycemia is a critical treatment strategy, overall glucose control remains an important goal. Blood glucose levels consistently over the renal threshold for glycosuria (>200 in chronic hyperglycemia, although variable) routinely increases the risk of dehydration, electrolyte abnormalities, urinary infections, dizziness, and falls. Hyperglycemic crises, including diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, and the combination of the two (hyperosmolar ketoacidosis), are severe complications of unrecognized or undertreated hyperglycemia in older adults. Older adults with these conditions have higher mortality rates than do younger individuals (77). Relaxing glycemic targets for older patients with a high burden of comorbidities and limited life expectancy may be appropriate, yet goals that minimize hyperglycemia are indicated for all patients.

Balancing risks and benefits of lower glycemic targets

As first noted in the Diabetes Control Complications Trial (DCCT), achieving a lower mean glucose to reduce complications may come at the cost of increased hypoglycemia risk (78). Because prevention of both microvascular and macrovascular disease via glycemic control may take years to realize, the health value of strict glycemic targets later in life has been controversial. National and international guidelines that address glycemic targets generally agree on individualizing care based on overall health status and weighing the expected timing of benefits against life expectancy (37, 79, 80).

Several studies have illustrated the clinical challenge of selecting glycemic targets by associating HbA1c achieved with mortality. One large retrospective analysis from the United Kingdom associated survival with HbA1c in a cohort of >40,000 individuals with T2D aged 50 years or older whose treatment had been intensified beyond oral monotherapy. The results showed a U-shaped association; the adjusted hazard ratios (HRs) of all-cause mortality were 1.52 (95% CI, 1.32 to 1.76) and 1.79 (95% CI, 1.56 to 2.06) in the groups with the lowest (median, 6.4%) and highest HbA1c (median, 10.5%) levels, respectively, compared with the group with a median HbA1c of 7.5% (81).

A secondary analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomized trial further highlighted the complexity of targets by addressing setting vs achieving HbA1c targets. This trial compared the outcomes of achieving a relatively low glycemic target of HbA1c <6.5% with those of achieving an HbA1c of 7% to 7.9%. Multiple treatment options were available to providers to achieve glucose goals. After ~5 years, the intensive treatment group had a 20% higher rate of mortality, which was significant, and subsequent analysis of 10,251 subjects enrolled in ACCORD indicated that the group of subjects who were unable to reach the intensive HbA1c target accounted for the excess mortality (82). This analysis also demonstrated that a higher average on-treatment HbA1c was a stronger predictor of mortality than was a lower HbA1c and that the risk of death with the intensive strategy increased linearly from 6% to 9% HbA1c (82). Of note, the progression of retinopathy was reduced by 30% with intensive control, although no measurements of functional status were reported for judging the impact on overall health (83). However, this finding was not reproduced in the recently published long-term results of the Veterans Affairs Diabetes Trial (VADT) (84).

Importantly, older individuals enrolled in diabetes clinical trials are more likely to have better overall health than are older individuals in the general population. Numerous studies successfully achieved standard glycemic targets without increased hypoglycemia in older adults with good or intermediate health (85, 86). Because these trials exclude older adults with poor health, they support the concept that intensive strategies for selected individuals can be effective and safe. The compendium of results from these and other published analyses suggests that although some patients may benefit from tighter targets, many are unable to reach these targets, and aggressive therapy may be harmful to some patients without the benefit of reducing complications.

Assessing glycemia in older adults with diabetes

4.2 In patients aged 65 years and older with diabetes who are treated with insulin, we recommend frequent fingerstick glucose monitoring and/or continuous glucose monitoring (to assess glycemia) in addition to HbA1c. (1|⊕⊕OO)

Evidence

Although measurement of HbA1c is a convenient and validated method for determining overall glycemic status,

it does not assist in identifying hypoglycemia. In one study, 40 patients aged 69 years or older with HbA1c values ≥8% were evaluated with blinded continuous glucose monitoring (CGM) for 3 days. Most (70%) had T2D, and nearly all (93%) were treated with insulin. Nearly 75% of subjects experienced a glucose level <60 mg/dL despite an elevated HbA1c. Importantly, of the 102 hypoglycemic episodes recorded, 93% were unrecognized by symptoms or by fingerstick glucose measurements performed four times a day (87). Detailed assessment of glycemia in older adults may also indicate glycemic variability, which is directly calculated by CGM systems and predicts hypoglycemia in older adults with T1D (88).

Older adults with T2D also tend to display unique glucose patterns, with relatively more postprandial hyperglycemia than fasting hyperglycemia (89). Knowledge of such patterns should lead to more tailored and potentially safer medication regimens, for example, adding premeal insulin to one large meal per day instead of progressive titration of long-acting basal insulin.

When available, CGM is an important tool for safely addressing high-risk glycemic patterns. CGM use in older adults is limited and is variable across populations, including patients with T1D, those with T2D, those using insulin pump therapy, and those using multiple daily injections of insulin. Clinicians who prescribe CGM for older adults need to consider many factors, including use of personal vs intermittent diagnostic CGM, patient selection and individualized goals of CGM, patient access and affordability, and involvement of family and/or caregivers in sharing of glucose data. For those older adults who have been enrolled in clinical trials, CGM used intermittently or continuously appears to be a useful tool for guiding therapy to allow improved glycemic control without increased hypoglycemia. In a clinical trial by Vigersky *et al.* (90), individuals with T2D, including older adults, were randomized to intermittent real-time CGM to test the impact on glycemic control. The population included individuals using various antihyperglycemic agents, including basal insulin but excluding prandial insulin. Interestingly, the results indicated that intermittent CGM can assist both patients and providers in adjusting diabetes regimens to achieve lower targets without increasing hypoglycemia risk (90). In the older adult cohort of the DIAMOND study, 116 individuals ≥60 years of age with both T1D and T2D on multiple daily injections of insulin were randomized to either personal real-time CGM or to continuation of self-monitored blood glucose. At the end of 6 months, the CGM group demonstrated high use (97% of participants used CGM at least 6 days per week), greater HbA1c reduction, and less glycemic variability (91).

In addition to its limitations in identifying glucose patterns, the HbA1c test must be interpreted with caution, which is particularly significant in older adults given the increased likelihood of relevant conditions that may alter red blood cell turnover (*e.g.*, advanced kidney disease, gastrointestinal bleeding, valvular heart disease). This topic has been explored in detail by others (92, 93).

Lifestyle interventions for older adults with diabetes

Lifestyle modifications

4.3 In patients aged 65 years and older with diabetes who are ambulatory, we recommend lifestyle modification as the first-line treatment of hyperglycemia. (1|⊕⊕⊕⊕)

Evidence

In overweight patients, lifestyle modifications resulting in as little as 5% weight loss can improve glycemic control and the need for medications to control glucose levels (94, 95). Nonetheless, older patients face a number of issues related to nutrition and exercise capacity. Weight loss should be approached with caution in older adults, as both intentional and unintentional weight loss may lead to severe nutritional deficiencies (40). The recommendation of a combination of physical activity and nutritional therapy, including the recommended intake of calcium, vitamin D, and other nutrients, is an appropriate strategy for this population. An increase in physical activity in older adults should reduce sedentary behavior, and moderate-intensity aerobic activity should be emphasized. Moreover, the activity plan must consider the older adult's abilities and aerobic fitness after careful medical evaluation, including exercise testing and heart rate/blood pressure (BP) monitoring as needed. Activities aimed at increasing flexibility, muscle strength, and balance are also recommended (96).

Intensive education regarding carbohydrate and calorie counting and meal planning can be useful for individuals with an active lifestyle to effectively modify insulin dosing and improve glycemic control (97, 98). A simpler diabetes meal planning approach emphasizing portion control and healthful food choices may be more suitable for older individuals with cognitive impairment or learning difficulties (99, 100). In the case of sarcopenia, nutritional therapy coupled with exercise training is thought to be beneficial.

Nutrition

Nutrition is an integral component of diabetes self-care for all people with diabetes regardless of age (79, 101). Notably, nutritional guidelines do not differ for

older adults with or without diabetes. However, older adults may experience unique challenges that impact their ability to follow a healthy diet (*i.e.*, finances, buying food, preparing meals) or have a higher risk of malnutrition due to taste and smell alteration, dysphagia, deficient dentition, gastrointestinal dysfunction, anorexia, cognitive dysfunction, and/or depression (40, 102).

4.4 In patients aged 65 years and older with diabetes, we recommend assessing nutritional status to detect and manage malnutrition. (1l⊕⊕⊕⊕)
Technical remark: Nutritional status can be assessed using validated tools such as the Mini Nutritional Assessment and Short Nutritional Assessment Questionnaire.

Evidence

Many studies support early screening for malnutrition in older patients, especially those at high risk for malnutrition (acute care-admitted patients and home-care residents) (103, 104). Malnutrition is an important problem in the older adult population and has potentially serious consequences, such as prolonged hospitalization, increased costs, and a higher number of readmissions (105, 106). Therefore, early detection and management of malnutrition are crucial for preventing future complications. Moreover, a number of screening tools are already available to assess nutritional status, and certain assessments, such as the Mini Nutritional Assessment and Short Nutritional Assessment Questionnaire, can be easily administered to older individuals.

4.5 In patients aged 65 years and older with diabetes and frailty, we suggest the use of diets rich in protein and energy to prevent malnutrition and weight loss. (2l⊕⊕OO)

Evidence

Low-quality studies suggest that consuming energy-dense and protein-rich food could improve food consumption and prevent weight loss and malnutrition risk. Approximately 40% of older adults do not meet the recommended 0.8 g/kg protein intake requirement. The PROT-AGE study group has recently recommended an average daily intake in the range of 1.0 to 1.2 g/kg body weight/d for healthy older people and even 1.2 to 1.5 g/kg body weight/d in older patients with acute or chronic diseases. Furthermore, experts have proposed a protein intake of at least 1.5 g/kg/d (15% to 20% of the total caloric intake) in sarcopenic or cachectic older individuals (107). Studies on specific nutrients (protein supplements, branched-chain amino acids, creatine) have not shown consistent benefits (108), although the Society for Sarcopenia, Cachexia, and Wasting Diseases recommends measuring 25-hydroxyvitamin D levels and replacing them if low in all sarcopenic patients (109).

Nutrition plans for patients with diabetes are generally individualized healthy diets based on preferences, abilities, and treatment goals. We must emphasize healthful eating patterns consisting of nutrient-dense, high-quality foods rather than specific nutrients to improve overall health regarding body weight; glycemic, BP, and lipid targets; and reductions in the risk of diabetes complications (101). The Mediterranean (110), Dietary Approaches to Stop Hypertension (DASH) (111, 112), and plant-based (113) diets are all examples of healthful eating patterns.

Dietary guidelines recommend an increase in fiber intake of 25 to 35 g/d (114). Choosing vegetables, legumes, whole grains, and high-fiber breakfast cereals is the best way to increase fiber consumption, although increasing fiber should be avoided in cases of delayed gastric emptying (gastroparesis). Additionally, meeting fluid intake recommendations is important for preventing constipation and fecal impaction in older adults (115).

People with diabetes should limit their sodium consumption to <2300 mg/d. Palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet are all important considerations (116). Additionally, older adults are much more likely to suffer the adverse effects of alcohol due to changes in their ability to metabolize alcohol, particularly those taking multiple medications and those who are at increased risk of adverse events (117, 118).

4.6 In patients aged 65 years and older with diabetes who cannot achieve glycemic targets with lifestyle modification, we suggest avoiding the use of restrictive diets and instead limiting consumption of simple sugars if patients are at risk for malnutrition. (2l⊕OOO)
Technical remark: Patients' glycemic responses to changes in diet should be monitored closely. This recommendation applies to both older adults living in the community and those in nursing homes.

Evidence

For nursing home residents, some studies (119–121) suggest that it is better to use regular diets for nursing home residents with diabetes. Diets tailored to a patient's culture, preferences, and personal goals might increase quality of life, satisfaction with meals, and nutritional status (119, 120). Moreover, short-term substitution of

controlled diets with "diabetic diets" was not found to modify the level of glycemic control (122).

As the most common fluid and electrolyte disturbance in older adults, dehydration needs to be prevented and managed in people living in long-term care facilities (123). Many interventions can reduce its prevalence (124, 125) in this population and, notably, diuretics and antihypertensives should be carefully managed after admission to avoid contributing to fluid and electrolyte depletion.

For community-dwelling older adults, maintaining a nutrient-dense diet is essential for promoting health and preventing nutrition-related complications (126). Evidence indicates that restrictive diets impose significant risks of sarcopenia and malnutrition in community-dwelling older adults (127).

Drug therapy for hyperglycemia

Glycemic management of diabetes in older individuals

Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older people with diabetes, especially those with CKD and heart disease.

4.7 In patients aged 65 years and older with diabetes, we recommend metformin as the initial oral medication chosen for glycemic management in addition to lifestyle management. (1|⊕⊕⊕O)
Technical remark: This recommendation should not be implemented in patients who have significantly impaired kidney function [estimated GFR (eGFR) <30 mL/min/1.73 m^2] or have a gastrointestinal intolerance.

Evidence

Metformin is highly effective, may reduce cardiovascular events and mortality, and does not cause hypoglycemia or weight gain (94, 95, 128, 129). As clinical events that may precipitate acute kidney injury, such as radiocontrast dye, nephrotoxic drugs, hypotension, heart failure, and surgery, may cause metformin accumulation, with a potential risk for lactic acidosis, metformin use is often stopped when patients are hospitalized. An additional concern is the development of vitamin B12 deficiency, and levels should be monitored yearly (130–133).

4.8 In patients aged 65 years and older with diabetes who have not achieved glycemic targets with metformin and lifestyle, we recommend that other oral or injectable agents and/or insulin should be added to metformin. (1|⊕⊕⊕⊕)
Technical remark: To reduce the risk of hypoglycemia, avoid using sulfonylureas (SUs) and glinides, and use insulin sparingly. Glycemic treatment regimens should be kept as simple as possible.

Evidence

SUs and glinides. SUs, repaglinide, and nateglinide can cause hypoglycemia and weight gain. Glyburide should be avoided in older individuals because of a substantially increased risk of hypoglycemia compared with that of glimepiride and glipizide (130, 131, 134, 135).

Thiazolidinediones. Pioglitazone and rosiglitazone can cause fluid retention and may precipitate or worsen heart failure; indeed, these drugs are contraindicated in patients with class III and IV heart failure (see "Management of congestive heart failure in older adults with diabetes" under section 5 on "Treating Complications of Diabetes") (136–138). Furthermore, these medications are associated with increased fracture rates and bone loss in women (139, 140); thus, use in older women with underlying bone disease, such as osteoporosis, could potentially be problematic.

α-Glucosidase inhibitors. α-Glucosidase inhibitors have only modest efficacy, and in older individuals, the gastrointestinal adverse effects of flatulence and diarrhea tend to cause a relatively high rate of nonadherence (141).

Dipeptidyl peptidase-4 inhibitors. Dipeptidyl peptidase-4 (DPP-4) inhibitors are generally well tolerated. Importantly, early concerns regarding an increased risk of pancreatitis have not been borne out (142, 143), although some DPP-4 inhibitors have been associated with heart failure (see "Management of congestive heart failure in older adults with diabetes" under section 5 on "Treating Complications of Diabetes").

Sodium-glucose cotransporter 2 inhibitors. Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce HbA1c by ~0.8%, can reduce weight, and do not cause hypoglycemia. Recently, both empagliflozin and canagliflozin have been shown to decrease major adverse cardiovascular events (MACE), heart failure, and the progression of CKD (144, 145). These compounds cause an obligate increase in urine volume and an increase in urogenital candida infections. Because adverse effects related to volume depletion were more frequent in older patients treated with canagliflozin, recommendations limit the dosage to 100 mg/d in such patients (146, 147). Canagliflozin has also been shown to be associated with a

decrease in bone mineral density at the hip, but not the femoral neck, lumbar spine, or distal radius (148), with a significant increase in fractures of arms and legs but not the spine (149). Very rare cases of diabetic ketoacidosis have been reported in patients with T2D taking SGLT2 inhibitors, including patients over the age of 65 years (150, 151).

Glucagon-like peptide 1 receptor agonists. Glucagon-like peptide 1 (GLP-1) receptor agonists increase insulin release, decrease glucagon secretion, delay gastric emptying, suppress appetite, and do not cause hypoglycemia; however, nausea is a common side effect (152). Initial concern about an increased risk for pancreatitis has not been proven (142, 143). Liraglutide and semaglutide have been found to improve cardiovascular outcomes (see "Congestive heart failure in older adults with diabetes" under section 5 on "Treating Complications of Diabetes").

Insulin. In patients with T2D, insulin therapy is usually initiated when oral agents do not provide sufficient glycemic control (153). Self-monitoring of blood glucose must be performed for insulin to be used safely and effectively.

Initially, a single long-acting insulin analog can be added as basal insulin therapy with dose adjustment to maintain fasting glucose in the desired range (79, 153, 154). Recently, insulin glargine U300 and insulin degludec, which are longer-acting basal insulins compared with insulin glargine U100, showed overall similar levels of glycemic control but with less variability and hypoglycemia (155, 156). If fasting glucose is near goal but the HbA1c remains above goal, rapid-acting insulin can be added first, prior to the largest meal and then prior to other meals, as necessary (79, 153, 154). Additionally, premixed insulins (neutral protamine hagedorn with regular or analog insulin) given twice daily may be a simpler approach (157), but the lack of flexibility, especially in patients who may skip or delay meals, may increase the risk of hypoglycemia (153).

Increasing from one to three or four injections per day means moving from a less complex to a more complex regimen, which may be limiting (79, 153, 154). The complexity of the treatment regimen must be balanced against the treatment goals and risks of hypoglycemia. For patients with arthritis of their hands, the use of insulin pens, or other assistive appliances, can be helpful.

Recently, fixed doses of GLP-1 receptor agonists and basal insulin, insulin degludec and liraglutide (IDegLira) and insulin glargine and lixisenatide (LixiLan), have become available in a single syringe, and thus only one injection is needed. A low dosage of the combination is started, and then the dosage is gradually titrated upward. Interestingly, studies have reported excellent reduction in HbA1c with less hypoglycemia and weight loss rather than weight gain compared with increased titration of basal insulin alone or intensification with basal/bolus insulin (158–160).

Values and preferences

Because T2D slowly worsens over time (161), increasing dosages and numbers of medications may be needed to control glucose levels. However, the sequence in which drugs should be added after metformin is not clear. Recent recommendations indicate that GLP-1 receptor agonists and SGLT2 inhibitors be prescribed early, given their beneficial cardiovascular outcomes (24, 162). In general, the more drugs that are prescribed, the poorer is adherence to a particular regimen (163). Of critical importance is the avoidance of hypoglycemia, which can have devastating outcomes in older patients. Thus, SUs and insulin should be avoided if at all possible.

5. Treating Complications of Diabetes

Macrovascular disease

Management of hypertension in older adults with diabetes

Hypertension is a well-known risk factor for cardiovascular and kidney disease. Lifestyle modification is generally advocated as the first treatment modality (see "Lifestyle interventions for older adults with diabetes" under section 4 on "Treatment of Hyperglycemia"), but one or more medications are usually needed for most patients. The goals of treatment and the specific medications used for treatment may differ between patients with diabetes and those without diabetes, particularly older adults.

5.1 In patients aged 65 to 85 years with diabetes, we recommend a target BP of 140/90 mm Hg to decrease the risk of CVD outcomes, stroke, and progressive CKD. (1|⊕⊕⊕O)

Technical remark: Patients in certain high-risk groups could be considered for lower BP targets (130/80 mm Hg), such as those with previous stroke or progressing CKD (eGFR <60 mL/min/1.73 m^2 and/or albuminuria). If lower BP targets are selected, careful monitoring of such patients is needed to avoid orthostatic hypotension. Patients with high disease complexity (group 3, poor health, Table 3) could be considered for higher BP targets (145 to 160/90 mm Hg). Choosing a BP

target involves shared decision-making between the clinician and patient, with full discussion of the benefits and risks of each target.

Evidence

In individuals who do not have diabetes (generally under the age of 65 years) many trials have shown that BP levels <140/90 mm Hg reduce mortality, MACE, and the progression of kidney disease. Thus, this level was recommended by the 2014 Eighth Joint National Committee evidence-based guideline for the management of high blood pressure in adults (164). In that guideline, the BP target for individuals >60 years of age is <150/90 mm Hg. However, the recent Systolic Blood Pressure Intervention Trial (SPRINT), which evaluated 9361 nondiabetic persons randomized to systolic BP (SBP) targets of <140 vs <120 mm Hg showed a 25% reduction in MACE and a 27% reduction in all-cause mortality with the more intensive treatment (165). The mean age of subjects entering SPRINT was 68.2 years, with 28% >75 years of age (165). Significant increases in rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure were observed in the more intensively treated group, but these increases were not significantly greater in participants >75 years of age (165). The way in which BP was measured in SPRINT (unattended automated machine) was subsequently noted to yield a SBP 16 mm Hg lower than a standard office BP measurement (*i.e.*, 136 vs 120 mm Hg) (166).

A systematic review and meta-analysis from the American College of Physicians and the American Academy of Family Physicians supported a level of <150/90 mm Hg for individuals aged 60 years or older with less consistent evidence for the SBP target of <120 mm Hg (167). The American College of Physicians and American Academy of Family Physicians guideline, titled "Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower BP targets," contained a strong recommendation for an SBP <150 mm Hg in all patients, and a recommendation for a SBP <140 mm Hg for patients with a history of stroke or transient ischemic attacks and those at high cardiovascular risk (168). The 2017 Diabetes and Hypertension Position Statement from the ADA supported a target of <140/90 mm Hg for "fitter" older individuals but a higher SBP (145 to 160 mm Hg) for individuals with loss of autonomy or major functional limitations (169). However, the 2017 high BP guideline from the American College of Cardiology/American Heart Association redefined BP categories as normal (SBP <120 mm Hg, diastolic BP <80 mm Hg), elevated (SBP 120 to 129 mm Hg, diastolic BP 80 to 89 mm Hg), and hypertension (SBP ≥130 or diastolic BP ≥90 mm Hg) and recommended a target of <130/80 mm Hg for all adults, including those with diabetes, because of the increased cardiovascular risk in such patients. This recommendation was based primarily on the SPRINT data; however, the guideline acknowledged the lack of randomized trial data supporting this target in patients with diabetes (170).

Four large prospective randomized studies have been performed in patients with diabetes and targeted two different BP goals: the United Kingdom Prospective Diabetes Study (UKPDS) (171), the ACCORD study (172), the ADVANCE trial (173), and the Hypertension Optimal Treatment (HOT) trial (174). Overall, these studies generally support the goal of <140/90 mm Hg, although a *post hoc* report of SPRINT-eligible ACCORD-BP patients suggested that the SBP goal of 120 mm Hg also applied to patients with diabetes (175).

Similarly, the goal of <140/90 mm Hg rather than lower goals is supported by *post hoc* analyses of several other studies in patients with diabetes, including the Irbesartan Diabetic Nephropathy Trial (IDNT) (176), INVEST (177), the VADT (178), the Louisiana State University Hospital–Based Longitudinal Study (179, 180), and the Veterans Affairs Nephropathy in Diabetes Trial (181).

Moreover, several systematic reviews and meta-analyses have shown that an SBP treatment goal of 130 to 140 mm Hg is optimal and that a goal of <130 mm Hg is associated with a decrease in stroke risk. However, these reports show higher adverse effects [and even higher risk (J-curve) in some reviews] (182–188) and no further benefit to other CVD outcomes and mortality when SBP is <120 mm Hg.

Values and preferences

Although most studies and guidelines have recommended a BP target of <140/90 mm Hg, the 2017 American College of Cardiology/American Heart Association guideline recommends a target of <130/80 mm Hg, even in older patients with diabetes (170). Thus, treatment approaches and goals are controversial. Many clinicians may opt for this lower target in patients at high CVD risk after careful discussion of the pros and cons of such increased intensity of treatment with the patient.

Importantly, consideration should also be given to a higher BP target if the patient develops symptomatic orthostatic hypotension, and medications that tend to cause orthostatic hypotension should be avoided (189). Additionally, prescribing one or more hypertension medications to be taken at bedtime may have additional CVD benefits (190).

5.2 In patients aged 65 years and older with diabetes and hypertension, we recommend that an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be the first-line therapy. (1|⊕⊕⊕O)

Technical remark: If one class is not tolerated, the other should be substituted.

Evidence

Several studies have demonstrated a reduction in the progression of diabetic CKD with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with hypertension and advanced CKD (191–193). Subsequent head-to-head studies have shown that these two drug classes are essentially equivalent for diabetic CKD (194). Moreover, ACE inhibitors have been shown to significantly reduce the risk of all-cause and CVD mortality, MACE, and heart failure, whereas ARBs significantly reduce only the risk of heart failure. Neither drug class has been shown to significantly reduce the risk of stroke (195–197). ACE inhibitors also appear to reduce the progression of retinopathy (see "Eye complications in older adults with diabetes" under section 5 on "Treating Complications of Diabetes"). Therefore, ACE inhibitors and ARBs should be the first-line therapy used for the treatment of hypertension in older patients with diabetes and should be included when more than one medication is needed, especially if albuminuria is present (169). Nonetheless, these two drug classes should not be used together, especially in patients with CKD, due to increased risks of hyperkalemia and acute kidney injury (198).

Values and preferences

The need for more than one drug to treat hypertension is common in patients with T2D (199). Two drugs should be started together if the initial BP is ≥160/100 mm Hg (170, 200). The calcium channel blocker amlodipine has been shown to provide better cardiovascular outcomes than other agents by the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study (201, 202) and is therefore commonly added as a secondary antihypertensive agent.

The question of the third or fourth drugs to be added after renin-angiotensin system blockers and calcium blockers has not been addressed in either controlled clinical trials or meta-analyses. Because hypertension involves a volume component in many patients with T2D, a thiazide diuretic is commonly recommended as the third drug unless the eGFR is <30 mL/min/1.73 m^2, in which case a loop diuretic might be more appropriate (169, 202–204). If coronary artery disease is significant, a beta-blocker may be appropriate and can be added as a fourth drug to a prior three-drug regimen (205). If a beta-blocker is used, carvedilol has been shown to have fewer metabolic effects than metoprolol (206). Notably, when BP is not controlled with three or more medications, referral to a hypertension specialist is indicated (169).

Management of hyperlipidemia in older adults with diabetes

5.3 In patients aged 65 years and older with diabetes, we recommend an annual lipid profile. (1|⊕⊕OO)

5.4 In patients aged 65 years and older with diabetes, we recommend statin therapy and the use of an annual lipid profile to achieve the recommended levels for reducing absolute CVD events and all-cause mortality. (1|⊕⊕⊕⊕)

Technical remark: The Writing Committee did not rigorously evaluate the evidence for specific LDL-C targets in this population, so we refrained from endorsing specific LDL-C targets in this guideline. For patients aged 80 years old and older or with short life expectancy, we advocate that LDL-C goal levels should not be so strict.

Evidence

Epidemiological evidence documents that diabetes is an independent risk factor for CVD in both men and women. Furthermore, in patients with diabetes, all major cardiovascular risk factors, including cigarette smoking, hypertension, and high serum cholesterol (207–209), add to the degree of risk for CVD in older patients with diabetes. Individuals with diabetes have more than twice the risk for CVD than do those who do not have diabetes.

Cholesterol-lowering treatment with statins is equally efficacious in reducing RR and more effective in reducing absolute CVD events in older adults than in younger individuals because the older patients have a higher absolute risk for CVD. Most studies indicate that diabetic dyslipidemia in older adults is undertreated (210).

Numerous studies have confirmed the relationship between hypercholesterolemia and CVD, including myocardial infarction and stroke. Similarly, in large RCTs and multiple meta-analyses, statin use has been found to be effective in primary and secondary prevention when using myocardial infarction, revascularization and stroke as endpoints (211, 212).

Most patients aged 65 years and older with diabetes do not have marked elevations of LDL-C, because the method of measuring LDL-C underestimates the LDL particle number. However, these LDL-C levels are high enough to support the development of atherosclerosis

(213). Because LDL-C may be normal but LDL particles may be small (213), risk stratification should be used to determine the level of LDL-C that should be achieved in older patients with diabetes using statins. Calculated non-HDL, which reflects all atherogenic particles, adds to the assessment of atherogenicity. Furthermore, risk stratification can be achieved by a number of CVD risk calculators, and, when indicated, coronary artery calcium may enhance risk stratification (214). Apolipoprotein B measurement can be useful in some patients to help refine their LDL treatment goal.

A role for LDL-C in hyperglycemic patients became apparent in several early large clinical trials [*e.g.*, the 4S trial (215, 216), the Cholesterol and Recurrent Events (CARE) trial (217, 218), and the LIPID trial (219) using pravastatin]. In all of these trials, aggressive LDL-C–lowering therapy reduced recurrent CHD events in patients with diabetes, including those >65 years of age, by ~25% to 35% (220, 221).

Additionally, the Treating to New Targets (TNT) study showed that patients with a high risk of CVD, including risk factors for diabetes and aging, should be treated with high doses of statins (atorvastatin at 80 mg vs atorvastatin at 10 mg) to reduce their LDL-C levels to <70 mg/dL and improve CVD outcomes (222). In contrast to statins, fibrates did not cause a significant reduction in stroke events compared with placebo in clinical trials.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial (223) included men and women, and the average age was 75 years. Approximately 8% of the participants had diabetes, and 3 years of pravastatin treatment reduced CVD during the subsequent 8 years. The average age in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (224) was 63 years, and ~16% of the patients had diabetes. High-dose atorvastatin was shown to reduce recurrent stroke by almost 25% in this trial. Most studies have included men and women >65 years of age, and subgroup analyses have also shown beneficial results for patients with known diabetes. Overall, older patients with diabetes experienced a 35% decrease in CVD events from statin therapy, and side effects were minimal. In general, high-dose statin therapy is indicated for all patients with diabetes, irrespective of age, unless specifically contraindicated. Furthermore, although LDL-C levels are not necessarily elevated in patients with diabetes, statins still have a profound effect on the prevention of CVD, and thus all patients with T2D should be treated with statins. (Caveat: Most, but not all, studies support the value of statin use in the prevention of CVD in patients with diabetes.)

As described in the technical remark, the Writing Committee did not rigorously evaluate the evidence for specific LDL-C targets in older patients with diabetes. Therefore, we refrained from proposing specific LDL-C targets. The reader is referred to numerous guidelines and consensus statements that address this important topic (Table 6).

5.5 In patients aged 65 years and older with diabetes, we suggest that if statin therapy is inadequate for reaching the LDL-C reduction goal, either because of side effects or because the LDL-C target is elusive, then alternative or additional approaches [such as including ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9)] should be initiated. (2l⊕OOO)

Evidence

In statin-intolerant patients, ezetimibe may be administered to inhibit cholesterol absorption from the gastrointestinal tract (225). The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that the addition of ezetimibe to statin therapy positively affected CVD in patients with acute coronary syndrome. The combination of these two agents decreased the LDL level to 53 mg/dL. In this trial, many of the patients were older than 65 years, and the CVD benefit was observed primarily in patients with diabetes (226, 227).

Additionally, PCSK9 inhibition has been shown to reduce LDL-C levels more than high-dose statins and to also reduce CVD outcomes. PCSK9 inhibitors have been approved for patients who are unable to reach the LDL goal with the maximally tolerated statin dose, those with clinical CVD on high-dose statins who have not reduced their LDL-C levels to target (228, 229), and those with familial hypercholesterolemia.

5.6 In patients aged 65 years and older with diabetes and fasting triglycerides >500 mg/dL, we recommend the use of fish oil and/or fenofibrate to reduce the risk of pancreatitis. (1l⊕⊕OO)

Evidence

The use of fibrates, as demonstrated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, resulted in no significant benefit regarding the primary endpoint or mortality, and it is therefore not recommended for CVD prevention in patients with diabetes. Importantly, fibrates in combination with statin therapy should be used together cautiously in view of an enhanced risk of myopathy, although this combination can be useful in treating patients with triglyceride

Table 6. Related Guideline Content Table

Rec. Number	Guideline Title	Publishing Organization	Publication Year
2.3, 5.10, 5.13	Standards of Medical Care in Diabetes 2019	American Diabetes Association	2019
3.2	Standards of Medical Care in Diabetes 2019	American Diabetes Association	2019
4.1	Management of Diabetes Mellitus in Primary Care (2017)	U.S. Department of Veterans Affairs and Department of Defense	2017
4.7	Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update from the American College of Physicians	American College of Physicians	2017
5.1	2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)	Eighth Joint National Committee (JNC 8)	2014
	2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines	American College of Cardiology/American Heart Association	2017
	Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher vs Lower Blood Pressure Targets: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians	American College of Physicians/American Academy of Family Physicians	2017
5.3, 5.4	American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease	American Association of Clinical Endocrinologists	2017
5.7	Treatment of Diabetes in People With Heart Failure: Diabetes Canada Clinical Practice Guideline	Diabetes Canada	2018
5.14	Standards of Medical Care in Diabetes 2019	American Diabetes Association	2019
6.3	Position Statement Executive Summary: Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus	National Academy of Clinical Biochemistry	2011

levels >500 mg/mL and who are at risk for pancreatitis (230, 231). There is also evidence that fenofibrate may be valuable in preventing the progression of retinopathy (232, 233).

Management of congestive heart failure in older adults with diabetes

Epidemiology, morbidity, and mortality. Aging and diabetes have a profound effect on the cardiovascular system structure and function that increases the risk of CHF. Aging increases vascular stiffness and reduces elasticity, leading to increased SBP, myocyte hypertrophy, and impaired diastolic function (234). Diabetes increases the risk of CHF due to associated comorbidities such as hypertension and complications such as macrovascular and microvascular disease and also directly affects the myocardium, causing cardiomyopathy (235–237). Therefore, the prevalence of CHF in older people with diabetes is high, reaching up to 30.6%, which is four times higher than expected in older adults without diabetes (238). Patients with both diabetes and CHF are at particular risk of adverse events. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, which included 19,699 patients with diabetes and a mean age of 68.4 years, diabetes was associated with a 33% higher risk of hospitalization for CHF (9.4% vs 5.9%; adjusted OR, 1.33; 95% CI, 1.18 to 1.50). CHF at baseline was independently associated with cardiovascular mortality (HR, 2.45; 95% CI, 2.17 to 2.77; $P < 0.001$) and hospitalization (adjusted OR, 4.72; 95% CI, 4.22 to 5.29; $P < 0.001$), highlighting the need for adequate treatment of CHF in this population (239).

5.7 In patients aged 65 years and older who have diabetes and CHF, we advise treatment in accordance with published clinical practice guidelines on CHF. (Ungraded Good Practice Statement)

Evidence

CHF medications act in essentially the same way in those with and without diabetes. Nevertheless, the

cardiovascular safety of the various classes of hypoglycemic medications is less well understood. Hyperglycemia increases the risk of CHF and hence should be controlled, although no direct evidence supports a reduction in the risk of CHF by treating hyperglycemia. Despite the common coexistence of diabetes and CHF in older people, optimal management is not fully evidence-based due to a lack of clinical trials in this age group. For this reason, treatment according to the recently published clinical practice guidelines is recommended (Table 6).

5.8 In patients aged 65 years and older who have diabetes and CHF, the following oral hypoglycemic agents should be prescribed with caution to prevent worsening of heart failure: glinides, rosiglitazone, pioglitazone, and DPP-4 inhibitors. (Ungraded Good Practice Statement)

Evidence

In a systematic review of observational studies including 34,000 patients with diabetes and CHF, metformin was associated with reduced mortality (23% vs 37%; adjusted risk estimate, 0.80; 95% CI, 0.74 to 0.87; $P < 0.001$), reduced all-cause hospitalizations (0.93, 95% CI, 0.89 to 0.98; $P = 0.01$), and low risk of lactic acidosis (240). No associations of SUs, insulin, acarbose, or glinides with CHF or mortality were found (241–243), but one study did suggest a possible link between glinides and heart failure (244). Moreover, rosiglitazone increased the risk of all-cause mortality (HR, 1.50; 95% CI, 0.49 to 4.59) and hospitalizations for CHF (RR, 1.30; 95% CI, 0.35 to 4.82) (245). A limited meta-analysis of seven RCTs reported that the risk for CHF was less with pioglitazone than with rosiglitazone (1.32, 1.04 to 1.68 vs 2.41, 1.61 to 3.61) and that the risk of cardiovascular death did not increase with either drug (0.93, 0.67 to 1.29, $P = 0.68$) (246). A more comprehensive meta-analysis of 94 RCTs demonstrated that pioglitazone was associated with reduced all-cause mortality (OR, 0.30; 95% CI, 0.14 to 0.63; $P = 0.05$) but with a nonsignificant increase in CHF (OR, 1.38; 95% CI, 0.90 to 2.12) (247).

Interestingly, the risk for hospitalization for CHF with DPP-4 inhibitors is inconsistent. The HR was significant for saxagliptin (HR, 1.27; 95% CI, 1.07 to 1.51) (248), marginally increased but not significant for alogliptin (HR, 1.19; 95% CI, 0.90 to 1.58) (249), and neutral for sitagliptin (HR, 1.00; 95% CI, 0.83 to 1.20) (250). Notably, the ability of these studies to detect CHF hospitalization risk with certainty may be limited, and further evidence is needed.

No increased risk of CHF hospitalization (HR, 0.96; 95% CI, 0.82 to 1.16) or mortality (HR, 0.94; 95% CI, 0.78 to 1.13) was found for the GLP-1 analog lixisenatide (251). In the recently published results of the LEADER trial, treatment with liraglutide compared with placebo was associated with significant cardiovascular benefits in high-risk T2D patients, although the mean age was ~64 years. Furthermore, the SGLT2 inhibitor empagliflozin showed a decreased HR for hospitalization for heart failure (0.65; 95% CI, 0.50 to 0.85) and all-cause mortality (0.68; 95% CI, 0.57 to 0.82). Canagliflozin showed a similar benefit for heart failure in the CANVAS study (144). In advanced CHF, palliative care with a focus on symptom control is effective in improving quality of life as well as reducing hypoglycemic medications in frail older people, as they are often unnecessarily overtreated (252, 253).

The cardiovascular safety profile of the SGLT2 inhibitor dapagliflozin has also recently been studied in a large randomized, placebo-controlled study (median duration of 4.2 years) of adults with T2D. A key result was a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR, 0.73; 95% CI, 0.61 to 0.88) (254). This appears to confirm a view held that these benefits are likely a class effect (255).

In contrast to the effects on the heart, an increase in lower extremity amputations was observed in patients taking canagliflozin in another long-term cardiovascular outcome study (CANVAS) (144), and the Food and Drug Administration (FDA) now requires a boxed warning regarding this effect of this medication (256).

Management of atherosclerosis in older adults with diabetes

Epidemiology, morbidity, and mortality. Aging and diabetes have a synergistic effect on the structure and function of the vascular system that increases the risk of vascular disease. Increased arterial wall thickening and stiffening and reduced compliance occur with aging (257). With diabetes, endothelin (vasoconstrictor and procoagulant) production increases, and nitric oxide production (vasodilator) decreases, shifting the balance toward a vasoconstrictor, procoagulant, proliferative, and proinflammatory state that leads to the development of atherosclerosis (258). Contributors to progressive atherosclerosis include hyperglycemia, dyslipidemia, obesity, and hypertension (259). Moreover, diabetes increases the risk of ischemic stroke by twofold, independently of BP, as well as the RR of in-hospital or 30-day stroke-related mortality. Diabetes substantially increases the risk of peripheral arterial disease and its associated mortality by nearly twofold and increases peripheral arterial disease–related costs and length of hospital stay (260, 261). According to one recent

study, there is little or no increase in risk of mortality, myocardial infarction, or stroke if the following five risk factors are within normal ranges in patients with T2D: HbA1c, LDL, albuminuria, smoking status, and BP (262). Although the available evidence suggests that large reductions in the classic complications of T2D, mainly myocardial infarction, stroke, amputations, and mortality, have occurred during the past 20 years (263), the burden of atherosclerosis in older patients with diabetes remains substantial, and multifactorial intervention in this age group is essential. Moreover, the ADA also notes that addressing multiple cardiovascular risk factors at the same time can lead to greater benefits (24).

Lifestyle interventions including exercise and weight loss in obese older patients reduce intrahepatic fat content, increase insulin sensitivity, and improve overall metabolic risk factors for atherosclerosis (11, 264). Clinical trials have shown that in older patients with diabetes, tight glycemic control with HbA1c no lower than 7.5% will have a cardiovascular benefit after at least 10 years of treatment (128, 265–267). Notably, patients >80 years old or those with multiple comorbidities were excluded from these trials. Furthermore, metformin treatment is associated with improved cardiovascular outcomes, regression of atherosclerosis, and low risk of lactic acidosis (268–270). In the EMPA-REG OUTCOME trial (271), the SGLT2 inhibitor empagliflozin showed lower rates of combined cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99; $P = 0.04$] and all-cause mortality (HR, 0.68; 95% CI, 0.57 to 0.82). In a recently completed randomized trial of canagliflozin vs placebo in T2D (mean age of 63.3 years) with high cardiovascular risk (CANVAS study), canagliflozin significantly reduced ($P < 0.001$ for noninferiority; $P = 0.02$ for superiority) the rate of the primary outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (144). Moreover, results from the LEADER trial demonstrated significant cardiovascular benefits from liraglutide in comparison with placebo (272).

The thiazolidinedione rosiglitazone was previously shown to increase the risk of myocardial infarction (OR, 1.43; 95% CI, 1.03 to 1.98; $P = 0.03$) and cardiovascular mortality (OR, 1.64; 95% CI, 0.98 to 2.74; $P = 0.06$) (273), but following extensive monitoring by the FDA, no new adverse safety data have been demonstrated. The FDA has now entirely lifted the risk evaluation and mitigation strategy for rosiglitazone. Pioglitazone has been shown to reduce the composite of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with T2D who have a high risk of macrovascular events following a large randomized controlled trial >5,000 patients with T2D with evidence of macrovascular disease (PROactive Study) (274).

Other hypoglycemic agents seem to have a neutral effect on cardiovascular outcome (247–251, 275), although the addition of glinides or α-glucosidase inhibitors to metformin therapy showed a reduction in risk of acute myocardial infarction (HR, 0.39, 95% CI, 0.20 to 0.75; and HR, 0.54; 95% CI, 0.31 to 0.95; respectively) (243). A meta-analysis of clinical trials of hypertension treatment in T2D showed that cardiovascular outcomes reached a plateau after attaining an SBP of 140 mm Hg. More intensive SBP control to ≤130 mm Hg was associated with a greater reduction in stroke but a significant increase in serious adverse events (276). A more recent meta-analysis confirmed the cardiovascular benefits of lowering SBP to 140 mm Hg but demonstrated that further reduction is associated with an increased risk of cardiovascular death, with no stroke reduction benefit (187). In a population-based cohort study of patients ≥85 years old, there was a U-shaped curve with a SBP of 164.2 mm Hg (95% CI, 154.1 to 183.8 mm Hg) being associated with the lowest mortality (277). All antihypertensive medications can be used in the treatment of hypertension in older people with diabetes, as no difference in mortality was observed with one drug class over the others, and the benefit may be due to the reduction in BP rather than a class effect (278). The benefit of statins in reducing cardiovascular risk is established. However, the evidence in older people is largely extrapolated from trials in younger populations. The PROSPER trial was designed for older people aged 70 to 82 years and showed 15% lower cardiovascular endpoints in the statin group (279). Interestingly, the addition of fibrate or niacin to statin therapy has shown no extra cardiovascular benefit (280, 281). Older patients with diabetes have a high burden of atherosclerosis and are likely to benefit from aspirin therapy after assessment of their bleeding risk (282, 283). Overall, frail older individuals with diabetes are unnecessarily overtreated, and reducing polypharmacy in this group may improve their quality of life.

5.9 In patients aged 65 years and older with diabetes and a history of atherosclerotic CVD, we recommend low-dosage aspirin (75 to 162 mg/d) for secondary prevention of CVD after careful assessment of bleeding risk and collaborative decision-making with the patient, family, and other caregivers. (1|⊕⊕OO)

Evidence

The primary prevention of cardiovascular events in older patients with diabetes is challenging because of a general lack of evidence for safe and effective treatment in

this age group. Older patients with diabetes have a higher baseline cardiovascular risk and therefore are likely to benefit more from risk reduction than are younger patients without diabetes. However, this group of patients is largely heterogeneous with various levels of functional ability and life expectancy, which should be considered, as the current evidence is not generalizable to patients with poor functional status or multiple comorbidities or those with limited life expectancy.

Aspirin use in secondary prevention of CVD is now well established and has been shown to be effective in reducing cardiovascular morbidity and mortality in patients with a history of CVD (282). The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1000 per year in real-world settings (24).

The evidence for use of aspirin in primary prevention, however, has been conflicting and unclear. In a recent randomized trial of aspirin vs placebo in >15,000 adults with diabetes but no evidence of CVD with a follow-up of 7.4 years, the aspirin group had significantly fewer serious vascular events [658 participants [8.5%] vs 743 [9.6%]; rate ratio, 0.88; 95% CI, 0.79 to 0.97; $P = 0.01$] but a significant excess of major bleeding events (rate ratio, 1.29; 95% CI, 1.09 to 1.52; $P = 0.003$) (284). Currently, the use of aspirin for primary prevention must remain a decision by the clinician on an individualized basis.

Microvascular disease

Eye complications in older adults with diabetes

Responses to standardized questionnaires suggest that vision loss due to diabetic retinopathy may significantly reduce quality of life and that treatment satisfaction may be significantly affected by the severity of macular edema (285–289). Retinopathy and neuropathy may affect the ability of a person to safely operate a motor vehicle (290).

The duration of diabetes predicts the presence of retinopathy, and control of hyperglycemia profoundly affects the onset and progression of diabetic retinopathy in both T1D and T2D (78, 231, 291–295). The beneficial microvascular effects of intensive glycemic control persisted after closeout of the DCCT research group, UKPDS, and ACCORD trials (128, 233, 296). In addition to poor glycemic control, the presence of albuminuria, hypertension, and dyslipidemia predict retinopathy (297–301). Furthermore, the observed present-day decline in the prevalence and incidence of retinopathy and vision impairment is thought to be the result of improved management of hyperglycemia, hypertension, and dyslipidemia (299, 302). In a Medicare study comparing 119 pairs of patients who received guideline care vs the closest matched controls who did not, low vision/blindness was substantially reduced during a 3-year period among persons who received recommended levels of care (300, 303, 304).

The benefit of strict BP control with respect to retinopathy, which was suggested in the UKPDS study (305) but not confirmed in the ACCORD study (231, 306), has not been consistently demonstrated. The use of ACE inhibitors or ARBs may have beneficial effects on retinopathy (307–310).

Treatment with fenofibrate in trials intended for assessing cardiovascular protection has suggested that this drug may reduce the progression of diabetic retinopathy, but continued treatment beyond the closing of the clinical trials may be required to confer this benefit (231–233, 301, 311, 312). There is worldwide interest in developing evidence to support the use of fenofibrate for limiting the progression of diabetic retinopathy, but its safety and efficacy might best be justified by evidence from trials that are designed to examine visual and retinal findings as their primary outcome measures.

5.10 In patients aged 65 years and older with diabetes, we recommend annual comprehensive eye examinations to detect retinal disease (1|⊕⊕⊕⊕). ***Technical remark:*** Screening and treatment should be conducted by an ophthalmologist or optometrist in line with present-day standards.

Evidence

Periodic screening is justified for detecting vision-threatening retinopathy at an early stage and for offering measures to reduce its progression (301). Panretinal photocoagulation is the mainstay of treatment of proliferative retinopathy but may produce an exacerbation of diabetic macular edema, a condition that affects a substantial number of older patients (313–316). A study of 76,127 patients with diabetes in a UK database reported that center-involving diabetic macular edema, potentially amenable to anti–vascular endothelial growth factor (VEGF) therapy, was present in the eyes of almost 10% of these patients (314). In an incident population of 64,983 patients with diabetes in a UK primary care setting, close to 28% of patients developed retinopathy, and close to 4% developed maculopathy (half were macular edema) within 9 years of diabetes diagnosis (315). Among persons ≥40 years of age in the United States with diabetes and retinal photographs, the prevalence of macular edema may be ~3.8%, with no differences among age groups. Rather, the risk is associated with duration of diabetes and HbA1c (316). Such data, together with the impact of retinal edema on vision,

suggest that a large number of older patients might experience improvements in vision and quality of life from anti-VEGF therapy. Intravitreal anti-VEGF therapy may be the most effective front-line modality for macular edema and may be an alternative to panretinal photocoagulation in the treatment of proliferative diabetic retinopathy (301, 317–324).

Notably, Medicare claims data suggest that diabetic retinopathy may be associated with an increased risk of age-related macular degeneration (325). Open-angle glaucoma and cataracts occur more commonly among persons with diabetes (326, 327). Moreover, the risk for glaucoma increases with the duration of diabetes and fasting hyperglycemia. Among older persons with T2D or T1D for 5 years, these additional risks lead us not only to endorse the recommendation of the ADA for an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist but also to suggest screening thereafter at least annually (300, 301).

Neuropathy, falls, and lower extremity problems in older adults with diabetes

5.11 In patients aged 65 years and older with diabetes and advanced chronic sensorimotor distal polyneuropathy, we suggest treatment regimens that minimize fall risk, such as the minimized use of sedative drugs or drugs that promote orthostatic hypotension and/or hypoglycemia. (2|⊕OOO)

5.12 In patients aged 65 years and older with diabetes and peripheral neuropathy with balance and gait problems, we suggest referral to physical therapy or a fall management program to reduce the risk of fractures and fracture-related complications. (2|⊕OOO)

Evidence

The prevalence of diabetic neuropathy appears to be increasing and is correlated with increased age, duration of diabetes, higher HbA1c, and lifelong glycemic control (328–332). Manifestations of the most common form of diabetic neuropathy, chronic sensorimotor distal polyneuropathy, may include not only a history of pain but also advanced findings of proprioceptive deficit, motor strength loss, contractures, deformities, weakness of the extremities, and/or Charcot arthropathies. Persons treated with metformin and having neuropathic manifestations should be evaluated because metformin may cause vitamin B12 deficiency. The heterogeneity of peripheral and autonomic neuropathies in diabetes necessitates consideration of a differential diagnosis, especially if manifestations are lateralized or atypical (333–337).

Persons with diabetes are at increased risk of falls and hip fracture (338–343). Thus, inquiry about falls should occur at least annually (344). Evidence is inconclusive on whether specific glycemic targets or antihyperglycemic treatment regimens promote falls (345–348). Thiazolidinediones and SGLT-2 inhibitors might worsen fall-related outcomes by increasing fracture risk (140, 347, 349). Furthermore, hypoglycemia may be a risk factor for adverse outcomes of falls (73–75). Pharmacologic therapy for painful diabetic neuropathy requires caution in older adults, with special concern for polypharmacy, oversedation, and orthostasis (342, 350–354).

Neuropathy is associated with increased risk of falls in older individuals with diabetes (345, 346, 355–358), and exploratory studies have found associations between diabetic neuropathy and abnormalities in gait, posture, and balance (359–362). Physical therapy interventions for those with functional deficits may reduce risk factors for falls and possibly the actual rate of falls and fractures (363–366). In the presence of advanced manifestations of distal polyneuropathy, we suggest consultation with physical therapists for improvement in balance, gait, posture, and strength and/or suggested use of assistive devices. Referrals might specify imbalance, unsteadiness on feet, abnormality in gait, foot drop, history of falling, neuropathic foot ulcer, lack of coordination, or other functional deficits or consequences traceable to neuropathy.

5.13 In patients aged 65 years and older with diabetes and peripheral neuropathy and/or peripheral vascular disease, we suggest referral to a podiatrist, orthopedist, or vascular specialist for preventive care to reduce the risk of foot ulceration and/or lower extremity amputation. (2|⊕⊕OO)

Evidence

Lower extremity amputation for nontraumatic indications is performed relatively infrequently but with higher incidence among individuals with diabetes, and individuals in some populations and geographic areas are at disproportionate risk for this situation (367–370). Among the 60- to 69-year-old group in a large cohort study, the incidence of lower extremity amputation was 290% greater for those with a longer duration of diabetes (371). Evidence possibly linking amputation to canagliflozin therapy is preliminary (144). Variably reported individual patient risk factors for lower extremity amputation may include peripheral sensory neuropathy, autonomic neuropathy, gait abnormalities, peripheral vascular disease, foot ulcer, history of previous amputation, certain foot deformities, greater body mass,

chronic renal failure, poor vision, older age, and higher HbA1c (372–379).

Foot ulcer increases amputation risk and utilization of medical care (380–383). However, further research is necessary to confirm trends in amputation rates and to establish whether a program of comprehensive foot care or specific management strategies for established foot complications may reduce the risk for amputation among older persons with diabetes (263, 330, 384–392). We endorse the standard of care concerning foot care as expressed by the ADA, which recommends patient self-care education, specifies the content and frequency of periodic comprehensive foot evaluations, recommends a multidisciplinary approach for foot ulcers and high-risk feet, and presents indications for referral for further vascular assessment, ongoing preventive care, and lifelong surveillance by foot care specialists (300). Examiners should identify any history of foot ulcer, poorly fitted footwear, loss of protective sensation, vascular insufficiency, foot deformity, or preulcerative lesion. For patients with altered gait due to neuropathy, local foot deformity, or unhealed ulcers, exercise programs may need to focus on non–weight-bearing activities (393). Furthermore, specialty care may be required to determine the appropriateness of off-loading devices, monitoring of foot skin temperature, use of therapeutic footwear, and need for vascular or podiatric surgical interventions (382, 394, 395).

Lower extremity amputation is associated with reduced survival and a reduction in physical health-related quality of life, as well as delayed recovery and impaired return to baseline function among nursing home residents (1, 396, 397).

The risk factor of vascular insufficiency must be considered among persons with diabetic foot ulcers (398, 399). The goals of lower extremity revascularization in older patients include maintenance of functional capacity and independent living status. Observational studies suggested similar limb salvage rates but less short-term mortality and morbidity after endovascular surgical revascularization (400, 401).

Chronic kidney disease in older adults with diabetes

GFR gradually decreases by ~0.75 to 1 mL/min/1.73 m^2 per year (402). The rate of GFR decline is accelerated in the 20% to 40% of older patients with diabetes and diabetic CKD (403). Notably, the decline in GFR reduces the clearance of insulin and many diabetes medications (404) and increases the risk of hypoglycemia (405, 406).

5.14 In patients aged 65 years and older with diabetes who are not on dialysis, we recommend annual screening for CKD with an eGFR and urine albumin-to-creatinine ratio. (1|⊕⊕⊕⊕)

5.15 In patients aged 65 years and older with diabetes who are in group 3 (poor health, see Table 3) of the framework and have a previous albumin-to-creatinine ratio of <30 mg/g, we suggest against additional annual albumin-to-creatinine ratio measurements. (2|⊕⊕OO)

Evidence

The general recommendation for annual measurement of urinary albumin-to-creatinine ratio and eGFR should also be carried out in older adults (300). However, progressive loss of GFR can occur in the absence of albuminuria (407).

In patients with an estimated limited lifespan who have normal urinary albumin excretion, the prognostic value of annual measurement of urinary albumin excretion over and above indicating an increased risk of CVD is likely minimal (408). Regardless, because a decrease in eGFR affects drug dosing and other aspects of care, at least annual testing should be performed, with more frequent testing if the eGFR is <60 mL/min/1.73 m^2.

5.16 In patients aged 65 years and older with diabetes and decreased eGFR, we recommend limiting the use or dosage of many classes of diabetes medications to minimize the side effects and complications associated with CKD. (1|⊕⊕OO)
Technical remark: Specific use/dosing guidance on each class of diabetes medication is provided in Table 7.

Evidence

Insulin. Reduced kidney function results in a prolongation of insulin half-life and a decrease in insulin requirements (409). All insulin preparations can be used in patients with CKD, and no specific reductions in dosing are necessary for patients. Patients with stages 4 to 5 CKD (eGFR <30 mL/min/1.73 m^2) often have delayed gastric emptying; administering rapid-acting insulin after the meal may be helpful for matching the insulin peak with the time of the postprandial blood glucose peak. Postprandial rapid-acting insulin with a dose adjustment for the amount eaten may help patients with varying food intakes.

Metformin. Because of drug accumulation with decreased clearance and therefore a potential risk for lactic acidosis, metformin can be used without dosage reduction down to an eGFR >45 mL/min/1.73 m^2 and with a reduction to 1000 mg daily if the eGFR is ≥30 to 44 mL/min/1.73 m^2. The drug should be stopped when

the eGFR is <30 mL/min/1.73 m^2 or in situations associated with hypoxia or an acute decline in kidney function such as sepsis/shock, hypotension, and use of radiographic contrast or other nephrotoxic agents (79, 410, 411) (see Table 7).

SUs and glinides. SUs and their metabolites are renally cleared, leading to an increased risk of hypoglycemia as GFR declines. Glyburide should be avoided with an eGFR <60 mL/min/1.73 m^2 (412). Glimepiride should be used with caution if the eGFR is <60 mL/min/1.73 m^2 and should not be used with an eGFR <30 mL/min/1.73 m^2. Less than 10% of glipizide is cleared renally, but it should still be used with caution with an eGFR <30 mL/min/1.73 m^2 (413, 414).

The active metabolite of nateglinide accumulates in CKD and should not be used with an eGFR <60 mL/min/1.73 m^2; however, the active metabolite is cleared by hemodialysis, and thus nateglinide can be used in patients on dialysis (415). Repaglinide appears safe for use in CKD but should be used with caution when the eGFR is <30 mL/min/1.73 m^2 (416).

Thiazolidinediones. Pioglitazone and rosiglitazone are hepatically metabolized and can be used in CKD without dosage adjustment (417, 418). However, fluid retention limits their use in CKD, and they are associated with increased fracture rates and bone loss (139). Thus, use in patients with underlying bone disease (such as renal osteodystrophy or osteoporosis) could potentially be problematic.

α-Glucosidase inhibitors. Neither acarbose nor miglitol has been studied long-term in patients with a creatinine level >2 mg/dL, and their use should be avoided in these patients (419).

DPP-4 inhibitors. The DPP-4 inhibitors sitagliptin, saxagliptin, and alogliptin undergo some renal clearance and require dosage adjustment in patients with reduced eGFR (420) (see Table 7). Only a small amount of linagliptin is cleared renally, and no dosage adjustment is indicated with a reduced GFR (420). In general, these drugs are very well tolerated.

SGLT2 inhibitors. SGLT2 inhibitors generally become less effective as GFR decreases (146). Because of a small increase in adverse events related to intravascular volume contraction, no more than 100 mg once daily of canagliflozin should be used in patients with an eGFR of 45 to <60 mL/min/1.73 m^2 (146, 421). Canagliflozin, empagliflozin, and ertugliflozin should be stopped if the eGFR is <45 mL/min/1.73 m^2, and dapagliflozin should be stopped at 60 mL/min/1.73 m^2, primarily because of a decrease in efficacy (146, 421). Interestingly, empagliflozin and canagliflozin have been shown to delay the progression of CKD (144, 145).

GLP-1 receptor agonists. The clearance of exenatide decreases as the GFR declines (422). Cases of acute renal failure associated with exenatide use have been reported, and thus exenatide should not be used if the GFR is <30 mL/min/1.73 m^2 (423). Lixisenatide should not be used if the GFR is <15 mL/min/1.73 m^2, but no dosage changes are needed for liraglutide (424), semaglutide, or dulaglutide as renal function worsens. Nausea is a common side effect of these drugs and could potentially be problematic in older patients with compromised intake, especially those with progressing CKD.

Other oral medications. Neither bromocriptine (dopamine receptor agonist) nor colesevelam (bile acid sequestrant) has been studied in patients with advanced CKD.

6. Special Settings and Populations

T1D

Although it is clear that life expectancy for patients with T1D is improving (425), the number of people reaching 60 years and older is unknown. There appears to be two reasons for the increasing number of older adults with T1D. First, those diagnosed with childhood T1D have taken advantage of the improved therapies for glycemic management and nonglycemic measures for the prevention and treatment of long-term complications. Second, for reasons that are unclear, the number of cases of adult-onset T1D has increased. Given these factors, "geriatric T1D" is anticipated to become more common over the next decade. In one large American T1D registry of 22,697 participants of all ages (T1D Exchange), 3445 individuals (15%) are >50 years of age (426). This phenomenon provides opportunities for the study of a population that numerically was not common in the past.

Hypoglycemia

No RCTs have assessed outcomes for older individuals with T1D. In general, near normal glycemic targets are reserved for individuals with shorter durations of diabetes prior to the development of microvascular or macrovascular complications. Furthermore, the aggressiveness of glucose control needs to be balanced against the risks of hypoglycemia, which is generally a more dangerous side effect of insulin therapy in an older population. In one survey of 510 individuals with T1D >65 years of age, the yearly frequency of severe

doi: 10.1210/jc.2019-00198

Table 7. Medications Used to Treat Hyperglycemia and Special Concerns With Use in Older Patients With CKD and CVD

Medication Class	Use in Older Patients	Use in Patients With CKD (Stages 3 to 5)	Use in Patients With CVD
Insulin	Can cause hypoglycemia	Decreased clearance. Increased risk of hypoglycemia. Dosages may need adjusting. Consider giving rapid-acting insulin postprandially because of gastroparesis.	May worsen fluid retention when used with thiazolidinediones. Hypoglycemia to be avoided because of potential arrhythmias and stroke
Metformin	Can cause gastrointestinal intolerance	Reduce dosage to 1000 mg/d if eGFR <45[a]; do not start if eGFR <45[a]	May be beneficial in patients with coronary artery disease. Avoid use in patients with severe CHF to avoid lactic acidosis
	Does not cause hypoglycemia	Stop if eGFR <30[a]	
	May cause vitamin B12 deficiency	Stop if increased risk of acute kidney injury (radiocontrast dye, hypotension, sepsis, shock, hypoxia).	
SUs	Can cause hypoglycemia	Glyburide: avoid if eGFR <60[a]	Can cause hypoglycemia, which is to be avoided because of potential arrhythmias and stroke
	Can cause weight gain	Glimepiride: avoid if eGFR <30[a]	
	Avoid glyburide	Glipizide: use with caution if eGFR < 30[a]	
Glinides	Can cause hypoglycemia	Nateglinide: stop if eGFR <60[a] but can use if patient is on dialysis	Can cause hypoglycemia, which is to be avoided because of potential arrhythmias and stroke
	May be useful for individuals who skip meals	Repaglinide: use with caution if eGFR <30[a]	
Thiazolidinediones	Does not cause hypoglycemia	No dosage adjustment needed. Can cause fluid retention. Can increase fractures.	Pioglitazone has been shown to reduce CVD mortality. Can cause fluid retention with potential to worsen heart failure
	Can increase fracture risk		
	Can cause fluid retention		
	Can cause weight gain		
α-Glucosidase inhibitors	Does not cause hypoglycemia	Avoid if serum creatinine >2.0 mg/dL because of lack of studies in such patients	
	Gastrointestinal side effects may cause nonadherence		
DPP-4 inhibitors	Does not cause hypoglycemia	Sitagliptin: eGFR >50[a]: 100 mg/d eGFR 30–50[a]: 50 mg/d eGFR <30[a]: 25 mg/d Saxagliptin: eGFR >50[a]: 2.5 or 5 mg daily eGFR ≤50[a]: 2.5 mg daily Alogliptin: eGFR >60[a]: 25 mg daily eGFR 30–60[a]: 12.5 mg daily eGFR <30[a]: 6.25 mg daily Linagliptin: No dosage adjustment needed	Saxagliptin has been shown to increase the risk of heart failure

(*Continued*)

Table 7. Medications Used to Treat Hyperglycemia and Special Concerns With Use in Older Patients With CKD and CVD (Continued)

Medication Class	Use in Older Patients	Use in Patients With CKD (Stages 3 to 5)	Use in Patients With CVD
SGLT2 inhibitors	Does not cause hypoglycemia Empagliflozin can reduce cardiovascular events and progression of CKD Volume depletion adverse effects more common in older patients Canagliflozin may increase fracture risk; has also been associated with an increased risk of toe and foot amputations May rarely cause ketoacidosis	Canagliflozin: eGFR 45–60[a]: 100 mg/d; eGFR <45[a]: avoid use Dapagliflozin: eGFR <60[a]: avoid use Empagliflozin: eGFR <45[a]: avoid use Ertugliflozin: eGFR <60[a]: avoid use Canagliflozin and dapagliflozin have been associated with acute kidney injury Empagliflozin and canagliflozin can reduce progression of CKD	Empagliflozin and canagliflozin have been demonstrated to reduce major adverse cardiovascular events and CHF
GLP-1 receptor agonists	Does not cause hypoglycemia May cause gastrointestinal side effects	Exenatide: eGFR <30[a]: avoid use Liraglutide, dulaglutide, semaglutide: no dosage adjustment needed Lixisenatide: avoid if eGFR <15[a]	Liraglutide and semaglutide have been demonstrated to reduce major adverse CVD events
Bromocriptine	May cause nausea Does not cause hypoglycemia	Use with caution. Not studied in CKD.	
Colesevelam	May cause gastrointestinal side effects Does not cause hypoglycemia	No dosage adjustment needed, but limited data are available	

[a]eGFR levels are all in mL/min/1.73 m^2.

hypoglycemia (seizure or coma) was 16.1% (427). The same survey found that the duration of diabetes was an even greater risk factor for severe hypoglycemia: for those with at least a 40-year duration of diabetes (N = 758), the yearly rate was 18.6% (427). A subsequent study of 101 subjects with a recent prior history of severe hypoglycemia (mean age and duration of diabetes were 69 and 41 years, respectively) wearing blinded CGM revealed hypoglycemic exposure of an average of 99 min/d <70 mg/dL and 65 min/d <60 mg/dL (88). Certain cognitive test scores were worse in these individuals than in a control group matched for age and duration of T1D.

Cognitive dysfunction

Routine self-care of T1D requires sufficient cognitive capabilities due to the complexity of disease management. One report noted that in a group of patients with T1D (mean age and duration of diabetes 60 and 38 years, respectively) over a 4-year period, the decline in cognitive function was no different from that in an aged-matched control group (428). However, patients with a history of severe hypoglycemia or CVD were more susceptible to cognitive decline than were the control patients. Cognitive decline in older adults with T1D often requires simplification of insulin regimens (*e.g.*, moving from carbohydrate and calorie counting to set meal-time dosing or moving from insulin pump to injections).

Functionality

The typical reduced physical function of older adults may be exacerbated by T1D. Neuropathy, visual impairment, and hypoglycemia unawareness may make driving an impossible task. In addition to these complications, arthritis, chronic pain, and other conditions are frequently observed in this population (diabetic cheiroarthropathy), presenting barriers to independent living. As functionality becomes more limited, the role of the caregiver becomes more critical. Due to to all of these concerns, less stringent glycemic targets are appropriate for older adults with T1D, particularly those with a >40-year duration of diabetes, when severe hypoglycemia becomes more common.

Hypertension and hypercholesterolemia

Even fewer data are available to guide clinicians for these common clinical problems. The presence of diabetic kidney disease generally results in lower BP targets, although the specific goals are controversial (429). BP targets with or without kidney disease have not been studied in older adults with T1D. Likewise, RCTs for the treatment of hypercholesterolemia have not been studied in patients with T1D, let alone in older patients with T1D. However, both proteinuria and obesity are accepted risk factors for CVD, and of the patients >50 years old in the T1D Exchange of 2014, 39% and 29% were overweight and obese, respectively (data for those >60 years old were not reported) (430). Because the duration of diabetes seems to be a risk factor for CVD, which is also the leading cause of mortality (431), it seems appropriate that most older adults with T1D should be treated similarly to those with T2D. Nevertheless, clinicians should evaluate each patient individually, especially those who are nonobese and diagnosed later in life where less aggressive treatment may be warranted.

Management of diabetes away from home—in hospitals and long-term care facilities—and transitions of care

More than 25% of people >65 years old have diabetes (120), and the prevalence of diabetes in the long-term care facility (LTCF) population has increased to 35% (432–434). Moreover, older patients with diabetes display various comorbid illnesses and functional impairments (435). Older patients with diabetes mellitus are frequently admitted to the hospital for non-diabetes–related problems such as cardiovascular and respiratory disorders and digestive, genitourinary, and infectious problems (436, 437).

Patients with diabetes may be admitted to general medical-surgical floors, straight to the intensive care unit, or to the operating room (438). Patients who are not eating or on steroids, pressors, tube feeding, total parenteral nutrition, special diets, hemotoneal or peritoneal dialysis, and/or other agents that modify glucose homeostasis and metabolic profiles. Frequently, hospitalized patients go from one condition or treatment to another in a very short time. Various specialists and teams may be involved in the treatment process, complicating communication and ordering processes. Thus, education of nursing and house staff as well as the contribution of so-called "Glucose Management Teams" cannot be overestimated (439). The benefits of glycemic control must be balanced with the adverse effects of glucose-lowering medications and a patient's age, overall health status, and functional and intellectual capacity (40, 79).

6.1 In patients aged 65 years and over with diabetes in hospitals or nursing homes, we recommend establishing clear targets for glycemia at 100 to 140 mg/dL (5.55–7.77 mmol/L) fasting and 140 to 180 mg/dL (7.77–10 mmol/L) postprandial while avoiding hypoglycemia. (1⊕⊕OO)
Technical remark: An explicit discharge plan should be developed to re-establish long-term

glycemic treatment targets and glucose-lowering medications as the patient transitions to post-hospital care.

Evidence

Glycemic targets for inpatient management of diabetes in older adults are established based on general guidelines while avoiding hypoglycemia (437). Best practice requires concrete strategies for transitions of care within the hospital and upon discharge (440–442).

The most common cause of glycemic variability in hospitalized patients with diabetes is a mismatch between caloric intake and insulin coverage. Alimentary intake is frequently a problem for hospitalized patients (443) and LTCF residents because of impaired appetite or inability to swallow or hold food down. Instead of a balanced meal, they might consume only fluids, frequently fruit juices, shakes, or dietary supplements that contain high concentrations of sugar and produce glycemic spikes. Using sliding scale regular insulin may lead to hypoglycemia and wide oscillations in blood glucose levels (444, 445). Nonetheless, holding insulin due to patients' complaints of poor appetite results in hyperglycemia and may precipitate diabetic ketoacidosis.

Patients on enteral or parenteral nutrition and insulin develop hypoglycemia when feeding is stopped abruptly for various reasons (438). Thus, safety measures must be in place at every institution. Continuous enteral or parenteral nutrition produces a constant "postprandial" state with glycemic targets between 140 and 180 mg/dL (7.77 to 10 mmol/L). Aiming at glycemia targets below this range is dangerous.

Point-of-care glucose monitoring is helpful only when it is performed frequently and when a knowledgeable person reviews the data and makes appropriate adjustments (439, 446–448). Most hospitalized patients with diabetes are treated with insulin (449). Most missteps in diabetes management occur not at the selection of the initial doses of insulin but because of poor follow-up and lack of appropriate and timely adjustments.

Whereas glycemia of critically ill patients is usually managed in the intensive care unit with IV insulin administration, most noncritically ill patients are treated with basal-bolus regimens. In a randomized multicenter trial comparing the efficacy of a basal-bolus insulin regimen with glargine once daily and glulisine before meals (n = 104) to sliding scale regular insulin four times daily (n = 107) in patients with T2D undergoing general surgery, Umpierrez *et al.* (450) demonstrated that basal-bolus insulin not only improved glycemic control but also significantly reduced hospital complications.

Moderate (41 to 70 mg/dL) and severe (<40 mg/dL) hypoglycemia is common in hospitalized patients with diabetes, including older patients (432, 451–455). Hypoglycemia increases length of hospital stay and mortality (456–459). The presence of renal failure, poor nutrition, and sepsis is highly predictive of a high risk of hypoglycemia in older individuals. Although a causal relationship between hypoglycemia and mortality has not been established, a strong association between hypoglycemia and more severe illness is likely (455, 460, 461).

An RCT comparing treatment with oral agents and basal insulin in older patients with T2D in LTCFs demonstrated that treatment within both arms resulted in a similar frequency of hypoglycemia (462), suggesting that a low daily dose of basal insulin is sufficient to achieve reasonable and safe glycemia in older patients. Clearly, patients with T1D in institutional settings should never be left without insulin.

6.2 In patients aged 65 years and older with diabetes and a terminal illness or severe comorbidities, we recommend simplifying diabetes management strategies. (1|⊕OOO)

Evidence

Patients with late-stage cancer, organ failure, or pre–solid organ or post–solid organ or bone marrow transplant, patients on dialysis, and those in the intensive care unit present unique challenges. Higher glycemic targets may be acceptable in patients with severe comorbidities and in terminally ill individuals. A simplified management approach is fully justified in these patients.

6.3 In patients aged 65 years and older without diagnosed diabetes, we suggest routine screening for HbA1c during admission to the hospital to ensure detection and treatment where needed (see the technical remark in recommendation 2.1). (2|⊕⊕OO)

Evidence

Although measurements of HbA1c have earned their recognition in the diagnosis of diabetes mellitus (463) and in the process of monitoring glycemic control in patients with diabetes (464), they can also help to assess the chronicity of hyperglycemia in patients admitted to the hospital who do not have a previous diagnosis of diabetes (465).

Admission HbA1c levels have been shown to correlate with greater morbidity and mortality in patients with acute myocardial infarction (466, 467), heart failure (468), and poor functional outcome after acute ischemic stroke (465). The exact mechanism of these associations

is not well understood, but one may surmise that chronic hyperglycemia has an adverse influence on the cardiovascular system in patients with undiagnosed diabetes or prediabetes.

Transitions of care

Transition of care from hospital to home or to an LTCF rightfully represents a critical element in the treatment of older patients with diabetes. The most important aspect of successful transition is effective, detailed, and thorough bidirectional communication between the discharging and receiving teams of health care providers. Excellent communication between the discharging team and patient as well as the patient's family or caregiver is also of paramount importance. Older patients newly diagnosed with diabetes during their hospital stay may present additional obstacles during transitions of care. These patients deal with the shock of a new chronic disease and may not have a clear ability to understand and integrate complicated medical regimens, changes in lifestyle, home glucose monitoring, and other challenges of diabetes. Finally, the number of comorbidities as well as patients' cognitive and functional status will dictate the appropriate steps in the transition of care offered to older patients with diabetes.

Methodology

Participants

The Writing Committee consisted of 10 content experts representing the following specialties: endocrinology, neurology, and geriatrics. Two of the committee members brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist who led the team of comparative effectiveness researchers that conducted the systematic reviews and meta-analyses.

Guideline development process

The Endocrine Society's guideline development process combines elements of the GRADE framework (469) with an approach that was thought to be more appropriate for the rare endocrine disease space where scientific evidence is limited or nonexistent. The Society applies the steps in the GRADE framework to research questions for which there is an ample body of knowledge of low-to-moderate quality or higher (Table 8 for descriptions of low- and moderate-quality evidence). In these situations, GRADE provides the methodological and statistical rigor that results in robust recommendations that are classified using quality of evidence and strength of recommendation as described in by Guyatt *et al.* (470) and represented graphically in Table 8.

Where evidence is extremely limited and/or not systematically analyzed, we provide recommendations based on an expert review of the limited data. This process is less systematic than the GRADE methodological framework; however, these recommendations are also clearly classified using the GRADE classification system.

Some of the Society's clinical practice guidelines also include Ungraded Good Practice Statements (471). This unclassified clinical guidance can include expert opinion statements on good practice, references to recommendations made in other guidelines, and observations on preventive care and shared decision-making.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, we include technical remarks. These provide supplemental information such as timing, setting, dosing regimens, and necessary expertise. All recommendations are followed by a synopsis of the evidence on which they are based. Authors may also include short statements on patients' values and preferences, the balance of benefits and harms, and minority opinions, where relevant.

Note that the Society's guideline development process is currently under review, and new approaches and processes are likely to be instituted in the coming months.

Conflicts of interest

1. To be considered for membership of a Writing Committee, nominees are required to disclose all relationships with industry for the 12-month period prior to guideline writing committee initiation. This is consistent with the reporting time frame for the National Institutes of Health and the FDA.
2. Conflicting relationships that should be declared include commercial, noncommercial, intellectual, institutional, and patient/public activities pertinent to the scope of the guideline.
3. The Chair of the Clinical Guidelines Subcommittee reviews these disclosed relationships and determines whether they are relevant to the topic of the guideline and present a relevant conflict of interest (COI).
4. The Chair of the Clinical Guidelines Subcommittee selects Co-Chairs and members based on the COI information received and the individuals' expertise and other skills. The Endocrine Society Council then reviews and endorses the nominees or makes appropriate changes.
5. The chair of the Writing Committee must be free of any COI or other biases that could undermine the integrity or credibility of the work.
6. At least half ($\geq$ 50%) of the Writing Committee members must be free of relevant COI.

Table 8. GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence from observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1): "We recommend…"** *Benefits clearly outweigh harms and burdens or vice versa*	**1|⊕⊕⊕⊕**	**1|⊕⊕⊕O**	**1|⊕⊕OO**	**1|⊕OOO**
	Conditional (2): "We suggest…" *Benefits closely balanced with harms and burdens*	**2|⊕⊕⊕⊕**	**2|⊕⊕⊕O**	**2|⊕⊕OO**	**2|⊕OOO**

7. Following initiation of the committee, members are asked to disclose any new relationships with industry at every in-person meeting and on most conference calls.
8. The authors who comprise the 50% or more without COIs must refrain from adding new relevant industry relationships throughout the guideline development process to ensure that the appropriate COI balance is preserved.
9. The authors who comprise the ≤50% with relevant COIs are required to declare the situation and recuse themselves from any relevant discussions, votes, and from drafting recommendations.
10. If a member is aware of another person who might have a conflict and has not declared it for some reason, they are obliged to bring this to the Chair's attention.
11. Staff, Writing Committee Chairs, and members must be alert for situations that might present a potential or perceived conflict of interest.

Appendixes

Appendix A. How to Use the Conceptual Framework

The guideline Writing Committee designed the framework (Table 3) to serve as a guide that encourages

the diabetes clinician to consider available evidence and a patient's overall health, likelihood to benefit from interventions, and personal values when considering treatment goals such as glucose, BP, and dyslipidemia. Consideration that the patient categories are general concepts and that individual patients may not fall clearly in one category is important. However, considering most patients in group 2 as prefrail and most in group 3 as frail with one or more disabilities may be helpful. Nevertheless, we recognize that neither the category nor patient values are necessarily static and may change over time with disease progression or may shift in either direction, for example, because of temporary disability.

Glucose targets

The framework prioritizes blood glucose targets over HbA1c, recognizing that both are important in clinical practice. However, owing to accuracy concerns of HbA1c as well as the failure of HbA1c to identify those at risk for hypoglycemia (see evidence statement in section 3 on "Assessment of Older Patients with Diabetes"), the framework intentionally places glucose values above HbA1c in the glucose target section.

Shared decision-making

Shared decision-making (SDM) is a collaborative, patient-directed decision-making process that helps the patient set goals and priorities with input from their health care team, family, and other caregivers. The objective is for the patient to make choices that meet his/her needs while honoring personal values and preferences. In the conceptual framework, the SDM arrow indicates that after consideration of these factors, some patients may have lower or higher targets.

SDM example

Mrs. Jones is a 72-year-old woman with T1D and rheumatoid arthritis who presents for the first time for ongoing management of her diabetes, which she has had for 40 years. She has retinopathy without impaired vision, peripheral polyneuropathy that has just become painful this past year, and stage 3 CKD with a GFR of 42. She has hypertension on two agents with SBP between 132 and 140 on recent checks. Owing to her rheumatoid arthritis, she uses a walker in the home and a wheelchair or scooter outdoors but is able to manage insulin and glucose monitoring independently, although some days her dexterity is so poor that she manages to only check twice. Her son pays her bills for her because she can no longer manage her online accounts due to MCI; otherwise, she is very involved in the local church and has evening activities three times a week.

Her HbA1c has been between 6.2 and 6.9 for the last 10 years, as you can see in the records, and she reports being pleased with her control. She uses long-acting basal insulin and rapid-acting insulin up to five times daily according to a carbohydrate ratio and correction factor, which, with further inquiry, you find that she applies very accurately; she declined an insulin pump and CGM in the past. From her glucose meter, her lowest glucose is 62 mg/dL, as measured in the fasting state, and she reports losing hypoglycemia awareness in the last 2 to 3 years; otherwise, her fasting mean glucose is 128 mg/dL.

You begin to discuss glucose goals, and she reports "Please don't tell me my HbA1c should be higher; that is what my previous doctor said." She reports feeling "fuzzy" and "clumsy" when her glucose is >200 mg/dL and attempts to loosen control have been difficult for her. You discuss the concerns around hypoglycemia, and she agrees that it is concerning. Together, you agree for her to wear a continuous glucose monitor for up to 10 days to evaluate her glucose patterns, and you place this device in the office. You agree on a glucose range of fasting, 100 to 150 mg/dL, and bedtime, 150 to 180 mg/dL (group 2 in framework), and she agrees to adjust as needed for safety while avoiding glucose levels >200 mg/dL as much as possible. You both agree to focus on the glucose ranges rather than HbA1c. You suggest that her son come with her to the next visit to discuss options for safe glucose monitoring going forward, as her rheumatoid arthritis is affecting her ability to self-monitor blood glucose.

Appendix B. Patient Voice Assessment

To include the patient's perspective in this guideline and to place the recommendations into the context of patient experience, we sought the collaboration of both organized groups and individuals with diabetes who were age 65 years or older. An anonymous, unvalidated survey was developed by members of the writing committee and administered electronically (via E-mail) and in person to 80 adults. The survey was designed to address specific aspects of the guideline, namely, the perception of how diabetes and treatment of diabetes impact overall health. As a group, the respondents represented the target population of the guideline, with most having T2D and reporting complex disease management (55% reported daily insulin use) and a significant prevalence of complications (41% with disease-specific microvascular complications and 51% with macrovascular complications). Based on the preponderance of responses, the committee identified four common themes: (i) many older adults do not anticipate changing their various treatment targets with advancing age; (ii) diabetes is often not listed as the top health condition by older patients with diabetes, as other conditions are often considered

more serious or important to them; (iii) most older patients with diabetes express significant fear of complications (microvascular and macrovascular) and primarily consider glucose control to be the most important factor for prevention; and (iv) lipid-lowering medications may be underused among older adults, which may be due to a lack of perceived benefit by themselves or their clinicians.

Methods

To include the patient's perspective in this guideline, we sought the collaboration of both organized groups and individual patients with diabetes who were age 65 years or older. The Writing Committee developed a 20-question anonymous survey that included demographics, diabetes-specific characteristics, and perspectives on the health problems addressed in the guideline. The survey was tested internally but was not formally validated. The participating organizations included the ADA's Senior Signature program (www.diabetes.org/in-my-community/awareness-programs/older-adults/) and the Diabetes Sisters (diabetessisters.org/). Individual patients were identified through a clinical database and were asked to submit the survey online. The survey was also administered in person to a focus group of older adults participating in a community program. All data collected directly from individuals did not include personal health information or identifiers.

Results

Overall, 80 respondents completed the survey, and 77 of them reported having diabetes (three reported taking the survey on behalf of a family member). Most respondents were women (88%) between the ages of 60 and 80 years (93%), and 7% were between 81 and 100 years old. Most were white (68%) and black and/or African American (26%), with 2.5% and 1% Native American and other, respectively. Self-reported diabetes type indicated that more than half of the respondents had T2D, as expected, and 31% reported having T1D (see Appendix Table 1).

Appendix Table 1. General Characteristics of the Survey Population

Characteristic	Value	(%)
Age, y (N = 80)	60–70	64
	71–80	29
	81–90	3.75
	91–100	3.75
	>100	0
Sex	Male	12
	Female	88
Race	Black and African American	26
	White	68
	Asian	1
	Native American	2.5
	Mixed race	0
	Latino or Hispanic	0
	Other	2.5
Self-reported diabetes type	T1D	31
	T2D	52
	Familial or "MODY"	0
	Due to pancreatic disease or removal	1.25
	Other type	9
	I do not know	6

Abbreviations: MODY, Maturity Onset Diabetes of Youth.

Diabetes self-management

Fifty-five percent of 75 respondents reported using insulin daily to manage diabetes, and ~40% reported taking more than one medication to treat diabetes, with 15% reporting taking three or more. Most respondents disagreed that forgetting medications was a concern, although 29% did report this as a concern.

Glucose targets and hypoglycemia

Patients generally reported agreement between themselves and their care providers on what their glucose target should be, with only 4% reporting disagreement. One-third of respondents either agreed or strongly agreed that they fear having low blood glucose on most days. Interestingly, when asked if they would agree to relax or loosen glucose targets with age, most (62%) reported that they would not.

Blood pressure and lipid control

Nearly all agreed (96%) that controlling BP will reduce their risk of stroke, and 100% of 78 respondents agreed that having a BP in the "target range" is important for overall health. Of these participants, 36% reported taking no medications for BP, 28% reported taking one medication, and 36% reported taking more than one medication. In contrast, a smaller majority agreed that maintaining lipids in the target range is important (87%) and that taking a lipid-lowering medication will reduce the risk of heart attack (67%). Although the majority reported taking one medication for lipid lowering (68%), a large minority reported taking none (24%).

Complications

Most respondents (85%) reported that they worry about the future with respect to the possibility of serious complications of diabetes. Forty-one percent reported having a diabetes-specific complication, with most (72%) reporting nerve-related discomfort or pain (neuropathy). Just more than half reported having macrovascular disease: peripheral vascular disease (24%) and heart disease (27%). Nearly all respondents (96%) agreed that

Appendix C. Conflicts of Interest

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info.
Derek LeRoith, Chair	Professor of Medicine, Endocrinology, Diabetes, and Bone Disease, Mount Sinai Medical Center	None	None	• Astrazeneca, consultant, Advisory Board • Merck Sharp & Dohme, faculty • MannKind, consultant	None	None
Geert-Jan Biessels	Professor of Neurology, University Medical Center Utrecht	None	None	None	• Boehringer Ingelheim, consultant and investigator	None
Susan Braithwaite	Emeritus Professor, Presence Saint Francis Hospital and Presence Saint Joseph Hospital	None	None	• ADA, book reviews • American Association of Clinical Endocrinologists and American College of Endocrinology, Associate Editor	None	None
Felipe Casanueva	Professor of Medicine, Santiago de Compostela University	None	• Pituitary Society, Board of Directors	• Pfizer, Advisory Board • Novo Nordisk, Advisory Board • Janssen Global Services, Advisory Board • Orexigen, speaker • Pronokal, speaker	None	None
Boris Draznin	Director, Adult Diabetes Program, School of Medicine, University of Colorado Denver	None	None	None	None	None
Jeffrey Halter	Professor of Internal Medicine and Director, Geriatrics Center, University of Michigan	None	None	None	None	None
Irl Hirsch	Professor of Medicine, University of Washington Medical Center–Roosevelt	None	None	• Abbott Laboratories, consultant • Roche Diabetes Care, consultant • BigFoot, consultant • Adocia, consultant	• Medtronic Diabetes, investigator	None
Marie McDonnell	Director, Brigham and Women's Diabetes Program, Brigham and Women's Hospital and Harvard Medical School	None	None	• American Association of Clinical Endocrinologists, Associate Editor	None	None

(*Continued*)

doi: 10.1210/jc.2019-00198

Appendix C. Conflicts of Interest (Continued)

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info.
Mark Molitch	Professor of Endocrinology, Northwestern University Feinberg Medical School	None	None	• Merck, member DSMB, consultant • Pfizer, member DSMB • Janssen Global Services, consultant • Chiasma, consultant • Novartis, consultant	• Bayer, investigator • Novo Nordisk, investigator • Calibra, investigator • Chiasma, investigator • Novartis, investigator	• Amgen, wife and daughter, stock ownership
M. Hassan Murad	Professor of Medicine, Mayo Clinic	None	None	None	None	None
Alan Sinclair	Director, Foundation for Diabetes Research in Older People, King's College, United Kingdom	None	None	• Eli Lilly, Speaker • Merck Sharp & Dohme, Advisory Board	• Merck Sharp & Dohme/Merck, sponsorship	None

blood glucose control reduces the risk of vision loss. Most, although a lower percentage (85%), also agreed that blood glucose control is the "most important factor" that will reduce heart disease risk.

Overall health

When asked how many other health problems they had, approximately half of the respondents reported having two or three, 13% reported four or five, and 10% reported having six or more other health problems. When asked whether they think that diabetes takes up too much mental and physical energy on a daily basis, the responses were broadly distributed: 58% agreed, 20% were undecided, and 20% disagreed. When asked to rank all of their health conditions in order of importance, 40% of the 69 respondents ranked diabetes first. Other conditions common among older adults that are potentially related to diabetes were also ranked high (hypertension, heart disease, bladder control, depression, and overweight).

There are several limitations to employing a limited survey approach to illustrate the patient experience. First, the population was largely ambulatory and did not represent nonambulatory older adults or those living in LTCFs. Additionally, this limited survey mostly included black and white individuals living in urban or suburban areas, with no Latino/Hispanic and minimal Asian representation, and may not be generalizable to many areas of the global community.

In summary, there appeared to be significant heterogeneity in perceived health and cognitive function (measured by a question related to forgetting medications), supporting the guideline's emphasis on tailoring treatment to the patient's level of overall health and functional status. Diabetes did not predominate the participants' perception of their overall health, possibly reflecting the accumulation of other conditions that impact health and quality of life with age. This finding may also suggest that some older adults may not be willing or able to invest the time and expense required to fulfill recommendations made in the guideline. Responses to the survey also highlight the potentially inconsistent messages heard by older patients regarding tailoring clinical targets (BP and glucose) and prevention of complications. Perhaps consistent with these results, most participants reported not being willing to relax glucose goals over time as they become older. Taken as a whole, the results highlight the importance of clear communication between clinicians and patients on the actual risks and benefits of different therapeutic strategies.

Acknowledgments

The guideline writing committee thanks the participating organizations and individuals with diabetes for their invaluable contribution to the patient voice in this guideline. We particularly thank the Reverend Albert Whitaker from the ADA's Senior Signature program, Ronald H. Lammy from the Total Wellness for Elders Program at the Elder HealthCare Disparities Coalition (Roxbury, MA), and Sarah Mart from Diabetes Sisters. The writing committee thanks the cosponsors of this guideline for their contribution to the development effort. The Endocrine Society acknowledges that the American Geriatrics Society (AGS) affirms the value of this document. (Affirmation of value means that AGS supports the general principles in this document and believes it is of general benefit to its membership.)

Financial Support: This guideline was supported by the Endocrine Society. No other entity provided financial support.

Correspondence: Derek LeRoith, MD, PhD, Mt. Sinai School of Medicine, Division of Endocrinology, Diabetes, and Bone Diseases, 1 Gustave Levy Place, Box 1055, New York, New York 10029. E-mail: derek.leroith@mssm.edu.

Disclosure Summary: See Appendix C.

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Thieme

Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Updated August 2018

Authors

Jean-Marc Dumonceau[1], Myriam Delhaye[2], Andrea Tringali[3,4], Marianna Arvanitakis[2], Andres Sanchez-Yague[5], Thierry Vaysse[6], Guruprasad P. Aithal[7], Andrea Anderloni[8], Marco Bruno[9], Paolo Cantú[10], Jacques Devière[2], Juan Enrique Domínguez-Muñoz[11], Selma Lekkerkerker[12], Jan-Werner Poley[9], Mohan Ramchandani[13], Nageshwar Reddy[13], Jeanin E. van Hooft[12]

Institutions

1 Gedyt Endoscopy Center, Buenos Aires, Argentina
2 Department of Gastroenterology Hepatopancreatology, and Digestive Oncology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium
3 Digestive Endoscopy Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
4 Centre for Endoscopic Research, Therapeutics and Training (CERTT), Università Cattolica del Sacro Cuore, Rome, Italy
5 Gastroenterology and Hepatology, Hospital Costa del Sol, Marbella, Spain
6 Service de Gastroentérologie, University Hospital of Bicêtre, Assistance Publique-Hopitaux de Paris, Université Paris Sud, Le Kremlin Bicêtre, France
7 Nottingham Digestive Diseases Centre, NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, UK
8 Endoscopy Unit, IRCCS Istituto Clinico Humanitas, Rozzano, Milan, Italy
9 Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands
10 Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
11 Gastroenterology Department, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain
12 Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, The Netherlands
13 Asian Institute of Gastroenterology, Hyderabad, India

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DOI https://doi.org/10.1055/a-0822-0832
Published online: 17.1.2019 | Endoscopy 2019; 51: 179–193

ISSN 0013-726X

Corresponding author

Jean-Marc Dumonceau, MD PhD, Gedyt Endoscopy Center, Beruti 2347 (C1117AAA), Buenos Aires, Argentina
Fax: +54-11-5288-6100
jmdumonceau@hotmail.com

Appendix 1s, Tables 1s – 8s
Online content viewable at:
https://doi.org/10.1055/a-0822-0832

MAIN RECOMMENDATIONS

ESGE suggests endoscopic therapy and/or extracorporeal shockwave lithotripsy (ESWL) as the first-line therapy for painful uncomplicated chronic pancreatitis (CP) with an obstructed main pancreatic duct (MPD) in the head/body of the pancreas. The clinical response should be evaluated at 6 – 8 weeks; if it appears unsatisfactory, the patient's case should be discussed again in a multidisciplinary team and surgical options should be considered.
Weak recommendation, low quality evidence.

ESGE suggests, for the selection of patients for initial or continued endoscopic therapy and/or ESWL, taking into consideration predictive factors associated with a good long-term outcome. These include, at initial work-up, absence of MPD stricture, a short disease duration, non-severe pain, absence or cessation of cigarette smoking and of alcohol intake, and, after initial treatment, complete removal of obstructive pancreatic stones and resolution of pancreatic duct stricture with stenting.
Weak recommendation, low quality evidence.

ESGE recommends ESWL for the clearance of radiopaque obstructive MPD stones larger than 5 mm located in the head/body of the pancreas and endoscopic retrograde

cholangiopancreatography (ERCP) for MPD stones that are radiolucent or smaller than 5 mm.
Strong recommendation, moderate quality evidence.

ESGE suggests restricting the use of endoscopic therapy after ESWL to patients with no spontaneous clearance of pancreatic stones after adequate fragmentation by ESWL.
Weak recommendation, moderate quality evidence.

ESGE suggests treating painful dominant MPD strictures with a single 10-Fr plastic stent for one uninterrupted year if symptoms improve after initial successful MPD drainage. The stent should be exchanged if necessary, based on symptoms or signs of stent dysfunction at regular pancreas imaging at least every 6 months. ESGE suggests consideration of surgery or multiple side-by-side plastic stents for symptomatic MPD strictures persisting beyond 1 year after the initial single plastic stenting, following multidisciplinary discussion.
Weak recommendation, low quality evidence.

ESGE recommends endoscopic drainage over percutaneous or surgical treatment for uncomplicated chronic pancreatitis (CP)-related pseudocysts that are within endoscopic reach.
Strong recommendation, moderate quality evidence.

ESGE recommends retrieval of transmural plastic stents at least 6 weeks after pancreatic pseudocyst regression if MPD disruption has been excluded, and long-term indwelling of transmural double-pigtail plastic stents in patients with disconnected pancreatic duct syndrome.
Strong recommendation, low quality evidence.

ESGE suggests the temporary insertion of multiple side-by-side plastic stents or of a fully covered self-expandable metal stent (FCSEMS) for treating CP-related benign biliary strictures.
Weak recommendation, moderate quality evidence.

ESGE recommends maintaining a registry of patients with biliary stents and recalling them for stent removal or exchange.
Strong recommendation, low quality evidence.

PUBLICATION INFORMATION

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the indications for, techniques, and results of treatment of chronic pancreatitis by extracorporeal shockwave lithotripsy and/or endoscopy.

ABBREVIATIONS

CP	chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESWL	extracorporeal shockwave lithotripsy
FCSEMS	fully covered self-expandable metal stent
LAMS	lumen-apposing metal stent
MPD	main pancreatic duct
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
OR	odds ratio
PFC	pancreatic fluid collection
PPC	pancreatic pseudocyst
RR	relative risk
RCT	randomized controlled trial
SEMS	self-expandable metal stents
S-MRCP	secretin-enhanced magnetic resonance cholangiopancreatography

1 Introduction

The Clinical Guideline on the endoscopic treatment of chronic pancreatitis (CP) published in 2012 by the European Society of Gastrointestinal Endoscopy (ESGE) made recommendations on the indications and modalities of treatment for CP [1]. New evidence has become available since then and is discussed in the present update, and new recommendations are issued.

2 Methods

ESGE commissioned this Guideline and appointed a Guideline leader (J.M.D.) who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (J.M.D., A.T., M.D.) and then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, who was assigned key questions (see Appendix 1s, online-only Supplementary Material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The literature search was performed using MEDLINE and Embase to identify new publications since January 2012 published in English. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendation and the quality of evidence [2]. Each task force proposed statements on their assigned key questions which were discussed during a meeting in Brussels, Belgium, in June 2017. Literature searches were re-run in August 2018. This time-point should be the starting point in the search for new evidence for future updates to this Guideline. In August 2018 a draft prepared by J.M.D. was sent to all group members for review. The draft was also reviewed by two members of the ESGE Governing Board, by external reviewers, and by the ESGE National Societies and

Individual Members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

This Guideline was issued in 2018 and will be considered for review in 2022, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim period will be noted on the ESGE website: https://www.esge.com/esge-guidelines.html.

3 Choice of treatment and initial work-up

RECOMMENDATION

ESGE suggests endoscopic therapy and/or extracorporeal shockwave lithotripsy (ESWL) as the first-line therapy for painful uncomplicated chronic pancreatitis (CP) with an obstructed main pancreatic duct (MPD) in the head/body of the pancreas. The clinical response should be evaluated at 6 – 8 weeks; if it appears unsatisfactory, the patient's case should be discussed again in a multidisciplinary team and surgical options should be considered.
Weak recommendation, low quality evidence.

The first step proposed to relieve pain in patients with uncomplicated CP includes lifestyle modifications plus, in selected patients, endoscopic therapy and/or ESWL [3]. If endoscopic therapy and/or ESWL provide no persistent pain relief or technically fail, or if the patient is not a good candidate for endoscopic therapy and/or ESWL, medical treatment including analgesics and adjunctive agents (e.g., pharmaceutical agents aimed to relieve neuropathic pain) are proposed, with the final step being early surgery for nonresponders. In a large prospective multicenter U.S. cohort (n = 521), medical therapy, endoscopic therapy, and pancreatic surgery were performed in 69 %, 52 %, and 18 % of patients, respectively [4]. Similarly, in 33 series of CP patients treated with endoscopic therapy and/or ESWL, surgery was performed during long-term follow-up in a minority of patients, less frequently in those with stones as the main obstructing factor (117 of 1695 [6.9 %], 13 series, **Table 1 s**, see Supplementary Material, online-only) as compared to those with strictures (157 of 1061 patients [14.8 %], 20 series, **Table 2 s**; $P < 0.001$).

Two trials have suggested that surgery was superior to endoscopic therapy and/or ESWL for pain relief [5 – 7]. In the first trial [5], pain was absent after 5 years of follow-up in 15 % vs. 34 % of patients treated with endoscopic therapy vs. surgery, respectively, showing that neither of these options is entirely satisfactory. Furthermore, neither ESWL nor cumulative stenting were used and the randomized design of the study is questionable. In the other trial [6, 7], only 39 patients were included; all of them had advanced CP and most were opioid-dependent. For these reasons, the results cannot be extrapolated to all patients with CP. A cost – effectiveness model based on data of this randomized controlled trial (RCT) unsurprisingly concluded that surgery was more effective and less costly than endoscopic therapy in CP [8], but another RCT has shown that ESWL could provide satisfactory clinical results at a relatively low cost in patients with obstructive stones in the main pancreatic duct (MPD) (62 % of patients with no pain relapse at 4-year follow-up after ESWL) [9]. Finally, a retrospective study (86 CP patients) reported similar pain relief 5.4 years after endoscopic therapy and/or ESWL vs. surgery, but surgery carried more complications and higher costs [10].

Endoscopic therapy and/or ESWL aim to relieve an obstruction in the MPD. They are proposed only to patients with marked ductal changes, mainly dilation, corresponding to the most severe grade in the Cambridge classification of pancreatitis [11]. No recent publications have reported the results of endoscopic therapy in patients with less severe changes [12 – 13]. In painless CP, endoscopic therapy and/or ESWL are not performed because the only potential benefit (preserving the pancreatic function) is uncertain: a single prospective nonrandomized comparative study examined this in 42 CP patients and found that the mean value of the N-benzoyl-L-tyrosyl para-aminobenzoic acid test was higher at 5-year follow-up after stenting vs. no stenting of a MPD stricture while no differences were observed for overt diabetes [14]. These results have not been confirmed and in most long-term studies the pancreatic function deteriorated during follow-up [15 – 19].

RECOMMENDATION

ESGE suggests, for the selection of patients for initial or continued endoscopic therapy and/or ESWL, taking into consideration predictive factors associated with a good long-term outcome. These include, at initial work-up, absence of MPD stricture, a short disease duration, a short disease duration, non-severe pain, absence or cessation of cigarette smoking and of alcohol intake, and, after initial treatment, complete removal of obstructive pancreatic stones and resolution of pancreatic duct stricture with stenting.
Weak recommendation, low quality evidence.

During the pretherapeutic evaluation of a patient, factors associated with a good long-term clinical outcome may help to select patients for endoscopic therapy and/or ESWL. These factors should be considered as orientative only as the differences in the proportions of patients with long-term success for an individual factor are small. The factors include absence of MPD stricture (see above) as well as short disease duration, non-severe pain (including low dose use of narcotics), the absence or cessation of cigarette smoking and of alcohol intake, cephalic location of stones, the absence of pancreas divisum if MPD stenting is required, and steatorrhea (4, 4, 3, 2, 1, 1, and 1 studies, respectively) (**Table 3 s**). Favorable prognostic factors related to endoscopic therapy and/or ESWL include complete stone removal and MPD stricture resolution after stenting (2 and 1 studies, respectively).

Patients with an MPD obstruction located only in the tail of the pancreas are not considered candidates for ESWL and/or endoscopic therapy by some groups of authors [20].

RECOMMENDATION

ESGE suggests performing a high quality pancreatic computed tomography (CT) scan and/or magnetic resonance imaging with cholangiopancreatography to reasonably rule out pancreatic cancer and to plan treatment in patients with chronic pancreatitis.

Weak recommendation, low quality evidence.

The risk of pancreatic cancer is increased in patients with CP, particularly in the first years following diagnosis [21]. A meta-analysis (52 studies, 5399 patients) found that endoscopic ultrasonography (EUS), CT scan, and magnetic resonance imaging (MRI) present similar diagnostic accuracies for the diagnosis of pancreatic cancer [22]. Imaging methods of the pancreas are constantly refined and they are often used in combination [23, 24]. In the particular context of CP, MRI with diffusion-weighted imaging has shown sensitivity and specificity for the diagnosis of malignancy of 86 % and 82 %, respectively, in a meta-analysis [25], while EUS-guided sampling seems to be less sensitive according to a retrospective and a prospective study (54 % and 74 % vs. 89 % and 91 % in the presence vs. the absence of CP, respectively) [26, 27]. The yield of EUS elastography and contrast-enhanced harmonic EUS as well as methods to improve the accuracy of EUS-guided sampling are discussed in dedicated ESGE Guidelines [28, 29].

Non-contrast CT scan accurately delineates calcified stones in the pancreas and allows measurement of stone density, a factor associated with the completeness of stone extraction [30]. Contrast enhancement may help to locate stones relative to the ducts [31, 32]. Magnetic resonance cholangiopancreatography (MRCP) identifies ductal abnormalities; in two retrospective studies its diagnostic accuracy for ductal abnormalities was 73.2 % (41 children with CP) and 92.2 % (30 adults with CP) [33, 34].

4 Pancreatic stone management

Pancreatic stones seem to arise as either direct and evenly calcified stones or as radiolucent protein plugs that may or may not become calcified during the course of the disease [35]. The vast majority of pancreatic stones are calcified and radiopaque; their prevalence increases with time to reach 50 % and 100 %, at 5 and 14 years after the onset of the disease, approximately [36]. In a multicenter survey (879 CP patients with a mix of newly diagnosed and long-standing disease), calcified pancreatic stones were detected in 62 % of patients; they were more frequent in men, heavy drinkers (> 80 g/day), and heavy smokers (≥ 20 cigarettes/day) [37]. Pancreatic stones in CP patients who undergo endoscopic therapy and/or ESWL are solitary in 10 % – 62 % of patients; they are most frequently located in the pancreatic head only, with a mean size of 10 mm, and they are associated with strictures in approximately 50 % of patients (Table **4 s**).

Successful stone fragmentation following ESWL has been defined as stones broken into fragments ≤ 2 or 3 mm, or by the demonstration at X-ray of decreased stone density, increased stone surface, and heterogeneity of the stone which may fill the MPD and adjacent side branches [38]. Ductal clearance has been defined as complete, partial, or unsuccessful if the proportion of stones cleared was > 90 %, 50 % – 90 %, or < 50 %, respectively [39].

RECOMMENDATION

ESGE recommends ESWL for the clearance of radiopaque obstructive MPD stones larger than 5 mm located in the head/body of the pancreas, and endoscopic retrograde cholangiopancreatography (ERCP) for MPD stones that are radiolucent or smaller than 5 mm.

Strong recommendation, moderate quality evidence.

Endoscopy alone, using pancreatic sphincterotomy and a basket or a balloon, allows stone extraction in a minority of CP patients: 9 % of 1041 patients in two retrospective series [40 – 41] and 14 % of 1834 patients in a survey of 125 hospitals [42]. Failed stone extraction using these techniques is associated with stones > 10 mm, diffuse location, stone impaction, and location upstream from a stricture [41, 43]. Furthermore, pancreatic mechanical lithotripsy carries a complication rate threefold higher compared with biliary mechanical lithotripsy according to a retrospective study of 712 patients [44]. Complications in the 69 patients with pancreatic stones included trapped or broken basket, traction wire fracture, and one pancreatic ductal leak which required surgery [44]. In one of the above-mentioned series, ESWL allowed the endoscopic extraction of pancreatic stones in > 80 % of the patients after failed stone extraction at primary endoscopy [40]. Similarly, a retrospective study (70 patients) found that performance of ESWL prior to the endoscopic attempt at stone extraction was the only independent factor associated with successful stone clearance [45]. Therefore, a primary endoscopic attempt at pancreatic stone extraction is reserved to selected patients, based on a reasonable expectation of success or on technical difficulty in performing ESWL as with radiolucent stones or stones < 5 mm that are difficult to target using X-rays.

A meta-analysis (27 studies including 6 prospective ones, in total 3189 patients with pancreatic stones > 5 mm) reported that pancreatic ESWL allowed complete/partial MPD clearance in 70 %/22 % of patients, respectively, that pain was absent or mild-moderate during the 2 years following treatment in 52.7 % and 33.4 % of patients, respectively, and that quality of life improved after ESWL in 88.2 % of patients [39]. ERCP was combined with ESWL in most studies. **Table 1 s** summarizes the outcomes of ESWL alone or combined with endoscopic stone extraction. Pain relapsed in 30 % – 50 % of patients dur-

ing a follow-up of 1 – 14 years and surgery was performed in 6.9 % of patients. Of note, the studies that reported the timing of pain relapse showed that patients with no pain relapse at 2-year follow-up rarely experience pain relapse thereafter [9, 16, 45], in particular if stone clearance has been complete [30]. Approximately half of patients with relapsing pain present with stone recurrence [46].

RECOMMENDATION

ESGE suggests restricting the use of endoscopic therapy after ESWL to patients with no spontaneous clearance of pancreatic stones after adequate fragmentation by ESWL. Weak recommendation, moderate quality evidence.

The addition of endoscopic therapy to ESWL provided no additional benefit in two studies that compared ESWL vs. ESWL systematically combined with endoscopic therapy [9, 47]. An RCT (55 patients) of ESWL alone vs. ESWL combined with endoscopic therapy reported similar decreases in MPD diameter and in number of pain episodes/year; patients who had ESWL combined with endoscopic therapy had a longer hospital stay and higher treatment costs [9]. Furthermore, a retrospective series (146 patients) found no differences in pain resolution 6 months after ESWL alone vs. combined with endoscopic therapy; the criteria for performing endoscopic therapy or not were not stated [47].

The first case series of ESWL alone for pancreatic stones was reported in 1996 from Japan; it reported pain relief in 22 of 28 patients (79 %) at 44-month follow-up [48]. Three surveys of the treatment of pancreatic stones in Japanese hospitals during 5-year periods were reported in 2018 (125 hospitals, 1834 patients), 2013 (34 hospitals, 916 patients) and 2005 (11 hospitals, 555 patients) [41, 42, 49]. The rates of spontaneous stone clearance after ESWL were 15 %, 49 %, and 70 %, respectively, and the proportions of patients who had endoscopic therapy after ESWL were 81 %, 56 %, and 43 %, respectively. The inclusion of a greater number of less specialized hospitals in the most recent survey might explain these differences [42]. In all of these studies, no differences in baseline characteristics of patients who had ERCP alone or combined with ERCP were reported except for gender in one study [47].

ESWL: technical factors, complications and contraindications

Pancreatic stone fragmentation is obtained after ESWL in approximately 90 % of patients [50]; this may require multiple ESWL sessions (up to 8 in a large series with a high rate of successful fragmentation) [20]. More shockwaves may be required for stones that are larger [51], multiple [52], or associated with a MPD stricture [53], while pancreatic stenting prior to ESWL seems to decrease the number of shockwaves and of ESWL sessions required [51]. Multicenter surveys have suggested that stone fragmentation is less frequently successful in low case volume centers while the role of the type of lithotripter has been controversial [41, 42, 49].

After ESWL, endoscopic clearance of stone fragments has been more frequently successful with solitary stones [17, 20, 30, 45, 53], stones located in the pancreatic head [20], stones with a density at CT scan of < 820.5 Hounsfield units [30], if a pancreatic stent had been inserted prior to ESWL [54, 55], if secretin had been administered at the beginning of ESWL [55], and if ERCP was delayed by more than 2 days after ESWL [56]. Pancreatic pseudocysts (PPCs) did not affect stone clearance or adverse events in a prospective series of 849 patients (59 with a PPC) [57].

The most frequent complication of ESWL is pancreatitis; it has been reported in 4.2 % of the patients in a meta-analysis, but most of the included studies were retrospective and did not allow the attribution of complications to either endoscopic therapy or ESWL as both were performed in most patients [39]. In a prospective study (634 patients, 1470 ESWL sessions), transient adverse events (asymptomatic hyperamylasemia, hematuria, gastrointestinal mucosal injury) and complications were detected in 21.2 % and 6.7 % of the procedures, respectively [58]. Complications included pancreatitis, infection, steinstrass (acute stone incarceration in the papilla), bleeding, and perforation; they were classified as moderate or severe in 1.1 % of the cases. Skin erythema and tenderness in the region in contact with the shockwave head were noted in most patients [58].

Contraindications to ESWL include non-correctable coagulation disorders, pregnancy, and presence in the shockwave path of bone, calcified vessels, or lung tissue [59]. Specific precautions should be taken for patients with implantable defibrillators and pacemakers [60].

RECOMMENDATION

ESGE suggests considering pancreatoscopy-guided lithotripsy when ESWL is not available or for stones that were not fragmented after adequately performed ESWL. Weak recommendation, low quality evidence.

Reports of intracorporeal lithotripsy using electrohydraulic or laser lithotripsy under peroral pancreatoscopy are sparse. A systematic review (10 studies, 87 patients) reported successful MPD clearance in 43 % – 100 % of patients [61]. Results may be biased as the reports included selected patients with anatomical features thought to permit passage of the pancreatoscope to the target stone in a stable position. The largest study reported complete and partial stone clearance in 24 (63 %) and 10 (26 %) of 38 patients, respectively, after a total of 280 endoscopic therapy sessions, including 88 with pancreatoscopy; complications (post-ERCP pancreatitis and one perforation) were reported for 20 procedures and the overall clinical success rate was 74 % [62].

5 Pancreatic strictures

Since the previous publication of this Guideline no new definitions of the types of MPD strictures in CP have been reported. Besides benign vs. malignant and single vs. multiple, strictures may be classified as either non-dominant or dominant [63]. Dominant MPD strictures are defined by the presence of at least one of the following characteristics: upstream MPD dilatation ≥ 6 mm in diameter, prevention of contrast medium outflow alongside a 6-Fr catheter inserted upstream from the stricture, or abdominal pain during continuous infusion of a nasopancreatic catheter inserted upstream from the stricture with 1 L saline for 12 – 24 h.

Stent insertion across a dominant MPD stricture (or the most proximal [tail] one in the case of multiple strictures) defines technical success. It aims to: (i) decompress the MPD, thereby ameliorating pain, and (ii) persistently dilate the stricture(s). Less frequent indications include facilitation of MPD stone clearance in association with ESWL as detailed above, and to bypass an obstruction in the ventral duct by inserting a stent through the minor papilla into the MPD [64]. A prospective non-randomized study showed in 42 patients with a dominant MPD stricture that pain recurred less frequently in patients who had received a temporary pancreatic stenting vs. those who had not (15 % vs. 50 % during a 5-year follow-up) [14]. Before stent dilation therapy is embarked upon, malignancy should be reasonably excluded, for example by brush cytology and cross-sectional imaging (see Section 3).

Refractory MPD strictures are defined as symptomatic dominant strictures that persist or relapse after 1 year of single pancreatic stent placement. A validated short-term definition for clinical success is still lacking. For long-term evaluation, the absence of pain during the year following stent removal still seems a reasonable and workable definition.

RECOMMENDATION

ESGE suggests treating painful dominant MPD strictures with a single 10-Fr plastic stent for one uninterrupted year if symptoms improve after initial successful MPD drainage. The stent should be exchanged if necessary, based on symptoms or signs of stent dysfunction at regular pancreas imaging at least every 6 months. ESGE suggests consideration of surgery or multiple side-by-side plastic stents for symptomatic MPD strictures persisting beyond 1 year after the initial single plastic stenting, following multidisciplinary discussion.

Weak recommendation, low quality evidence.

Insertion of a single plastic stent has been used as the initial endoscopic therapy for MPD strictures (**Table 2 s**); these strictures were single in > 80 % of the patients [65 – 66], and some studies explicitly excluded patients with multiple strictures [67]. After temporary insertion of a single plastic stent in the MPD, stricture resolution was achieved in 9 % [68] to 50 % [6] of 145 patients in five studies [6, 67 – 70] but this is not required for long-term pain relief [67]. Long-term pain relief was reported in 67.5 % of 536 patients (95 % confidence interval [CI] 51.5 % – 80.2 %) in a meta-analysis of 9 studies [71]. The follow-up duration after stent removal was not calculated but in most studies it was ≥ 24 months, the period during which almost all pain relapses occur [6, 14, 66, 70, 72 – 74].

Refractory strictures may be treated by surgery, multiple side-by-side plastic stents (**Table 5 s**), or self-expandable metal stents (SEMSs) (**Table 6 s**).

The temporary insertion of multiple side-by-side plastic stents in 48 patients yielded stricture resolution and pain relief at 9.5-year follow-up in 89.5 % and 77.1 % of the patients, respectively [75 – 76].

With respect to SEMSs, uncovered and partially covered types have provided disappointing results [77] but temporary placement of a fully covered SEMS (FCSEMS) has provided pain improvement in 85 % of patients according to a systematic review of four prospective series (total 61 patients) [78]. These studies were limited by a very short follow-up, and three more recent studies (n = 41) have reported pain improvement in 37 % – 88 % of patients during a follow-up of 3 – 4 years [79 – 81]. Pancreatic FCSEMS need further evaluation in the setting of clinical trials because of potential complications as listed below.

Pancreatic stenting: technical factors and complications

Whether or not a pancreatic sphincterotomy should be performed before pancreatic stent insertion has not been addressed in any study, but both methods have been reported for the insertion of a single plastic stent as well as for a SEMS [18, 65, 79, 82 – 85]. With respect to the performance of a biliary sphincterotomy prior to pancreatic sphincterotomy, this should only be performed in selected cases, according to a small RCT, mostly if biliary drainage is indicated or to facilitate access to the MPD [86].

In many but not all studies [51, 54, 55], pancreatic stenting was performed after stone fragmentation and removal. In prospective series, technical success was reported in 92 % of attempted insertions of a first stent [6, 14, 67, 87]. The stenting duration averaged 10.6 months (range 3.2 – 23 months) in 18 series totaling 811 patients [5, 6, 14, 64 – 67, 70, 72 – 74, 82, 87 – 92].

Multiple stent designs have been proposed, including straight, S-shaped, and winged stents, and stents with or without sideholes [93 – 94]. Few comparative studies have been reported; in a prospective study, stents with large sideholes have been suggested to occlude less frequently compared to other types, but only a minority of patients had CP [95]. With respect to stent diameter, CP patients treated with stents ≤ 8.5-Fr were 3.2 times more likely to be hospitalized for abdominal pain than those who had received 10-Fr stents in a retrospective study of 163 CP patients [96].

"On-demand" stent exchange consists of exchanging pancreatic stents when deemed necessary, based on patient symptoms and/or additional investigations at 1 – 6-month intervals (i. e., secretin-enhanced MRCP [S-MRCP] [66], abdominal ultra-

sound alone [68] or supplemented either with abdominal plain film [66] or with blood/urinary amylase measurements [69]). With this stent exchange policy, sepsis of pancreatic origin was reported in 15 (5.2 %) of 288 patients in four series [66, 68 – 69, 72] and surgery was required in two patients for pancreatic abscesses; this was reported in the only series in which no additional investigations at regular intervals were performed [72]. On the other hand, in 12 series (521 patients) with stent exchange scheduled at shorter intervals, usually 3 months, septic complications have not been reported [5, 14, 65, 67, 70, 73, 74, 88, 90, 92, 97, 98].

Compared with surgery, hospital stays and medical expenses were similar for patients who had pancreatic stenting for less than 1 year (n = 19) but higher for those who required longer pancreatic stenting (n = 15), in a retrospective study [97]. In that study, a single plastic stent was re-inserted if a stricture persisted at pancreatography after stent removal within 3 months of the first ERCP.

With respect to FCSEMSs, stents of 6 – 10 mm in diameter have been used (**Table 6 s**); the mean stenting duration was 2 – 6 months and stents were removed uneventfully in 108 (98 %) of 110 patients. (The stent-in-stent technique was used in the two remaining patients and distal FCSEMS migration had occurred in 6 other patients.) Finally, in a pilot study, a biodegradable non-covered self-expandable stent has provided clinical success in 10 of 19 patients (53 %) who had no stricture resolution at least 6 months after plastic stent insertion (median 10 months); adverse events were reported in 4 patients (21 %) [99].

Regarding complications with plastic stents, mild pancreatitis or worsening of pancreatic pain were most commonly reported at short term (average 6.2 %, range 4 % – 39 %) followed by sepsis, cholangitis, and post-sphincterotomy bleeding (average, 2.6 %, 2.3 %, and 1.5 %, respectively) (**Table 2 s**). Severe pancreatitis has been rarely reported [73]. During follow-up, proximal and distal stent migration is reported in 2.7 % and 3.6 % of cases respectively, and bench tests using a column of water at a pressure lower than that observed in patients with CP [89, 100] have shown that almost all stents become obstructed at 3 months. However stent obstruction does not correlate with symptoms [82, 89, 100]. Stent-induced ductal lesions were described in 18 % of patients (range 0 – 26 %) and mortality was reported in 0.4 % (7/1620) (**Table 2 s**).

With SEMSs, stent migration (15 % – 46 %) and de novo strictures (16 % – 27 %) have also been reported and specific complications include severe pain (7 % – 20 %) leading to cholestasis and FCSEMS removal (15 %) (**Table 6 s**).

RECOMMENDATION

ESGE recommends performance of endosonography-guided access and drainage of the MPD only in tertiary centers after multidisciplinary discussion and preferably in a research setting.

Strong recommendation, low quality evidence.

Potential indications for endosonography-guided access and drainage of the MPD include patients with symptomatic MPD obstruction and failed conventional transpapillary drainage. Briefly, the technique consists of puncturing the MPD through the gastric or duodenal wall and advancing a guidewire into the MPD to proceed with transpapillary (rendezvous technique) or transmural drainage using a plastic stent [50], or more recently a FCSEMS [101]. It is recognized as one of the most difficult techniques of EUS-guided therapy [102].

Endosonography-guided access and drainage of the MPD has been reported in retrospective, small, single-center studies [103 – 107] or larger multicenter studies (36 to 80 patients) [108 – 110] with a follow-up ranging from a few weeks up to 55 months (median 1 year). In all these series, the annual inclusion rate per center was always below 4, illustrating the rarity of the indications.

Immediate pain relief after successful endosonography-guided access and drainage of the MPD has been reported in a majority of patients with obstructive CP (range 50 % – 100 %). In the two series to date with available long-term follow-up, complete or major pain relief was achieved in 70 % – 90 % of patients but the probability of remaining free of pain dropped sharply over time [108, 109].

Failed endosonography-guided access and drainage of the MPD occurs in approximately 10 % of cases and the incidence of moderate to severe complications also averages 10 % in the largest series, including severe pancreatitis, perforation, bleeding, and hematoma [103 – 110]. No procedure-related mortality has been reported. Migration and occlusion of stents necessitating endoscopic re-intervention frequently occur (20 % – 55 % of patients).

6 Pseudocyst management

Approximately one third of CP patients develop PPC during the course of their disease [36]. PPCs should be differentiated from cystic neoplasms such as potentially malignant mucinous neoplasms, particularly when they present for the first time.

Endoscopic therapy of PPCs consists of inserting a drain from the digestive lumen into the PPC, through the digestive wall (“transmural drainage”), through the papilla (“transpapillary drainage”), or using a combination of these routes. Transpapillary PPC drainage is feasible only if the PPC communicates with the MPD, a situation detected in approximately half of PPCs [111]. Technical and clinical success are usually defined, respectively, as the insertion of at least one stent between the PPC and the digestive lumen (plus removal if indicated) [112], and disappearance of symptoms with complete resolution of the PPC or a decrease in size to less than 2 cm [113].

RECOMMENDATION
ESGE recommends treating CP-related pseudocysts if they are symptomatic (abdominal pain, gastric outlet obstruction, early satiety, weight loss or jaundice) or present with complications (infection, bleeding, rupture, or fistulization to adjacent hollow structures).
Strong recommendation, low quality evidence.

Spontaneous regression of chronic PPCs is infrequent (0 to 27 %) and occurs most commonly for PPCs smaller than 4 cm and/or located within the pancreas [114 – 115]. The indications for treatment listed above are commonly accepted. In asymptomatic patients with a PPC compressing a major vessel, the risk – benefit ratio of any intervention should be thoroughly analyzed; progressively enlarging collections are considered a valid indication by some authors while others suggest that such patients be followed until symptoms develop [116 – 117].

RECOMMENDATION
ESGE recommends endoscopic drainage over percutaneous or surgical treatment for uncomplicated CP-related pseudocysts that are within endoscopic reach.
Strong recommendation, moderate quality evidence.

A meta-analysis of 7 retrospective studies (490 patients with various types of pancreatic fluid collections [PFCs]) found that, compared with percutaneous drainage, endoscopic drainage was associated with a higher clinical success rate, fewer re-interventions, shorter hospital stay, and similar morbidity and recurrence rates [118]. Although percutaneous drainage has mostly been abandoned for the definitive treatment of CP-related pseudocysts because it often results in an external fistula [119], it may be useful as an emergency measure (e. g., for infected PPC not accessible to endoscopic drainage in a frail patient).

A meta-analysis (5 comparative studies including one RCT, 255 patients) found that, compared with endoscopic therapy, surgery has a higher success rate (odds ratio [OR] 0.43, 95 %CI 0.20 – 0.95), but is associated with a longer length of hospital stay and higher hospital costs as well as similar rates of morbidity (18.0 % vs. 11.5 %) and recurrence (3.2 % vs. 3.1 %) [120]. A more recent multicenter prospective cohort study (71 patients) reported a similar overall success rate and a shorter hospital stay for endoscopic therapy vs. surgery [121].

RECOMMENDATION
ESGE suggests MRI with secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP) for characterizing pancreatic fluid collections and the MPD anatomy before endoscopic drainage of CP-related pseudocysts.
Weak recommendation, low quality evidence.

CT scan, MRI, and EUS allow the characterization of PFCs but the assessment of their solid content is less precise with CT scan [122 – 124]; this is important only in subacute PFCs where necrotic debris may impede endoscopic drainage. S-MRCP also allows diagnosis of MPD rupture. This has important consequences for treatment planning: (i) in the absence of MPD rupture, endoscopic drainage can be transmural only; (ii) if a partial MPD rupture is present, insertion of a stent bridging the rupture (as opposed to below it) is associated with treatment success [63, 64]; and (iii) in the case of a complete MPD rupture (disconnected pancreatic duct syndrome), removal of transmural stents is associated with PFC recurrence so that long-term indwelling of transmural double-pigtail plastic stents should be considered [125, 126]. Therefore, some centers perform imaging of the MPD by S-MRCP and/or ERCP prior to drainage of and/or stent removal from PFCs.

Although ERCP is still considered to be the gold standard for the diagnosis of MPD disruption, it presents limitations including an accuracy rate of approximately 75 % and adverse events such as infection of a sterile PFC [127, 128]. In small series, S-MRCP showed an accuracy of > 90 % for diagnosing MPD disruption in patients with PFCs [123, 129].

These imaging modalities have not been compared for the detection of pseudoaneurysms close to pseudocysts, which is another important consideration when planning treatment.

RECOMMENDATION
ESGE suggests transpapillary drainage for small (< 50 mm) CP-related pseudocysts communicating with the MPD in the head or body of the pancreas and transmural drainage for other CP-related pseudocysts.
Weak recommendation, low quality evidence.

Compared with transmural drainage, transpapillary drainage provides similar success with a similar morbidity rate but fatal or surgical complications are less frequent (1/176 vs. 15/283; $P = 0.007$); however, transpapillary drainage as the only endoscopic therapy has been performed for relatively smaller collections (generally ≤ 50 mm) than those managed by transmural drainage alone or combined transpapillary and transmural drainage (**Table 7 s**). If transmural drainage is performed, the addition of transpapillary drainage seems to add no benefit according to a meta-analysis of 9 non-randomized comparative studies (7 including PPCs exclusively, 604 drainage procedures)

[130]. No definitive conclusion can be drawn as the proportion of patients in whom a transpapillary stent was inserted across as opposed to below a partial MPD disruption, a predictor of success following transpapillary drainage [131, 132], was not known. However, this factor may be of marginal importance as the insertion of a stent across a partial MPD rupture succeeds in only 33 % – 67 % of the patients [131, 132].

RECOMMENDATION

ESGE recommends endosonography-guided over conventional access for the transmural drainage of CP-related pseudocysts.

Strong recommendation, moderate quality evidence.

For the transmural drainage of PPCs, a systematic review (four studies, 229 patients) found a higher technical success rate for EUS vs. conventional approach (relative risk [RR] 12.38, 95 %CI 1.39 – 110.22) and no other significant differences (complications, short and long-term clinical success) [133]. The difference in technical success was due to the presence of non-bulging collections which account for approximately half of PFCs [111]; EUS guidance is the only option for transmural drainage in these cases.

RECOMMENDATION

ESGE suggests the use of double-pigtail plastic stents for the transmural drainage of CP-related pseudocysts; a fully covered biliary SEMS can be considered if disconnected pancreatic duct syndrome has been excluded and indwelling duration is expected to be less than 6 weeks.

Weak recommendation, low quality evidence.

Plastic stents are generally used for the transmural drainage of PPCs. Three retrospective studies examined the role of the number or diameter of plastic stents in a total of 307 patients; all studies included patients with various types of PFCs [134 – 136]. Double-pigtail stents of 7 – 10 Fr were used in the two most recent series as straight stents may migrate and erode large vessels [135]. One study found that the insertion of a single stent was associated with failure of endoscopic therapy (defined as severe procedure-related complication or need for another treatment modality) [135] while two studies found no differences according to the number and diameter of plastic stents [134, 136].

Plastic stents and FCSEMSs have been compared for the transmural drainage of PPCs in three meta-analyses [113, 137, 138]. The two most recent meta-analyses included comparative studies exclusively but only approximately 10 % of patients had CP. These two meta-analyses reported: (i) a similar success and a lower morbidity rate with FCSEMSs vs. plastic stents (OR 0.4, 95 %CI 0.21 – 0.73) (three studies, 301 patients) [138]; and (ii) a higher success rate with FCSEMSs vs. plastic stents (OR 5.35, 95 %CI 1.35 – 21.19) (morbidity analysis not reported) (two studies, 250 patients) [113]. Biliary FCSEMSs were used in most patients while lumen-apposing metal stents (LAMSs) were used in 5 % [138] and 6 % of the patients [113]; in the studies that used a standard biliary FCSEMS, a double-pigtail plastic stent was inserted through the FCSEMS to prevent its migration. The older meta-analysis included non-comparative studies only and it found no differences between stents in terms of success rates or morbidity [137].

A meta-analysis (6 retrospective studies, 504 patients) compared LAMSs with multiple plastic stents for the treatment of PFCs but only 11 % of patients had a PPC; LAMSs were associated with a higher clinical success rate (RR 2.70, 95 %CI 1.49 – 5.00) and a lower morbidity rate (RR 0.39, 95 %CI, 0.18 – 0.84) [139]. A decision model analysis concluded that LAMSs were less cost-effective than plastic stents [140].

RECOMMENDATION

ESGE recommends retrieval of transmural plastic stents at least 6 weeks after pancreatic pseudocyst regression if MPD disruption has been excluded, and long-term indwelling of transmural double-pigtail plastic stents in patients with disconnected pancreatic duct syndrome.

Strong recommendation, low quality evidence.

Transmural plastic stents are generally removed at least 6 weeks after insertion as a retrospective study showed that earlier plastic stent removal was associated with treatment failure [135]. In an RCT (28 patients, 15 of whom had a CP-related PPC), PFCs recurred more frequently in patients randomized to stent removal 2 months after drainage vs. no stent removal (38 % vs 0); PFC recurrence tended to be associated with MPD rupture as identified at S-MRCP (4/5 vs 2/9, $P = 0.063$) [126].

Disconnected pancreatic duct syndrome generally results from severe necrotizing pancreatitis and has been discussed in a dedicated ESGE Guideline [141]. Retrospective studies have shown that long-term indwelling of double-pigtail transmural plastic stents is effective, with PFC recurrence being uncommon and associated with stent migration < 6 months after PFC resolution and MPD disruption at the pancreatic head level [142, 143].

With respect to LAMSs, an RCT reported LAMS-related severe adverse events in 6 of 12 patients (50 %), including bleeding, buried stent syndrome, and biliary stricture, all occurring > 3 weeks after LAMS placement [144, 145]. Stent-related morbidity dropped to levels similar to those observed with plastic stents after the study protocol was changed to removal of LAMSs within 4 weeks. The placement of a coaxial double-pigtail stent through the LAMS has also been proposed to prevent delayed adverse events [146].

RECOMMENDATION

ESGE recommends the use of endosonographic guidance if the transmural route is selected for draining CP-related pseudocysts in patients with portal hypertension. In the case of arterial pseudoaneurysm close to a CP-related pseudocyst, ESGE recommends arterial embolization prior to endoscopic drainage.

Strong recommendation, low quality evidence.

Extrahepatic portal hypertension develops during the course of CP in ≥15% of patients [147]. The only two series that reported the results of endoscopic drainage for PFCs in patients with portal hypertension used EUS guidance; bleeding was reported in 1 of 26 patients (4%) [148, 149].

Pseudoaneurysms complicate the course of CP in 1%–10% of patients, mostly those with a PPC, and their rupture is associated with a high mortality [150]. Therefore, some authors recommend embolization of arterial pseudoaneurysms before attempting endoscopic therapy of PPC close to pseudoaneurysms [151]. This strategy has not been tested but, in patients with bleeding pseudoaneurysms, two retrospective series have reported a 94%–100% mid-term success rate with arterial embolization followed by endoscopic therapy of the PPC in a total of 40 patients [152, 153].

7 Biliary strictures

RECOMMENDATION

ESGE suggests performance of an ERCP when a CP patient presents with a ≥4-week biliary obstruction (jaundice, asymptomatic elevation of serum alkaline phosphatase [>2 or 3 times the upper limit of normal values] and/or bilirubin) to achieve biliary decompression by means of stent placement. If follow-up shows that the obstruction is caused by a genuine fibrosis rather than transient inflammatory compression, endoscopic stent treatment should be continued in order to dilate the stricture. After 1 year of unsuccessful endotherapy, surgery should be considered.

Weak recommendation, low quality evidence.

Biliary strictures complicate the course of CP in 3%–23% of patients, with studies reporting a prevalence as high as 46% [154]. Symptoms may be absent or include jaundice, cholangitis or choledocholithiasis. Jaundice resolves spontaneously in 20%–50% of patients within 1 month, because of resolution of edema or of a PPC in the head of the pancreas but secondary biliary cirrhosis is relatively frequent (7.3% of 288 patients in a review of 11 studies) [154]. Therefore, an asymptomatic elevation of serum alkaline phosphatase (>2 or 3 times the upper limit of normal values) and/or bilirubin for longer than 1 month are usually accepted as an indication for bile duct drainage [155].

As underlined in Section 3, an underlying malignancy should be reasonably excluded.

A single retrospective study compared surgery vs. endoscopic therapy (multiple side-by-side plastic stents or FCSEMS) for the treatment of CP-related biliary strictures in 39 patients [156]. Compared with surgery, endoscopic therapy presented a lower procedural morbidity rate (21% vs. 83%) and a lower success rate at 2 years (15% vs. 66%). The success rate was noticeably lower than in other studies (**Table 8s**), including an RCT, maybe because incomplete stricture resolution at ERCP was considered a failure. Outcomes were similar in patients who had surgery as a primary treatment or following unsuccessful endoscopic therapy. The authors proposed to attempt endoscopic therapy first in the absence of associated lesions (e.g., inflammatory cephalic mass), and to evaluate its success after 12 months or three endoscopic procedures.

RECOMMENDATION

ESGE suggests the temporary insertion of multiple side-by-side plastic stents or of a FCSEMS for treating CP-related benign biliary strictures.

Weak recommendation, moderate quality evidence.

The strategy of endoscopic therapy for benign biliary strictures is detailed in a dedicated ESGE Clinical Guideline [157]; it consists of temporarily dilating the stricture using multiple side-by-side plastic stents or a FCSEMS (single plastic stents or uncovered SEMSs have long been abandoned because of poor long-term results (**Table 8s**) [158]. An RCT (60 CP patients) found that multiple plastic stents and covered SEMSs provided similar success rates 2 years after stent removal (88.0% vs. 90.9%, respectively), with similar treatment-related morbidity (23.3% vs. 28.6%, respectively) [159]. The stenting duration was 6 months in both groups. Various stenting durations have not been compared in the literature (scheduled stenting durations with multiple plastic stents and covered SEMSs have generally been for 1 year and for 6–12 months, respectively). Short biliary strictures may respond better than longer ones to stenting, as suggested by a small study (10 CP patients) [160].

RECOMMENDATION

ESGE recommends maintaining a registry of patients with biliary stents and recalling them for stent removal or exchange.

Strong recommendation, low quality evidence.

Patient compliance with stent exchange may be poor, giving rise to potentially fatal complications [161, 162]. To prevent this, various recall systems have proven useful in pilot studies [163, 164]. Removable FCSEMSs can result in better patient compliance since the number of ERCPs is reduced to two. Of course, patient compliance with repeat interventions should be ensured prior to endoscopic therapy and hepaticojejunostomy remains a valid option for noncompliant patients or if the stricture does not respond to endoscopic therapy.

Disclaimer

The legal disclaimer for ESGE guidelines [165] applies to the current Guideline.

Acknowledgments

The authors gratefully acknowledge Dr. Lars Aabakken, GI Endoscopy, OUS-Rikshospitalet University Hospital, Oslo, Norway, and Dr. Kazuo Inui, Department of Gastroenterology, Second Teaching Hospital, Fujita Health University, Nagoya, Japan, for their critical review of the Guideline.

Competing interests

G. P. Aithal receives consultancy fees from Shire (September 2015 to present), Pfizer (July 2018 to present), and GSK and Agios (February 2018 to present). A. Anderloni has provided consultancy to Boston Scientific (2017 – 2018). M. J. Bruno has received lecturing and consultancy fees from Boston Scientific, Cook Medical, and Pentax Medical (ongoing) and consultancy fees from Mylan (ongoing); his department is involved in investigator- and industry-initiated studies with Boston Scientific, Cook Medical, and Pentax Medical (ongoing); he is a member (no financial benefit) of the Dutch Pancreatitis Study Group J. Devière receives research support from Olympus for institutional review board-approved studies (ongoing); his department receives research support from Boston Scientific for institutional review board-approved studies (ongoing). J. E. Domínguez-Muñoz has received speaker's honoraria from Boston Scientific (2018); his department has received financial support for educational activities from Pentax and Boston Scientific (2017 – 2018) and Medtronic (2018). J.-W. Poley receives speaker's fees and travel expenses from Pentax, Boston Scientific, and Cook Endoscopy (ongoing), and consultancy fees from Boston Scientific and Cook Endoscopy (ongoing). A. Sanchez-Yague has provided paid consultancy to Boston Scientific (2015 – 2018). J. E. van Hooft has received lecture fees from Medtronic (2014 – 2015) and consultancy fees from Boston Scientific (2014 – 2016); her department has received research grants from Cook Medical (2014 – 2018) and Abbott (2014 – 2017). M. Arvanitakis, P. Cantú, M. Delhaye, J.-M. Dumonceau, S. Lekkerkerker, M. Ramchandani, N. Reddy, A. Tringali, and T. Vaysse have no competing interests.

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Rev Esp Cardiol. 2019;72(1):16-20

Editorial

Comments on the 2018 ESC/EACTS Guidelines for Myocardial Revascularization

Comentarios a la guía ESC/EACTS 2018 sobre revascularización miocárdica

SEC Working Group for the 2018 ESC/EACTS Guidelines for Myocardial Revascularization, Expert Reviewers for the 2018 ESC/EACTS Guidelines for Myocardial Revascularization, and the SEC Guidelines Committee[*,◊]

Article history:
Available online 20 december 2018

INTRODUCTION AND COMMENTARY ON THE METHODOLOGY

The Spanish Society of Cardiology endorses the clinical practice guidelines (CPG) published by the European Society of Cardiology (ESC). As part of this policy, ESC guidelines are translated into Spanish and published in the online version of *Revista Española de Cardiología*, with the aim of increasing their accessibility and facilitating their implementation.[1] The translated articles are accompanied by an editorial authored by a panel of Spanish experts that highlights the most important content of each CPG document, details changes and innovations introduced since the previous edition, and discusses the more contentious aspects and possible limitations. The editorial also seeks to evaluate and adapt the recommendations to the context of health care organization and clinical practice in Spain.

The latest ESC guidelines for myocardial revascularization[1] update the previous CPG published in 2014.[2] It should be noted that a major effort has been made to maintain coherence with previous guidelines.

DIAGNOSTIC TOOLS TO GUIDE MYOCARDIAL REVASCULARIZATION

Noninvasive diagnostic tools

For patients with angina symptoms, the guidelines recommend a noninvasive imaging test as an initial diagnostic measure. In patients undergoing coronary angiography by computed tomography (CT), regional ischemia can be revealed by myocardial perfusion or the determination of fractional flow reserve (FFR-CT).

Patients with advanced heart disease (HD) and maintained myocardial viability should be revascularized before being considered for mechanical circulatory support or heart transplant.

Invasive diagnostic tools

The most notable change in this section concerns the introduction of the instantaneous wave-free ratio (iFR), a new measure that does not require adenosine induced hyperemia. In the new guidelines, iFR is included in the class I A recommendation for assessing the functional impact of intermediate-grade lesions. The guidelines consider FFR and iFR as equivalent, and the cutoffs for defining a lesion as hemodynamically significant are iFR ≤ 0.89 and FFR ≤ 0.8.

For the use of FFR to guide percutaneous treatment of multivessel disease, the new CPG document maintains the recommendation established previously (IIa B).[2]

The new guidelines place great value on pressure-derived functional indices (FFR and iFR), whose use in clinical practice has increased sharply. A clear example of this is provided by experience in Spain, where data from 2017 reveal a 23% increase compared with the previous year.[3]

A separate section is devoted to the assessment of stenosis severity in the left main coronary artery (LMCA), mostly involving ostial lesions. Functional assessment by FFR or iFR can be technically complex, and the evidence supporting their use in this setting is scarce. Consequently, intravascular ultrasound (IVUS) is a class IIa B recommendation, and revascularization should be excluded when the minimal luminal area is > 6 mm^2. For all lesions outside the LMCA, functional assessment is preferable to intracoronary imaging.

PROCESS FOR DECISION-MAKING AND PATIENT INFORMATION

In line with the 2014 guidelines,[2] the new CPG document emphasizes the importance of giving patients up-to-date evidence-based information about treatment options. The guidelines stress the need for treatments to be decided by a multidisciplinary Heart Team. This decision-making process is designed not only to ensure routine adherence to guideline recommendations, but also to establish defined decision-making algorithms, the measurement and short-term and long-term communication of results, and the consideration of patient preferences.

The recommended timing of revascularization (ad hoc vs deferred) depends on the clinical presentation. For patients with acute coronary syndrome (ACS) or shock, it is acceptable to perform ad hoc revascularization according to a protocol established by the multidisciplinary Heart Team. In contrast, delayed revascularization

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*Corresponding author.
E-mail address: bibanez@cnic.es (B. Ibáñez).
◊The names of all authors of this article are listed in the Appendix.

http://dx.doi.org/10.1016/j.rec.2018.11.010

is recommended for most patients with stable angina, with a deferral period of 2 to 6 weeks depending on the clinical and anatomical characteristics and ventricular function. In general, ad hoc revascularization (within the same procedure as the angiographic diagnosis) is not recommended for patients with stable angina and complex coronary anatomy.

For a number of reasons, fewer coronary artery bypass grafting (CABG) procedures are performed in Spain than in comparable countries, which is reflected in a lower rate of CABG relative to percutaneous coronary intervention (PCI), according to data from the Organisation for Economic Co-operation and Development.[4]

REVASCULARIZATION FOR STABLE CORONARY ARTERY DISEASE

Important changes have been introduced in this section, which now incorporates discussion about the assessment of surgical risk and anatomical complexity. A new figure (Figure 3 in the CPG document) summarizes the clinical and anatomical factors influencing the decision between CABG and PCI, and the guidelines also evaluate the benefits of complete revascularization. The CPG document evaluates the alternative definitions of complete revascularization, and the preferred strategy is complete revascularization based on the functional rather than the anatomical definition. Moreover, the probability of complete revascularization is given priority in decision-making between CABG and PCI (class IIa B). Despite the benefits of this recommendation, it can conflict with the indication for revascularization in specific anatomical situations that require CABG or PCI independently of the possibility of complete revascularization.

Recommendations according to the extent and anatomical complexity of coronary artery disease (CAD) remain unaltered except for diabetes patients with 3-vessel CAD and a SYNTAX score ≤ 22, for whom the recommendation for PCI has been downgraded from IIa B in 2014 to IIb B in the current CPG. This change is somewhat surprising because 3-vessel CAD and a SYNTAX score ≤ 22 indicates low anatomical complexity and a low future rate of revascularization and thrombosis. CABG remains an optimal treatment for LMCA and 3-vessel disease. PCI and CABG are both class I A recommendations for LMCA disease with a SYNTAX score ≤ 22 and for 3-vessel CAD without diabetes and a SYNTAX score ≤ 22. For most other patients with LMCA or 3-vessel disease, PCI is contraindicated if CABG is possible; the exception is LMCA patients with an intermediate SYNTAX score, for whom PCI retains a class IIa recommendation.

Compared with the previous guidelines,[2] the new guidelines give less weight to the EuroSCORE II in the prediction of surgical mortality (IIa B in 2014 vs IIb B in 2018), whereas the STS and SYNTAX scores maintain a class I B recommendation. The logistic EuroSCORE and other scores are no longer considered, and the use of the SYNTAX-II score is not recommended. The ESC Task Force members acknowledge the major limitations of the SYNTAX score, but nonetheless still regard it as a basic tool in the choice of revascularization method, a conclusion supported by data from a recent collaborative individual patient pooled analysis of randomized trials.[5] To date, only 1 study has compared CABG and PCI specifically in relation to the SYNTAX score.[6] The new guidelines reduce the left ventricular ejection fraction (LVEF) cutoff for indicating revascularization in patients with multivessel disease and documented ischemia; the cutoff was previously ≤ 40% and is now ≤ 35% (I A). The new guidelines add the possibility of revascularization of lesions with FFR < 0.75 (I B).

This section of the CPG document addresses the controversial issue of the possible placebo effect of PCI, indicated by the ORBITA study.[7] The Task Force members conclude that, despite its elegant design, the ORBITA study has major limitations that make it unsuitable for guiding changes to clinical practice. Nevertheless, the ORBITA study underlines the importance of optimal medical treatment for patients with stable CAD.

The new ESC guidelines incorporate data from a network meta-analysis of 100 studies confirming that new-generation drug-eluting stents (DES) improve survival compared with medical treatment, although this has not been demonstrated in any individual study.[8]

REVASCULARIZATION IN NON–ST-ELEVATION ACUTE CORONARY SYNDROME

The invasive strategy remains the standard treatment for most patients with non–ST-segment elevation acute coronary syndrome (NSTEACS). The early invasive strategy (intervention in the first 24 hours) is recommended for most NSTEACS patients, including those with elevated troponins, repolarization changes, or a GRACE score > 140. The debate about the basis for intervention within 24 hours is an old one, and this strategy has well-known logistic and procedural implications that may significantly contribute to its incomplete implementation in Spain. Therefore, in Spain, the decision on whether to use the early invasive strategy should be informed by consideration of regional health care organization and the type of hospital to which the patient is admitted.

Radial access and the use of new-generation DES are recommended for all patients. The guidelines highlight the usefulness of FFR for identifying functionally significant lesions in NSTEACS patients, although the prognostic value of this approach is unknown.

Complete revascularization is recommended for patients with multivessel disease and should be carried out in a single procedure except in patients with cardiogenic shock.

CABG is required in only 5% to 10% of NSTEACS patients, and the ideal timing of intervention should be carefully determined for each individual. The guidelines give no specific recommendation for preoperative antiplatelet therapy; however, they do remind readers that, whereas the incidence of preoperative ischemic events is < 0.1%, the incidence of perioperative bleeding is above 10%. Even so, dual antiplatelet therapy does not justify delaying surgery in patients with active ischemia and hemodynamic instability. There is no evidence favoring a choice between PCI or CABG for patients with stable NSTEACS, and physicians should therefore apply the same criteria used for patients with stable CAD.

REVASCULARIZATION IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

This section introduces several changes compared with the previous CPG document. The most important changes include the promoted recommendations for radial access and DES use (both of which are now class I A); the recommendation against the systematic use of thrombus aspiration (relegated from class IIa A to III A), while allowing for its use in selected patients; and the use of unfractionated heparin as the anticoagulant of choice (class I C), with enoxaparine and bivalirudin as alternatives in decreasing order of preference (class IIa and class IIb, respectively). Another major change compared with the 2014 guidelines relates to the treatment of severe stenosis in nonculprit vessels in STEACS patients. For stable patients, the recommendation is to revascularize nonculprit vessels before hospital discharge (class IIa A). The basis for recommending revascularization during hospitalization is that this is the procedure used in trials; however, there is no reason to expect that results would be different if revascularization were performed after hospital discharge. For patients in shock, the new guidelines advise against the systematic practice of multivessel PCI in this setting (class III B).

MYOCARDIAL REVASCULARIZATION IN PATIENTS WITH HEART FAILURE

Chronic heart failure

CABG is the preferred revascularization procedure for HD patients with reduced LVEF or multivessel disease and acceptable

surgical risk (class I B). PCI is recommended as an alternative to CABG (IIa C) for patients with 1-vessel or 2-vessel disease when complete revascularization can be achieved. PCI is similarly recommended for patients with 3-vessel disease based on the Heart Team's assessment of the surgical risk (comorbidities), coronary anatomy, the predicted completeness of revascularization, and above all diabetes status. PCI should also be considered for elderly patients with diabetes when complete revascularization can be achieved, whereas CABG is recommended for younger patients with extensive CAD and for patients with diabetes. There has been no trial comparing CABG and PCI in heart failure patients with reduced LVEF, and the evidence gap in this area should to some degree influence the application of these recommendations.

Acute heart failure and cardiogenic shock

The most notable feature of this section is the maintenance of the low recommendation for short-term mechanical circulatory support (class IIb C) and its restriction to a set of defined patient characteristics. The document includes no recommendations about the use of intra-aortic balloon pumps in patients with shock in the peri-infarct period and mechanical complications.

The CPG document mentions that extracorporeal membrane oxygenation support appears to provide superior clinical benefit vs intra-aortic balloon pumping in observational studies; in contrast, no such advantage has been reported for percutaneous left ventricular assist devices (Impella and TandemHeart).

Revascularization in special patient groups

Patients with diabetes

The only specific recommendation in this section retained from the previous guidelines is to check renal function if patients have taken metformin immediately before angiography and to suspend metformin if renal function deteriorates. Other recommendations for diabetes patients are included in the general sections of the document. The discussion of the evidence favoring revascularization in diabetes patients has been simplified, and concludes that the recommendations for this patient group are similar to those for the general population in light of a meta-analysis showing no significant interaction between diabetes and the benefits of revascularization. The guideline authors note that this meta-analysis included only patients with ACS and that the largest study designed to compare revascularization and medical treatment in diabetes patients showed no benefit.

CABG remains the recommended revascularization method for multivessel disease in diabetes patients. As previously mentioned, the guidelines recommend PCI for diabetes patients with a SYNTAX score ≤ 22 (class IIb A), based on several studies in a variety of clinical contexts. New studies are needed to explore whether functional revascularization and new-generation DES also provide a benefit in patients with low anatomical complexity.

Patients with chronic kidney disease

Like previous editions, the new guidelines highlight the underrepresentation of this patient group in clinical trials. The need to prevent contrast-induced nephropathy in all patients is addressed by raising the recommendation class for preoperative risk assessment (from class IIa C in 2014 to class I C in the new CPG document) and ensuring adequate hydration (class I C). For patients with moderate or severe chronic kidney disease, the guidelines recommend prehydration and posthydration with isotonic saline if the expected contrast volume is > 100 mL (IIa C).

Patients requiring valve interventions

There are no major changes in this section. Coronary stenosis severity can be assessed with FFR or iFR in patients with severe aortic stenosis; however, the current evidence in insufficient to support the use of these approaches in this setting.

For patients with moderate aortic stenosis/regurgitation undergoing CABG, the Heart Team should carefully assess the potential for transcatheter aortic valve implantation on a case-by-case basis. The guidelines introduce a new indication for mitral valve repair at the time of CABG in patients with concomitant severe primary mitral regurgitation. However, a general recommendation for mitral valve repair applies only if the effective regurgitant orifice area (EROA) is > 0.4 cm^2, and the decision to combine mitral valve repair with CABG should be individualized for patients with an EROA between 0.2 and 0.4 cm^2. A class IIa C recommendation has been added for mitral valve repair in patients with severe mitral regurgitation and LVEF < 30% accompanied by evidence of myocardial viability.

Patients with peripheral artery disease

The myocardial revascularization guidelines endorse the 2017 ESC peripheral arterial diseases guidelines.[9] The current CPG authors note the higher incidence of stroke in patients undergoing CABG and discuss the causes and available preventive strategies. The new guidelines do not tackle the frequent problem of myocardial revascularization in patients who also require surgical or percutaneous vascular intervention, the evidence for which is well established.

REPEAT REVASCULARIZATION

Clinically apparent early graft failure after CABG is a rare event (≈3%). For patients with suspected severe myocardial ischemia immediately after CABG, perioperative angiography is recommended to detect the cause and inform joint decision-making between the surgeon and the catheterization specialist. In this situation, it is better to target treatment to the native vessels or the internal mammary artery (IMA) and avoid the occluded saphenous veins.

Repeat CABG increases the mortality risk between 2 and 4 times relative to the initial surgery, and therefore patients with early graft failure should always be considered for PCI. However, PCI in saphenous vein bypass grafts is associated with a high risk of complications. Although procedures to prevent distal coronary embolization are effective, the current recommendation for the systemic use of PCI in this situation is class IIa B, reduced from I B in the previous guidelines. In venous bypass grafts, DES produce superior initial results to metallic stents and are therefore recommended; however, the relative benefit of DES over the very long-term (5 years) has not been confirmed. When repeat revascularization surgery is indicated, the IMA should be used whenever possible.

Patients treated by PCI can develop angina during follow-up due to restenosis, incomplete revascularization, or disease progression, with disease progression being the most frequent cause in the long-term. In patients with restenosis, repeat PCI remains the strategy of choice. Both DES and drug-coated balloon angioplasty are recommended for patients with restenosis of a bare-metal stent or a DES (class I A).[10] Intracoronary imaging provides useful information about the mechanism of stent failure caused by restenosis or thrombosis and aids decision-making about optimal treatment (IIa C).

ARRHYTHMIAS

Coronary revascularization should always be considered for CAD patients with LVEF < 35% before they are fitted with an implantable

cardioverter-defibrillator for primary prevention. CABG reduces 10-year mortality in patients with reduced LVEF. Irrespective of the ECG pattern, survivors of out-of-hospital cardiac arrest with no obvious noncardiac cause of the arrhythmia should undergo early coronary angiography (IIa C). Patients who develop atrial fibrillation (AF) as a complication of PCI or CABG should be assessed for anticoagulation. Beta-blocker therapy should be considered as a measure to prevent the appearance of AF after CABG (I B).

PROCEDURAL ASPECTS OF CORONARY ARTERY BYPASS GRAFTING

The new guidelines omit recommendations on perioperative medication and the handling of periprocedural blood products in favor of a focus on surgical techniques. Regarding the selection of the second coronary graft, the CPG document recommends bilateral IMA grafts in patients younger than 70 years, stating that "a second arterial graft should be considered" depending on patient characteristics and other factors. The recommendation for the skeletonized IMA harvesting technique is limited to patients with a high risk of infection. Hybrid revascularization (CABG and PCI performed consecutively as part of the same procedure or sequentially in separate operating environments) retains a low recommendation (IIb) for selected patients treated in experienced centers; nonetheless, the evidence level has been changed from C in 2014 to B in the current document.

The recommendations for fully arterial revascularization (with no saphenous vein grafts) are based exclusively on the 5-year results of the Arterial Revascularization Trial.[11]

Spain has a low per capita rate of CABG, and it is therefore difficult for Spanish centers to follow the recommendation to assemble specialist teams in minimally invasive revascularization, surgery without extracorporeal circulation, or endoscopic dissection.

PROCEDURAL ASPECTS OF PERCUTANEOUS CORONARY INTERVENTION

The use of balloon angioplasty is now relegated to vessels unsuitable for stent implantation due to technical difficulties or because they are too narrow. As already mentioned, radial access has been upgraded to a class I A recommendation, and is already used in 88% of procedures in Spain.[3]

The maximum recommendation (class I A) is maintained for the use of DES in all clinical contexts and for all lesion types. However, implementation of this recommendation could be limited by spending restrictions in the health care sector. Despite this concern, DES are very widely used in Spain.[3] The guidelines discuss the polymers used or their absence in the different types of DES available; studies published to date have shown no significant clinical differences between the new-generation DES devices. This applies even to the high bleeding risk and the subsequent reduction in dual antiplatelet therapy duration, although the evidence in this area is limited to specific types of DES.[12] The use of bioresorbable scaffolds is not recommended (class III C) except in clinical trials.

The use of IVUS and optical coherence tomography (OCT) is recommended to optimize stent implantation (class IIa B). The 2014 guidelines already included this recommendation for IVUS, and now OCT has been upgraded to the same recommendation class (from IIb C in the previous guidelines). Reclassification to a firmer recommendation (class I) is impeded by the predominance of observational studies.[13]

Regarding specific lesion subsets, the guidelines increase the recommendation for main branch-only stenting with provisional stenting of the side branch (class IIa A in 2014; upgraded to I A in the new guidelines). In the specific case of true distal LMCA bifurcation lesions, the double-kissing crush technique is recommended (class IIb B) in preference to the provisional T-stent strategy. Although only class IIb, the recommendation of a specific method for true distal LMCA bifurcation lesions is contentious given the complexity and operator dependency of the double-kissing crush technique; moreover, the cited trial used lesion profiles unsuitable for provisional T-stenting, and the results in this treatment branch were worse than those obtained in other studies.

The guidelines maintain the class IIa B recommendation for the treatment of chronic total occlusions in patients with refractory chest pain or a large ischemic area near the occluded vessel. No distinction is made between anterograde and retrograde access. Since the evidence for a benefit associated with PCI mostly derives from registry data, the recommendation is lower than class I.

ANTITHROMBOTIC TREATMENTS

Recommendations for antiplatelet therapy have undergone no major changes with respect to the previous guidelines. The $P2Y_{12}$ receptor inhibitors of choice for ACS are ticagrelor and prasugrel, except in patients with a high bleeding risk or other contraindications. For patients with stable CAD treated by PCI, clopidogrel remains the preferred medication; however, for patients at high ischemic risk, more potent $P2Y_{12}$ receptor inhibitors should be considered (IIb C). A weak recommendation (IIb A) is made for cangrelor as an alternative medication for patients undergoing PCI and who have no history of $P2Y_{12}$ receptor inhibitor therapy, independently of their clinical presentation. This option is unavailable in Spain until this drug is commercialized. Recommendations for the duration of dual antiplatelet therapy after PCI retain the starting points of 6 months for stable CAD and 12 months for ACS; however, the guidelines stress the need to individualize treatment duration according to ischemia and bleeding risk.

Regarding anticoagulant treatment during PCI, the only major change is the relegation of bivalirudin to a class IIb A recommendation for STEACS and NSTEACS patients.

The new CPG document updates recommendations regarding the use of platelet function testing to guide antiplatelet therapy. These changes include a class IIb B recommendation to consider "downscaling" $P2Y_{12}$ receptor inhibitor therapy in ACS patients to less potent drugs. Moreover, the use of platelet function testing to guide antiplatelet therapy interruption in patients undergoing cardiac surgery has been downgraded from a class IIa recommendation to class IIb. Thus in both cases, the recommendation is weak.

For nonvalvular AF patients requiring simultaneous antiplatelet therapy, nonvitamin K oral anticoagulants (NOAC) are preferred over vitamin K antagonists and should be used at the minimum dose shown to prevent stroke. Moreover, NOACs are recommended in triple therapy (aspirin, clopidogrel, and an oral anticoagulant), although none of the published trials of triple therapy used NOACs at an appropriate dose for stroke prevention. This recommendation has major cost implications in Spain, where the current level of NOAC prescription is low and varies between the different autonomous communities.

VOLUME-OUTCOME RELATIONSHIP FOR REVASCULARIZATION PROCEDURES

The new guidelines maintain the previous recommendation that surgical revascularization be performed in centers with an annual volume of ≥ 200 patients (IIa C). A new recommendation has been introduced for periodic monitoring of performance measures to promote continuous improvement (class I C). There is no standard European training program in CABG; however, the guidelines recommend that trainee surgeons perform at least 200 procedures under supervision before working independently. Because of the fragmented organization of cardiac surgery centers

in Spain, it is difficult for our cardiac surgeons to achieve these numbers.

The guidelines also maintain the recommendations for training in PCI, both for ACS (≥ 75 procedures per operator in centers with at least 400 PCI procedures per year and a 24-hour on-call service) and for stable CAD (≥ 75 procedures per operator in centers with at least 200 PCI procedures per year). For the first time, the guidelines recommend that PCI treatment of LMCA disease be carried out by experienced operators (IIa C), defined in the article cited by the guidelines as those who treat at least 15 patients per year.[14] An especially notable modification has been introduced into the recommendation regarding the treatment of elective PCI patients considered complex. The guidelines maintain the requirement for PCI in these patients to be performed by experienced operators, with access to circulatory support and intensive care treatment; however, the requirement in the previous guidelines for an on-site surgical team has been eliminated.

For training in interventional cardiology, the guidelines propose a standardized program based on that put forward by the European Association of Percutaneous Cardiovascular Interventions (EAPCI). This program stipulates a minimum of 200 procedures as lead operator in a center performing more than 800 angioplasty procedures annually and an established 24-hour angioplasty service. This proposal provides support for the accreditation scheme run by the SEC Working Group on Cardiac Catheterization and Interventional Cardiology and should strengthen moves to give it legal standing.

MEDICAL THERAPY, SECONDARY PREVENTION, AND FOLLOW-UP STRATEGIES

Recommendations for cardiac rehabilitation are strengthened in the new guidelines for all patients treated for ACS with CABG or PCI, rising from class IIa in 2014 to class I A currently. This is a challenging recommendation in Spain because some centers lack a cardiac rehabilitation unit, and efficient implementation of these programs is impeded due to limited funds and a lack of infrastructure, patient care time, and multidisciplinary teams. Nonetheless, adherence to this recommendation may be improved with the advent of supervised telematic cardiac rehabilitation programs available to patients in their own homes.

Although the restenosis rate has decreased with the use of DES, it is important to check for the recurrence of ischemia symptoms, together with other secondary prevention measures. These concerns require clearly defined follow-up strategies, but there are numerous evidence gaps in this area.

Finally, the guidelines do not recommend systematic invasive or noninvasive screening for ischemia in asymptomatic patients.

CONFLICTS OF INTEREST

None declared.

APPENDIX: AUTHORS

SEC Working Group for the 2018 ESC/EACTS Guidelines for Myocardial Revascularization: Borja Ibáñez (Co-ordinator), Victor Bautista-Hernández (Co-ordinator), Fernando Alfonso, Gemma Berga Congost, Héctor Bueno, Manuel Carnero, Belén A. Cid-Álvarez, José María de la Torre Hernández, Juan Antonio Franco-Peláez, and Soledad Ojeda.

Expert Reviewers for the 2018 ESC/EACTS Guidelines for Myocardial Revascularization: Vivencio Barrios, Armando Pérez de Prado, Eduardo Armada, Carlos Escobar, Juan Cosin Sales, Raúl Moreno, José María García Acuña, Rosa María Lidón, Esteban López de Sá, Oriol Rodríguez Leor, and Alessandro Sionis.

SEC Guidelines Committee: Fernando Alfonso, Borja Ibáñez, Fernando Arribas, Gemma Berga Congost, Héctor Bueno, Arturo Evangelista, Ignacio Ferreira-González, Manuel Jiménez Navarro, Francisco Marín, Leopoldo Pérez de Isla, Antonia Sambola, Rafael Vázquez, and Ana Viana-Tejedor.

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Rev Esp Cardiol. 2019;**72(2)**:104-108

Editorial

Comments on the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension

Comentarios a la guía ESC/ESH 2018 sobre el diagnóstico y tratamiento de la hipertensión arterial

*SEC Working Group for the 2018 ESC/ESH Guidelines on Arterial Hypertension, Expert Reviewers for the 2018 ESC/ESH Guidelines on Arterial Hypertension, and the SEC Guidelines Committee**,◊

Article history:
Available online 15 January 2019

INTRODUCTION

Following established practice, the Spanish Society of Cardiology endorses and translates the clinical practice guidelines (CPG) published by the European Society of Cardiology (ESC) and convenes a panel of Spanish specialists with expertise in each topic. This expert panel reviews and summarizes the CPGs from a Spanish perspective, and its reflections are published as an editorial commentary in *Revista Española de Cardiología*.

The present commentary highlights the main changes and implications for clinical practice in the 2018 ESC/European Society of Hypertension (ESH) guidelines on the management of arterial hypertension (HT).[1] This commentary is not intended to provide an exhaustive review, and readers seeking more comprehensive information should consult the original CPG document.

A table near the start of the 2018 ESC/ESH CPG summarizes innovations and changes introduced since the 2013 edition,[2] thus providing an overview of the guidelines. This table uses the ESC color code for classes of recommendation and includes sections on "New sections/recommendations" and "New concepts".

The following paragraphs outline the features regarded by the expert review panelists as the most important changes and new content in the latest guidelines.

DEFINITION, CLASSIFICATION, AND EPIDEMIOLOGICAL ASPECTS OF HYPERTENSION

The definition of HT remains unchanged from the previous European guidelines: systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg. This marks a clear divergence from the latest US guidelines,[3] which now define hypertension as blood pressure (BP) readings > 130/80 mmHg, a change that has stimulated intense debate over the past year.[4] The European guidelines use the same values in younger, middle-aged, and older adults, whereas BP centiles are used in children and adolescents because interventional trial data are unavailable for these 2 groups. There are no changes in the thresholds used to define optimal, normal, and high–normal BP and the different grades of hypertension.

A notable change in this section is the recommendation to assess cardiovascular (CV) risk in patients with no known CV disease using the SCORE scale,[5] which provides an estimate of the 10 year risk of a fatal first atherosclerotic event.

The new guidelines also place great emphasis on the need for CV risk estimation to include assessment of what earlier guidelines called target organ damage, and which the 2018 CPG document identifies as hypertension-mediated organ damage (HMOD). HMOD describes alterations to all major organs potentially damaged by HT (heart, brain, retina, kidneys, and blood vessels), some of which are not considered in the SCORE scale. In addition, HMOD is common and frequently goes undetected, and multiple HMODs often occur in the same patient. For these reasons, it is important to exclude the presence of HMOD in patients classified at low risk on the SCORE scale and to identify HMOD in patients with a high or very high SCORE risk. It should also be remembered that an adapted version of the SCORE scale is available for patients older than 65 years; the SCORE OP (older persons) scale is based on patient data from several European countries and has been evaluated in a Spanish population.[6,7] Another change is the proposed use of the term "CV risk age" as a useful way to communicate risk and support treatment decision-making. This is illustrated by the example of a younger patient (40 years old) with risk factors but low absolute risk whose CV risk is equivalent to that of a person aged 60 years with optimal risk factors; the younger patient's CV risk age is thus 60 years.

BLOOD PRESSURE MEASUREMENT

As in previous editions, the guidelines pay close attention to the method used to measure BP, devoting an extensive section to this question. A diagnosis of HT should be confirmed by repeat office BP measurements (at least 2), with at least 3 readings per visit, separated by 1 to 2 minutes. On each visit, the recorded BP should be the mean of the last 2 readings (discarding the first). An exception is made for patients with severe HT (grade 3), for whom repeat determinations

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*Corresponding author.
E-mail address: fr.marino@um.es (F. Marín).
◊The names of all authors of this article are listed in the Appendix.

http://dx.doi.org/10.1016/j.rec.2018.12.001

Table
Key Features and New Content

Diagnosis	HT diagnosis threshold values are maintained at SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. HT classification is maintained: HT grades 1-3, isolated systolic HT, optimal BP, normal BP, and high–normal BP
BP measurement	• Repeat office BP measurements (at least 3 per visit, separated by 1-2 minute intervals) and at least 2 visits; the BP value is the mean of the last 2 readings in each visit (except for grade 3 HT) • ABPM and HBPM recommended to confirm HT when the office diagnosis is uncertain and to exclude white-coat HT and masked HT • BP monitoring at least every 5 years in patients with BP < 120/80 mmHg, every 3 years for BP = 120-129/80-84 mmHg, and annually for BP = 130-139/85-89 mmHg
Risk stratification	• SCORE risk should be complemented with assessment of HMOD • Atrial fibrillation is included as an established cardiovascular disease
Lifestyle	Daily salt intake < 5 g/d (class I recommendation)
	• Limit alcohol intake (class I A recommendation): o Fewer than 14 units per week for men (1 unit = 125 mL of wine or 250 mL of beer) o Fewer than 8 units per week for women • Recommendation against concentrated consumption of all alcohol units at the weekend (III C) • Body weight control indicated to prevent obesity (defined as BMI > 30 or WC > 102 cm in men and > 88 cm in women), with the aim of achieving a healthy body weight profile (BMI 20-25 and WC < 94 cm for men and < 80 cm for women) • Recommendation for regular aerobic exercise: at least 30 min moderate dynamic exercise 57 days per week
Pharmacological treatment	The 5 classes of drugs for initial therapy are maintained: ACEI, ARA-II, calcium antagonists, diuretics, and beta-blockers (used only when specifically indicated)
	• Treatment initiation for patients with high–normal BP (130-139/85-89 mmHg) • Treatment initiation for patients at very high cardiovascular risk due to concomitant cardiovascular disease, especially those with coronary artery disease (class IIb recommendation) • Treatment initiation for patients with grade 1 hypertension (140-159/90-99 mmHg) at low–moderate cardiovascular risk, alongside lifestyle changes; recommendation upgraded from class II in the previous guidelines to class I currently • Less conservative treatment of elderly patients with hypertension • Decisions should be based more on biological age than chronological age (emphasizing the importance of considering frailty, independence, and treatment tolerance). A patient's age should never be a cause for interrupting well tolerated treatment; elderly patients benefit from appropriate BP control through improved prognosis • Reduced BP target values for most patients • For patients younger than 65 years at any cardiovascular risk level, the target SBP should be < 130 mmHg and never < 120 mmHg for most patients, so long as treatment is well tolerated (class I recommendation). The exception is patients with chronic kidney disease, for whom the target SBP is between 140 and 130 mmHg • Combination therapy with a polypill encouraged to improve BP control (class I recommendation)
Interventional treatment	Use of devices is discouraged (class III recommendation) except in clinical trials until there is evidence confirming safety and efficacy

ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HBPM; home blood pressure monitoring; HMOD, hypertension-mediated organ damage; HT, hypertension; SBP, systolic blood pressure; WC, waist circumference.

are not required. The guidelines also encourage the wider use of ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) to confirm a diagnosis of HT, maintaining the same thresholds as the previous CPG document. The guideline authors note that these out-of-office BP measurements are more reproducible and have a higher prognostic value than office BP measurement; however, some authorities would go further and recommend routine confirmation of an HT diagnosis with ABPM, especially in patients with grade 1 HT values, in line with the NICE guidelines.[8] The use of HBPM is encouraged in light of evidence of its positive impact on treatment adherence and BP control; however, this recommendation is accompanied by a warning against inappropriate use, which can lead to clinical problems. Precise instructions are given, similar to those in the Spanish consensus document published a few years ago.[9]

Following the publication of the SPRINT study,[10] the new guidelines incorporate automated (unattended) BP measurement in the physician's office. As the authors remark, unattended BP measurement has been linked to BP values lower than those obtained by conventional office BP measurement. It should be noted, however, that unattended measurement was not used by all participating centers in the SPRINT study, and a recently published analysis shows that the BP readings were independent of the measurement method used.[11] Like its predecessor, the new CPG document lacks a list of BP measuring devices validated for use in Europe.

Finally, the guidelines highlight the importance of early detection of HT. Blood pressure monitoring is recommended at least every 5 years for people with values < 120/80 mmHg, every 3 years for those with BP values in the range of 120-129/80-84 mmHg, and annually for those whose BP values fall in the range of 130-135/85-89 mmHg.

CLINICAL EVALUATION AND ASSESSMENT OF HYPERTENSION-MEDIATED ORGAN DAMAGE IN PATIENTS WITH HYPERTENSION

In this largely unaltered section, the standout change is the inclusion of atrial fibrillation (AF) as a CV disease that should be assessed during patient clinical evaluations. Although AF is routinely assessed in clinical practice, this is the first time that the ESC guidelines specifically identify AF as a cardiac disorder that should be taken into consideration. HT is the most prevalent risk factor among AF patients, and the evidence links HT directly to the origin and maintenance of this arrhythmia.[12] It is therefore a very positive move that the HT guidelines now recommend the inclusion of AF in risk stratification.

As in previous editions, the guidelines recommend that all patients undergo a 12-lead electrocardiogram examination to test for left ventricular hypertrophy voltage criteria (including Cornell criteria) and indicators of other heart conditions. A table is included showing the definitions of echocardiographic definitions of left ventricular hypertrophy and left atrial dilatation; these parameters were mentioned in previous guideline documents but were not described in such detail.

Likewise, the 2018 guidelines specify the need to record heart rhythm and diagnose cases of asymptomatic AF.

Finally, it is worth reproducing the recommendations included in this section on the types of patients with hypertension who require referral for more specific, hospital-based care:

- Patients with suspected secondary hypertension
- Younger patients (<40 years) with grade 2 or more severe hypertension in whom secondary hypertension should be excluded
- Patients with treatment-resistant hypertension
- Patients in whom detection of HMOD would substantially influence treatment decisions
- Patients with sudden onset hypertension in whom BP has previously been normal
- Patients with other clinical circumstances that the referring physician feels require more specialist evaluation

GENETICS AND HYPERTENSION

The new guidelines comment briefly on the genetic determinants of HT. The evidence points to a strong hereditary component in HT, and between 35% and 50% of patients have a first degree relative also affected by the condition. However, HT has a multifactorial etiology, and accumulated genetic analyses explain only about 3.5% of HT cases. Routine genetic testing is therefore not recommended for HT patients (class III, level C); nevertheless, for specific patients with a suspected rare monogenic cause of secondary HT, genetic testing is recommended in class IIa, evidence level B.

TREATMENT OF HYPERTENSION

This section covers all aspects of HT therapy: its medical basis, when to initiate antihypertensive treatment, treatment goals and target BP values, lifestyle changes, drug treatment strategies, and the current role of interventional treatments in the management of HT patients.

There are 2 key aspects. The first and most important is the treatment goal. The target "blood pressure value" has been changed from the more uniform and simplified target in the 2013 guidelines and for most patients is now set at 130/80 mmHg or even lower. For patients older than 65 years, the guidelines stipulate a target SBP between 120 and 129 mmHg. Moreover, treatment initiation is now recommended for patients between the ages of 65 and 80 years with grade 1 HT, whereas the previous CPG document indicated only that treatment should be "considered" in these patients. Unlike the previous edition, the new CPG document includes a recommendation to consider treating patients with high–normal BP (130–139/85–89 mmHg) when this is accompanied by a high CV risk, especially in patients with coronary artery disease. These changes have been introduced to reflect the results of meta-analyses of randomized, controlled clinical trials published in recent years.[13]

The second key aspect is the rational maintenance of 2 main subsections dealing with treatment strategies: lifestyle changes and BP-lowering drug therapy.

For most patients, the new guidelines tend to recommend the simultaneous introduction of lifestyle changes and pharmacological treatment.

Lifestyle recommendations have been updated in light of recent publications and are now stricter, both for reducing salt and alcohol intake and for targeting waist circumference through weight loss and regular physical activity. The guidelines also bring together important recent advances in pharmacological treatment identified in recent clinical trials and meta-analyses; these studies have addressed the prevention of morbidity and mortality in patients with high–normal BP, the treatment of patients with grade 1 HT and low risk, as well as the treatment of elderly patients with HT and patients with hypertension and diabetes. Although somewhat lacking in scientific consistency, the available data indicate a reduction in the thresholds for initiating treatment with BP-lowering drugs, as well as lower target values for both SBP (130-120 mmHg) and DBP (80-70 mmHg) for most patients who tolerate treatment. The exceptions to these strict goals are hypertensive patients older than 65 years or those with chronic kidney disease; for these patients, a target SBP of 130-139 mmHg is more beneficial than lower values.

The most important change with respect to the previous edition is the new recommendation to use combination therapy as the first-line pharmacological treatment. This strategy seeks to achieve target BP values earlier and to improve control, and is applicable to most patients. Possible exceptions are elderly patients with grade 1 HT and younger patients with grade 1 HT, SBP < 150 mmHg, and low risk; for these patients, an SBP < 130 mmHg may be achievable with monotherapy. To improve treatment adherence, the guidelines also recommend that drugs for combination therapy be included in a single pill, containing 2 or 3 antihypertensive drugs. This may turn out to be the most difficult recommendation to implement in daily practice, particularly in a country like Spain, where the use of fixed dose drug combinations receives insufficient support from the health care authorities.[14] This could be one of the greatest challenges we face over the coming years.

HYPERTENSION IN SPECIFIC CIRCUMSTANCES

The new guidelines present several clinical scenarios not considered in the previous guidelines, such as ethnicity, the coexistence of HT with valve disease or aortic disease, and HT related to anticancer drug therapy. Other content has been removed, including the specific subsections on metabolic syndrome, obstructive sleep apnea, renovascular disease, and primary hyperaldosteronism.

Recommendations for the pharmacological treatment of resistant hypertension center on the results of the PATHWAY-2 study.[15] Invasive strategies such as renal denervation are discouraged because the available evidence raises questions about their clinical role. The guidelines highlight the importance of volume overload as a cause of resistant HT and recommend salt restriction and intensified diuretic therapy as appropriate treatments. Mineralocorticoid receptor antagonists effectively control many cases of resistant HT and are recommended as the fourth-line treatment.

The guidelines cover several specific aspects of HT in daily clinical practice. For white-coat HT, the guidelines recommend assessment of individual CV risk profiles, including a screen for HMOD; white-coat HT patients with a higher CV risk or organ damage should be considered for antihypertensive drug therapy, alongside lifestyle recommendations. Poorly controlled masked HT is very common, and the guidelines underline the need for out-of-office BP measurement; however, masked HT is usually caused by poorly controlled nocturnal BP, and can therefore only be detected with ABPM. Since the publication of these latest ESC/ESH guidelines, the results of the Spanish CARDIORISC registry have been released.[16] The CARDIORISC findings confirm that white-coat HT is nonbenign and that masked HT is associated with a higher mortality risk than persistently elevated BP.

This section also makes recommendations for the treatment of HT in specific age groups. Despite the lack of evidence from clinical outcome trials, antihypertensive treatment is recommended in younger adults (< 50 years) with grade 1 HT because of the linear relationship between elevated BP and long-term CV events and death. Isolated systolic HT in young patients is closely associated with smoking, and the guidelines advise against routine assessment of central BP because it is normal in this patient group and the methodology for measuring it is usually unavailable.

For the treatment of HT in older patients (≥ 65 years < 80 years), the new guidelines reject the excessively conservative recommendations of previous guidelines in favor of an approach similar to that

used in adult patients younger than 65 years. This change was prompted by recent evidence supporting the treatment of HT in elderly patients, including those who are frail.[17] The new CPG document rightly introduces the concept of frailty, which is a more important factor in decision-making than chronological age. Periodic functional and cognitive assessments are recommended, and the value of these evaluations increases with patient age (although this is not clearly expressed in the text). Unlike the previous CPGs, the latest document recommends antihypertensive therapy for grade 1 HT in patients between the ages of 65 and 80 years who tolerate the treatment well; the goal is to achieve an SBP in the range of 130-139 mmHg, and the guidelines even advise this treatment for patients older than 80 years who tolerate it well.

The recommendations on HT in pregnancy have been extensively revised. Important changes include the specific recommendation to monitor uric acid in pregnant hypertensive women, the advisability of Doppler ultrasound of the uterine arteries to identify women at risk of complications, and the recommendation to use angiogenic markers to predict pre-eclampsia. Based on the results of a clinical trial published in 2017,[18] the guidelines recommend a daily aspirin dose of 100–150 mg in weeks 12 to 36 of pregnancy for women with a high or moderate pre-eclampsia risk. A low evidence level is maintained for recommendations on target BP values and the timing of treatment initiation. In contrast with the mild hypertensive effect of estrogens in contraceptive pills, hormone replacement therapy in postmenopausal women does not increase HT. Other noteworthy content in this section includes the link between ethnicity and comorbidities such as diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and anticancer drugs that can increase BP, such as proteasome or angiogenesis inhibitors. There are no major changes to the recommendations for the treatment of pregnant women with heart disease.

Regarding HT and cerebrovascular disease, the new guidelines reject the previous recommendation for immediate and intense BP reduction in all patients with acute intracerebral hemorrhage and high BP. (This change follows the rejection of routine antihypertensive therapy for acute ischemic stroke in the previous guidelines.) In its place, the new guidelines recommend a more conservative approach, although an exception is made for patients with BP ≥ 220 mmHg, who might benefit from BP reduction < 180 mmHg. In acute ischemic stroke, BP reduction is only recommended for patients scheduled for thrombolysis, in whom BP should be lowered and maintained at < 180/105 mmHg for at least the first 24 hours after the procedure. In the period starting several days after ischemic stroke (or immediately after a transient ischemic attack), BP-lowering drug therapy is strongly recommended for hypertensive patients; the goal should be to reduce SBP < 130 mmHg, as indicated by the results of the Secondary Prevention of Small Subcortical Strokes Trial.[19] The guidelines also contain a new set of recommendations for patients taking anticoagulants. These include reducing BP to < 130/80 mmHg and proceeding with extreme caution at BP ≥ 180/100 mmHg; both these recommendations have a low level of evidence (the second of them is derived from the exclusion criteria for morbidity and mortality trials with anticoagulant drugs).

The new CPG document devotes a long subdivided section to the management of HT in patients with vascular disease. The guideline authors remark on the knowledge gap regarding the treatment of HT in patients with tight carotid stenosis, especially when bilateral. Physicians are advised to adopt a cautious approach to the speed and degree of BP lowering. A cautious approach is also recommended for the treatment of lower extremity arterial disease in the presence of critical ischemia. For arterial stiffness, indirect evidence suggests that renin-angiotensin system (RAS) blockers may be more potent than antihypertensive drugs; however, there is no evidence to indicate that they are more beneficial. Moreover, centers commonly lack the technology to measure arterial stiffness. Taken together, these considerations justify the exclusion of this parameter from decision-making. The recommendations for BP management in patients with aortic diseases are taken from the recent ESC guidelines on this topic.[20] These recommendations include reducing BP to < 130/80 mmHg in patients with aortic dilatation or bicuspid aortic valve disease, although the supporting evidence is weak in both settings. The guideline authors challenge the mistaken view that BP-lowering treatment is deleterious in patients with aortic stenosis and hypertension. Similar misconceptions occur in relation to the use of beta-blockers to treat chronic obstructive pulmonary disease or symptomatic peripheral arterial disease, conditions in which this treatment benefits most patients.

The section on sexual dysfunction has been revised and expanded. The guidelines mention the prognostic value of erectile dysfunction and its negative influence on treatment adherence and describe the effects of available treatments. Nonetheless, the information presented is old and rather inconsistent, reflecting the conflicting published data, which do not identify the simple fact of lowered BP as possible major cause of erectile dysfunction.

The final part of this section updates the approach to the perioperative management of HT, presenting recommendations that are sometimes unclear and have a low level of evidence. Recent data suggest that the perioperative use of beta-blockers is linked to an increased risk of complications; nonetheless, the guidelines recommend against either abrupt or programmed gradual discontinuation. Transient preoperative discontinuation of RAS blockers is recommended, as these drugs appear to be associated with an elevated incidence of complications.

MANAGING CONCOMITANT CARDIOVASCULAR DISEASE RISK

The recommendations for statin therapy are adjusted to the latest guidelines in this area.[21] For patients with a very high CV risk, the goal of statin therapy should be to achieve a low-density lipoprotein cholesterol (LDL-C) level of < 70 mg/dL or a reduction of at least 50% from a baseline level between 70 and 135 mg/dL. For patients at high risk, the LDL-C goal is < 100 mg/dL or a ≥ 50% reduction from a baseline level between 100 and 200 mg/dL; for patients at intermediate or low risk, the goal is LDL-C < 115 mg/dL. Antiplatelet therapy in patients with HT is indicated only for secondary prevention, and the recommended treatment is low dose aspirin; there is no identified patient subgroup with an indication for primary prevention (previously a contentious issue in the literature).

PATIENT FOLLOW-UP

The standout feature of the section on patient follow-up is its emphasis on patient assessment and its influence on treatment adherence. A new consideration introduced in these guidelines is the key role of nurses and pharmacists in the long-term treatment of HT. These professionals have an important role to play in patient instruction, support, and follow-up as part of a general strategy to improve BP control and achieve better adherence to treatment.

The section includes a table detailing the main interventions that could be implemented not only by physicians and health care systems, but also by patients and their support network. These interventions include strategies to facilitate adoption of a healthy lifestyle, promote patient empowerment, set up group sessions, and increase treatment accessibility. The guideline authors consider treatment nonadherence to be one of the most common causes of inadequate BP control.

FINAL SECTIONS

Like other ESC guidelines, the current document ends with 3 summary sections: “Gaps in the evidence”, which includes 26 questions

(compared with half this number in the previous edition); "Key messages"; and a tabulated section listing "'What to do' and 'what not to do' messages", each presented with its corresponding recommendation class and evidence level.

CONCLUSIONS

In this commentary on the latest ESC/ESH guidelines on HT, we have attempted to highlight the most important content in the new CPG document, which is even more extensive than the 2013 edition. An important point of clinical interest in the new CPG is the maintenance of the previous diagnostic threshold values for HT; publication of these thresholds has been eagerly awaited in view of the debate triggered by the revised values adopted in the USA. Moreover, the European diagnostic thresholds have been maintained at the same time as target BP values for most patients have been reduced; the revised treatment targets are mostly based on the results of meta-analyses, since there have been very few new clinical trials in recent years. It might appear inconsistent to maintain a diagnostic threshold of 140/90 mmHg while setting the target for BP control at < 130/80 mmHg; however, the evidence indicates that these lower values have a superior prognostic value.

The treatment recommendations strengthen measures to promote lifestyle changes. Moreover, in the absence of new antihypertensive drugs in the therapeutic arsenal, the guidelines recommend combination therapy from the outset; the preferred treatment route is a polypill containing several drugs, with the aim of improving treatment adherence and thus BP control, an area that requires further attention. In addition to other treatment recommendations for specific situations, the guidelines propose follow-up norms and interventions to improve treatment adherence.

CONFLICTS OF INTEREST

None declared.

APPENDIX: AUTHORS

SEC Working Group for the 2018 ESC/ESH Guidelines on Arterial Hypertension: Pilar Mazón (coordinator), Francisco Marín (coordinator), Juan Cosín-Sales, Alberto Cordero, Inmaculada Roldán, Xavier García-Moll, Carmen Suárez, and Antonio Coca.

Expert Reviewers for the 2018 ESC/ESH Guidelines on Arterial Hypertension: Carlos Escobar, Vivencio Barrios, Rafael Vidal, Pablo Díez-Villanueva, Clara Bonanad, Alberto Esteban, Pilar Zuazola, Vicente Bertomeu, Manuel Abeytua, and Pilar Zuazola.

SEC Guidelines Committee: Fernando Alfonso, Borja Ibáñez, Fernando Arribas, Gemma Berga Congost, Héctor Bueno, Arturo Evangelista, Ignacio Ferreira-González, Manuel Jiménez Navarro, Francisco Marín, Leopoldo Pérez de Isla, Antonia Sambola, Rafael Vázquez, and Ana Viana-Tejedor.

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World Journal of Emergency Surgery

REVIEW Open Access

2019 update of the WSES guidelines for management of *Clostridioides* (*Clostridium*) *difficile* infection in surgical patients

Massimo Sartelli[1*], Stefano Di Bella[2], Lynne V. McFarland[3], Sahil Khanna[4], Luis Furuya-Kanamori[5], Nadir Abuzeid[6], Fikri M. Abu-Zidan[7], Luca Ansaloni[8], Goran Augustin[9], Miklosh Bala[10], Offir Ben-Ishay[11], Walter L. Biffl[12], Stephen M. Brecher[13], Adrián Camacho-Ortiz[14], Miguel A. Caínzos[15], Shirley Chan[16], Jill R. Cherry-Bukowiec[17], Jesse Clanton[18], Federico Coccolini[8], Maria E. Cocuz[19], Raul Coimbra[20], Francesco Cortese[21], Yunfeng Cui[22], Jacek Czepiel[23], Zaza Demetrashvili[24], Isidoro Di Carlo[25], Salomone Di Saverio[26], Irina M. Dumitru[27], Christian Eckmann[28], Edward H. Eiland[29], Joseph D. Forrester[30], Gustavo P. Fraga[31], Jean L. Frossard[32], Donald E. Fry[33,34], Rita Galeiras[35], Wagih Ghnnam[36], Carlos A. Gomes[37], Ewen A. Griffiths[38], Xavier Guirao[39], Mohamed H. Ahmed[40], Torsten Herzog[41], Jae Il Kim[42], Tariq Iqbal[43], Arda Isik[44], Kamal M. F. Itani[45], Francesco M. Labricciosa[46], Yeong Y. Lee[47], Paul Juang[48], Aleksandar Karamarkovic[49], Peter K. Kim[50], Yoram Kluger[11], Ari Leppaniemi[51], Varut Lohsiriwat[52], Gustavo M. Machain[53], Sanjay Marwah[54], John E. Mazuski[55], Gokhan Metan[56], Ernest E. Moore[57], Frederick A. Moore[58], Carlos A. Ordoñez[59], Leonardo Pagani[60], Nicola Petrosillo[61], Francisco Portela[62], Kemal Rasa[63], Miran Rems[64], Boris E. Sakakushev[65], Helmut Segovia-Lohse[53], Gabriele Sganga[66], Vishal G. Shelat[67], Patrizia Spigaglia[68], Pierre Tattevin[69], Cristian Tranà[1], Libor Urbánek[70], Jan Ulrych[71], Pierluigi Viale[72], Gian L. Baiocchi[73] and Fausto Catena[74]

Abstract

In the last three decades, *Clostridium difficile* infection (CDI) has increased in incidence and severity in many countries worldwide. The increase in CDI incidence has been particularly apparent among surgical patients. Therefore, prevention of CDI and optimization of management in the surgical patient are paramount. An international multidisciplinary panel of experts from the World Society of Emergency Surgery (WSES) updated its guidelines for management of CDI in surgical patients according to the most recent available literature. The update includes recent changes introduced in the management of this infection.

Keywords: Clostridioides difficile infection, *Clostridium difficile* infection, Pseudomembranous colitis, Antimicrobial treatment, Fecal microbiota transplantation, Infection control, Antimicrobial stewardship

Introduction

In the last three decades, the dramatic worldwide increase in incidence and severity of *Clostridium difficile* infection (CDI) [1] has made CDI a global public health challenge [2–14]. Surgery is a known risk factor for development of CDI yet surgery is also a treatment option in severe cases of CDI [15–18]. The World Society of Emergency Surgery (WSES) guidelines for management of CDI in surgical patients were published in 2015 [19]. In 2019, the guidelines have been revised and updated. A multidisciplinary expert panel worldwide prepared the manuscript following an in-depth review of the most recent current literature using MEDLINE, EMBASE, and Cochrane Database and aimed to provide an insight into these complex issues. The expert panel met via email to prepare, discuss, and revise the paper. The manuscript was successively reviewed by all members and ultimately re-formulated as the present manuscript.

* Correspondence: massimosartelli@gmail.com
[1]Department of Surgery, Macerata Hospital, Via Santa Lucia 2, 62100 Macerata, Italy
Full list of author information is available at the end of the article

These guidelines outline clinical recommendations based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) hierarchy criteria from Guyatt et al. [20, 21] (Table 1).

Clostridioides difficile (formerly *Clostridium difficile*) is an anaerobic, spore-forming, Gram-positive bacillus, which may be part of the normal intestinal microbiota in healthy babies [22–25]. The organism is spread via the oral-fecal route and in hospitalized patients may be acquired through the ingestion of spores from other patients, healthcare personnel's hands, or from environmental surfaces [26, 27]. *C. difficile* is the main pathogen associated with nosocomial infections and is the most common cause of diarrhea in hospitalized patients [28]. CDI can present as a spectrum of symptoms ranging from an asymptomatic carriage to fulminant disease with toxic megacolon. The basis for this range of clinical manifestations is not fully understood but is likely related to host and pathogen interactions.

The rapid evolution of antibiotic resistance in *C. difficile* and the consequent effects on prevention and treatment of CDIs are a matter of concern for public health. Multi-drug resistant (MDR) *C. difficile* strains are increasing (about 60% of the epidemic strains circulating in hospital settings show resistance to three or more antibiotics) [29].

Pathogenesis

C. difficile spores survive the acidic environment of the stomach and germinate in the intestine [30], which act as a reservoir for *C. difficile* and can facilitate spread among patients, as well as contribute to the high recurrence rates observed in CDI. The primary toxins produced by this bacterium are toxins A and B [31]. Toxins A and B act as glucosyltransferases, promoting the activation of Rho GTPases leading to disorganization of the cytoskeleton of the colonocyte, and eventual cell death [32]. Since CDI is a toxin-mediated infection, non-toxigenic *C. difficile* strains are non-pathogenic. The respective roles and importance of toxins A and B have been debated. Toxin A was thought to be the major virulence factor for many years [33–35]. It is now established that both toxins A and B are important for inducing colonocyte death and colitis, and there is increasing evidence pointing toward their role in CDI extra-intestinal effects [36]. In addition to toxins A and B, some strains

Table 1 Grading of recommendations from Guyatt and colleagues [20, 21]

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A			
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1B			
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1C			
Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but subject to change when higher quality evidence becomes available
2A			
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2B			
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2C			
Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; alternative treatments may be equally reasonable and merit consideration

produce a third toxin known as binary toxin [37–41]. Binary toxin has an ADP-ribosyltransferase function, which also leads to actin depolymerization [42, 43]. However, its pathogenetic role is still debated [44, 45].

Asymptomatic *C. difficile* colonization occurs when *C. difficile* is detected in the absence of symptoms of infection. Asymptomatic colonized individuals with no clinical signs of CDI can still act as an infection reservoir and transmit *C. difficile* to others [46, 47]. Asymptomatic colonization with *C. difficile* may be a crucial factor in the progression to CDI, as carriers of toxigenic strains may be at a higher risk for the development of an infection compared to non-colonized patients [48]. Other data suggests that carriage of non-toxigenic *C. difficile* may be protective against toxigenic ribotypes [49]. Estimates of prevalence of asymptomatic *C. difficile* colonization vary considerably between different patient groups. Among healthy adults with no prior risk factors for CDI, asymptomatic colonization prevalence varied between 0 and 15% [50–56].

Risk factors

Risk factors for CDI may be divided into three general categories: host factors (immune status, comorbidities), exposure to *C. difficile* spores (hospitalizations, community sources, long-term care facilities), and factors that disrupt normal colonic microbiome (antibiotics, other medications, surgery) [57].

Patient factors

Risk factors identified to date include age > 65 years, comorbidity or underlying conditions, inflammatory bowel diseases, immunodeficiency (including human immunodeficiency virus infection), malnutrition, obesity, female sex, and low serum albumin level [3, 58]. Patients with comorbidities may have distinct characteristics of their CDI, for example, in type 2 diabetes mellitus, patients with CDI were younger, and sepsis and proton pump inhibitors (PPIs) were important causes, but fever was not a dominant feature [59].

The effects of prior appendectomy on the development of *C. difficile* colitis have been debated [60]. A review by Seretis et al. [61] of five studies conducted retrospectively and published in 2014 reported that an in situ appendix did not impact on the development of CDI. In the retrospective analysis by Clanton et al. [62] on 55 patients who underwent colectomy for CDI between 2001 and 2011, a prior appendectomy was noted in 24 of 55 patients (44%, 99% CI 0.280–0.606). In another retrospective study of 507 patients [63], 13 of 119 patients (10.9%) with a previous appendectomy required colectomy compared to 20 of 388 patients (5.2%) with an intact appendix developing fulminant infection and requiring colectomy and increased disease severity, indicated by increased rates of colectomy, occurred in the group with a history of appendectomy ($p = 0.03$). A sub-group analysis of a large population-based study published in 2013 [64] showed that appendectomy was not associated with adverse outcomes in CDI. Patients with appendectomy before CDI showed no differences in risk factors, treatment, or outcomes including treatment failure, development of severe or severe-complicated CDI, or recurrence rates as compared with patients without appendectomy. Larger prospective studies are needed to assess the impact of prior appendectomy on the development and severity of CDI.

Exposure to *Clostridium difficile* spores

Factors that increase risk of exposure to *C. difficile* spores, such as increased duration of hospital stay, increase the risk of CDI. A length of stay > 2 weeks has been shown to be a risk factor for CDI [65]. Hospitals with well-implemented infection prevention and control measures are at lower risk of nosocomial CDI [66].

Normal flora disruption

The indigenous gut microbiota is a complex community of microorganisms that populates the gastrointestinal tract in a healthy person. This micro-ecosystem plays a crucial role in protecting the intestines by providing resistance to colonization and infection by pathogenic organisms [67]. Gut microbiota has also immeasurable effects on homeostasis of the host [68]. Under normal conditions, the human gut microbiota may impede pathogen colonization through general mechanisms such as direct inhibition through bacteriocins, nutrient depletion (consuming growth-limiting nutrients), or stimulation of host immune defenses [57], though the exact mechanism by which the microbiota protects against CDI is unknown [69]. Disruption of the normal balance of colonic microbiota as a consequence of antibiotic use or other stressors is, however, of major importance [70].

Antibiotic exposure

Disruption of the normal gut flora allows *C. difficile* to proliferate and produce toxins. In 1974, Tedesco et al. published a prospective study of clindamycin-associated colitis, which had become endemic in many hospitals [71]. In 200 consecutive patients, administration of clindamycin resulted in diarrhea in 21% and the incidence of endoscopy-diagnosed pseudomembranous colitis was 10%. The study led to a search for an infectious cause of colitis, and it identified *C. difficile* as the main causative agent [72].

The risk of CDI is increased up to sixfold during antibiotic therapy and in the subsequent month afterwards [73]. Although nearly all antibiotics have been associated with CDI, clindamycin, third-generation cephalosporins,

penicillins, and fluoroquinolones have traditionally been considered to pose the greatest risk [74–80]. An association between CDI and antimicrobial treatment > 10 days has also been demonstrated [81, 82]. Antibiotics which have been less commonly associated with CDI include macrolides, sulfonamides, and tetracyclines [83]. Even very limited exposure, such as single-dose surgical antibiotic prophylaxis, can increase patients risk for both *C. difficile* colonization or infection [84–86].

Other medications

Exposure to gastric acid-suppressive medications, such as histamine-2 blockers and PPIs, may be a potential risk factor for development of CDI. Several studies have suggested the association between use of stomach acid-suppressive medications, primarily PPIs, and CDI [87, 88]. In 2012, a systematic review of incident and recurrent CDI in PPI users was published [89]. Forty-two observational studies (30 case-control, 12 cohort) totaling 313,000 participants were evaluated. Despite the substantial statistical and clinical heterogeneity, the findings indicated a probable association between PPI use and incident and recurrent CDI. This risk was further increased by concomitant use of antibiotics and PPI. Other studies suggested that this association may be the result of confounding with the underlying severity of illness and duration of hospital stay [90]. Another meta-analysis about a plausible link between CDI and PPIs was recently published [91]. Pooled analysis of 50 studies showed a significant association between PPI use and risk of developing CDI (odds ratio [OR] = 1.26, 95% confidence interval (CI), 1.12–1.39) as compared with non-users.

Even when compared to other gastric acid-suppressive medication, a recent meta-analysis showed that the use of PPI increased the risk of hospital-acquired CDI (OR = 1.386, 95% CI 1.152–1.668) when compared to H2-antagonist [92].

Given that PPIs are overprescribed in surgical settings, consideration should be given to stop PPIs, when they are not necessary, especially in patients at high risk of CDI.

Nasogastric tube

The risk of poor clinical outcomes of CDI in patients with nasogastric tube (NGT) insertion is still controversial. In order to assess the outcomes of CDI in patients with NGT insertion, a systematic review and meta-analysis was recently published [93].

Eight observational studies were included in the analysis to assess the association between NGT insertion and risk of poor outcome of CDI. The pooled relative risk (RR) of severe or complicated clinical outcomes of CDI in patients with NGT insertion was 1.81 (95% CI 1.17–2.81).

This study demonstrated a statistically significant association between NGT insertion and risk of poor outcomes of CDI. This finding may impact clinical management and primary prevention of CDI. Avoidance of unnecessary NGT uses would improve the clinical outcomes of CDI.

Surgery

Reports have linked the development of CDI in surgical patients to the widespread use of broad-spectrum antibiotics, and the increasing number of elderly and immunocompromised patients undergoing surgical interventions [17, 94, 95].

Abdelsattar et al. [18] prospectively identified postoperative patients with laboratory-confirmed CDI following general, vascular, or gynecological surgeries at 52 academic and community hospitals in the state of Michigan, USA between July 2012 and September 2013. The highest rates of CDI occurred after lower-extremity amputation (2.6%), followed by bowel resection or repair (0.9%) and gastric or esophageal surgeries (0.7%). Gynecological and endocrine surgeries had the lowest rates of CDI (0.1% and 0%, respectively). Multivariate analysis identified increasing age, chronic immunosuppression, hypoalbuminemia (≤ 3.5 g/dL), and preoperative sepsis to be associated with postoperative CDI.

Zerey et al. [15] performed a 5-year retrospective analysis of the Agency for Healthcare Research and Quality's National Inpatient Sample Database representing a stratified 20% sample of hospitals in the United States, from 1999 to 2003. Emergency surgery was at higher risk of CDI than elective surgery. Colectomy, small-bowel resection, and gastric resection were associated with the highest risk of CDI. Patients undergoing cholecystectomy and appendectomy had the lowest risk.

In 2010, Rodriguez et al. [96] published a retrospective analysis of all general surgery in patients admitted to a large tertiary referral general surgical unit in the UK, between March 2005 and May 2007. Multivariate analysis identified malignancy, gastrointestinal disease, anemia, respiratory disease, cardiovascular disease, diabetes mellitus, gastrointestinal surgery, and age as independently associated with *C. difficile*.

To assess risk factors for CDI on a surgical ward, in 2012 Kim et al. conducted a retrospective chart review of all patients admitted between January 2010 and July 2011 [97]. The rate of CDI was 0.4% (19/4720 patients). Multivariate analysis showed that colectomy and hospital stays > 10 days were the main risk factors for CDI in the surgical ward.

Using the Japanese Diagnosis Procedure Combination inpatient database, Yasunaga et al. [98] analyzed factors associated with CDI incidence and outcomes following digestive tract surgery. Of 143,652 patients undergoing

digestive tract surgery, CDI was identified in 409 (0.28%) patients. High mortality, long hospital stay, and high costs were associated with post-surgical CDI.

Colorectal surgery is a documented risk factor for CDI [99, 100]. Damle et al. [101] published a retrospective analysis of patients who developed CDI following colorectal resection. The authors identified adult patients undergoing colorectal surgery between 2008 and 2012 from the US University Health System Consortium database. A total of 84,648 patients met study inclusion criteria. CDI occurred in 1266 (1.5%) patients. The strongest predictors of CDI were emergency procedure, inflammatory bowel disease, and severity of illness score. CDI was associated with a higher rate of complications, intensive care unit (ICU) admission, longer preoperative inpatient stay, 30-day readmission rate, and death within 30 days compared to non-CDI patients.

Recently, a retrospective colectomy database review of the 2015 American College of Surgeons National Surgical Quality Improvement Project [102] demonstrated that stoma reversal (OR = 2.701, 95% CI 1.966–3.711; $p < 0.001$), smoking (OR = 1.520, 95% CI 1.063–2.174; $p = 0.022$), steroids (OR = 1.677, 95% CI 1.005–2.779; $p = 0.048$), and disseminated cancer (OR = 2.312, 95% CI 1.437–3.719; $p = 0.001$) were associated with CDI in the 30-day postoperative period.

In 2008, Lumpkins et al. published a retrospective observational study on the incidence of CDI in the critically injured trauma population [103]. Five hundred eighty-one consecutive critically injured trauma patients were followed prospectively for development of CDI, diagnosed by toxin assay. Among 581 patients, 19 cases of CDI were diagnosed (3.3%). ICU length of stay, duration of mechanical ventilation, and hospital length of stay were associated with CDI. The diagnosis was documented with a median delay of 17 days after admission. Fourteen patients (74%) had received antibiotics for confirmed or suspected infection prior to CDI; 4 patients (21%) received only intraoperative prophylaxis, and 1 patient had no antibiotic exposure.

Obesity and bariatric surgery

Obesity as a risk factor for CDI has been debated. Several reports have recently proposed obesity as a novel risk factor for CDI [104–106]. On the other hand, Punni et al. [107], in a case-control study, showed that obesity is not a risk factor for CDI. Importantly, body mass > 35 index has been shown to be an independent risk factor for CDI [108].

To investigate the impact of the two most common bariatric surgeries on CDI, Roux-en-Y gastric bypass (RYGB), and vertical sleeve gastrectomy (VSG), a retrospective cohort study was recently published [109]. CDI rates were higher after RYGB than VSG in the first 30 days (OR = 2.10; 95% CI, 1.05–4.20) with a similar but not significant trend within 31–120 days.

Knowledge about the link between obesity, bariatric surgery, and CDI is still evolving. Further studies are needed to reveal the exact mechanisms underlying this association. At this stage, we suggest high suspicion for CDI when managing patients with obesity and undergoing bariatric surgery.

Inflammatory bowel disease

Patients with inflammatory bowel disease (IBD) retain an increased risk of developing CDI, along with worse outcomes, higher rates of colectomy, and higher rates of recurrence [110–115].

Patients with IBD also appear to have higher rates of asymptomatic carriage of *C. difficile* [116]. These patients commonly receive various types of immunosuppressive drugs including steroids which have been found to increase the risk of CDI. In addition, they have a different microbiota compared to healthy subjects [117, 118].

A recent retrospective study evaluated the impact of CDI on in-hospital outcomes among adults with IBD hospitalized in the USA [119]. Using the 2007–2013 Nationwide Inpatient Sample, hospitalizations among US adults with Crohn's disease (CD), ulcerative colitis (UC), and CDI were identified using ICD-9 coding. Hospital charges, hospital length of stay (LOS), and in-hospital mortality was stratified by CD and UC and compared. Predictors of hospital charges, LOS, and in-hospital mortality were evaluated with multivariate regression models and were adjusted for age, sex, race/ethnicity, year, insurance status, hospital characteristics, and CDI. Among 224,500 IBD hospitalizations (174,629 CD and 49,871 UC), overall prevalence of CDI was 1.22% in CD and 3.41% in UC. On multivariate linear regression, CDI was associated with longer LOS among CD (coefficient: 5.30, 95% CI 4.61–5.99; $p < 0.001$) and UC (coefficient 4.08, 95% CI 3.54–4.62; $p < 0.001$). Higher hospital charges associated with CDI were seen among CD (coefficient $35,720, 95% CI $30,041–$41,399; $p < 0.001$) and UC (coefficient $26,009, 95% CI $20,970–$31,046; $p < 0.001$). CDI among IBD was associated with almost threefold greater risk of in-hospital mortality.

The clinical presentation of an IBD exacerbation and CDI often is indistinguishable and requires a high index of suspicion for adequate treatment [6]. As the symptoms of CDI and an exacerbation of IBD (diarrhea, abdominal pain, fever, and leukocytosis) overlap, the diagnosis of CDI may be delayed [120]. In addition, in IBD patients with ileostomies, the development of acute enteritis manifested as an increase in ileostomy output,

nausea, fever, and leukocytosis may also indicate CDI. The same is true for pouchitis, which presents as an increase in the number of stools per day [121]. In one study, 10.7% of patients with ileal pouch anal anastomosis, presenting with pouchitis, were found to have CDI [122].

Due to high rates of asymptomatic colonization by *C. difficile* in patients with IBD, only patients with increased diarrhea or new symptoms potentially due to CDI should be tested for *C. difficile* toxin. Typical findings of CDI on colonoscopy are often absent in patients with IBD (0–13% of cases) [123] which may be attributed to a weakened inflammatory response. There is no evidence that one antibiotic regimen is better than another for the treatment of CDI in IBD patients. In a survey of North American gastroenterologists, there was no agreement on combination of antibiotics and immunomodulators in patients with an IBD flare and CDI [124]. The American College of Gastroenterology recommended with low-quality supporting evidence, that ongoing immunosuppression can be maintained in patients with CDI and that escalation of immunosuppression should be avoided [125].

An expert review to synthesize the existing evidence on the management of CDI in patients with underlying inflammatory bowel disease was published in 2017. The review suggested six simple advices of best practice [126].

Physicians should remain alert to the possibility of CDI in a patient with an IBD exacerbation to ensure rapid diagnosis and treatment. Early surgical consultation is also key for improving outcomes of patients with severe disease. Colectomy with preservation of the rectum may need to be considered for severely ill IBD patients with CDI.

Immunocompromised patients

The rate of CDI is increased in solid organ transplant recipients due to ongoing immunosuppression and antibiotic use [127].

It has also been reported that cancer patients have a higher risk compared with non-cancer patients [128] due to chemotherapy causing immunosuppression [129, 130].

Patients with HIV/AIDS are also at high risks of being infected with *C. difficile* too. The risk is stronger in those with low absolute CD4 T cell counts or those who meet clinical criteria for AIDS [131].

The increased risk may be partially attributed to frequent hospitalization, exposure to antibiotics, and antibiotic prophylaxis for opportunistic infections, but HIV-related alterations in fecal microbiota, gut mucosal integrity, and humoral and cell-mediated immunity may also likely play a role [132].

Risk factors for community-acquired *C. difficile* infection

Although predominantly associated with the inpatient health care population, CDI originating in the community has been increasingly reported. The predominant *C. difficile* ribotypes isolated in the hospital setting correspond with those isolated in the community, suggesting that transmission between these two settings is occurring [133].

In 2011, an estimated 159,000 community-associated CDI (CA-CDI) occurred in the USA, representing 35% of the total CDI burden [134].

Risk factors may include increasing outpatient antibiotic prescriptions, acid-suppression medications, asymptomatic carriers in the community, and food or water contamination [135]. A sub-group analysis of a population-based epidemiological study of CDI in Olmsted County, Minnesota in 1991–2005 [136], identified 157 CA-CDI cases (75% women), with a median age of 50 years. Among them, 40% required hospitalization, 20% had severe, and 4.4% severe-complicated infection, while 20% had treatment failure and 28% had recurrent CDI.

A case-control study from ten US sites from October 2014 to March 2015 analyzed risk factors for CA-CDI [137]. Case patients were defined as persons aged ≥ 18 years with a positive *C. difficile* specimen collected as an outpatient or within 3 days of hospitalization who had no admission to a health care facility in the prior 12 weeks and no prior CDI diagnosis. Each case patient was matched to one control (persons without CDI). Participants were interviewed about relevant exposures; multivariate conditional logistic regression was performed. More case patients than controls had prior outpatient health care (82.1% vs. 57.9%; $p < 0.0001$) and antibiotic (62.2% vs. 10.3%; $p < 0.0001$) exposures. In multivariate analysis, antibiotic exposure—that is, cephalosporin (adjusted matched odds ratio [AmOR], 19.02; 95% CI 1.13–321.39), clindamycin (AmOR, 35.31; 95% CI 4.01–311.14), fluoroquinolone (AmOR, 30.71; 95% CI 2.77–340.05), and beta-lactam and/or beta-lactamase inhibitor combination (AmOR, 9.87; 95% CI 2.76–340.05)—emergency department visit (AmOR, 17.37; 95% CI 1.99–151.22), white race (AmOR 7.67; 95% CI 2.34–25.20), cardiac disease (AmOR, 4.87; 95% CI 1.20–19.80), chronic kidney disease (AmOR, 12.12; 95% CI 1.24–118.89), and IBD (AmOR, 5.13; 95% CI 1.27–20.79) were associated with CA-CDI.

A systematic review and meta-analysis investigated the association between medications and comorbidities with CA-CDI [138]. Twelve publications ($n = 56,776$ patients) met inclusion criteria. Antimicrobial (OR = 6.18, 95% CI 3.80–10.04) and corticosteroid (OR = 1.81, 95% CI 1.15–2.84) exposure were associated with increased risk of

CA-CDI. Among the comorbidities, IBD (OR = 3.72, 95% CI 1.52–9.12), renal failure (OR = 2.64; 95% CI 1.23–5.68), hematologic malignancy (OR = 1.75; 95% CI 1.02–5.68), and diabetes mellitus (OR = 1.15; 95% CI 1.05–1.27) were associated with CA-CDI. Antimicrobial exposure was associated with a higher risk of CA-CDI in the USA, whereas PPI exposure was associated with a higher risk in Europe. The risk of CA-CDI associated with antimicrobial exposure greatly increased in adults older than 65 years.

Risk factors for recurrent CDI

Recurrent CDI (RCDI) can be defined as reappearance of symptoms within eight weeks following the completion of a course of therapy with complete resolution of symptoms.

The key to preventing recurrent infection is identifying those patients at the greatest risk [139].

In a meta-analysis, Garey et al. [140] found that continued use of non-*C. difficile* antibiotics after diagnosis of CDI (OR = 4.23; 95% CI 2.10–8.55; $p < 0.001$), concomitant receipt of antacid medications (OR = 2.15; 95% CI 1.13–4.08; $p = 0.019$), and older age (OR = 1.62; 95% CI 1.11–2.36; $p = 0.0012$) were associated with increased risk of recurrent CDI. Other factors identified in individual studies include age, hospital exposure, comorbid conditions, severe underlying illness, hypoalbuminemia, impaired humoral immunity, poor quality of life, disease severity, and previous recurrent CDI [141–144].

In order to evaluate current evidence of risk factors for recurrent CDI, a systematic review and meta-analysis [145] analyzed 33 studies (18,530 patients). The most frequent independent risk factors for recurrent CDI were age ≥ 65 years (RR = 1.63, 95% CI 1.24–2.14; $p = 0.0005$), additional antibiotics during follow-up (RR = 1.76; 95% CI 1.52–2.05; $p < 0.001$), use of PPIs (RR = 1.58; 95% CI 1.13–2.21; $p = 0.008$), and renal failure (RR = 1.59; 95% CI 1.14–2.23; $p = 0.007$). The risk was also increased in patients previously on fluoroquinolones (RR = 1.42; 95% CI 1.28–1.57; $p < 0.001$).

Clinical manifestations

The spectrum of symptomatic CDI ranges from mild diarrhea to severe disease or fulminant colitis and as many as 30% of patients may develop recurrent CDI [146, 147].

Though diarrhea is the hallmark symptom of CDI, it may not be present initially, possibly due to colonic dysmotility either from previous underlying conditions or possibly from the disease process itself [148].

This is especially important in surgical patients who may have a concomitant ileus. Therefore, in surgical patients, it is important to have a high index of suspicion for the development of CDI.

Mild-moderate CDI

Diarrhea may be accompanied by mild abdominal pain and cramps and if prolonged may result in altered electrolyte balance and dehydration. When this occurs in patients with severe comorbidity, particularly after surgery, non-severe CDI may increase morbidity significantly [149].

Severe CDI

Severe CDI is associated with increased abdominal cramping and pain as well as systemic features such as fever, leukocytosis, and hypoalbuminemia. The absence of diarrhea may signal a progression to fulminant infection [150]. Though a wide variety of severity predictors for severe CDI has been described [151–156], international consensus for the definition of severe CDI is lacking [6, 7].

A systematic review identifying risk factors for adverse outcomes of CDI was published by Abou Chakra et al. in 2012 [154]. Except for leukocytosis, albumin, and age, there was much heterogeneity in the data and most studies were limited by small sample sizes.

To investigate the prognostic value of fever, leukocytosis, and renal failure, in 2012 Bauer et al. [153] analyzed the database of two randomized controlled trials, which contained information on 1105 patients with CDI. They found that both leucocytosis and renal failure were useful predictors of in severe CDI. Miller et al. [155] in 2013 subsequently published an analysis of the same two clinical therapeutic trials to validate a categorization system to stratify CDI patients into severe or mild-moderate groups. A combination of five simple and commonly available clinical and laboratory variables (ATLAS) measured at the time of CDI diagnosis were able to accurately predict treatment response to CDI therapy. The ATLAS criteria included age, treatment with systemic antibiotics, leucocyte count, serum albumin, and serum creatinine levels.

Any of the following may be predictors of severe CDI:

- WBC > 15×10^9/L
- Rise in serum creatinine level (≥ 133 μM/L or ≥ 1.5 times premorbid level)
- Temperature > 38.5 °C
- Albumin < 2.5 g/dL

It has been recently demonstrated that human serum albumin is capable to bind *C. difficile* toxin A and B thus impairing their internalization into host cells; this could partially explain the increased CDI severity experienced by hypoalbuminemic patients [157].

The progression to fulminant *C. difficile* colitis is relatively infrequent [158] (1–3% of all CDI) though mortality in this group of patients remains high due to the

development of toxic megacolon with colonic perforation, peritonitis, and septic shock and subsequent organ dysfunction. Systemic symptoms may not merely result from toxin-induced inflammatory mediators released locally in the colon but likely to the toxins spread into the bloodstream [36, 159, 160].

Studies have demonstrated a significant rise in the number of cases of fulminant colitis associated with multiple organ failure and increased mortality in recent years associated with the hypervirulent 027 strain of *C. difficile* [161, 162]. Early diagnosis and treatment is therefore important in reducing the mortality associated with fulminant colitis. Patients who present organ failure including increased serum lactate or vasopressor requirements should be assessed immediately with regard to early operative intervention [162].

Recurrent CDI

Recurrence of symptoms after initial therapy for *C. difficile* develops in 10–30% of cases, and presents a clinical challenge [144, 163–167]. For a patient with 1–2 previous episodes, the risk of further recurrences is 40–65%.

Recurrences are associated with an impaired immune response to *C. difficile* toxins and/or alteration of the colonic microbiota.

RCDI may be either a consequence of germinating resident spores remaining in the colon after antibiotic treatment has stopped, or re-infection from an environmental source.

Even though consensus regarding factors associated with CDI recurrence is not universal, algorithms have been developed to predict CDI recurrence with good sensitivity [168].

Ultimately, distinction between recurrence and re-infection can only be achieved if the strain of *C. difficile* is "typed" using molecular epidemiology [169].

Recurrent episodes are less severe compared to initial episodes: in a Canadian study, the authors reported a decline in the proportion of severe cases according to the number of recurrent episodes (47% for initial episodes, 31% for first recurrences, 25% for second, and 17% for third) [170].

Additional significant consequences of CDI

Patients who develop CDI have increased hospital length-of-stay, higher medical care costs, more hospital re-admissions, and higher mortality [171–173]. These consequences are also found in surgical patients with CDI.

In the Zerey et al. analysis [15], CDI was an independent predictor of increased length of stay, which increased by 16.0 days (95% CI 15.6–16.4 days; $p < 0.0001$). Total charges increased by $77,483 (95% CI $75,174, $79,793; $p < 0.0001$), and there was a 3.4-fold increase in the mortality rate (95% CI 3.02–3.77; $p < 0.0001$) compared with patients who without *C. difficile infection*.

In the Abdelsattar et al. study [18], postoperative CDI was independently associated with increased length of stay (mean, 13.7 days vs. 4.5 days), emergency department presentations (18.9 vs. 9.1%), and readmissions (38.9% vs. 7.2%, all $p < 0.001$).

Data from Nationwide Inpatient Sample database in 2011 of patients who underwent vascular surgery [174] showed that in patients who had experienced CDI, the median length of stay was 15 days (IQR 9, 25 days) compared to 8.3 days for matched patients without CDI, in-hospital mortality 9.1% (compared to 5.0%), and $13,471 extra cost per hospitalization. The estimated cost associated with CDI in vascular surgery in the USA was about $98 million in 2011. Similarly, data from the National Inpatient Sample in patients undergoing lumbar surgery found that CDI increased length of stay by 8 days, hospital costs by 2-fold, and increased inpatient mortality by 36-fold [175].

Higher mortality was also observed for liver transplant recipients (from 2000 to 2010) at a Detroit hospital [176].

The ACS-NSQIP database from 2005 to 2010 was used by Lee et al. to study emergently performed open colectomies for a primary diagnosis of *C. difficile* colitis in the USA [177]. The overall mortality was 33% (111/335).

A study was performed to quantify additional hospital stay attributable to CDI in four European countries, by analyzing nationwide hospital-episode data [5]. Patients in England had the longest additional hospital stay attributable to CDI at 16.09 days, followed by Germany at 15.47 days, Spain at 13.56 days, and The Netherlands at 12.58 days. Propensity score matching indicated a higher attributable length of stay of 32.42 days in England, 15.31 days in Spain, and 18.64 days in the Netherlands. Outputs from this study consistently demonstrate that in European countries, in patients whose hospitalization is complicated by CDI, the infection causes a statistically significant increase in hospital length of stay.

Recommendations for the management of CDI

Infection prevention and control

An infection control "bundle" strategy should be used to successfully control CDI outbreaks. The "bundle" approach should include multifaceted interventions including antibiotic stewardship, hand hygiene, isolation measures, and environmental disinfection.

1. Proper antibiotic stewardship in both selecting an appropriate antibiotic and optimizing its dose and

duration to prevent and cure an infection may prevent the emergence of *C. difficile* (Recommendation 1 B).

As CDI is thought to follow disruption of normal bacterial flora of the colon, a consequence of antibiotic use [178], it is logical that antibiotic stewardship programs may be useful in preventing CDI [179]. Good antibiotic stewardship involves ensuring appropriate antibiotic choices and optimizing antibiotic doses and duration of treatment to prevent and cure an infection while minimizing toxicity and conditions conducive to the development of CDI.

In order to estimate the effectiveness and safety of interventions to improve antibiotic prescribing practices in hospital inpatients in 2017, a systematic review including 221 studies (58 RCTs, and 163 NRS) was published [180]. The results showed a very low level of evidence regarding the effect of interventions to reduce CDI (median − 48.6%, interquartile range − 80.7% to − 19.2%; seven studies).

Another systematic review and meta-analysis quantified the effect of both persuasive (education and guidance) and restrictive (approval required, removal) antimicrobial stewardship programs for CDI [179]. A significant protective role (overall RR = 0.48, 95% CI 0.38–0.62) was found, with the strongest evidence for restrictive program and those with the longest duration. Cephalosporins and quinolones reduction should be an important target for stewardship programs, with a significant expected impact on the incidence of CDI [181, 182].

2. *C. difficile* carriers should be placed in contact (enteric) precautions (Recommendation 1 B). Even if further studies are warranted to establish the benefit of screening and the efficacy of infection control measures for asymptomatic carriers.

Prompt identification of patients with CDI is essential, so that appropriate isolation precautions can be put into effect [183].

This is particularly important in reducing environmental contamination as spores can survive for months in the environment [184], despite regular use of environmental cleaning agents.

It is important to place patients suspected of having CDI on contact precautions before diagnostic laboratory test confirmation if there is a lag before test results are available [185].

Contact (enteric) precautions in patients with CDI should be maintained until the resolution of diarrhea, which is demonstrated by passage of formed stool for at least 48 h. There are no studies demonstrating that further extension of contact precautions results in reductions in CDI incidence.

C. difficile carriers should be placed in a private room [186] with en-suite hand washing and toilet facilities. If a private room is not available, known CDI patients may be cohorted in the same area [187] though the theoretical risk of transfection with different strains exists. This is supported by a retrospective cohort of 2859 patients published by Chang et al. [188]. Non-infected patients who were roommates or neighbors of a patient with CDI were at higher risk of nosocomial acquisition of CDI (RR 3.94; 95% CI 1.27–12.24).

Recently, there has been growing interest in asymptomatic carriage/colonization of *C. difficile* since asymptomatic carriers are considered a reservoir for *C. difficile*. Colonization by toxigenic *C. difficile* strain seems to be associated with increased risk of progressing to CDI. Zacharioudakis et al. [48] showed that carriers of toxigenic strains are at a higher risk for the development of an infection compared to non-colonized patients. On the other hand, patients colonized by non-toxigenic strains may be even protected from developing CDI [189]. Conversion of a non-toxigenic strain to a toxin producer by horizontal gene transfer makes the risk assessment of colonization really challenging [190]. More data are needed to assess the precise role of the microbiota and the conditions allowing progression from asymptomatic colonization to CDI, in particular the recognition of the mechanism which may trigger toxin production. Based on current data, screening for asymptomatic carriers and an eradication of *C. difficile* is not indicated because *C. difficile* colonization is not believed to be a direct independent precursor for CDI. *C. difficile* asymptomatic carriers may also play a role in spore dissemination in the hospital and many cases of CDI are thought to be attributable to cross-contamination from asymptomatic carriers. Curry et al. [191] examined patients for *C. difficile* colonization and found that 29% of CDIs were linked to asymptomatic *C. difficile* carriers. Asymptomatic carriers who are colonized at admission appear to contribute to sustaining *C. difficile* transmission in the ward by the shedding of spores to the environment. The frequency of environmental contamination depends on the *C. difficile* status of the patient—34% of rooms of patients with asymptomatic colonization and 49% of rooms of CDI patients were found to be contaminated with *C. difficile* [192]. Infection control measures for asymptomatic carriers may be effective by limiting contamination of the hospital environment and health care workers' hands, as well as by preventing direct patient-to-patient transmission. Longtin et al. [185] reported that screening of *C. difficile* colonization at hospital admission and contact precautions were associated with a significant decrease in the HA-CDI incidence rate (6.9 per 10,000 patient-days in the pre-intervention period vs. 3.0 per 10,000 patient-days during the intervention period;

$p < 0.001$). This study provides the most convincing evidence to date for the significant effect of isolating asymptomatic *carriers*.

3. Hand hygiene with soap and water is the cornerstone of the prevention of *C. difficile* infection. Hand hygiene, contact precautions, and good cleaning and disinfection of patient care equipment and the environment should be used by all health-care workers in contact with any patient with known or suspected CDI (Recommendation 1 B).

In a health-care setting, transmission of *C. difficile* spores occurs primarily via the contaminated hands of health-care workers, but contact with a contaminated environment, contaminated utensils or medical devices has also been implicated. Hand hygiene with soap and water and the use of contact precautions along with good cleaning and disinfection of the environment and patient equipment should be used by all health-care workers in contact with any patient with known or suspected CDI. Hand hygiene is a cornerstone of prevention of nosocomial infections, including infection due to *C. difficile*. Alcohol-based hand sanitizers are highly effective against non-spore-forming organisms, but they do not kill *C. difficile* spores or remove *C. difficile* from the hands [193].

Though disposable glove use during care of a patient with CDI may be effective in preventing the transmission of *C. difficile*, these must be removed at the point of use and the hands should then be thoroughly decontaminated with soap and water.

For environmental cleaning, disinfection with sodium hypochlorite solutions are usually recommended in patient areas where *C. difficile* transmission is ongoing [194].

In 2016, a cross-sectional study was conducted in a tertiary care hospital to analyze the impact of location of sinks on hand washing compliance after caring for patients with CDI. Healthcare workers' hand washing compliance was low, and a poor access to sinks was associated with decreased hand washing compliance [195].

Environmental decontamination of clinical areas, ideally using hypochlorite agents or a sporicidal product, is recommended; however, in practice, compliance with cleaning protocols is often suboptimal.

In 2017, a qualitative systematic review including 46 studies investigated the impact of specific interventions on CDI rates in acute-care hospitals. The most effective interventions, resulting in a 45% to 85% reduction in CDI, included daily to twice daily disinfection of high-touch surfaces (including bed rails) and terminal cleaning of patient rooms with chlorine-based products. Chlorhexidine bathing and intensified hand-hygiene practices were not effective for reducing CDI rates [196].

Newer alternatives for environmental decontamination have been introduced, notably hydrogen peroxide vapor (HPV) and, more recently, UV decontamination [197].

In a study conducted by McCord et al., breakpoint time series analysis indicated a significant reduction ($p < 0.001$) in the CDI rate at the time when HPV disinfection was implemented, resulting in a reduction in the CDI rate from 1.0 to 0.4 cases per 1000 patient-days in the 24 months before HPV usage compared with the first 24 months of HPV usage [198].

Recently, a systematic literature review and meta-analysis on the impact of no-touch disinfection methods to decrease HAIs was performed [199]. Statistically significant reduction in CDI (RR = 0.64; 95% CI 0.49–0.84) was observed using UV light no-touch disinfection technology. Important to point out that the new no-touch methods for room disinfection supplement, but do not replace, daily cleaning [200].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group for *C. difficile* (ESGCD) recently published a set of guidelines regarding measures for prevention of *C. difficile* infection in acute healthcare settings [201]. According to the committee, it is recommended:

- To use personal protective equipment (gloves and gowns/disposable aprons) to decrease transmission of *C. difficile* or incidence of CDI
- To use contact precautions to decrease the transmission of *C. difficile* and reduce the incidence of CDI
- To introduce daily environmental sporicidal disinfection and terminal disinfection of rooms of patients with CDI to decrease the transmission of CDI
- To perform surveillance of CDI in combination with timely feedback of infection rates on both the hospital and ward level
- To implement restriction protocols of antibiotic agents/classes (effective in reducing CDI rates)
- To implement protocols to reduce the duration of antibiotic therapy (effective in reducing CDI rates)
- Educate healthcare workers on prevention of CDI to enhance their knowledge and skills on prevention strategies

It is not recommended:

- To screen for *C. difficile* to identify colonized/carrier patients as a way of altering the risk of developing CDI in either colonized subjects or other patients and thus reducing CDI rates
- To screen health care workers for *C. difficile* gut colonization as a routine control measure for CDI

Diagnosis

4. The diagnosis of CDI should be based on clinical signs and symptoms in combination with laboratory tests. Stool testing should only be performed on diarrheal stools from at-risk patients with clinically significant diarrhea (≥ 3 loose stools in 24 h) with no obvious alternative explanation (Recommendation 1 C).
5. For patients with ileus who may be unable to produce stool specimens, polymerase chain reaction testing of perirectal swabs provides an acceptable alternative to stool specimen analysis (Recommendation 2B).

Typing is useful to differentiate *C. difficile* strains and to obtain epidemiological information. Different typing methods for *C. difficile* currently available are: restriction endonuclease analysis (REA), pulsed-field gel electrophoresis (PFGE), multi-locus sequence typing (MLST), repetitive-element PCR typing, toxin-typing, multi-locus variable-number tandem-repeat analysis (MLVA), and PCR-ribotyping [201]. *C. difficile* strains with increased virulence traits (hypervirulent) have been described in the last 15 years. In particular, PCR-ribotype 027, also known as North American pulsed-field gel electrophoresis type 1 (NAP1) or restriction endonuclease analysis group BI, has been associated with increased disease severity, recurrence, and significant mortality [202].

The diagnosis of *C. difficile* infection should be suspected in patients with acute diarrhea (≥ 3 loose stools in 24 h) with no obvious alternative explanation (such as laxative use), particularly in the setting of relevant risk factors (including recent antibiotic use, hospitalization, and advanced age).

Prompt and precise diagnosis is important for the effective management of CDI. An accurate diagnosis of CDI requires both clinical symptoms and a positive laboratory test.

Early identification of CDI allows early treatment and can potentially improve outcomes. Rapid isolation of infected patients is important in controlling the transmission of *C. difficile* [203].

The diagnosis of CDI is based on the presence of a clinical picture compatible with CDI and microbiological evidence of free toxin and/or the demonstration of toxigenic *C. difficile* in a diarrhea stool sample [203]. Clinical features include diarrhea (defined as by passage of three or more unformed stools in 24 h), abdominal pain and cramps, abdominal distension, ileus (signs of severely disturbed bowel function), and toxic megacolon.

Since *C. difficile* can colonize the intestinal tract of healthy individuals, diagnostic testing for CDI should be performed only on diarrheic stools from symptomatic patients. Testing of formed stool can result in false positive tests, which may result in unnecessary antibiotic therapy.

One limitation of the reliance on stool specimens involves patients with suspected severe CDI complicated by ileus as those patients may be unable to produce specimens for testing. For those patients, testing of perirectal swabs may be an accurate and efficient method to detect toxigenic *C. difficile*. In 2012, Kundrapu et al. [204] described the results of a prospective study of 139 patients being tested for *C. difficile* infection by polymerase chain reaction. The sensitivity, specificity, positive predictive value, and negative predictive value of testing perirectal swabs were 95.7%, 100%, 100%, and 99.1%, respectively. The authors concluded that for selected patients, perirectal swabs provided an acceptable alternative to stool specimen analysis.

Clinical context such as a history of recent antibiotic administration and/or residence in hospital are useful in selecting patients for testing. Other signs such as fever, abdominal pain, leukocytosis, in combination with other laboratory tests (e.g., creatinine and serum lactate) are useful for defining the severity of infection.

6. Nucleic acid amplification tests (NAAT) for *C. difficile* toxin genes appear to be sensitive and specific and may be used as a standard diagnostic test for CDI. NAAT as single-step algorithm can increase detection of asymptomatic colonization, therefore it should be performed in patients with high suspicion for CDI or included in two-step algorithm starting with toxin-EIA (Recommendation 1 B).
7. Glutamate dehydrogenase (GDH) screening tests for *C. difficile* are sensitive but do not differentiate between toxigenic and non-toxigenic strains. They may be used in association with toxin A/B enzyme immunoassays (EIA) testing. Algorithms including screening with an EIA for GDH followed by a toxin assay may be suggested (Recommendation 1 B).
8. EIA for toxin A/B is fast and inexpensive and has high specificity but it is not recommended alone due to its relatively low sensitivity (Recommendation 1 B).
9. *C. difficile* culture is relatively slow but sensitive. It is rarely performed today as a routine diagnostic test. *C. difficile* culture is recommended for subsequent epidemiological typing and characterization of strains (Recommendation 1 C).
10. Repeat testing after a first negative sample during the same diarrheal episode may be useful only in selected cases with ongoing clinical suspicion during an epidemic situation or in cases with high clinical suspicion during endemic situations (Recommendation 1 C).

The best standard laboratory test for diagnosis of CDI has not been clearly established [205].

Currently, there is no single stool test that can be relied upon as the reference standard for the diagnosis of CDI. Several methods are suggested for the diagnosis of CDI, including toxinogenic culture (TC), cell cytotoxicity neutralization assay (CCNA), enzyme immunoassays (EIA) for toxins A, B, and/or glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAATs).

In the past, TC was accepted by many microbiologists as the method of choice for diagnosis of CDI. The procedure includes stool culture for *C. difficile* on a selective differential medium (cycloserine, cefoxitin, fructose agar, or CCFA) and an assay to test the colonies for the ability to produce toxins. Despite TC is considered the gold standard method, there are significant issues with TC including slow turnaround time and its inability to detect the presence of toxins in stool. This may also lead to false positive results as up to 7% of asymptomatic hospitalized patients may be colonized with toxigenic *C. difficile* [206].

C. difficile culture is also necessary for subsequent epidemiological typing and characterization of strains.

The EIA for toxin A/B has been adopted by most clinical laboratories because it is fast, convenient, and inexpensive [207]. However, studies have shown that sensitivity can be low. Toxin A + B EIA tests have a described sensitivity of 32–98% and a specificity of 84–100% [208].

GDH is an enzyme produced by *C. difficile* in relatively large amounts compared with toxins A and B [209, 210]. A positive GDH assay only documents the presence of *C. difficile* but it does not discriminate between toxigenic and non-toxigenic strains (about 20% of the *C. difficile* population). Therefore, a second test for toxin production is necessary for confirmation. GDH screening tests for *C. difficile* used in association to toxin A + B EIA testing gives an accurate test result quickly [207, 208] even if the sensitivity of such strategy is lower than NAATs.

The use of NAATs for the detection of *C. difficile* from diarrheal stool specimens was documented in the early 1990s. NAATs possess a series of advantages such as excellent sensitivity and specificity, low complexity, simplified reporting, reduced need for repeat testing, and improved turnaround time [209–212].

In particular, some NAATs such as multiplex NAATs can simultaneously detect *C. difficile* strains and toxin encoding genes from stool samples [213].

There are several commercially available NAATs, including a real-time PCR (RT-PCR) assay and loop-mediated isothermal amplification (LAMP) assay, both of which have an overall high analytical sensitivity (80–100%) and specificity (87–99%).

However, although NAATs have a high sensitivity and specificity, not all laboratories routinely perform this assay [214]. Moreover, some limitations have been associated with NAATs [215].

Although NAAT methods are considered superior to other methods of diagnosing CDI, this testing strategy is unable to accurately distinguish between *C. difficile* colonization and active disease, which may result in both over diagnosis and overtreatment of CDI, delaying recognition of other causes of diarrheal illness/outbreaks, and resulting in unnecessary exposure to antibiotics used to treat CDI.

A current topic of debate is whether a stool sample that was positive by a molecular assay needs to be tested with a confirmatory toxin assay [216] given it can also identify toxigenic *C. difficile* in asymptomatic patients. This underscores the importance of only testing patients with symptoms. There is no evidence suggesting that surgical patients should be diagnosed any differently than general medical patients [217]. It has already been highlighted that immunocompromised patients including those on glucocorticoids, or chemotherapy and post-transplant patients are at increased risk for CDI.

The issue of if or when to retest for CDI is inherently linked to the accuracy of the employed routine testing method. Methods with suboptimal sensitivity for *C. difficile* (e.g., stand-alone toxin EIAs) led to frequent retesting in some settings. In the absence of clear changes to the clinical presentation of suspected CDI (i.e., change in character of diarrhea or new supporting clinical evidence), repeating testing should not be performed.

11. CT imaging is suggested for patients with clinical manifestations of severe-complicated *C. difficile* colitis; however, its sensitivity is not satisfactory for screening purposes (Recommendation 2 B).

In certain clinical settings, adjunct testing methods such as radiologic diagnostic imaging may be useful for diagnosing CDI. Diagnostic computed tomography (CT) imaging can assist with an early diagnosis and may help determine the severity of the disease in patients with CDI [218].

CT has been studied as an imaging modality for diagnosing *C. difficile* colitis [219–222]. Typical CT findings of CDC include colonic wall thickening, dilation, peri-colonic stranding, “accordion sign” (high-attenuation oral contrast in the colonic lumen alternating with low-attenuation inflamed mucosa), “double-halo sign, target sign” (intravenous contrast displaying varying degrees of attenuation caused by submucosal inflammation and hyperemia), and ascites [223]. However, the most common finding, colonic wall thickening, is non-specific and can be found in other forms of colitis, although it may be more pronounced with CDI.

In the study by Kirkpatrick et al. [224], CT diagnosis of CDC had a sensitivity of 52%, a specificity of 93%, and positive and negative predictive valued 88%, and 67% respectively. Sensitivity would have been increased to 70% with no change in specificity if colonic wall thickness of greater than 4 mm had been used as a diagnostic criteria, in conjunction with the presence of the following factors, colon wall nodularity, accordion sign, peri-colonic stranding, or otherwise unexplained ascites.

12. Ultrasound may be useful in critically ill patients suspected to have pseudomembranous colitis who cannot be transported to the CT scan suite (Recommendation 2 C).

Point-of-care ultrasound may be useful in diagnosing and managing critically ill patients who cannot be moved to the radiology department [225].

Ultrasound findings of pseudomembranous colitis in severe cases include a thickened colonic wall with heterogeneous echogeneity as well as narrowing of the colonic lumen [226]. Pseudomembranes can also be visualized as hyperechoic lines covering the mucosa [226–229].

In the early stages of pseudomembranous colitis, the texture of the colonic wall is preserved. The hypoechoic edematous mucosa and muscularis propria may be thickened with the echogenic submucosa sandwiched between them. The presence of submucosal gaps may indicate extension of tissue damage into deeper structures. Intraperitoneal free fluid is seen in more than 70% of cases [224–227].

13. Flexible sigmoidoscopy may be helpful in the diagnosis of *C. difficile* colitis when there is a high level of clinical suspicion for *C. difficile* infection (Recommendation 2 B).

Endoscopy should be used sparingly to confirm the diagnosis of CDI since the diagnosis can be usually made by laboratory tests, clinical findings, and imaging. However, colonoscopy may be hazardous in the setting of fulminant colitis where there may be increased risk of perforation [169].

A study by Johal et al. [230] described the use of flexible sigmoidoscopy as a tool for the diagnosis of *C. difficile* colitis when stool assays were negative suggesting that sigmoidoscopy should be considered in all hospitalized patients with diarrhea in whom the stool tests for *C. difficile* cytotoxin and enteric pathogens are negative.

Antibiotic therapy

14. Unnecessary antibiotic agent(s) should be discontinued if CDI is suspected (Recommendation 1 B).
15. Unnecessary PPIs should always be discontinued in patients at high risk for CDI (Recommendation 1 C).
16. Empirical therapy for CDI should be avoided unless there is a strong suspicion for CDI. If a patient has a strong suspicion for severe CDI, empirical therapy for CDI should be considered while awaiting test results (Recommendation 1 C).

In cases of suspected severe CDI, antibiotic agent(s) should be discontinued, if possible [231].

A meta-analysis addressing factors associated with prolonged symptoms and severe disease due to *C. difficile* showed that continued use of antibiotics for infections other than CDI is significantly associated with an increased risk of CDI recurrence [232].

If continued antibiotic therapy is required for treatment of the primary infection, antimicrobial therapy with agents that are less frequently implicated with antibiotic-associated CDI should be used; these include parenteral aminoglycosides, sulfonamides, macrolides, vancomycin, or tetracycline/tigecycline.

Although there is a clinical association between PPI use and CDI [89], no RCTs studies have studied the relationship between discontinuing or avoiding PPI use and risk of CDI. Thus, a strong recommendation to discontinue PPIs in patients at high risk for CDI regardless of need for PPI will require further evidences. However, stewardship activities to discontinue unneeded PPIs are strongly warranted.

Antibiotic therapy is the first choice for CDI, and specific antibiotic therapy guideline recommendations should be based on the severity of the disease.

When antibiotic therapy is indicated for symptomatic cases with a positive *C. difficile* toxin result, options include metronidazole, oral or intraluminal vancomycin, and oral fidaxomicin [233–239].

17. Oral metronidazole should be limited to the treatment of an initial episode of mild-moderate CDI (Recommendation 2A). Oral vancomycin is recommended for treatment of patients with mild-moderate disease who do not respond to metronidazole (Recommendation 1 A). Repeated or prolonged courses of metronidazole should be avoided due to risk of cumulative and potentially irreversible neurotoxicity (Recommendation 1 B).

Although metronidazole may be associated with more frequent side effects, and there has been a significant increase in treatment failures (especially in patients infected with the emergent 027/BI/NAP1 strain), oral metronidazole 500 mg three times per day for 10 days has been used for treating mild-to-moderate cases of CDI [240]. Repeated or prolonged courses of metronidazole

should be avoided due to risk of cumulative and potentially irreversible neurotoxicity [241].

In recent IDSA guidelines, metronidazole is suggested only for patients with an initial episode of non-severe CDI in settings where access to vancomycin or fidaxomicin is limited [242].

In 2015, a systematic review and meta-analysis comparing the efficacy and safety of metronidazole monotherapy with vancomycin monotherapy and combination therapy in CDI patients was published [243]. No statistically significant difference in the rate of clinical cure was found between metronidazole and vancomycin for mild CDI (OR = 0.67, 95% CI 0.45–1.00; $p = 0.05$) or between either monotherapy and combination therapy for CDI (OR = 1.07, 95% CI 0.58–1.96; $p = 0.83$); however, the rate of clinical cure was lower for metronidazole than for vancomycin for severe CDI (OR = 0.46, 95% CI 0.26–0.80; $p = 0.006$). No significant difference in the rate of CDI recurrence was found between metronidazole and vancomycin for mild CDI (OR = 0.99, 95% CI 0.40–2.45; $p = 0.98$) or severe CDI (OR = 0.98, 95% CI (0.63, 1.53); $p = 0.94$) or between either monotherapy or combination therapy for CDI (OR = 0.91, 95% CI (0.66, 1.26); $p = 0.56$). In addition, there was no difference in the rate of adverse events (AEs) between metronidazole and vancomycin (OR = 1.18, 95% CI 0.80–1.74; $p = 0.41$). In contrast, the rate of adverse effects was significantly lower for either monotherapy than for combination therapy (OR = 0.30, 95% CI 0.17–0.51; $p < 0.0001$).

However, recent data have suggested an overall superiority of vancomycin to metronidazole for the treatment of patients with CDI and oral vancomycin 125 mg four times per day for 10 days is recommended as first choice antibiotic also for moderate cases.

In 2017, in an update of a previously published Cochrane review, moderate quality evidence suggested that vancomycin is superior to metronidazole in all cases of CDI [244]. The differences in effectiveness between these antibiotics were not too large and the advantage of metronidazole is its far lower cost even if liquid vancomycin is cheaper and reduces the cost.

18. Both oral vancomycin or fidaxomicin are recommended for treatment of all patients with severe CDI (Recommendation 1 A).
19. In patients in whom oral antibiotics cannot reach the colon, vancomycin may be administered as retention enema via a large rectal tube or catheter (Recommendation 1 B).
20. Fidaxomicin may be used to treat CDI, especially in patients at higher risk for recurrence (e.g., elderly patients or those receiving concomitant antibiotics) (Recommendation 1A).

Vancomycin orally 125 mg four times daily for 10 days is considered superior to metronidazole in severe *C. difficile* disease [245–247]. This may reflect the superior pharmacokinetic properties of vancomycin which is concentrated in the gut lumen. Doses of up to 500 mg have been used in some patients with severe or fulminant, as defined as hypotension or shock, ileus or megacolon, CDI [7], although there is little evidence for this in the literature.

Unlike vancomycin delivered enterally, intravenous vancomycin has no effect on CDI since the antibiotic is not excreted into the colon. Vancomycin enema may be an effective therapy for patients who cannot tolerate the oral preparation or patients with ileus who have delayed passage of oral antibiotics from the stomach to the colon [248].

Trans-stoma vancomycin may also be effective in surgical patients with Hartmann resection, ileostomy, or colon diversion. A single-hospital, retrospective chart review on 47 consecutive patients with *C. difficile* colitis treated with intracolonic vancomycin (ICV) was published by Kim et al. in 2013 [249]. Thirty-three of 47 patients (70%) with severe *C. difficile* colitis responded to adjunct intracolonic vancomycin with complete resolution without surgery. Multivariate analysis suggested that failures to intracolonic vancomycin enemas occurred in patients who were older and frail with albumin < 2.5 g/dl. Early surgery should be considered for those patients. Early surgery should also be offered to those patients who are failing maximal medical therapy including ICV enemas.

Fidaxomicin orally 200 mg twice daily for 10 days may be a valid alternative to vancomycin in patients with CDI [250, 251]. Fidaxomicin was non-inferior to vancomycin for initial cure of CDI in two prospective trials [235, 236]. In a first double-blind, randomized, non-inferiority trial [237], 629 adults with acute symptoms of *C. difficile* infection and a positive result on a stool toxin test were enrolled and randomly assigned to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis and the per-protocol analysis. In a second multicenter, double-blind, randomized, non-inferiority trial [238], 535 patients, 16 years or older with acute, toxin-positive CDI were randomly allocated (1:1) to receive oral fidaxomicin (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days.

Non-inferiority was shown for both the modified intention-to-treat analysis (15.4% vs. 25.3%; $p = 0.005$) and the per-protocol analysis (13.3% vs. 24.0%; $p = 0.004$). Patients receiving concomitant antibiotics for other infections had a higher cure rate with fidaxomicin (46 [90.2%] of 51) than with vancomycin (33 [73.3%] of 45; $p = 0.031$).

A randomized, controlled, open-label, superiority study, recruited hospitalized adults aged 60 years and older with confirmed CDI at 86 European hospitals extended-pulsed fidaxomicin demonstrated to be superior to standard-dose vancomycin for sustained cure of CDI [252]. Between Nov 6, 2014, and May 5, 2016, 364 patients were enrolled and randomly assigned to receive extended pulsed fidaxomicin or vancomycin. Then, 362 patients received at least one dose of study medication (181 in each group). Further, 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI, 1.0–20.7]; $p = 0.030$; OR 1.62 [95% CI, 1.04–2.54]). Incidence of treatment-emergent adverse events did not differ between extended-pulsed fidaxomicin (121 [67%] of 181) and vancomycin (128 [71%] of 181) treatment arms.

Fidaxomicin may be useful for treating patients who are considered at high risk for recurrence (elderly patients with multiple comorbidities who are receiving concomitant antibiotics). However, it is important to note that no data on the efficacy of fidaxomicin in severe life-threatening disease are available.

The use of other antibiotics such as tigecycline [253, 254], fusidic acid, teicoplanin, rifamixin [238], and nitazoxanide [255] has been described in the literature, but they are not currently recommended for general use.

Surgical management

Patients with fulminant colitis (FC) who progress to systemic toxicity require surgical intervention.

To determine clinical predictors for the development of fulminant colitis in patients with CDI, a 10-year retrospective review of FC patients who underwent colectomy was performed and compared with randomly selected age- and sex-matched non-fulminant CDI patients at a single institution study by Girotra et al. in 2012 [256]. Predictive clinical and laboratory features included age (> 70 years), prior CDI, profound leukocytosis (> 18,000/mm^3), hemodynamic instability, use of anti-peristaltic medications, and a clinical trial of increasing abdominal pain, distension and diarrhea.

Another important clinical feature that should be taken into account in patients who are going to experience fulminant colitis is the occurrence of a change in mental status that could reflect significant toxemia [257].

21. Patients with severe CDI who progress to systemic toxicity should undergo early surgical consultation and should be evaluated for potential surgical intervention (Recommendation 1 C).

Patients with severe CDI who progress to systemic toxicity are likely to have serious comorbidities. Delaying surgery in this group leads to increased likelihood of adverse outcomes [258], although some reports show that a short period of medical optimization can improve outcomes before colectomy [259].

There are no reliable clinical and/or laboratory findings that can predict those patients who will respond to medical therapy and those who will need surgery [260].

Data comparing mortality rates between surgical and medical treatment for fulminant *C. difficile* colitis were published in a systematic review by Stewart et al. [261]. Five hundred ten patients with fulminant colitis were identified in 6 studies. Emergency colectomy for patients with FC provided a survival advantage compared with continuing antibiotics. When all 6 studies numbering 510 patients were analyzed, the pooled adjusted odds ratio of mortality comparing surgery with medical therapy, and weighted by the contribution of each study, was 0.70 (0.49–0.99) leading the authors to conclude that emergency colectomy has a therapeutic role in treating complicated CDI.

Patients presenting with organ failure (acute renal failure, mental status changes, or cardiopulmonary compromise) also need prompt intervention since the timing of surgical intervention is the key for survival of patients with FC [262–265].

Seder et al. [266] described 6841 patients with CDI and showed a decreased mortality associated with surgery performed before the need for vasopressor requirement, especially in the patients < 65 years old. Hall et al. [264] reviewed 3237 consecutive cases of CDI and showed an increased mortality rate when surgical exploration was performed after intubation or the development of respiratory failure and the use of vasopressors.

Recently, a risk scoring system (RSS) for daily clinical practice was designed by van der Wilden et al. [267]. Age greater than 70 years was assigned 2 points, white blood cell counts equal to or greater than > 20,000/μL or equal to or less than 2000/μL was assigned 1 point, cardiorespiratory failure was assigned 7 points, and diffuse abdominal tenderness on physical examination was assigned 6 points. A value of 6 points was determined to be the threshold for reliably dividing low-risk (< 6) from high-risk (≥ 6) patients. Only patients with cardiorespiratory failure or diffuse abdominal tenderness were high risk.

Ferrada et al. [268] reviewed the existing literature on the treatment of CDI and published practice management

guidelines (PMG) for the Eastern Association for the Surgery of Trauma (EAST). The authors strongly recommended that adult patients with CDI undergo early surgery before developing shock and requiring vasopressors. Although optimal timing remains controversial, the authors found that it was between 3 and 5 days after diagnosis in patients who are worsening or not clinically improving [268].

Many factors have been described as predictors of mortality in patients who undergo emergency surgery.

Sailhamer et al. [269] reviewed the records of 4796 inpatients diagnosed with *C. difficile* colitis. In 199 patients (4.1%) with fulminant CDI, the in-hospital mortality rate was 34.7%. Independent predictors of mortality included age 70 years or older, severe leukocytosis or leukopenia (white blood cell count, > or = 35,000/μL or < 4000/μL) or bandemia (neutrophil bands, > or = 10%), and cardiorespiratory failure (intubation or vasopressors). Survival rates were higher in patients who were cared for by surgical vs. nonsurgical departments.

The ACS-NSQIP database from 2005 to 2010 was used by Lee et al. to study emergency open colectomies performed for *C. difficile* colitis in the USA [177]. The overall mortality was 33% (111/335). Age 80 years or older, preoperative dialysis dependence, chronic obstructive pulmonary disease, and wound class III were associated high patient mortality. Thrombocytopenia (platelet count $< 150 \times 10^3/mm^3$), coagulopathy (international normalized ratio > 2.0), and renal insufficiency (blood urea nitrogen > 40 mg/dL) were also associated with a higher mortality.

A systematic review and meta-analysis of outcomes following emergency surgery for CDI was published by Banghu et al. [270]. Thirty-one studies were included, which presented data for 1433 patients. The authors concluded that the strongest predictors for postoperative death were those relating to preoperative physiological status: preoperative intubation, acute renal failure, multiple organ failure and shock requiring vasopressors.

22. Early diagnosis and treatment is important to reduce the mortality associated with fulminant colitis.
23. Resection of the entire colon should be considered to treat patients with fulminant colitis (Recommendation 1 B). However, diverting loop ileostomy with colonic lavage is a useful alternative to resection of the entire colon (Recommendation 1 B).
24. Patients with fulminant colitis should be treated with high dose vancomycin (500 mg, 6 hourly), oral and/or by enema, in combination with intravenous metronidazole (500 mg, 8 hourly) (Recommendation 1 C).

In the Bhangu et al. meta-analysis [270], the most commonly performed operation for treatment of fulminant colitis (FC) was total colectomy with end ileostomy (89%, 1247/1401). When total colectomy with end ileostomy was not performed, reoperation to resect further bowel was needed in 15.9% (20/126). In the recent meta-analysis by Ferrada et al. [268], 17 studies comparing colectomy versus other procedures or no surgery as treatment for CDI were analyzed. The authors recommended that total colectomy (versus partial colectomy or other surgery) is the procedure of choice for patients with *C. difficile* colitis.

To evaluate the role of emergency colectomy in patients with FC, and to identify subgroups of patients that may benefit from it, Lamontagne et al. [271] published a retrospective observational cohort study of 165 cases of FC requiring ICU admission or prolongation of ICU stay in 2 tertiary care hospitals in Quebec, Canada. Eighty-seven (53%) patients died within 30 days of ICU admission, of whom almost half (38 of 87, 44%) died within 48 h of ICU admission. The independent predictors of 30-day mortality were leukocytosis $\geq 50 \times 10^9/L$, lactate ≥ 5 mmol/L, age ≥ 75 years, immunosuppression, and shock requiring vasopressors. Patients who underwent an emergency colectomy were less likely to die than those treated medically. Colectomy was more beneficial in patients aged 65 years or more, in immunocompetent patients and in patients with a leukocytosis $\geq 20 \times 10^9/L$ or lactate between 2.2 and 4.9 mmol/L.

Diverting loop ileostomy with antegrade colonic lavage may be a colon-preserving alternative to total colectomy [272, 273]. A prospective, nonrandomized, historical control group study was performed at the University of Pittsburgh Medical Center and the Veterans' Administration Healthcare System, in Pittsburgh between June 2009 and January 2011 [272]. Forty-two patients with FC were managed by a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, and postoperative antegrade instillation of vancomycin flushes via the ileostomy. There was no significant difference in age, sex, pharmacologic immunosuppression, and Acute Physiology and Chronic Health Evaluation-II scores between the studied cohort and historical controls. The operation was accomplished laparoscopically in 35 patients (83%). This treatment strategy resulted in reduced mortality compared to their historical controls. Preservation of the colon was achieved in 39 of 42 patients (93%). Of note, vancomycin antegrade enemas were continued via the ileostomy every 6 h for 10 days and this likely augmented the effect of the defunctioning surgery.

A retrospective multicenter study conducted under the sponsorship of the Eastern Association for the Surgery

of Trauma to compare loop ileostomy versus total colectomy as surgical treatment for CDI was published in 2017 [274]. Data from ten centers of patients who presented with CDI requiring surgery between July 1, 2010 and July 30, 2014 were collected. When comparing colectomy and loop ileostomy, there was no statistical difference between these two operative strategies. Univariate pre-procedure predictors of mortality were age, lactate, timing of operation, vasopressor use, and acute renal failure. There was no statistical difference between the APACHE score of patients undergoing either procedure (TC, 22 vs. LI, 16). Adjusted mortality (controlled for pre-procedure confounders) was significantly lower in the loop ileostomy group (17.2% vs. 39.7%; $p = 0.002$).

Supportive care

25. Early detection of shock and aggressive management of underlying organ dysfunction are essential for improved outcomes in patients with fulminant colitis (Recommendation 1 C). Supportive measures, including intravenous fluid resuscitation, albumin supplementation, and electrolyte replacement, should be provided to all patients with severe *C. difficile* infection (Recommendation 1 C).

Early detection and prompt aggressive treatment of the underlying organ dysfunction is an essential component in the management of CDI in critically ill patients.

Severe CDI may present with a fulminant course and may be associated with great morbidity and high mortality. Physiologic support including invasive monitoring in an intensive care unit and aggressive resuscitation are often necessary in fulminant colitis. Diarrhea results in significant volume depletion and electrolyte abnormalities, and fluid and electrolyte imbalance should be promptly corrected.

Although it has been debated, albumin supplementation in patients with severe hypoalbuminemia (< 2 g/dl) should be considered as a supportive measure and also to exploit its anti-toxin properties [275].

The expert panel suggests measuring intra-abdominal pressure (IAP) when any known risk factor for intra-abdominal hypertension (IAH)/abdominal compartment syndrome (ACS) is present.

RCDI

Recurrence is diagnosed when CDI recurs < 8 weeks after the resolution of a previous episode, provided the symptoms from the previous episode resolved after completion of the initial treatment and other causes have been excluded. Symptomatic recurrent *C. difficile* infection (RCDI) occurs in approximately 20% of patients and is challenging [141]. Therefore, patients with recurrent CDI should therefore be treated by experienced clinicians.

26. Agents that may be used to treat the first recurrence of CDI include vancomycin (particularly if metronidazole was used for the first episode) or fidaxomicin. (Recommendation 1 B).
27. Antibiotic treatment options for patients with > 1 recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen (Recommendation 1C).

For recurrent cases of CDI, oral vancomycin 125 mg four times per day for 14 days or oral fidaxomicin 200 mg twice a day for 10 days is recommended for first recurrence.

Metronidazole is not recommended as initial treatment of recurrent CDI as sustained response rates are lower than those with vancomycin. Furthermore, metronidazole should not be used for long-term therapy because of the potential for cumulative neurotoxicity.

Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms but fidaxomicin has been shown to be associated with a lower likelihood of CDI recurrence after a first recurrence [237, 238, 276]. However, there are no prospective randomized controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI. Vancomycin is often administered using a prolonged tapered and/or pulsed regimen which may be more effective than a standard 10 to 14 days course, although no RCTs have been reported in second or subsequent CDI recurrences [146].

Probiotics

28. Limited direct evidence exists to support the use of probiotics in the management of a first episode of CDI as an adjunctive treatment to antibiotics for immunocompetent patients Recommendation 2 B).

The altered composition of gut microbiota in the setting of *C. difficile* infection has raised interest in the potential role of probiotics [163]. Their use aims to re-colonize and restore the diversity of flora following the disruption due to antibiotic treatment and *C. difficile* overgrowth.

There is limited direct evidence to support the use of probiotics in the primary prevention of CDI.

Data for primary prevention of CDI often arises from prevention of antibiotic-associated diarrhea trials with CDI as a secondary outcome and are often underpowered for CDI. Thus, meta-analyses may be useful to evaluate if specific probiotics are efficacious for CDI, as

this statistical method utilizes the increase in power resulting from pooling different studies together. However, since the recent finding that the efficacy of probiotics are both strain-specific and disease-specific [277], for valid conclusions to be reached, the meta-analysis must assess efficacy within subgroups of identical probiotic strains (or mixture of strains) and for the same type of disease. A meta-analysis of 22 randomized controlled trials using sub-group analysis for 5 different types of probiotics for primary prevention of CDI found 4/5 (*Saccharomyces boulardii* I-745, *Lactobacillus casei* DN114001, a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, and another mixture of three Lactobacilli strains [*L. acidophilus* CL1285, *L. casei* LBC80R, *Lactobacillus rhamnosus* CLR2]) were effective and one type (*L. rhamnosus* GG) was not effective [278]. Other systematic reviews and meta-analyses report a protective effect of probiotics [279–284], but reviews exploring the contribution of probiotics in CDI prevention can be limited due to heterogeneity between studies, inadequate study power, or significant levels of missing outcome data. In addition, many reviews still fail to account for strain-specificity and pool different types of probiotics together in their analysis [280, 281, 284]. The short-term use of probiotics appeared to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Probiotics should not be administered to patients at risk of bacteremia or fungemia.

29. Prophylactic probiotics may be considered for inpatients receiving antibiotics during high-risk period (such as outbreaks) before the disease develops (Recommendation 2 C). Probiotics should be not used in immunocompromised patients (Recommendation 2 C).

Several types of probiotics have been tested on a facility-level intervention as part of an infection control bundle for CDI. In an effort to reduce hospital-wide CDI rates (especially in hospitals having CDI outbreaks), probiotics were given to newly admitted patients receiving antibiotics and continued during either the duration of the antibiotic or duration of the patient's stay. Although lacking in the rigorous strength from randomized trials, these hospital studies showed a significant reduction of CDI rates for some types of probiotics (*L. casei* Shirota, *Lactobacillus plantarum* 299v, and a mixture of three lactobacilli strains, Bio-K+) [278]. This three lactobacilli strain mixture (*L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2) has been tested in seven other hospitals and found to be effective in reducing CDI rates [285]. However, other types of probiotics need further research, particularly in those at high risk of CDI. Probiotics are contraindicated for immunocompromised patients due to a rare, but serious risk of bacteremia.

30. Probiotics for prevention of recurrent CDI may be an effective adjunct to standard antibiotic treatment (vancomycin) in patients with at least one prior episode of CDI (Recommendation 2 B).

There have been many case reports and case series reporting fewer recurrences of CDI when some probiotics were used as an adjunctive treatment with vancomycin or metronidazole. However, there are fewer randomized trials for this adjunctive therapy. Two randomized controlled trials found significantly fewer CDI patients developed recurrences when *Saccharomyces boulardii* I-745 was combined with standard antibiotic therapy [286, 287]. The first trial demonstrated a lower CDI recurrence rate compared with a placebo control group (26% vs. 45%, respectively) [283] and the second trial found that the combination of *S. boulardii* (1 g/day) with high dose vancomycin (2 g/day) was more effective than high dose vancomycin and placebo (17% vs. 50% recurrence rate) [284]. The probiotic was not able to reduce CDI recurrences when combined with a lower dose of vancomycin (500 mg/day) or with metronidazole (1 g/day). Other studies with Lactobacillus strains (*L. rhamnosus* GG or *L. plantarum* 299v) were stopped prematurely due to enrollment problems [146]. There have no published trials currently combining probiotics with fidaxomicin.

Fecal microbiota transplantation

31. Fecal microbiota transplantation (FMT) may be an effective option for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments (Recommendation 2 C).

FMT has been considered as an alternative therapy to treat RCDI [283–293]. It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of patients to restore the intestinal microbiota.

The rationale of FMT is that disruption of the normal balance of colonic flora allows *C. difficile* strains to grow and produce CDI. By reintroducing normal flora via donor feces, the imbalance may be corrected, and normal bowel function re-established [288].

FMT has not been widely adopted as a therapeutic tool probably due to concerns regarding safety and acceptability [258].

A systematic literature review of FMT treatment for RCDI and pseudomembranous colitis was published in 2011 by Gough et al. [289]. In 317 patients treated

across 27 case series and reports, FMT was highly effective, showing disease resolution in 92% of cases. In those studies, 35% of patients received FMT via enema, with a response rate of 95%; 23% patients received FMT via naso-jejunal tube by gastroscope, with a response rate of 76%; and 19% via colonoscopy, with a response rate of 89%. Effectiveness varied by route of instillation, relationship to stool donor, volume of FMT given, and treatment before infusion.

Another systematic review was published by Cammarota et al. [290]. Twenty full-text case series, 15 case reports, and 1 randomized controlled study were included for the final analysis. Almost all patients treated with donors' fecal infusion had experienced recurrent episodes of CD-associated diarrhea despite standard antibiotic treatment. Of a total of 536 patients treated, 467 (87%) had resolution of diarrhea. Diarrhea resolution rates varied according to the site of infusion: 81% in the stomach, 86% in the duodenum/jejunum, 93% in the cecum/ascending colon, and 84% in the distal colon. No severe adverse events were reported with the procedure.

Recently, a review to evaluate the efficacy of FMT in treating recurrent and refractory CDI was published [291]. Thirty-seven studies were included; 7 randomized controlled trials and 30 case series. FMT was more effective than vancomycin (RR = 0.23, 95% CI 0.07–0.80) in resolving recurrent and refractory CDI. Clinical resolution across all studies was 92% (95% CI 89–94%). A significant difference was observed between lower gastrointestinal (GI) and upper GI delivery of FMT 95% (95% CI 92–97%) vs. 88% (95% CI 82–94%) respectively ($p = 0.02$). There was no difference between fresh and frozen FMT 92% (95% CI 89–95%) vs. 93% (95% CI 87–97%) respectively ($p = 0.84$). Administering consecutive courses of FMT following failure of first FMT resulted in an incremental effect. Donor screening was consistent but variability existed in recipient preparation and volume of FMT. Serious adverse events were uncommon.

Although FMT has high success rates with long-term durability [292], few disadvantages still exist. In particular, the manipulation of feces and the classical enteral administration methods are not only laborious but tend to make the procedure rather unattractive for physicians and patients.

In the context of these disadvantages, few efforts have been made to enhance the feasibility and social acceptance of microbiota transplantation.

FMT may be administered via enemas or as a slurry given via a nasogastric tube.

One systematic review which compared various routes of administration included a total of 182 patients (148 received FMT via colonoscopy and 34 received FMT via nasogastric tube) from 12 published studies [293]. Recurrence of CDI after FMT was similar in both the colonoscopy group (8/148, 5.4%) versus the nasogastric tube group (2/34, 5.9%) ($p = 1.000$). However, the overall rate of cure after FMT was slightly higher in patients receiving FMT by colonoscopy: 85.3% (29 patients, 29/34) in the nasogastric tube group and 93.2% (138 patients, 138/148) in the colonoscopy group ($p = 0.162$).

A larger and more recent systematic review of 14 studies including 305 patients and comparing FMT delivery by upper and lower gastrointestinal routes also favored lower gastrointestinal delivery [294]. At 30 and 90 days, the risk of clinical failure was 5.6% and 17.9% in the upper gastrointestinal group compared with 4.9% and 8.5% in the lower GI delivery route group, respectively.

More recently, encapsulated preparations of FMT have been used with success. This strategy has the advantage of being less invasive and simpler, which may also result in improved cost-effectiveness [295–298].

In 2014, Youngster et al. [296] reported their experience with frozen FMT capsules in 20 patients who had RCDI. Fourteen patients (70%) had resolution of diarrhea after a single treatment, and 4 patients responded after a second treatment, with a clinical resolution rate of 90%.

Patients who are immunocompromised are at increased risk of CDI. During the last 2 years, the first data on FMT in immunocompromised patients began to appear in the medical literature [299].

A multicenter retrospective series on the use of FMT in immunocompromised patients with recurrent, refractory, or severe CDI was published in 2014 [300]. Immunosuppression included HIV/AIDS (3), solid organ transplantation (19), oncologic condition (7), immunosuppressive therapy for IBD (36), and other medical conditions/medications (15). This series demonstrated the effective use of FMT for CDI in immunocompromised patients with few serious adverse events.

With the increased awareness of the role of native gut microbiome and its role in the gut brain axis, there have been concerns about the long-term effect of transplanted stool, and how the new gut microbiome can affect brain function and immune responses.

Monoclonal antibodies

32. Coadjuvant treatment with monoclonal antibodies (bezlotoxumab) may prevent recurrences of CDI, particularly in patients with CDI due to the 027 epidemic strain, in immunocompromised patients and in patients with severe CDI (Recommendation 1 A).

Since the expression of clostridial toxins (TcdA and TcdB) is mandatory for the development of CDI, the

development of monoclonal antibodies aimed at preventing the cytotoxic effect of these toxins is a potential strategy for controlling the disease. In 2016, the FDA approved bezlotoxumab to reduce the recurrence of CDI in adult patients receiving antimicrobial therapy for CDI who are at high risk of CDI recurrence. Bezlotoxumab (MK-6072) is a human monoclonal antibody which reduces recurrent CDI by blocking the binding of *C. difficile* toxin B to host cells, thus limiting epithelial damage and facilitating recovery of the microbiome [301]. Besides bezlotoxumab, another human monoclonal antibody, actoxumab (MK-3415), was recently designed to neutralize *C. difficile* toxin.

The data from two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection showed that bezlotoxumab achieved a significant benefit over placebo in the treatment of recurrent CDI. Participants received an infusion of bezlotoxumab (10 mg/kg of body weight), actoxumab plus bezlotoxumab (10 mg/kg each), or placebo; actoxumab alone (10 mg/kg) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population [302].

In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, − 10.1 percentage points; 95% CI, − 15.9 to − 4.3; $p < 0.001$; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, − 9.9 percentage points; 95% CI, − 15.5 to − 4.3; $p < 0.001$) [303].

A post-hoc analysis of pooled monoclonal antibodies for *C. difficile* therapy (MODIFY) I/II data assessed bezlotoxumab efficacy in participants with risk factors for RCDI including age ≥ 65 years, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244 [304]. Although the patients with only one of the risk factors may benefit from bezlotoxumab, patients with at least three risk factors appeared to have the greatest risk reduction with bezlotoxumab.

Intravenous immunoglobulin

33. Intravenous immunoglobulin (IVIG) should only be used as adjunct therapy in patients with multiple recurrent or fulminant CDI until results from large, randomized controlled trials are available (Recommendation 2 C).

Novel treatment modalities for management of CDI have been developed. IVIG treatment is based on evidence that the level of immune response to *C. difficile* colonization is the major determinant of the magnitude and duration of clinical manifestations. Passive immunization with IVIG has been successful in several small series. A review by Abourgergi et al. [305] of 15 small, mostly retrospective and non-randomized studies, documented success with IVIG in the treatment of protracted, recurrent, or severe CDI. The authors concluded that IVIG should only be used as adjunct therapy until results from large, randomized controlled trials are available. Two small retrospective matched cohort studies were published that compared the clinical efficacy of the addition of IVIG to conventional CDI treatment [306, 307]. Neither of these studies found significant differences between the compared cohorts in the main clinical outcomes, although Shahani et al. [306] noted that in their IVIG cohort, there were significantly older patients with more severe CDI than in the control group. It is reasonable to utilize IVIG therapy in patients diagnosed with hypogammaglobuminemia based on the confirmation of IgG levels below the normal laboratory range.

Enteral nutrition in CDI

34. Tube feeding patients should be clinically assessed due to their risk for developing CDI (Recommendation 2 C).

It is widely accepted that enteral nutrition (EN) maintains gut mucosal integrity which leads to decreased intestinal permeability, decreased infections, and an improved immunological status. EN during episodes of diarrhea may be well tolerated and may improve enterocyte healing and maintenance of enzyme activity [308–310]. Enteral nutrition, however, has also been associated with increased risk of CDI [310]. Bliss et al. evaluated 76 tube-fed and non-tube-fed hospital patients for the development of CDI [311]. Patients were controlled for age, severity of illness, and duration of hospitalization. Patients who were tube-fed were statistically more likely to develop CDI (20% vs. 8% $p = 0.03$). One of the reasons may be prolonged use of elemental diets. It is known that critically ill patients tolerate feeding well if the feed is given in elemental form and delivered beyond the stomach into the jejunum because it is totally absorbed within the upper small intestine [312], depriving the colonic microbiota of their source of nutrition, such as dietary fibers, fructose oligosaccharides, and resistant starch [313]. The resultant suppression of colonic fermentation may therefore lead to the disruption of the normal gut flora and the creation of a "permissive" environment for *C. difficile* colonization and subsequent infection. In feeding tube patients, the conversion of elemental diet feeding to a diet containing adequate

indigestible carbohydrate after the first week of critical illness may, in theory, be beneficial.

Puri et al. [314] reported that daily concomitant treatment with 4 g cholestyramine in patients receiving long-term intravenous ceftriaxone (2 to 4 g ceftriaxone daily, for an average of > 10 weeks) was associated with CDI in only 3 out of 46 patients (6.5%) compared with 23.1% of those receiving ceftriaxone alone. Cholestyramine (or colestyramine) is a hydrophilic, water insoluble, non-digestible basic anion-exchange resin which can bind luminal TcdA and TcdB.

Anti-motility agents

35. The use of anti-peristaltic agents for the treatment of CDI should be discouraged. If anti-peristaltic agents are used to control persistent symptoms in patients with CDI, they must always be accompanied by medical therapy (Recommendation 2 C).

A review of the literature regarding anti-motility treatment of CDI found 55 patients with CDI who were exposed to anti-motility agents [315]. Nine patients (16%) died, and 27 patients (49%) had unknown outcomes. Seventeen patients (31%) with CDI developed colonic dilation; 5 of these patients with severe CDI died. However, all patients who experienced complications or died were given anti-motility agents alone initially, without an appropriate antibiotic and 23 patients who received metronidazole or vancomycin co-administered with the anti-motility agent experienced no complications. Further study of the role of anti-motility agents in providing symptomatic relief and reducing environmental contamination with infectious stool may be warranted though, until there is clear evidence of benefit, their use in patients with CDI should be avoided.

Conclusions

In the last three decades, the worldwide increase in CDI incidence has been particularly apparent among surgical patients, becoming a global public health challenge. Therefore, prompt and precise diagnosis is paramount for the effective management of CDI, allowing both the immediate implementation of infection prevention and control strategies, and the optimization of treatment in surgical patients, considering the most recent changes introduced in the management of this infection.

Abbreviations

CDI: *Clostridium difficile* infection; FC: Fulminant colitis; RCDI: Recurrent *Clostridium difficile* infection

Acknowledgements

Not applicable.

Funding

Not applicable.

Availability of data and materials

The authors are responsible for the data described in the manuscript and assure full availability of the study material upon request to the corresponding author.

Authors' contributions

MS wrote the first draft of the manuscript. All the authors reviewed the manuscript and approved the final draft.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Department of Surgery, Macerata Hospital, Via Santa Lucia 2, 62100 Macerata, Italy. [2]Infectious Diseases Department, Trieste University Hospital, Trieste, Italy. [3]Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, WA, USA. [4]Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN, USA. [5]Research School of Population Health, Australian National University, Acton, ACT, Australia. [6]Department of Microbiology, Faculty of Medical Laboratory Sciences, Omdurman Islamic University, Khartoum, Sudan. [7]Department of Surgery, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates. [8]Department of General Surgery, Bufalini Hospital, Cesena, Italy. [9]Department of Surgery, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia. [10]Trauma and Acute Care Surgery Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel. [11]Department of General Surgery, Rambam Health Care Campus, Haifa, Israel. [12]Trauma and Acute Care Surgery, Scripps Memorial Hospital La Jolla, La Jolla, CA, USA. [13]Pathology and Laboratory Medicine, VA Boston Healthcare System, West Roxbury MA and BU School of Medicine, Boston, MA, USA. [14]Department of Internal Medicine, University Hospital, Dr. José E. González, Monterrey, Mexico. [15]Department of Surgery, University of Santiago de Compostela, A Coruña, Spain. [16]Department of General Surgery, Medway Maritime Hospital, Gillingham, Kent, UK. [17]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, MI, USA. [18]Department of Surgery, West Virginia University Charleston Division, Charleston, WV, USA. [19]Faculty of Medicine, Transilvania University, Infectious Diseases Hospital, Brasov, Romania. [20]Riverside University Health System Medical Center and Loma Linda University School of Medicine, Moreno Valley, CA, USA. [21]Emergency Surgery Unit, San Filippo Neri's Hospital, Rome, Italy. [22]Department of Surgery, Tianjin Nankai Hospital, Nankai Clinical School of Medicine, Tianjin Medical University, Tianjin, China. [23]Department of Infectious Diseases, Jagiellonian University, Medical College, Kraków, Poland. [24]Department of Surgery, Tbilisi State Medical University, Kipshidze Central University Hospital, Tbilisi, Georgia. [25]Department of Surgical Sciences, Cannizzaro Hospital, University of Catania, Catania, Italy. [26]Department of Surgery, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. [27]Clinical Infectious Diseases Hospital, Ovidius University, Constanta, Romania. [28]Department of General, Visceral and Thoracic Surgery, Klinikum Peine, Hospital of Medical University Hannover, Peine, Germany. [29]Vital Care, Inc, Meridian, MS, USA. [30]Department of Surgery, Stanford University, Stanford, CA, USA. [31]Division of Trauma Surgery, Hospital de Clinicas, School of Medical Sciences, University of Campinas, Campinas, Brazil. [32]Service of Gastroenterology and Hepatology, Geneva University Hospital, Genève, Switzerland. [33]Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. [34]University of New Mexico School of Medicine, Albuquerque, NM, USA. [35]Critical Care Unit, Instituto de Investigación Biomédica de A Coruña

(INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), A Coruña, Spain. [36]Department of Surgery Mansoura, Faculty of Medicine, Mansoura University, Mansoura, Egypt. [37]Surgery Department, Hospital Universitario (HU) Terezinha de Jesus da Faculdade de Ciencias Medicas e da Saude de Juiz de Fora (SUPREMA), Hospital Universitario (HU) Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, Brazil. [38]Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK. [39]Unit of Endocrine, Head, and Neck Surgery and Unit of Surgical Infections Support, Department of General Surgery, Parc Taulí, Hospital Universitari, Sabadell, Spain. [40]Department of Medicine, Milton Keynes University Hospital NHS Foundation Trust, Milton Keynes, Buckinghamshire, UK. [41]Department of Surgery, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany. [42]Department of Surgery, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea. [43]Department of Gastroenterology, Queen Elizabeth Hospital, Birmingham, UK. [44]General Surgery Department, Magee Womens Hospital, UPMC, Pittsburgh, USA. [45]Department of Surgery, VA Boston Health Care System, Boston University and Harvard Medical School, Boston, MA, USA. [46]Global Alliance for Infections in Surgery, Porto, Portugal. [47]School of Medical Sciences, University Sains Malaysia, Kota Bharu, Kelantan, Malaysia. [48]Department of Pharmacy Practice, St Louis College of Pharmacy, St Louis, MO, USA. [49]Faculty of Mediine University of Belgrade Clinic for Surgery "Nikola Spasic", University Clinical Center "Zvezdara" Belgrade, Belgrade, Serbia. [50]Department of Surgery, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA. [51]Abdominal Center, Helsinki University Hospital Meilahti, Helsinki, Finland. [52]Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. [53]Department of Surgery, Universidad Nacional de Asuncion, Asuncion, Paraguay. [54]Department of Surgery, Post-Graduate Institute of Medical Sciences, Rohtak, India. [55]Department of Surgery, Washington University School of Medicine, Saint Louis, USA. [56]Department of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey. [57]Department of Surgery, University of Colorado, Denver Health Medical Center, Denver, CO, USA. [58]Department of Surgery, University of Florida, Gainesville, FL, USA. [59]Department of Surgery, Fundación Valle del Lili, Hospital Universitario del Valle, Universidad del Valle, Cali, Colombia. [60]Infectious Diseases Unit, Bolzano Central Hospital, Bolzano, Italy. [61]National Institute for Infectious Diseases - INMI - Lazzaro Spallanzani IRCCS, Rome, Italy. [62]Gastroenterology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. [63]Department of Surgery, Anadolu Medical Center, Kocaali, Turkey. [64]Department of Abdominal and General Surgery, General Hospital Jesenice, Jesenice, Slovenia. [65]Department of Surgery, Medical University of Plovdiv, Plovdiv, Bulgaria. [66]Division of Emergency Surgery, Department of Surgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. [67]Department of Surgery, Tan Tock Seng Hospital, Singapore, Singapore. [68]Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy. [69]Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France. [70]First Department of Surgery, Faculty of Medicine, Masaryk University Brno and University Hospital of St. Ann Brno, Brno, Czech Republic. [71]First Department of Surgery, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic. [72]Clinic of Infectious Diseases, St Orsola-Malpighi University Hospital, Bologna, Italy. [73]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [74]Emergency Surgery Department, Maggiore Parma Hospital, Parma, Italy.

Received: 28 January 2019 Accepted: 17 February 2019
Published online: 28 February 2019

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Circulation

ORIGINAL RESEARCH ARTICLE

Risk Categorization Using New American College of Cardiology/American Heart Association Guidelines for Cholesterol Management and Its Relation to Alirocumab Treatment Following Acute Coronary Syndromes

BACKGROUND: The 2018 US cholesterol management guidelines recommend additional lipid-lowering therapies for secondary prevention in patients with low-density lipoprotein cholesterol ≥70 mg/dL or non–high-density lipoprotein cholesterol ≥100 mg/dL despite maximum tolerated statin therapy. Such patients are considered at very high risk (VHR) based on a history of >1 major atherosclerotic cardiovascular disease (ASCVD) event or a single ASCVD event and multiple high-risk conditions. We investigated the association of US guideline-defined risk categories with the occurrence of ischemic events after acute coronary syndrome and reduction of those events by alirocumab, a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor.

METHODS: In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), patients with recent acute coronary syndrome and residual dyslipidemia despite optimal statin therapy were randomly assigned to alirocumab or placebo. The primary trial outcome (major adverse cardiovascular events, ie, coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina) was examined according to American College of Cardiology/American Heart Association risk category.

RESULTS: Of 18924 participants followed for a median of 2.8 years, 11935 (63.1%) were classified as VHR: 4450 (37.3%) had multiple prior ASCVD events and 7485 (62.7%) had 1 major ASCVD event and multiple high-risk conditions. Major adverse cardiovascular events occurred in 14.4% of placebo-treated patients at VHR versus 5.6% of those not at VHR. In the VHR category, major adverse cardiovascular events occurred in 20.4% with multiple prior ASCVD events versus 10.7% with 1 ASCVD event and multiple high-risk conditions. Alirocumab was associated with consistent relative risk reductions in both risk categories (hazard ratio=0.84 for VHR; hazard ratio=0.86 for not VHR; $P_{interaction}$=0.820) and by stratification within the VHR group (hazard ratio=0.86 for multiple prior ASCVD events; hazard ratio=0.82 for 1 major ASCVD event and multiple high-risk conditions; $P_{interaction}$=0.672). The absolute risk reduction for major adverse cardiovascular events with alirocumab was numerically greater (but not statistically different) in the VHR group versus those not at VHR (2.1% versus 0.8%; $P_{interaction}$=0.095) and among patients at VHR with multiple prior ASCVD events versus a single prior ASCVD event (2.4% versus 1.8%; $P_{interaction}$=0.661).

CONCLUSIONS: The US guideline criteria identify patients with recent acute coronary syndrome and dyslipidemia who are at VHR for recurrent ischemic events and who may derive a larger absolute benefit from treatment with alirocumab.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01663402.

Matthew T. Roe, MD, MHS
Qian H. Li, ScD
Deepak L. Bhatt, MD, MPH
Vera A. Bittner, MD, MSPH
Rafael Diaz, MD
Shaun G. Goodman, MD, MSc
Robert A. Harrington, MD
J. Wouter Jukema, MD, PhD
Patricio Lopez-Jaramillo, MD
Renato D. Lopes, MD, PhD
Michael J. Louie, MD, MPH, MSc
Patrick M. Moriarty, MD
Michael Szarek, PhD
Robert Vogel, MD
Harvey D. White, DSc
Andreas M. Zeiher, MD
Marie T. Baccara-Dinet, MD
Ph. Gabriel Steg, MD
Gregory G. Schwartz, MD, PhD
For the ODYSSEY OUTCOMES Investigators*

*The ODYSSEY OUTCOMES Committee members, investigators, and contributors are listed in the online-only Data Supplement.

Key Words: alirocumab ■ acute coronary syndrome ■ dyslipidemias ■ guideline

Sources of Funding, see page 1587

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- We evaluated the application of the 2018 American College of Cardiology/American Heart Association cholesterol management guideline recommendations for additional lipid-lowering therapies in patients with established atherosclerotic cardiovascular disease and residual dyslipidemia despite maximum tolerated statin therapy who were enrolled in the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab).
- Patients classified as very high risk, either because of a history of multiple atherosclerotic cardiovascular disease events or a single atherosclerotic cardiovascular disease event (trial-qualifying acute coronary syndrome) and multiple high-risk conditions, had more than double the risk of recurrent cardiovascular events as patients classified as not very high risk.
- The very-high-risk category also had a larger absolute benefit of alirocumab treatment.

What Are the Clinical Implications?

- Application of the new guideline recommendations for the risk stratification and use of additional lipid-lowering therapies in patients with established atherosclerotic cardiovascular disease clearly identifies patients at very high risk of recurrent cardiovascular events after an acute coronary syndrome, and who may derive substantial benefit from treatment with a proprotein convertase subtilisin/kexin type 9 inhibitor.

Secondary prevention treatment options for patients with established atherosclerotic cardiovascular disease (ASCVD) and elevated serum cholesterol values have evolved beyond statins since the publication of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines.[1] In the interim, large cardiovascular outcomes trials have evaluated nonstatin medications in patients with established ASCVD, including ezetimibe and inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9).[2–4] These trials demonstrated further reductions in the occurrence of major adverse cardiovascular events (MACE) when these therapies were added to statins.[2–4] Consequently, an update to the ACC/AHA cholesterol guidelines was published in 2018,[5] which specifically recommended shared decision making by clinicians and patients with established ASCVD to decide on the use of these nonstatin medications, informed by expected future risks of recurrent cardiovascular events. The guidelines categorize patients with established ASCVD as very high risk (VHR) or not VHR based on the presence of multiple prior ASCVD events or a single prior ASCVD event and multiple high-risk concomitant clinical conditions.

We evaluated the application of the 2018 ACC/AHA cholesterol guideline recommendations for patients with established ASCVD using data from the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab).[4] The trial compared alirocumab, a PCSK9 inhibitor, with placebo in patients on optimized statin therapy after a recent acute coronary syndrome (ACS). A high percentage of these patients had been treated with revascularization for the index ACS event, and they were well treated with other secondary prevention medications. Specifically, we analyzed the association of the VHR categorization with the occurrence of cardiovascular events and the influence of this categorization on the treatment effect of intensive low-density lipoprotein cholesterol (LDL-C) lowering with alirocumab.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Qualified researchers may also request access to study documents, including the clinical study report, study protocol with amendments, blank case report form, statistical analysis plan, and data set specifications.

Study Design and End Points

The design and primary findings from the ODYSSEY OUTCOMES trial have been published.[4,6] The trial was approved in each center by the responsible Institutional Review Board or Ethics Committee, and all patients provided written informed consent. A total of 18924 patients ≥40 years of age with a prior ACS hospitalization within 1 to 12 months on intensive or maximum tolerated statin therapy with residual dyslipidemia (LDL-C ≥70 mg/dL, non–high-density lipoprotein cholesterol ≥100 mg/dL, or apolipoprotein B ≥80 mg/dL) were randomly assigned to blinded treatment with alirocumab 75 mg every 2 weeks or placebo and followed for a median of 2.8 years. The dose of alirocumab was blindly adjusted during follow-up to target an on-treatment LDL-C level of 25 to 50 mg/dL.

The primary composite end point was MACE, comprising death attributable to coronary heart disease, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization.[6] All end points were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

Risk Categorization According to Guideline Recommendations

Patients were categorized as VHR with multiple major ASCVD events if they had at least 1 prior ASCVD event before the qualifying index ACS, including myocardial infarction,

ischemic stroke, or peripheral artery disease.[5] Patients who did not have multiple major ASCVD events could also be categorized as VHR based on the combination of 1 major ASCVD event (the qualifying index ACS for the trial) and at least 2 high-risk conditions (age ≥65 years, revascularization before the index ACS, diabetes mellitus, history of hypertension, baseline estimated glomerular filtration rate of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥100 mg/dL despite maximum tolerated statin therapy).[5] The presence of heterozygous familial hypercholesterolemia (another high-risk clinical condition specified in the guidelines) was not captured on the trial case report form. Analyses were performed by the categorization of VHR versus not VHR and then with further stratification of the patients at VHR according to the presence of multiple major ASCVD events versus 1 major ASCVD event with at least 2 high-risk clinical conditions.

Statistical Analysis

Summary statistics, such as mean values and proportions, were used to compare the baseline clinical characteristics of

Table 1. Baseline Clinical Characteristics by Very-High-Risk Categorization and by Substratification of Very-High-Risk Patients

Variable	All Patients		Non-VHR		VHR*		VHR* (Multiple Prior Major ASCVD Events)		VHR* (1 Major Prior ASCVD Event + Multiple High-Risk Conditions)	
	Placebo (n=9462)	Alirocumab (n=9462)	Placebo (n=3525)	Alirocumab (n=3464)	Placebo (n=5937)	Alirocumab (n=5998)	Placebo (n=2241)	Alirocumab (n=2209)	Placebo (n=3696)	Alirocumab (n=3789)
Demographics										
Age, y	58.6±9.4	58.5±9.3	54.7±7.6	54.6±7.5	61.0±9.6	60.8±9.5	60.2±9.5	60.6±9.2	61.4±9.6	60.9±9.6
Male sex	7090 (74.9)	7072 (74.7)	2876 (81.6)	2808 (81.1)	4214 (71.0)	4264 (71.1)	1749 (78.0)	1677 (75.9)	2465 (66.7)	2587 (68.3)
Cardiovascular risk factors										
Smoking status										
Current	2278 (24.1)	2282 (24.1)	576 (16.3)	548 (15.8)	1702 (28.7)	1734 (28.9)	544 (24.3)	521 (23.6)	1158 (31.3)	1213 (32.0)
Former or never	7183 (75.9)	7180 (75.9)	2948 (83.6)	2916 (84.2)	4235 (71.3)	4264 (71.1)	1697 (75.7)	1688 (76.4)	2538 (68.7)	2576 (68.0)
Hypertension	6044 (63.9)	6205 (65.6)	1079 (30.6)	1099 (31.7)	4965 (83.6)	5106 (85.1)	1766 (78.8)	1801 (81.5)	3199 (86.6)	3305 (87.2)
Diabetes mellitus	2751 (29.1)	2693 (28.5)	255 (7.2)	242 (7.0)	2496 (42.0)	2451 (40.9)	852 (38.0)	776 (35.1)	1644 (44.5)	1675 (44.2)
Prior medical history										
Peripheral artery disease	386 (4.1)	373 (3.9)	0	0	386 (6.5)	373 (6.2)	386 (17.2)	373 (16.9)	0	0
Congestive heart failure	1449 (15.3)	1365 (14.4)	79 (2.2)	62 (1.8)	1370 (23.1)	1303 (21.7)	596 (26.6)	545 (24.7)	774 (20.9)	758 (20.0)
Myocardial infarction	1843 (19.5)	1790 (18.9)	0	0	1843 (31.0)	1790 (29.8)	1843 (82.2)	1790 (81.0)	0	0
PCI	1615 (17.1)	1626 (17.2)	26 (0.7)	20 (0.6)	1589 (26.8)	1606 (26.8)	1262 (56.3)	1244 (56.3)	327 (8.8)	362 (9.6)
CABG	526 (5.6)	521 (5.5)	4 (0.1)	6 (0.2)	522 (8.8)	515 (8.6)	402 (17.9)	374 (16.9)	120 (3.2)	141 (3.7)
Ischemic stroke	256 (2.7)	268 (2.8)	0	0	256 (4.3)	268 (4.5)	256 (11.4)	268 (12.1)	0	0
Laboratory values										
eGFR, mL/min	79.8±19.1	79.5±19.4	84.9±16.0	84.5±16.0	76.8±20.2	76.6±20.5	77.2±20.1	76.3±19.8	76.6±20.2	76.7±21.0
LDL-C, mg/dL	92.3±30.8	92.4±31.1	89.8±28.6	89.8±27.5	93.8±31.9	94.0±32.9	96.1±32.7	98.1±35.6	92.4±31.4	91.5±31.0
Non–HDL-C, mg/dL	122±35.5	122±35.0	118±32.9	118±31.4	125±36.7	125±36.7	128±38.0	130±39.6	123±35.8	122±34.7
HDL-C, mg/dL	44.2±11.4	44.4±11.3	44.2±11.2	44.6±11.2	44.1±11.5	44.2±11.4	43.6±11.2	44.2±11.4	44.5±11.7	44.3±11.4
Triglycerides, mg/dL, median (quartile 1, quartile 3)	129 (94.7,183)	129 (93.8, 181)	121 (89.4, 172)	122 (88.5, 169)	135 (97.0, 188)	135 (97.0, 188)	136 (98.0, 193)	136 (97.3, 189)	133 (96.5, 186)	133 (97.0, 187)
Apolipoprotein B, mg/dL	83.3±21.6	83.0±21.3	80.6±20.1	80.2±19.1	84.9±22.3	84.6±22.3	86.6±22.4	87.6±23.7	83.8±22.1	82.9±21.3

Data presented as n (%) or mean±SD unless otherwise indicated.

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; and VHR, very high risk.

*Patients were categorized as very-high-risk with (a) multiple major ASCVD events if they had ≥1 prior ischemic event before the qualifying index ACS event, including myocardial infarction, ischemic stroke, or peripheral artery disease; or (b) 1 major ASCVD event (the qualifying index ACS event) and ≥2 high-risk conditions (age ≥65 years, revascularization before the index ACS event, diabetes mellitus, history of hypertension, baseline eGFR of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe).[5]

patients among the categorized subgroups by risk status. The background frequencies in incidence rates of MACE and its components, also cardiovascular and all-cause death, among the categorized subgroups by risk status were compared only among patients receiving placebo to limit confounding by randomized treatment. The association of baseline LDL-C values and the absolute risk increase in MACE and death among the categorized subgroups by risk status was evaluated by using generalized linear regression models by treatment groups separately. Kaplan-Meier curves for survival probability over time were plotted by treatment groups and by risk status. Both relative risk reductions (RRRs) and absolute risk reductions (ARRs) by treatment assignment were calculated to evaluate the alirocumab treatment effect by subgroup interaction. The estimates and tests for hazard ratios (HRs) between treatment groups and treatment by risk status interaction used proportional hazard models for RRRs and the Gail-Simon method for ARRs.[7] Marginal Cox regression models were used to estimate treatment HRs and testing of treatment by risk status interaction for total (ie, first and potentially subsequent) nonfatal MACE and all-cause death events. Nonparametric mean cumulative function curves were created for total events, representing the expected (ie, mean) cumulative number of events per 100 patients at a given point in time after randomization. The SAS 9.4 analytic software package was used to perform the statistical analyses.

Table 2. Frequency of Ischemic Events Among Placebo-Treated Patients by Very-High-Risk Categorization and by Substratification of Very-High-Risk Patients

End Point	All Patients	Non-VHR	VHR	VHR* (Multiple Prior Major ASCVD Events)	VHR* (1 Major Prior ASCVD Event + Multiple High-Risk Conditions)
MACE					
Events	1052	198	854	458	396
Patient-years	25271	9699	15571	5720	9851
Incidence rate, /100 patient-years	4.16	2.04	5.48	8.01	4.02
Myocardial infarction					
Events	756	150	606	349	257
Patient-years	25530	9754	15776	5820	9955
Incidence rate, /100 patient-years	2.96	1.54	3.84	6.00	2.58
Stroke					
Events	152	13	139	68	71
Patient-years	26501	9974	16526	6250	10277
Incidence rate, /100 patient-years	0.57	0.13	0.84	1.09	0.69
CHD death					
Events	222	31	191	105	86
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	0.82	0.31	1.13	1.64	0.82
Unstable angina requiring hospitalization					
Events	60	15	45	25	20
Patient-years	26601	9969	16632	6302	10330
Incidence rate, /100 patient-years	0.23	0.15	0.27	0.40	0.19
Cardiovascular death					
Events	271	33	238	127	111
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	1.01	0.33	1.41	1.99	1.06
All-cause death					
Events	392	56	336	169	167
Patient-years	26915	10074	16842	6396	10446
Incidence rate, /100 patient-years	1.46	0.56	2.00	2.64	1.60

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; and VHR, very high risk.

*Patients were categorized as very high risk with (a) multiple major ASCVD events if they had ≥1 prior ischemic event before the qualifying index ACS event, including myocardial infarction, ischemic stroke, or peripheral artery disease; or (b) 1 major ASCVD event (the qualifying index ACS event) and ≥2 high-risk conditions (age ≥65 years, revascularization before the index ACS event, diabetes mellitus, history of hypertension, baseline eGFR of 15–59 mL·min^{-1}·1.73 m^{-2}, current smoking, history of heart failure, or LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe).[5]

RESULTS

A total of 18 924 patients were randomly assigned at 1315 sites in 57 countries, with 9462 patients randomly assigned to alirocumab and 9462 patients to placebo. Median (quartile 1, quartile 3) follow-up was 2.8 (2.3, 3.4) years. Among the overall population, 11 935 patients (63.1%) were categorized as VHR, with 4450 of these (37.3%) having multiple major ASCVD events and 7485 (62.7%) having 1 major ASCVD event (index ACS event) and at least 2 high-risk clinical conditions. Among the 7485 patients classified as at VHR because of 1 major ASCVD event and at least 2 high-risk clinical conditions, 2568 (41.2%) qualified because of the presence of age ≥65 years and hypertension, 1045 (14.0%) qualified because of age ≥65 years and diabetes mellitus, and 403 (5.4%) qualified because of age ≥65 years and current smoking (the 3 qualification categories may not be mutually exclusive). In comparison with patients categorized as not VHR, patients at VHR were older, more commonly female, and more likely to have cardiovascular risk factors and prior cardiovascular events and procedures, and, in general, they had higher baseline lipid values (Table 1). Comparing patients in the VHR group with multiple major ASCVD events to those with a single ASCVD event and multiple risk factors, the former were more frequently male and had fewer cardiovascular risk factors.

Among patients in the placebo group, the rates of all events were substantially higher in the patients at VHR than in those categorized as not VHR (Table 2). When placebo-treated, patients at VHR were further stratified by the presence of multiple major ASCVD events or 1 major ASCVD event and multiple risk factors; the frequencies of ischemic end points were higher among those with multiple major ASCVD events.

Treatment with alirocumab was associated with similar reductions in LDL-C levels among patients categorized as VHR or not VHR (Figure 1A), and also among the patients at VHR further stratified by the presence of multiple major ASCVD events or 1 major ASCVD event and multiple risk factors (Figure 1B).

The Kaplan-Meier curves depicting the longitudinal occurrence of MACE events over time demonstrate a substantially higher risk of events among those categorized as VHR in comparison with those categorized as not VHR, with an earlier and more sustained separation of the event curves by alirocumab versus placebo treatment among the patients at VHR (Figure 2A). Similarly, the risk of death was greater among patients categorized as VHR, with a separation of the event curves by alirocumab versus placebo treatment observed only in the VHR group (Figure 2B).

The HR for MACE observed with alirocumab treatment was similar in the VHR (HR, 0.84; 95% CI, 0.76–0.93) and not VHR (HR, 0.86; 95% CI, 0.70–1.06; $P_{interaction}$=0.820) categories and was also similar among the patients at VHR further stratified by the presence of multiple major ASCVD events (HR, 0.86; 95% CI, 0.75–0.98) or 1 major ASCVD event and multiple risk factors (HR, 0.82; 95% CI, 0.71–0.95; $P_{interaction}$=0.672) (Figure 3A). A greater ARR in MACE was observed with alirocumab among those categorized as VHR (ARR, 2.13%; 95% CI, 0.91–3.35) versus those not at VHR (ARR, 0.77%; 95% CI, –0.28 to 1.81), but it was not statistically different ($P_{interaction}$=0.095). The ARR for alirocumab treatment was similar among the patients at VHR with multiple major ASCVD events (ARR, 2.42%; 95% CI, 0.11–4.73) or with 1 major ASCVD event and multiple risk factors (ARR, 1.82%; 95% CI, 0.47–3.17; $P_{interaction}$=0.661) (Figure 3A). Similar findings were observed with alirocumab treatment for all-cause death (Figure 3B).

An exploratory analysis that stratified patients as VHR by the presence of baseline (prerandomization) LDL-C levels ≥100 mg/dL demonstrated higher MACE and death rates among those with baseline LDL-C levels above this threshold and significantly greater RRRs and ARRs for both MACE and all-cause death with alirocumab treatment (Figure 3A and 3B). Nonsignificant but numerically greater RRR and ARR results were observed with alirocumab treatment in the patients not at VHR among those with baseline LDL-C levels ≥100 mg/dL.

The treatment effect of alirocumab according to risk status was further investigated by total nonfatal MACE events and all-cause death (Figure 4A). The RRR was identical irrespective of risk status (HRs 0.84 for both VHR and not VHR; $P_{interaction}$=0.98). However, the accrual of events was markedly higher among patients classified as VHR, with greater ARR by alirocumab, with nearly 5 events avoided over 4 years per 100 patients in the VHR subgroup in comparison with 1.6 events avoided over 4 years per 100 patients in the not VHR patient subgroup (Figure 4B).

DISCUSSION

Approximately two-thirds of patients with recent ACS and residual dyslipidemia despite optimal statin therapy who were enrolled in a contemporary cardiovascular outcomes trial were categorized as VHR for future ASCVD events based on recently published updates to the ACC/AHA cholesterol treatment guidelines.[5] The guideline-defined risk categories correlated well with the observed risk in this post-ACS population. Moreover, we observed that in the VHR category, patients with multiple major ASCVD events had an even greater risk of MACE and all-cause death during longitudinal follow-up than patients who had only 1 prior major ASCVD event (the qualifying index ACS event) with at least 2 high-risk clinical conditions. Although alirocumab was

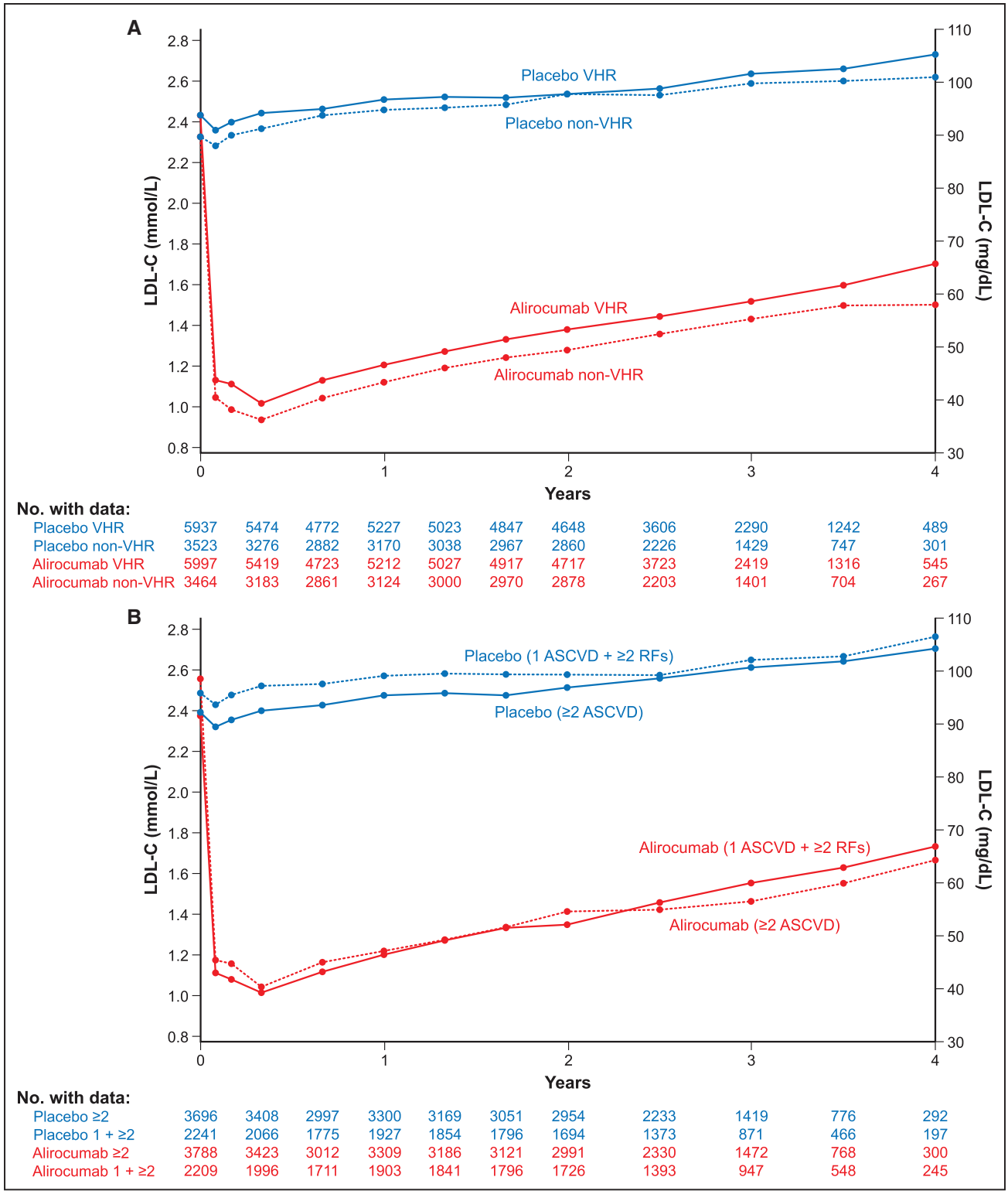

Figure 1. Impact of alirocumab treatment on temporal changes in achieved LDL-C values.
Very high-risk categorization (**A**) and substratification of very high-risk patients (**B**). ASCVD indicates major atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; and VHR, very high risk.

associated with consistent LDL-C lowering and relative reductions in the risk of MACE and all-cause death across guideline-defined risk categories, we observed a numerically greater, but not statistically different, ARR for time to first event with alirocumab in patients categorized as VHR in comparison with those categorized as not at VHR. These findings were further informed by a total events analysis that demonstrated a larger

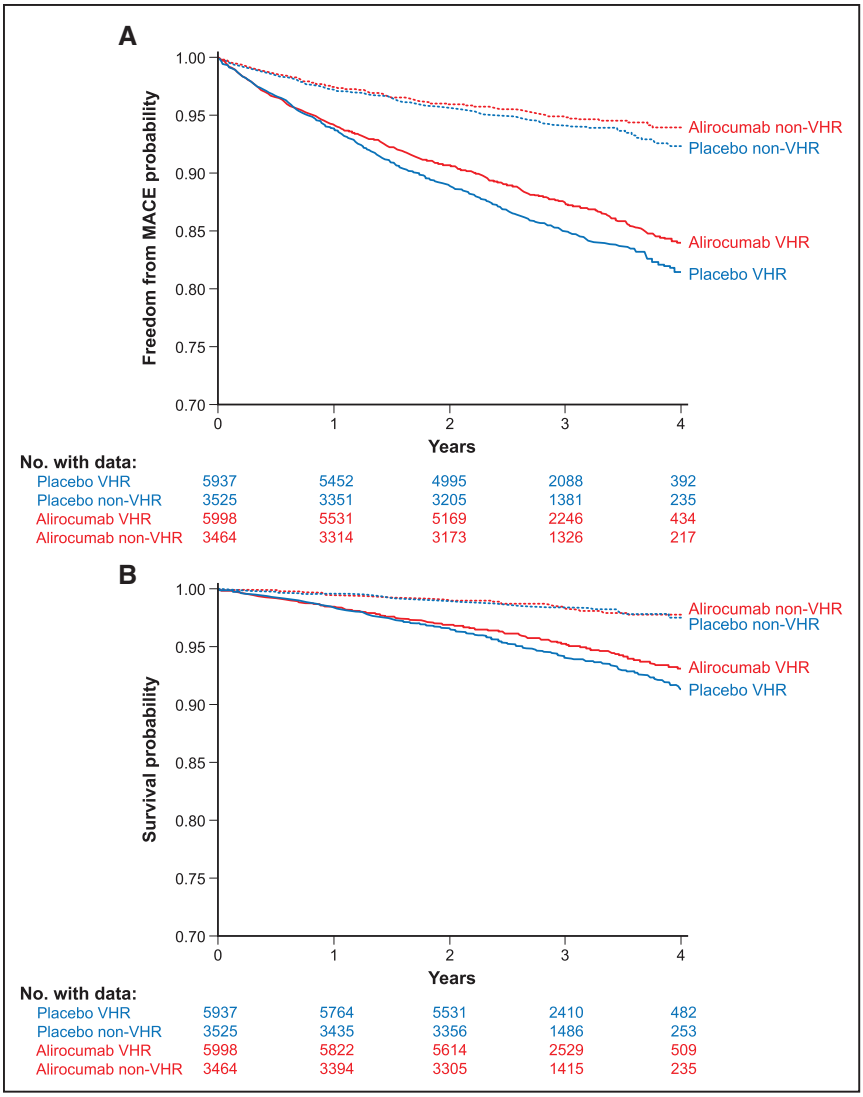

Figure 2. Occurrence of recurrent ischemic events by alirocumab treatment by very-high-risk categorization and by substratification of very-high-risk patients.
The frequency of MACE (**A**) and all-cause death (**B**). MACE indicates major adverse cardiovascular event; and VHR, very high risk.

number of events avoided over 4 years with alirocumab in the VHR versus not VHR subgroups. Furthermore, within the VHR category, we observed similar ARRs for time to first event with alirocumab among those who had multiple major ASCVD events and those who had only 1 prior major ASCVD event and multiple risk factors. In summary, these findings provide support for the application of the updated ACC/AHA cholesterol treatment guidelines[5] to select the highest-risk patients for treatment with additional LDL-C–lowering therapies (beyond statins) in the post-ACS setting.

Contemporary trials that evaluated further LDL-C lowering with ezetimibe or PCSK9 inhibitors, in addition to statin therapy, focused on patients with established ASCVD confirmed by a prior ischemic event.[2–4] Within this context, secondary analyses from these trials have shown that multiple high-risk subgroups derive enhanced benefit from additional LDL-C lowering, including those with peripheral artery disease, diabetes mellitus, multivessel coronary disease with prior coronary artery bypass surgery, and multiple prior myocardial infarction events.[8–13] Our findings provide further confirmation of the incremental benefit of additional LDL-C lowering for patients with established ASCVD (leveraging both time to first event and total events analyses) using a comprehensive, integrated risk-stratification approach recommended by recently updated cholesterol guidelines in comparison with binary attributions of risk based on the presence or absence of a single high-risk clinical characteristic.[5] Thus, the present data indicate the utility of the ACC/AHA cholesterol treatment guidelines[5] risk categories to inform decisions on the selection of patients with established ASCVD for PCSK9 inhibitor therapy to achieve the greatest benefits of intensive LDL-C–lowering therapies.

In the post-ACS setting, the risk of recurrent ischemic events is greatest in the first 3 to 6 months following the index ACS event, so the timing and sequencing of additional LDL-C–lowering therapies may need to be more front-loaded to have the greatest treatment benefit and impact. Treatment with high-intensity statin therapy starting at the time of ACS has been shown to be superior to placebo and to moderate-intensity statin

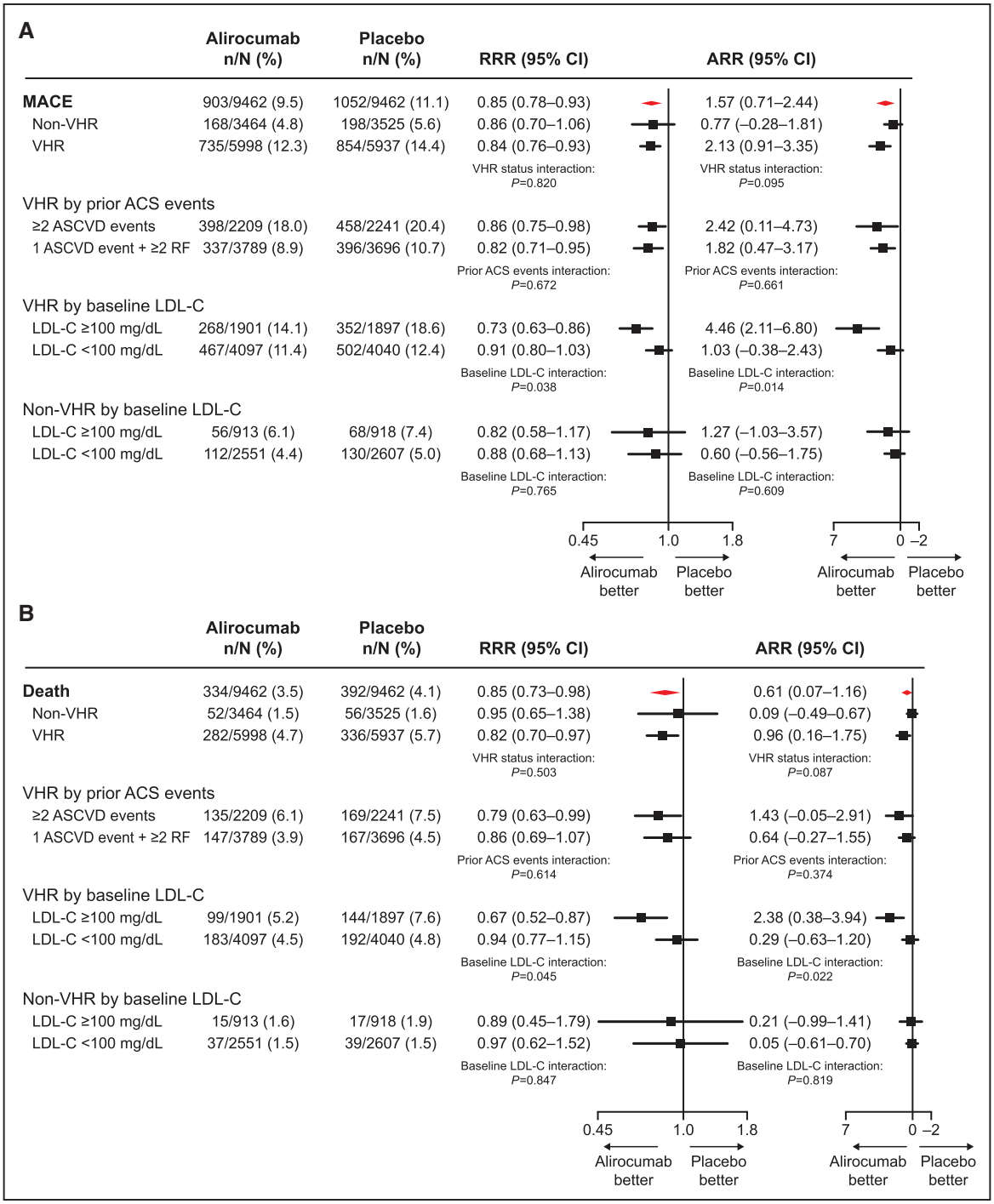

Figure 3. Risk reductions associated by treatment, and very-high-risk categorization, substratification of very-high-risk patients, and baseline LDL-C for very-high-risk and non–very-high-risk patients.

MACE (**A**) and all-cause death (**B**). An LDL-C value of 100 mg/dL equates to 2.6 mmol/L. ACS indicates acute coronary syndrome; ARR, absolute risk reduction; ASCVD, major atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; RF, risk factor; RRR, relative risk reduction; and VHR, very high risk.

therapy for reducing the early risk of recurrent ischemic events and correlated with greater relative reductions in LDL-C values in the MIRACL trial (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) and PROVE IT–TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22), respectively.[14,15] Further LDL-C lowering with ezetimibe, added to statin therapy, started within 10 days of an ACS event, is associated with a modest reduction in LDL-C values and recurrent ischemic events, but the benefits observed were apparent only after 1 year of treatment exposure.[2] Similar findings were observed in the ODYSSEY OUTCOMES trial with alirocumab, in which treatment was initiated at a

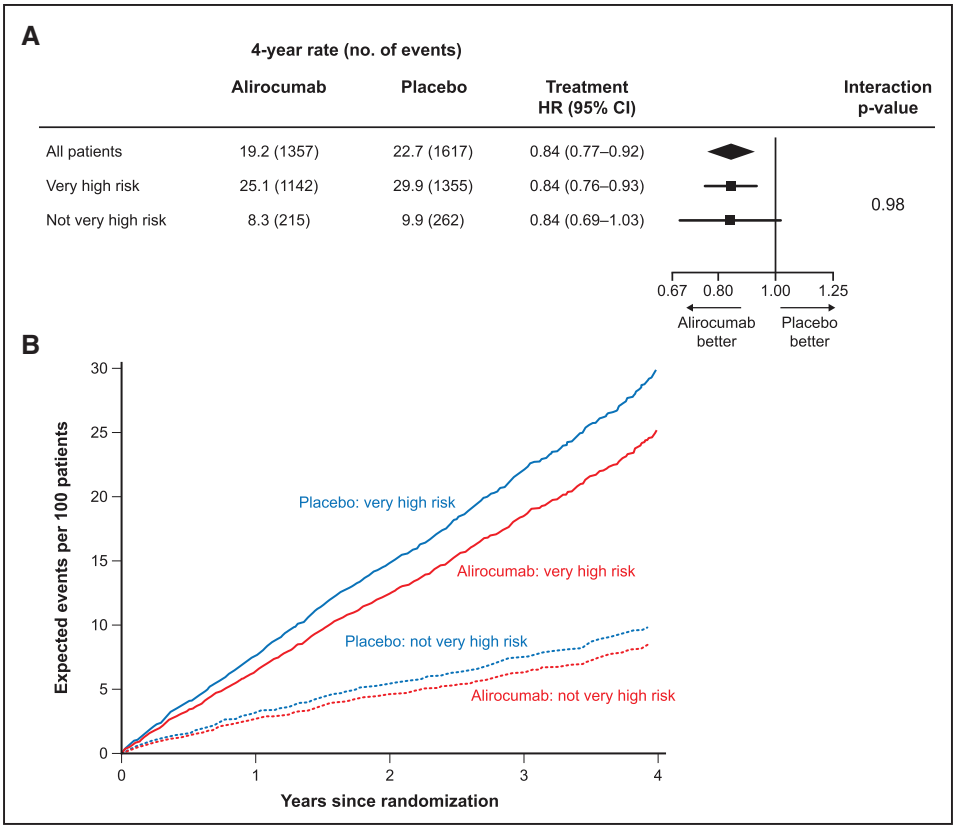

Figure 4. Total nonfatal MACE events and death by very high-risk categorization and treatment assignment to 4 years.
A, Treatment group rates represent the expected number of events per 100 patients for total nonfatal MACE and all-cause death events based on mean cumulative function estimates at 4 years; the total number of events observed are in parentheses. Treatment HRs and associated CIs and high-risk categorization by treatment assignment interaction *P* value are from marginal Cox regression models. **B**, Accrual of events per 100 patients. The expected number of nonfatal MACE and all-cause death events per 100 patients in the placebo and alirocumab groups at 4 years were 29.9 and 25.1, respectively, for patients classified as very high risk and 9.9 and 8.3, respectively, for patients classified as not very high risk. HR indicates hazard ratio; and MACE, major adverse cardiovascular event.

median of 2.6 months after the index ACS event and a separation of event curves became apparent at ≈1 year.[4] In this context, when considering additional LDL-C–lowering therapies for patients at VHR with ASCVD, the 2018 ACC/AHA cholesterol treatment guidelines recommend starting with high-intensity statin therapy, then adding ezetimibe if LDL-C values remain ≥70 mg/dL, and finally adding a PCSK9 inhibitor if LDL-C values continue to remain ≥70 mg/dL.[5] No clinical trial has investigated such a sequential approach to the addition of lipid-lowering therapies to intensive statin treatment. Nonetheless, LDL-C reduction with ezetimibe reaches a steady state ≈2 weeks after commencing treatment,[16] allowing assessment of the need for further addition of a PCSK9 inhibitor within a relatively short period of time, perhaps as early as 4 weeks after commencing treatment, and in line with the recommended time window of 4 to 12 weeks for repeat LDL-C measurement in the 2018 guidelines.[5] In this regard, the new ACC/AHA guidelines[5] are logical and pragmatic.

The ODYSSEY OUTCOMES trial showed that patients with ACS and LDL-C ≥100 mg/dL despite high-intensity statin therapy derived a greater absolute treatment benefit with alirocumab than those with LDL-C in the 70 to 100 mg/dL range.[4,17] In the present analysis, we demonstrate that, among patients with recent ACS classified as VHR according to ACC/AHA criteria, the benefit of alirocumab treatment was particularly pronounced among those statin-treated patients with LDL-C ≥100 mg/dL. Therefore, the presence of residual elevated LDL-C levels ≥100 mg/dL despite optimal statin therapy may be an important criterion to select those patients at VHR who will derive substantial benefit from the addition of a PCSK9 inhibitor.[5,18]

Limitations

Limitations of this analysis include insufficient data elements to identify patients in the ODYSSEY OUTCOMES trial with heterozygous familial hypercholesterolemia, which is 1 of the designated criteria for VHR. Second, the current analysis applies guideline categories only to patients with recent ACS, and not to the broader population of patients with chronic ASCVD. Third, the analysis of treatment benefit in patients at VHR according to baseline LDL-C should be considered in the context of trial design. The ODYSSEY OUTCOMES protocol specified blinded substitution of placebo for alirocumab in

patients with persistent on-treatment LDL-C levels <15 mg/dL. As attainment of LDL-C <15 mg/dL on alirocumab was infrequent among patients with baseline LDL-C levels >100 mg/dL, that subgroup was more likely to have persistent alirocumab treatment than those with baseline LDL-C levels <100 mg/dL. Finally, the present results should be considered hypothesis-generating because the analyses were not prespecified, but rather were conducted in an ad hoc manner in response to publication of the 2018 cholesterol guidelines update[5] in November 2018 (after conclusion of the trial earlier in 2018). Future studies may prespecify analyses of data according to guideline criteria for risk categories. In addition, meta-analyses of patient-level data from existing PCSK9 inhibitor trials may help to generalize the observations from the present analysis, which are limited to patients with recent ACS.

CONCLUSIONS

New recommendations for the risk stratification of patients with established ASCVD from the 2018 ACC/AHA cholesterol guidelines[5] for the selection of LDL-C–lowering therapies appear to identify patients with recent ACS and dyslipidemia who are at VHR for recurrent cardiovascular events and who may have an accentuated benefit from alirocumab treatment. Within this context, prospective evaluation of decision-support tools based on these guidelines will be helpful to determine the optimal approaches for improving the cholesterol management of patients in the post-ACS setting.

ARTICLE INFORMATION

Received July 2, 2019; accepted August 1, 2019.

Guest Editor for this article was Christie M. Ballantyne, MD.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.119.042551.

Correspondence

Matthew T. Roe, MD, MHS, 200 Morris St, Rm 7410, Durham, NC 27701. Email matthew.roe@duke.edu

Affiliations

Duke Clinical Research Institute, Durham, NC (M.T.R., R.D.L.). Regeneron Pharmaceuticals, Tarrytown, NY (Q.H.L., M.J.L.). Brigham and Women's Hospital, Boston, MA (D.L.B.). University of Alabama at Birmingham (V.A.B.). Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Argentina (R.D.). St Michael's Hospital, Toronto, Canada (S.G.G.). Stanford University Medical Center, CA (R.A.H.). Leiden University Medical Center, the Netherlands (J.W.J.). Fundación Oftalmológica de Santander (FOSCAL), Medical School (UDES), Floridablanca, Colombia (P.L.-J.). University of Kansas Medical Center, Kansas City, MO (P.M.M.). State University of New York (SUNY) Downstate Medical Center, Downstate School of Public Health, Brooklyn (M.S.). University of Colorado, Aurora (R.V., G.G.S.). Green Lane Cardiovascular Services, Auckland City Hospital, New Zealand (H.D.W.). Department of Medicine III, Goethe University, Frankfurt am Main, Germany (A.M.Z.). Sanofi, Montpellier, France (M.T.B.-D.). Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Université de Paris, FACT (French Alliance for Cardiovascular Trials), Institut National de la Santé et de la Recherche Médicale (INSERM) U1148, France (P.G.S.). National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London, UK (P.G.S.).

Acknowledgments

We thank the patients, study coordinators, and investigators who participated in this trial. S. K. Rushton-Smith and J. Lloyd (MedLink Healthcare Communications, London, UK) provided editorial assistance in the preparation of the article (limited to formatting, editing for style, referencing, and figure and table editing and submission) and were funded by Fondation Assistance Publique–Hôpitaux de Paris, Paris, France.

Sources of Funding

This work was supported by Sanofi and Regeneron Pharmaceuticals.

Disclosures

Dr Roe reports research grant funding from Sanofi-Aventis, Janssen Pharmaceuticals, AstraZeneca, Patient Centered Outcomes Research Institute, Ferring Pharmaceuticals, Myokardia, American College of Cardiology, American Heart Association, Familial Hypercholesterolemia Foundation; consulting or honoraria from AstraZeneca, Amgen, Eli Lilly, Roche-Genentech, Janssen Pharmaceuticals, Regeneron, Ardea Biosciences, Novo Nordisk, Flatiron, Merck, Pfizer, Sanofi-Aventis, Signal Path, and Elsevier Publishers. All conflicts of interest are listed at https://www.dcri.org/about-us/conflict-of-interest. Dr Li is an employee of and stockholder in Regeneron Pharmaceuticals. Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO IDE trial (Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial), funded by St Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial [CENTERA THV System in Intermediate Risk Patients Who Have Symptomatic, Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement], funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE-TAVI AF trial [Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation], funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; REDUAL-PCI clinical trial (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) steering committee funded by Boehringer Ingelheim; AEGIS-II trial (Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome) executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS trial [Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease] operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi-Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Biotronik, Boston Scientific, St Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda. Dr Bittner reports research grants from Amgen, DalCor, Esperion, Sanofi, AstraZeneca, Bayer Healthcare, and The Medicines Company; honoraria from the American College of Cardiology, American Heart Association, and National Lipid Association; and serving as a consultant and on an advisory board for Sanofi. Dr Diaz reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center and Lepetit and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius. Dr Goodman reports research grants from Daiichi-Sankyo, Luitpold Pharmaceuticals, Merck, Novartis, Servier, Regeneron Pharmaceuticals,

Sanofi, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Eli Lilly, Pfizer, and Tenax Therapeutics; honoraria from Bristol-Myers Squibb, Eli Lilly, Esperion, Fenix Group International, Ferring Pharmaceuticals, Merck, Novartis, Pfizer, Servier, Regeneron Pharmaceuticals, Sanofi, Amgen, AstraZeneca, Bayer, and Boehringer Ingelheim; and serving as a consultant or on advisory boards or both for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, HLS Therapeutics, Pfizer, Servier, Tenax Therapeutics, Sanofi, Amgen, and Bayer. Dr Harrington reports research grants (all Data and Safety Monitoring Board–related) from AstraZeneca, Janssen, and Bristol-Myers Squibb, serving on advisory boards for Gilead (uncompensated) and WebMD; and serving on the boards of directors (unpaid) for the American Heart Association and Stanford HealthCare. Dr Jukema reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. Dr Lopez-Jaramillo reports honoraria for speaking from Sanofi, Merck, Boehringer Ingelheim, Menarini, Amgen, and Servier. Dr Lopes has received research grants from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, and Sanofi-Aventis; and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, and Portola. Dr Louie is an employee of and holds shares in Regeneron Pharmaceuticals. Dr Moriarty reports speaker fees from Academic CME, Amarin, Ambry Genetics, National Lipid Association; research grants from Akcea, Familial Hypercholesterolemia Foundation, GB Life Sciences (genetic testing kits), Ionis, Kowa, Novartis, RegenXBio, Stage 2 Innovations/Renew; research grants and consultant fees from Amgen, Kaneka, Regeneron Pharmaceuticals, RegenXBio; consulting fees from Esperion, Lilly, Sanofi, and Stage II Innovations/Renew; and advisory fees from BioPharma. Dr Szarek reports serving as a consultant or on advisory boards or both for CiVi, Resverlogix, Baxter, Esperion, and Regeneron Pharmaceuticals. Dr Vogel reports research grants and speaker fees from Sanofi and Regeneron Pharmaceuticals. Dr White reports receiving grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals, for the SPIRE trial (The Evaluation of Bococizumab [PF-04950615; RN 316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) from Pfizer USA, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent; for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc, for the dal-GenE study (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc, for the AEGIS-II study from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc. He was on the Advisory Board for Acetelion and Sirtex and received lecture fees from AstraZeneca. Dr Zeiher reports receiving fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi, and advisory board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. Dr Baccara-Dinet is an employee of and holds shares in Sanofi. Dr Steg reports grants and nonfinancial support (cochair of the ODYSSEY OUTCOMES trial; as such he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for some travel related to trial meetings) from Sanofi; research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (cochair of the ODYSSEY OUTCOMES trial; cochair of the SCORED trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial]; consulting); and personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca. Dr Steg also has a European application number/patent number, issued on October 26, 2016 (No. 15712241.7), for a method for reducing cardiovascular risk. Dr Schwartz reports research grants to the University of Colorado from Resverlogix, Sanofi, The Medicines Company, and Roche; and is coinventor of pending US patent 14/657192 ("Methods of Reducing Cardiovascular Risk") assigned in full to the University of Colorado.

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Neurología. 2019;34(6):408—417

NEUROLOGÍA

www.elsevier.es/neurologia

CONSENSUS STATEMENT

Evidence and experience with onabotulinumtoxinA in chronic migraine: Recommendations for daily clinical practice☆

A.B. Gago-Veiga[a], S. Santos-Lasaosa[b], M.L. Cuadrado[c,d], Á.L. Guerrero[e], P. Irimia[f], J.M. Láinez[g], R. Leira[h], J. Pascual[i], M. Sanchez del Río[j], J. Viguera[k], P. Pozo-Rosich[k,l,*]

[a] *Unidad de Cefaleas, Servicio de Neurología, Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain*
[b] *Unidad de Cefalea, Servicio de Neurología, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain*
[c] *Unidad de Cefaleas, Servicio de Neurología, Hospital Clínico San Carlos, Madrid, Spain*
[d] *Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain*
[e] *Unidad de Cefaleas, Servicio de Neurología, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*
[f] *Departamento de Neurología, Clínica Universidad de*
[g] *Servicio de Neurología, Hospital Clínico Universitario, Departamento de Neurología, Universidad Católica de Valencia, Valencia, Spain*
[h] *Servicio de Neurología, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain*
[i] *Hospital Universitario Marqués de Valdecilla e IDIVAL, Santander10, Programa de Cefaleas, Servicio de Neurología, Hospital Ruber Internacional, Madrid, Spain*
[j] *Consulta de Cefalea, Servicio de Neurología, Unidad de Gestión Clínica de Neurociencias, Hospital Universitario Virgen Macarena, Sevilla, Spain*
[k] *Unidad de Cefalea, Servicio de Neurología, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[l] *Grupo de Investigación en Cefalea; VHIR; Universitat Autònoma de Barcelona, Barcelona, Spain*

Received 31 August 2017; accepted 7 September 2017
Available online 4 April 2019

KEYWORDS
Consensus;
Chronic migraine;
OnabotulinumtoxinA;
Botulinum neurotoxin A;

Abstract OnabotulinumtoxinA has been demonstrated to be effective as a preventive treatment in patients with chronic migraine (CM). Five years after the approval of onabotulinumtoxinA in Spain, the Headache Study Group of the Spanish Society of Neurology considered it worthwhile to gather a group of experts in treating patients with CM in order to draw up, based on current evidence and our own experience, a series of guidelines aimed at facilitating the use of the drug in daily clinical practice. For this purpose, we posed 12 questions that we ask

☆ Please cite this article as: Gago-Veiga AB, Santos-Lasaosa S, Cuadrado ML, Guerrero ÁL, Irimia P, Láinez JM, et al. Evidencia y experiencia de bótox en migraña crónica: Recomendaciones para la práctica clínica diaria. Neurología. 2019;34:408—417.

* Corresponding author.
E-mail address: ppozo@vhebron.net (P. Pozo-Rosich).

Preventive treatment;
Guidelines

ourselves as doctors, and which we are also asked by our patients. Each author responded to one question, and the document was then reviewed by everyone. We hope that this review will constitute a practical tool to help neurologists treating patients with CM.

PALABRAS CLAVE
Consenso;
Migraña crónica;
OnabotulinumtoxinA;
Toxina botulínica A;
Tratamiento preventivo;
Recomendaciones

Evidencia y experiencia de bótox en migraña crónica: Recomendaciones para la práctica clínica diaria

Resumen OnabotulinumtoxinA ha demostrado ser eficaz como tratamiento preventivo en pacientes con migraña crónica (MC). El Grupo de Estudio de Cefalea de la Sociedad Española de Neurología ha considerado que sería de interés, a los 5 años de la aprobación en España de la onabotulinumtoxinA, reunir a un grupo de expertos en el tratamiento de pacientes con MC para elaborar con la evidencia actual y nuestra experiencia unas recomendaciones dirigidas a facilitar su uso en la práctica clínica diaria. Con este fin planteamos 12 preguntas que nos hacemos como médicos y que también nos realizan nuestros pacientes. Cada autor ha contestado una pregunta y luego el documento ha sido revisado por todos. Esperamos que esta revisión constituya una herramienta práctica para ayudar a los neurólogos que tratan a pacientes con MC.

Introduction

One of the objectives of the Spanish Society of Neurology's Headache Study Group (GECSEN) is to issue consensus statements in order to establish good practice guidelines based on evidence and experience. The consensus statement on anaesthetic peripheral nerve block[1] was the first of these; this document is intended to be a continuation of this work. The topics addressed in these documents were selected mainly due to the lack of clear consensus on how these techniques should be applied and assessed in clinical practice.

We also took into account the insight of neurologists working in reference headache units and who have published research on the subject; this expertise sheds light on the real-life effects of treatments administered after their approval in clinical trials.

This study aims to provide adequate answers to neurologists' questions regarding the therapeutic management of chronic migraine (CM) with onabotulinumtoxinA (OnabotA), with a view to providing the best possible treatment and minimising the impact of migraine and the associated disability.

Methods

A group of neurologists specialising in the management and treatment of CM worked collaboratively to respond to the 12 questions considered most important regarding the use of OnabotA to treat CM, with answers drawing from their own expertise and the published evidence.

The issues addressed are grouped into 6 areas: (1) the action mechanism of OnabotA; (2) factors related to treatment response; (3) dosage and adjuvant treatments; (4) cost-effectiveness of the treatment; (5) safety of OnabotA; and (6) information for patients.

We performed a literature search on the MedLine database, including articles published up to April 2017. We also included bibliographical references cited in the articles identified, as well as databases pertaining to neurology organisations and societies, and clinical practice guidelines.

Each neurologist answered one question. Each response was critically reviewed by another expert blinded to the identity of the respondent; the final document was reviewed by all members of the panel.

1. What is the action mechanism of onabotulinumtoxinA?

OnabotA (Botox®) is one form of botulinum toxin type A (BoNTA), which belongs to the large family of neurotoxins synthesised by the bacterium *Clostridium botulinum*. The protein is composed of one heavy- and one light-chain polypeptide, connected by a disulfide bond.[2,3] Upon contact with presynaptic nerve terminals, the heavy chain binds to membrane receptors, and the toxin-receptor complex enters the neuron by endocytosis. The protein then undergoes a conformational change, with the disulfide bond breaking and the light chain being released into the neuronal cytoplasm.[3,4] The light chain subsequently interacts with the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which is composed of a group of vesicular and membrane proteins and enables

synaptic vesicle fusion with the synaptic membrane. Specifically, BoNTA cleaves synaptosomal associated protein-25 (SNAP-25), an essential SNARE complex protein which is anchored to the cytosolic face of the plasma membrane.[5] By damaging the SNARE complex, the toxin prevents exocytosis of neurotransmitters and neuropeptides from nerve terminals into the synaptic cleft.[3]

The best understood effect of OnabotA is its capacity to inhibit acetylcholine release at the neuromuscular junction. This effect has been exploited extensively in the treatment of neurological conditions involving muscle hyperactivity. OnabotA also inhibits acetylcholine release from nerve terminals of the autonomic nervous system, hence its use in certain conditions presenting with autonomic dysfunction.[4,6] Pain was recently included among the indications for OnabotA, given the drug's demonstrated efficacy for treating CM and other pain syndromes. Experimental studies have shown that BoNTA interferes with the transmission of painful stimuli.[7–9] The exact mechanism of this antinociceptive effect is not fully understood. In vitro and animal studies have shown that BoNTA blocks the peripheral release of neuropeptides involved in neurogenic inflammation, such as substance P[10,11] and calcitonin gene-related peptide (CGRP),[11,12] and such excitatory neurotransmitters as glutamate.[13,14] It can also block the translocation of membrane receptors to the surface of sensory neurons; examples are the transient receptor potential vanilloid 1 (TRPV1)[15–17] receptor or the P2X3 purinergic receptor.[16] These mechanisms enable BoNTA to reduce the sensitisation of peripheral nerve terminals, indirectly blocking central sensitisation.[18] This appears to be the mechanism underlying the application of pericranial OnabotA infiltrations to treat CM. In fact, the Phase 3 Research Evaluating Migraine Prophylaxis Theory (PREEMPT) protocol establishes infiltration points near pericranial nerves with afferent fibres supplying the spinal trigeminal nucleus.[19] Some experimental studies also suggest that BoNTA may directly modulate meningeal nociceptor signals through collateral branches crossing the cranial sutures.[20,21] Regardless of the effects on peripheral nerves, experiments with high doses of BoNTA have found that it can reach the central nervous system via retrograde axonal transport and interneuronal transfer.[22] However, experimental animals only display cleaved SNAP-25 fragments in the most peripheral neurons, making it unlikely that BoNTA infiltrations should have significant effects on the central nervous system.[23]

2. Which factors predict response to onabotulinumtoxinA?

Since the first studies into the use of OnabotA as a possible treatment for CM, multiple study groups have searched for predictors of treatment response. We propose the following classification for analysing these factors:

Clinical/demographic factors

Several clinical variables have been proposed; these include markedly unilateral headache or allodynia,[24] ocular or imploding migraine,[25] and pericranial sensitivity during examination.[26] These variables have not been confirmed in subsequent studies.[27] Shorter progression time for migraine[28] or CM[29] is reported to be associated with better response.

Analytical factors

Levels of CGRP and to a lesser extent vasoactive intestinal peptide are reported to be predictive of response to OnabotA in patients with CM.[30]

Neuroradiological factors

A neurosonology study found a significantly higher ratio between flow velocity (measured by interictal transcranial Doppler ultrasound) in the middle cerebral artery and in the ipsilateral internal carotid artery in responders.[31]

A study published by Borsook's research group reports structural and functional differences between responders and non-responders in resting-state studies.[32] This study included a small patient sample, and further study is needed to confirm the findings.

3. When should we ideally start treatment with onabotulinumtoxinA?

In Spain, OnabotA was approved as a preventive treatment for CM in 2012 ''in patients not responding satisfactorily or who are intolerant to preventive drug therapy for migraine.'' GECSEN's 2015 Official Clinical Practice Guidelines for Headache,[33] published after the PREEMPT studies,[34,35] recommend starting treatment in patients with an intolerance, contraindication, or lack of response to at least 2 preventive drugs (topiramate and one beta-blocker) administered at the minimum recommended dose for at least 3 months (level of evidence IV, grade of recommendation: GECSEN) (Fig. 1).[36]

There is growing evidence that shorter progression time of migraine[28,31] and particularly CM[37] is associated with favourable progression and better response to OnabotA; early onset of preventive treatment is therefore recommended.[38]

4. How should we assess treatment response?

When assessing a patient's response to treatment with OnabotA, we should consider subjective variables, as well as objective, functional, and operative variables. Objective

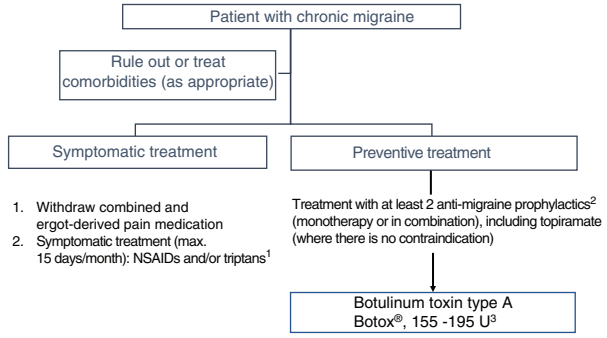

Figure 1 Therapeutic algorithm for the initial treatment of patients with chronic migraine. NSAIDs: non-steroidal anti-inflammatory drugs.

Table 1 Response criteria for treatment of chronic migraine with onabotulinumtoxinA.

Objective variables	
Primary	Reduced number of headache days and migraine days per month Reduced pain intensity Reduced use of symptomatic medication (days used per month, number of doses) Improved MIDAS and HIT-6 scores Presence/absence of adverse effects
Secondary	Reduced economic cost of drug: Direct (related to disease) and indirect (loss of productivity)
Subjective variable	Patient's decision as to whether to continue with treatment

HIT-6: Headache Impact Test-6; MIDAS: Migraine Disability Assessment Test.

variables are quantified using a calendar on which patients mark days on which they experienced pain and disability, which assists the neurologist, together with the patient, in establishing treatment response.[39]

Subjective variables include headache intensity, tolerability, and the overall assessment of whether or not to continue treatment.[40] Table 1 summarises the main objective and subjective variables.

5. If the patient initially shows no response, how many cycles of onabotulinumtoxinA should we try?

According to data from the PREEMPT programme,[40] approximately 15% of patients (depending on the measurement of effectiveness used) begin to respond to the second cycle. In the light of this evidence, we should always administer a second cycle in patients apparently unresponsive to the first; increasing the dose to 195 U should also be considered. On the one hand, these results should be expected, given the intrinsic variability of CM (which may mean that an apparent lack of response can be misleading); on the other, they suggest that the effect of OnabotA is cumulative, at least in the first treatment cycles.

The post hoc analysis of patients included in the PREEMPT study demonstrates that a third cycle of treatment can salvage as many as 10% of patients with apparently refractory migraine (Fig. 2).[41] Therefore, the PREEMPT findings (which

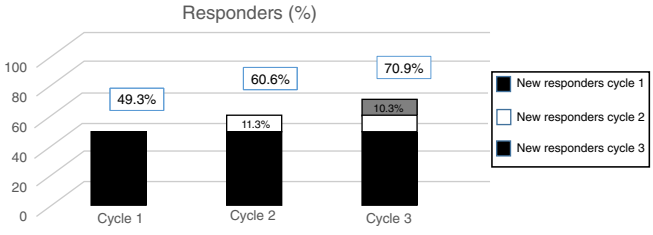

Figure 2 Percentage of responders (≥50% reduction in headache frequency with respect to the baseline rate) for each cycle of treatment.

are consistent with observations from everyday practice) support administering at least 3 cycles of OnabotA, increasing dosage to 195 U (even when treatment response is not satisfactory after 24 weeks),[42] before establishing lack of response to this treatment (level of evidence IV, grade of recommendation: GECSEN).[33]

6. When should onabotulinumtoxinA be administered in doses above 155 U?

The current recommended dose of 155-195 U is based on data obtained in various clinical trials on the use of OnabotA to treat migraine.[43,44] Studies using higher doses (225-260 U), which do not follow the PREEMPT injection paradigm, have demonstrated the safety of higher doses despite not achieving the primary objective of efficacy.[45,46]

PREEMPT studies[34,35] use an initial dose of 155 U, administered to fixed points. At the discretion of the researcher, and in accordance with pain location, an additional dose of 40 U may be administered to the temporal, occipital, or trapezium regions, reaching a maximum dose of 195 U. No clinical series have compared the different doses, although most authors recommend higher doses in patients not responsive to the initial low dose.[47]

A recent study demonstrated the sustained efficacy of a 195 U dose over a period of 2 years in 143 patients with CM and medication overuse.[42] Compared to a cohort of patients treated with 155 U, patients receiving 195 U showed greater treatment response from the first cycle, in terms of number of headache days, number of migraine days, and Headache Impact Test (HIT-6) scores. No significant difference was observed in the use of symptomatic medication until the fourth cycle.[42]

According to published data and clinical experience, there are 2 indications for increasing the dose after the first cycle: lack of response or insufficient response to the first infiltration, or insufficient duration of treatment response (worsening of symptoms 8-10 weeks after infiltration following initial good response).

7. How should oral preventive treatment be managed in patients receiving onabotulinumtoxinA?

It is relatively common in clinical practice to maintain oral treatment, despite suboptimal response, when starting treatment with OnabotA.[48,49] Withdrawal or dose reduction may be justified by response to a first or second cycle of OnabotA. According to the literature, this is achieved in more than half of patients (complete withdrawal in 45.2% and dose reduction in 13.9%).[49]

Patients starting treatment with OnabotA will fall into one of the following 2 categories:

- Patients not receiving oral treatment due to intolerance, contraindication, or lack of response after at least 6 weeks of treatment.
- Patients receiving oral preventive medication in monotherapy or combined treatment, with some degree of response.

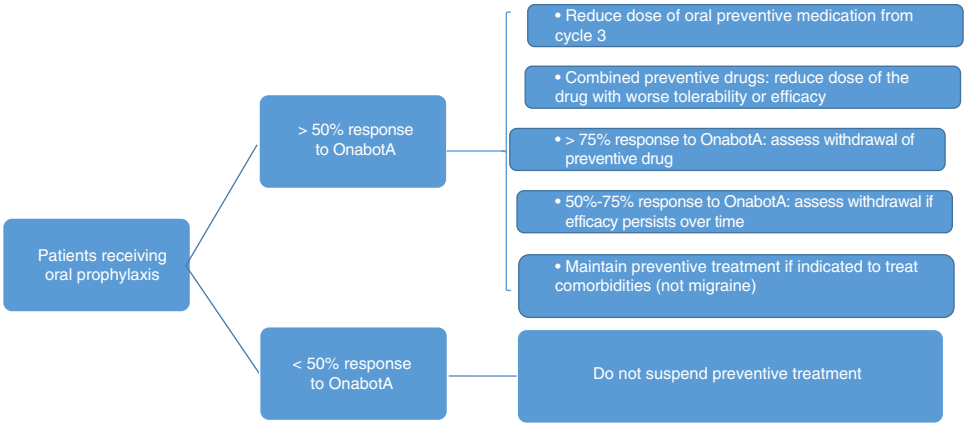

Figure 3 Management of patients receiving oral preventive treatment. OnabotA: onabotulinumtoxinA.

Fig. 3 summarises the protocol for withdrawing oral preventive treatment. The following must also be taken into account:

- The patient's opinion and consent.
- If symptoms worsen, the dose should be returned to the previous level.
- In patients receiving combined therapy, topiramate should be maintained if effectiveness and tolerability are equal.
- Preventive treatment may be indicated for concomitant diseases.

8. Is response to onabotulinumtoxinA cumulative?

According to the published evidence, predicting when a patient will achieve maximum response to OnabotA treatment remains a challenge. The results of the PREEMPT study and patient series from clinical practice suggest that the number of headache days, pain intensity, and consumption of symptomatic medication may decrease progressively up to the fourth cycle of treatment.[50–53] However, these studies are not directly comparable, as treatment response is measured in different ways. In the PREEMPT study,[54] patients continued to improve from treatment onset, at least for the duration of the study's follow-up period. The prospective, observational, multi-centre REPOSE study[52] included data from 783 patients treated with OnabotA for CM for one year, and found that effectiveness (reduction in the number of headache days and improvement in quality of life) persisted throughout the follow-up period. While these differences were calculated against baseline values, they do appear to increase progressively over the first 4 visits.

Guerzoni et al.[50] published a prospective study in which 57 patients treated for CM with OnabotA were followed up for 18 months. The number of headache/migraine days per month significantly and progressively decreased with respect to baseline levels. At 6 months from treatment onset, pain days decreased by 22%, and consistently reduced by a further 18% after each cycle of treatment. Symptomatic medication use decreased by 26% at 6 months and 67% at 18 months.

The COMPEL study is a prospective, observational, multicentre, open-label study including 715 patients treated with OnabotA, with a 108-week follow-up period and 9 cycles of treatment.[51] The authors of the study conclude that treatment efficacy increased sequentially, peaking after the ninth cycle.

Negro et al.[53] performed a prospective, observational study, following up 132 patients with CM for a period of 2 years. Significant reductions from baseline values were observed for all the variables analysed (number of headache and migraine days per month and HIT-6 score), although increases in this benefit were less marked after the first year.

9. How should responders be managed in the long term?

Given the long progression times characterising CM, we should consider how to manage these patients after the first year of treatment. There is no established consensus on this issue due to the lack of placebo-controlled studies of over one year's duration.[55] However, recommendations can be made based on clinical data from patients receiving treatment for up to 5 years.

Several non-placebo-controlled studies report objective (>50% reduction in migraine days in 3 of 4 treatments) and subjective treatment response in around 70% of patients in the first year of treatment.[47,56–59]

Can the treatment be suspended at the end of the first year?

The available data show that half of patients need to continue with quarterly OnabotA infiltrations, as they present systematic worsening of symptoms after 12 weeks. Of the remaining patients, injections can be postponed by one month (3 infiltrations per year) in 40%, and the treatment may be withdrawn in 10%.[48]

What happens to treatment response after one year?

Clinical experience shows that only one in 10 patients who respond to treatment in the first year stop responding in the second year.[48] Evidence from patients with 5 years' follow-up suggests that loss of treatment response is highly unlikely after the second year. In the same series, no patient stopped

responding to OnabotA between the third and fifth years of treatment. In addition to the reduced number of headache days, the long-term benefits include an over 50% decrease in the use of symptomatic medication and the number of emergency department visits for severe headache.[48,60]

OnabotA continues to show excellent tolerability after the first year. Adverse reactions are observed at a rate below 20%, accounting for very few cases of treatment withdrawal; the profile does not change with regard to those reported in short-term studies, with the exception of the potential for local muscle atrophy, which should lead us to reduce the dose administered to the affected muscle.[48]

What should be done if a patient does not respond to a given cycle of treatment?

Treatment response may not be apparent. As CM can fluctuate and worsen over time, the proposed indicator of treatment response is an over 50% reduction in migraine days after at least 3 of 4 treatments.[48] In the event of insufficient or absent response, OnabotA dose should be increased to 195 U (see question 6).[42]

10. Is onabotulinumtoxinA a cost-effective treatment for chronic migraine?

Recent studies show that the annual cost of CM ranges from €1500 to €3700, tripling that of episodic migraine.[61] CM has higher direct costs, due to patients' greater need for medical attention (at outpatient clinics, emergency departments, and inpatient wards) and complementary studies to confirm diagnosis, and significantly higher indirect costs due to absences from work and loss of productivity, which represents over 70% of the overall cost of migraine.[62] Given the finite resources available to healthcare systems, controlling expenditure is one of the pillars of health policy.[63] Therefore, treatments to be introduced into clinical practice must be both efficacious and cost-effective, particularly in relation to diseases that are prevalent, disabling, or associated with high levels of comorbidities and long duration, as is the case with CM.[63,64]

The first economic studies, based on estimates, demonstrate the cost-effectiveness of treatment with OnabotA, with reductions in both direct and indirect costs[65,66]; subsequent studies in the clinical setting have confirmed these findings.[67,68] In a study comparing OnabotA to oral preventive treatments, only patients receiving the former showed a decrease in emergency department visits and hospital admissions.[69] Various Spanish studies have shown that the treatment reduced the direct cost of CM, fundamentally due to the decreases in triptan use and emergency visits.[48,69]

Indirect cost is also considerably lower due to a marked reduction in rates of disability associated with migraine and patients' improved quality of life.[40] Therefore, it seems reasonable to conclude that the treatment has an impact beyond merely reducing direct costs; in parallel with the reduction in disability, there is a decrease in indirect costs associated with absence from work and loss of productivity.

11. Is treatment with onabotulinumtoxinA safe?

According to the safety and tolerability analysis performed as part of the 5 trials conducted prior to the drug's indication for CM,[70] the rate of treatment withdrawal due to adverse reactions was 3.4%. The most frequent issues were neck pain (12.6%), muscle weakness (8%), muscle stiffness (6.1%), and ptosis (4.6%). Although 72.9% of patients receiving OnabotA reported at least one adverse effect, only 5.4% considered it serious (vs 3% in the placebo group).

In the PREEMPT programme, the treatment-related adverse event rate for patients undergoing 5 injection cycles was only 34.8%. The percentage of patients with adverse reactions decreased in successive cycles, from 48.3% in the first to 19.1% in the fifth.[54]

Neck stiffness and ptosis were somewhat more prevalent in the prospective study with the largest patient series published to date than in clinical trials, affecting 14.5% and 11% of patients, respectively. The authors also report occasional migraine exacerbations in the first days after injection (4.3%), and dysphagia (1.96%).[59]

Pascual et al.[48] described frontotemporal muscle atrophy in 2 patients treated with OnabotA for longer than 5 years. Both cases were merely observations, with no functional or aesthetic impact, and did not require treatment discontinuation. Finally, Negro et al.[42] observed similar rates of adverse reactions in patients receiving 155- and 195-U doses.

12. How should we manage patients' expectations? How should patients be informed?

Regarding the management of expectations in patients treated with OnabotA, the questions listed below should be answered with the following information:

How much better will I get, and how long will it take?

Both clinical trials and everyday practice have found OnabotA to achieve a 50% reduction in the number of headache and migraine days per month, and to decrease pain intensity (number of days using symptomatic medication and doses).[28,42,48,58,59,71–74] Approximately 80% of patients respond to OnabotA infiltration during and after the first year of treatment.[38,42,48,58,71–75] In some cases, this enables progressive withdrawal of preventive medication after the third cycle of treatment; these drugs can be fully suspended in almost half of patients.[42] This improvement is also observed on scales measuring quality of life and headache impact, and persists over time.[49,71]

Therapeutic compromise

Recent studies report that shorter progression time of migraine in general[28,76] and CM in particular, as well as earlier onset of treatment, are associated with better treatment response.[38] After an initial cycle with 155 U of OnabotA, we should consider increasing the dose to 195 U in patients with no response, suboptimal response, or if response does not persist until the next cycle (worsening at 8-10 weeks following a good initial response).[42,47]

Is this treatment safe?
Yes. Data from clinical trials[34,35] and everyday practice[52,59] suggest that adverse reactions are mild and transient: neck pain, muscle weakness, muscle stiffness, and ptosis. These effects do not change for long-term treatment[48] or at higher doses,[42] which shows that OnabotA is a safe treatment for CM; treatment discontinuation due to adverse reactions is anecdotal.

How often and for how long do I need the treatment?
There is no consensus as to when OnabotA should be withdrawn in responders. It is apparent that the interval between cycles can be extended to 4 or 5 months in approximately 20% of cases.[75] Therefore, the effect of the drug appears to be cumulative over successive cycles, although it continues to be difficult to establish when the maximum benefit is reached. Loss of response is rare after the first year of treatment; where it does occur, we should consider increasing the dose to 195 U. Once the response returns, the dose may be readjusted according to the patient's needs. Five-year follow-up data suggests that the excellent tolerability of the drug persists over time.[48]

Conclusions

Table 2 shows the conclusions of this consensus statement, which are derived from the questions initially presented and are based on published evidence and clinical experience.

Table 2 Conclusions.

Mechanism of action in chronic migraine	BoNTA blocks the exocytosis of neuropeptides and neurotransmitters involved in the generation and propagation of pain impulses (substance P, CGRP, glutamate) and the translocation of membrane receptors to the surface of sensory neurons (TRPV1, P2X3).
Predictors of treatment response	Predictors of response to the drug are related to its mechanism of action (plasma CGRP levels) and parameters potentially related to reduced possibility of ''dechronification'' of migraine (age, progression time, and structural or functional neuroimaging changes).
When to start OnabotA	Early treatment is recommended for all patients with CM with no response, intolerance, or contraindications for 2 oral preventive treatments.
Variables related to response	In addition to objective and quantitative variables (reduced number of headache/migraine days per month and number of pain-free days), it is important to consider subjective variables (patient's decision to continue with the treatment).
How many cycles should be tried if there is no initial response?	Even in the absence of a satisfactory response at 24 weeks, it is reasonable to complete 3 cycles of treatment with OnabotA, increasing the dose to 195 U before concluding that it is ineffective. We should also assess the presence of factors related to chronic or refractory pain, comorbidities, or the co-presence of another cause of pain or primary headache.
When to administer over 155 U of OnabotA	A dose of 195 U is recommended if there is no response to the first infiltration, or if the response is suboptimal or does not persist (pain worsens 8-10 weeks after infiltration following an initial good response). It is important to assess the correct development of the neck muscles, given the increased risk of adverse reactions.
How should oral preventive treatment be managed in patients receiving OnabotA?	In patients with persisting improvement (>75%), it is recommended to completely withdraw the oral preventive drug. In patients showing improvement of 50%-75%, we should aim to reduce doses in patients receiving monotherapy or to remove one of the 2 drugs in patients receiving combined therapy. In the latter case, topiramate should be maintained if effectiveness and tolerability are equal. Oral prophylaxis should be continued in patients with <50% improvement.
Is response to OnabotA cumulative?	The effect of OnabotA in preventing CM appears to be cumulative over successive cycles, although it continues to be difficult to establish at which point the maximum benefit is reached.
How should responders be managed in the long term?	After the first year of treatment, OnabotA is withdrawn in 10% of patients due to good response; in 40% of patients the infiltration can be administered one month later per cycle; around half of patients continue with quarterly cycles. Loss of response after the first year is rare; where it does occur, we should consider increasing the dose to 195 U.
Is OnabotA a cost-effective treatment for chronic migraine?	Yes. Data from clinical practice have confirmed that the treatment reduces both the direct and the indirect costs of CM. Given its excellent tolerability, it is not associated with increased resource use due to adverse reactions, as these are infrequent and mild.
Is OnabotA safe?	Yes. The treatment is rarely withdrawn due to adverse effects in patients with CM, although no data is available for follow-up periods of over 5 years.

CGRP: calcitonin gene-related peptide; CM: chronic migraine; OnabotA: onabotulinumtoxinA; TRPV1: transient receptor potential vanilloid 1.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors are grateful to Allergan S.A. for their assistance in the editorial process and the logistics of meetings.

Allergan was not involved in drafting the document and had no influence over the conclusions reached.

Dr Antonio Martínez of Ciencia y Deporte S.L. provided assistance in the preparation of the manuscript, with funding from Allergan.

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INR INTERVENTIONAL NEURORADIOLOGY

Interventional Neuroradiology
2019, Vol. 25(1) 31–37

DOI: 10.1177/1591019918800457
journals.sagepub.com/home/ine
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Standards of practice in acute ischemic stroke intervention: International recommendations

This article was first published in JNIS. Cite this article as: Pierot L, Jayaraman MV, Szikora I, et al. Standards of practice in acute ischemic stroke intervention: international recommendations. Journal of NeuroInterventional Surgery. Published Online First: 28 August 2018. doi: 10.1136/neurintsurg-2018-014287.

Laurent Pierot[1], Mahesh V Jayaraman[2], Istvan Szikora[3], Joshua A Hirsch[4], Blaise Baxter[5], Shigeru Miyachi[6], Jeyaledchumy Mahadevan[7], Winston Chong[8], Peter J Mitchell[9], Alan Coulthard[10], Howard A Rowley[11], Pina C Sanelli[12], Donatella Tampieri[13], Patrick A Brouwer[14], Jens Fiehler[15], Naci Kocer[16], Pedro Vilela[17], Alex Rovira[18], Urs Fischer[19], Valeria Caso[20], Bart van der Worp[21], Nobuyuki Sakai[22], Yuji Matsumaru[23], Shin-ichi Yoshimura[24], Rene Anxionnat[25], Hubert Desal[25], Luisa Biscoito[26], José Manuel Pumar[27], Orlando Diaz[28], Justin F Fraser[29], Italo Linfante[30], David S Liebeskind[31], Raul G Nogueira[32], Werner Hacke[33], Michael Brainin[34], Bernard Yan[35], Michael Soderman[14], Allan Taylor[36], Sirintara Pongpech[37], Michihiro Tanaka[38] and Terbrugge Karel[39]; Asian-Australasian Federation of Interventional and Therapeutic Neuroradiology (AAFITN), Australian and New Zealand Society of Neuroradiology (ANZSNR), American Society of Neuroradiology (ASNR), Canadian Society of Neuroradiology (CSNR), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Japanese Society for NeuroEndovascular Therapy (JSNET), French Society of Neuroradiology (SFNR), Ibero-Latin American Society of Diagnostic and Therapeutic Neuroradiology (SILAN), Society of NeuroInterventional Surgery (SNIS), Society of Vascular and Interventional Neurology (SVIN), World Stroke Organization (WSO) and World Federation of Interventional and Therapeutic Neuroradiology (WFITN)

[1]Hôpital Maison-Blanche, Université Reims-Champagne-Ardenne, Reims, France
[2]Warren Alpert School of Medicine at Brown University, Providence, Rhode Island, USA
[3]National Institute of Clinical Neurosciences, Budapest, Hungary
[4]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
[5]Erlanger Medical Center, Chattanooga, Tennessee, USA
[6]Neuroendovascular Therapy Center, Aichi Medical University, Aichi-gun, Japan
[7]Pantai Hospital, Kuala Lumpur, Malaysia
[8]Monash University, Clayton, Victoria, Australia
[9]The University of Melbourne, The Royal Hospital of Melbourne, Parkville, Victoria, Australia
[10]University of Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia
[11]University of Wisconsin, Madison, USA
[12]Northwell Health Donald and Barbara Zucker School of Medicine, New York, USA
[13]Queen's University, Kingston, Canada
[14]Karolinska University Hospital, Stockholm, Sweden
[15]University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[16]Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey
[17]Hospital Garcia de Orta, Hospital da Luz, Lisbon, Portugal
[18]Hospital Universitari Vall d'Hebron, Barcelona, Spain
[19]Neurology, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland
[20]University of Perugia, Perugia, Italy
[21]University Medical Center, Utrecht, The Netherlands
[22]Kobe City Medical Center General Hospital, Kobe, Japan
[23]University of Tsukuba, Tsukuba, Japan
[24]Hyogo College of Medicine, Nishinomiya, Japan
[25]CHU Nantes, Nantes, France
[26]Hospital Universitário Santa Maria, Lisbon, Portugal
[27]Hospital Clinico Universitário, Santiago de Compostela, Spain
[28]The Methodist Hospital, Houston, USA
[29]University of Kentucky, Lexington, USA
[30]Herbert Wertheim College of Medicine, Florida International University, Miami Cardiac and Vascular Institute, Baptist Hospital, Miami, USA
[31]University of California Los Angeles, Los Angeles, USA
[32]Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, Atlanta, Georgia, USA
[33]University of Heidelberg, Heidelberg, Germany
[34]Danube University Krems, Krems, Austria
[35]Melbourne Brain Center at Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
[36]Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
[37]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[38]Kameda Medical Center, Kamogawa, Japan
[39]University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada

Corresponding author:
Laurent Pierot, Department of Neuroradiology, University Hospital Reims, 51100, France.
Email: ilierot@gmail.com

Keywords
Acute ischemic stroke, emergent large vessel occlusion, mechanical thrombectomy, standards of practice

Received 5 August 2018; accepted 6 August 2018

Preamble

After the five positive randomized controlled trials showing the benefit of mechanical thrombectomy (MT) in the management of acute ischemic stroke (AIS) with emergent large vessel occlusion (ELVO), a multisociety meeting was organized during the 16th Congress of the World Federation of Interventional and Therapeutic Neuroradiology (WFITN), October 2015, Gold Coast, Australia. This meeting was dedicated to the training of physicians performing MT, and recommendations were published thereafter in multiple scientific journals.[1]

The same group of scientific societies decided to organize a similar meeting during the 17th WFITN Congress, October 2017, Budapest, Hungary. This multisociety meeting was dedicated to standards of practice in AIS intervention (AISI), aiming for a consensus on the minimum requirements for centers providing such treatment.

In an ideal situation, all patients would be treated at a center offering a full spectrum of neuroendovascular care (a level 1 center). However, for geographical reasons, some patients are unable to reach such a center in a reasonable period of time. With this in mind, the group paid special attention to define recommendations on the prerequisites of organizing stroke centers providing MT for AIS, but not for other neurovascular diseases (a level 2 center). Finally, some centers will have a stroke unit and offer intravenous thrombolysis, but not any endovascular stroke therapy (a level 3 center). Together, these level 1, 2, and 3 centers form a complete stroke system of care. The requirements for these centers are summarized in Table 1.

Due to the relatively short time elapsed since the evidence in favor of MT has been published, some organizational aspects still require scientific validation. However, considering the extremely fast growth of such activities around the world, the multisociety group considered it timely and rational to set up recommendations and a framework for the development of MT services in all parts of the world. The requirements included in this document are proposed to help countries and centers to properly implement MT.

Composition of the consensus group

This working group is composed of delegates from the following societies: Asian-Australasian Federation of Interventional and Therapeutic Neuroradiology

Table 1. General summary of capabilities of level 1, 2, and 3 centers.

	Level 1 center	Level 2 center	Level 3 center
Offers full spectrum of neuroendovascular therapy (including aneurysm treatment, surgical and endovascular, arteriovenous malformations, arteriovenous fistulas, etc.)	Yes	No	No
Offers endovascular stroke therapy	Yes	Yes	No
Offers intravenous tissue plasminogen activator	Yes	Yes	Yes
Minimum number of stroke patients per year	250	100	50
Minimum thrombectomy volume per year	50	50	N/A
Dedicated neurointensive care unit	Yes	Optional	Not needed
Dedicated stroke unit	Yes	Yes	Yes
Open neurosurgical services on site	Yes	Optional	Not needed
Geographic restriction?	No	Yes (should be more than 2 hours' transport time from a level 1 center)	No
Interfacility transfers	Receives cases from level 1 and level 2 centers	Will transfer some cases to a level 1 center. Will occasionally receive transfers from level 3 centers if no level 1 center is available within 2 hours from the level 3 center	Has standardized transfer processes in place with a level 1 center (preferable) or a level 2 center

(AAFITN), Australian and New Zealand Society of Neuroradiology (ANZSNR), American Society of Neuroradiology (ASNR), Canadian Society of Neuroradiology (CSNR), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Japanese Society for NeuroEndovascular Therapy (JSNET), Ibero-Latin American Society of Diagnostic and Therapeutic Neuroradiology (SILAN), Society of NeuroInterventional Surgery (SNIS), Society of Vascular and Interventional Neurology (SVIN), World Stroke Organization (WSO), and World Federation of Interventional and Therapeutic Neuroradiology (WFITN).

Definitions

Neuroendovascular procedures: minimally invasive, image-guided procedures to treat diseases of the brain and spinal cord. These include embolization, for treatment of intracranial aneurysms, arteriovenous malformations, tumors, and revascularization techniques, such as angioplasty and stenting for atherosclerotic disease.

AISI: involves percutaneous endovascular procedures to treat ischemic stroke in adults and children, and may involve thrombectomy, aspiration, percutaneous transluminal angioplasty, and stent implantation, as well as superselective drug infusion.

Stroke unit: a dedicated, geographically clearly defined area or ward in a hospital where stroke patients are admitted and cared for by a multiprofessional team (medical, nursing, and therapy staff) who have specialist knowledge, training, and skills in stroke care with well defined individual tasks, regular interaction with other disciplines, and stroke leadership. This team shall coordinate stroke care through regular (weekly) multiprofessional meetings (http://stroke.ahajournals.org/content/44/3/828#T1).

Stroke center: a hospital infrastructure and related processes of care that provide the full pathway of stroke unit care. A stroke center is the coordinating body of the entire chain of care. This covers prehospital care, emergency room assessment and diagnosis, emergency medical treatment, stroke unit care, ongoing rehabilitation, secondary prevention, and access to related neurosurgical and vascular intervention. A stroke unit is the most important component of a stroke center. A stroke center provides stroke unit services for the population of its own catchment area and serves as a referral center for peripheral hospitals with stroke units in case their patients need services that are not locally available (http://stroke.ahajournals.org/content/44/3/828#T1).

Background and significance

AIS caused by ELVO is the leading cause of adult disability in the world.[2] Strokes caused by occlusion of the large intracranial vessels, such as the internal carotid artery, proximal middle cerebral artery, or basilar artery, have low rates of response to intravenous tissue plasminogen activator and, subsequently, poor outcomes.[3] The major revolution in acute stroke intervention began in 2015 when five randomized trials showed that rapid MT significantly improves outcomes in anterior circulation (internal carotid artery, M1) ELVO stroke patients.[4–8] The degree of benefit is profound, with a number needed to treat as low as 2.5 to have one patient be less disabled.[9,10] Few, if any, therapies in medicine can approach that level of benefit. Two additional trials have further confirmed that indeed rapid thrombectomy dramatically improves outcomes, including up to 24 hours from the last known normal.[11–14]

Training guidelines for physicians performing AISI were already proposed by the same working group.[1] Delivering the benefit of this therapy to a population that is applicable in diverse localities throughout the world, as reflected by the breadth of international societies sponsoring this guideline, requires a concerted effort. Critical to this is ensuring the proper facility capabilities to deliver this treatment in a safe yet timely fashion.

The goal of this document is to provide recommendations that outline the minimum requirements to provide AISI to as large a population as possible, including those that do not have timely access to a level 1 center, which is capable of treating all vascular diseases of the brain and spine.

Purpose

This is a document which provides recommendations based on expert opinions and best available evidence, in relation to the optimal conditions for the safe practice of AISI.

In order to replicate the dramatic results of the major randomized trials, we must ensure patients throughout the world are treated in a center with the capabilities necessary to handle not just the procedural aspects, but also the medical management of the patient prior to, during, and post-thrombectomy.

These general recommendations are not a substitute for existing national and regional guidelines, recommendations, and regulations in the field of AIS. Rather, this describes the minimum organization and workload that, based on expert consensus, is necessary for a hospital to practice AISI.

The best option for the management of AIS is to have patients transferred to and treated in high-volume level 1 centers, as demonstrated by scientific evidence.[15] However, in some situations, specifically due to geographical, traffic, and transportation conditions, access of patients to such centers in an acceptable time frame may not be possible. In that case, it would be wise to have a system of care that incorporates level 2 centers, able to provide AISI but not

necessarily the full spectrum of neuroendovascular procedures.

Where is AISI performed?

The practice of AISI should ideally take place in healthcare institutions that routinely provide services for all neurological disorders and neurointerventional treatments to patients with all kinds of neurovascular disorders (level 1 centers). Recommendation for these centers have been recently published.[16]

However, if a level 1 center is not regionally available, a center treating only ischemic stroke (level 2) can be established under the following conditions:

- There is no level 1 center available within 2 hours of interfacility transport time.
- The level 2 center must care for a reasonable number of AIS treatments a year (at least 100 treatments, including intravenous thrombolysis and AISI).
- The institution must incorporate an acute stroke center or stroke unit with fully trained stroke physicians.
- It is highly recommended that the level 2 center is organized in cooperation with a level 1 center, and should pursue the objective of collaborative work with the level 1 center for neurointervention training, continuous medical education, mortality and morbidity rounds, expertise advice by tele-consultations or by practice, 24-hour 7-week-day coverage, referrals, among other.

Level 2 center: standards of practice

For those centers established under these conditions the standards of practice described below apply.

Facilities

Facilities that must be available on site include:

- Stroke unit beds: a sufficient number of stroke unit beds should be available in stroke units to accommodate interventionally treated stroke patients at any time.
- Intensive care unit.
- A radiology/neuroradiology service, with competence in neuroimaging, and a suitable angiography room (as defined below): high quality, rapidly available non-invasive imaging is vital to the management of the acute stroke patient. At a minimum, computed tomography (CT) scanners should be available on a 24/7 basis to image patients with non-contrast CT and CT angiography. The availability of CT perfusion and/or magnetic resonance imaging may also assist in patient selection for AISI beyond 6 hours from onset. The necessary technologists and support personnel for this imaging should be available and onsite at the time of patient admission. Diagnostic radiologists/neuroradiologists with sufficient training and experience in the interpretation of these imaging studies shall be available on a 24/7 basis. Finally, cerebrovascular ultrasound facilities will be available.
- A team of trained acute stroke neurointerventionists.
- A dedicated 'stroke unit' and a 'stroke team' with fully trained stroke physicians.
- A department of neurosurgery ideally inhouse or, if that is not possible, in a nearby hospital.

Angiography suite

A suitable interventional angiographic suite implies the ability to routinely accommodate general anesthesia. Optimally, procedures should be carried out under the image guidance of a biplane digital angiography unit with flat panel CT capabilities and necessary software and hardware in order to perform high quality cerebral angiography.

As a minimum, each suite should include a single-plane high-resolution digital subtraction angiography unit with road-mapping capabilities.

Radiation protection measures in accordance with national regulations should be in place with designated individuals responsible for carrying out the necessary checks and audits.

Treatment availability

AISI should be offered to every appropriate patient according to international guidelines, not excluding/discriminating against any patient, appropriate at the right time to obtain the best results, with population treatment access equity, in centers providing safe, effective, and efficient treatment.

A suitable level 2 center should be able to provide the services defined in the definition section, on a full-time basis, 24/7, all year around.

Procedural volume

The randomized trials demonstrating a clear benefit from thrombectomy were almost exclusively performed in high-volume centers. It has been shown that high-volume centers have a significantly lower mortality, even if the patient has to be transferred from a low-volume center. Rinaldo et al. found that centers performing 35 or more thrombectomy cases per year would classify as 'high volume' and offer the lowest mortality rate for patients.[15] Similarly, the American College of Cardiology Foundation, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions suggest a minimum of 36 percutaneous coronary interventions for acute myocardial infarction per year per center as a minimum requirement.[17]

We acknowledge that the thresholds listed below are generally low. Multiple regional/national recommendations with higher limits are available and should be observed in regions/countries having already advanced healthcare networks providing services for AIS patients. The current recommendations are international and have to be compatible with the development of this new activity in areas and countries where there had been previously limited availability. Subsequently, these thresholds should be considered as the minimum caseload providing the lowest limit of safe operation. With the increased implementation of AISI in the world, it may be desirable to revise these thresholds in the future.

On the other hand, we also acknowledge that these thresholds are potentially difficult to reach in newly created level 2 centers and recognize that, during a transitory period, the activity can be below the threshold numbers, as long as it is expected that the volumes would be reached within 12–24 months.

With all of the above in mind, the suggested thresholds for annual procedure volume in order to maintain the competence for AIS endovascular treatment are the following:

- Each level 2 center shall perform a minimum number of intracranial thrombectomy procedures for ELVO per year. The global consensus group recommends a minimum of 50 procedures per center per year.
- Including the aforementioned thrombectomy procedures, each level 2 center shall perform a minimum total number of neuroendovascular procedures (diagnostic and interventional) per year according to national requirements. The global consensus group recommends a minimum of 120 procedures per center per year.
- Each neurointerventionist working in a level 2 center must perform a minimum number of acute intracranial thrombectomy procedures per year, in accordance with national requirements. The global consensus group recommends a minimum of 15 procedures per neurointerventionist per year.
- In addition to the aforementioned thrombectomy procedures, each neurointerventionist in a level 2 center should perform a minimum number of total neuroendovascular procedures per year according to national requirements. The global consensus group recommends a minimum of 50 procedures per neurointerventionist per year.

Operational guidelines/medical personnel

Stroke team. Outstanding stroke care does not exist in a vacuum solely focused on the procedure but instead is part of a successful multidisciplinary team. The stroke team comprises fully trained stroke physicians (vascular neurologists or neurointensivists), allied professionals, and nurse that are all led by a stroke physician with a strong background in the management of neurovascular disease.

Level 2 stroke intervention team

- The team should have a minimum of three clinicians with training and qualification in AISI.[18]
- The team should organize 24/7/365 acute ELVO stroke coverage (possibly in a rotation system organized with other level 2 centers or a level 1 center).
- It is recommended that stroke neurointerventionists involved in AISI maintain outpatient clinics for follow-up and have admitting privileges either in units/beds dedicated to interventional neuroradiology or in other appropriate inpatient facilities.
- The stroke neurointerventionist/interventionist, in collaboration with the stroke team, should have shared responsibility for preoperative and postoperative patient care with input from the appropriate specialties.
- AISI should ideally be practiced in neurointerventional teams with the possibility to exchange experience and knowledge. Clinical research should be encouraged. The solitary practice of AISI is strongly discouraged.

Anesthesia team. There shall be 24/7 inhospital anesthesia coverage with anesthetists with experience in caring for patients undergoing AISI. At many centers, the use of anesthesia, whether monitored anesthetic care or general anesthesia, is routine during thrombectomy. Even at centers primarily using moderate sedation, patients may deteriorate clinically prior to, or during, the procedure such that immediate access to general anesthesia is necessary to safely complete the procedure.

Others. Given the significant amount of assistance stroke patients need reintegrating into the community, the center should have access to physical therapy, speech therapy, and occupational therapy services, as well as a coordinated plan for assessment for rehabilitation needs.

Individual procedures. With regard to individual procedures, ideally the following staff roles are present for each case:

- One first operator: a neurointerventionist
- One assistant: a second scrubbed individual (i.e. a supporting AIS interventionist, physician in training (resident or fellow), nurse practitioner, physician assistant, scrub nurse, or a radiographer)
- One radiographer
- One nurse or nurse assistant
- Regardless of the type of anesthesia, an anesthesiology service must be readily available 24/7.

As a minimum, a neurointerventionist, a radiographer, and an appropriately trained nurse must be present.

Quality improvement processes. Treatment of AIS using AISI techniques is a novel method that involves the consumption of significant human and material resources and carries the risk of severe complications. Accurate documentation of medical and technical details as well as patient outcome and follow-up results is inevitable to ensure the highest benefit of such complex and demanding procedures.

To secure such documentation and data management, it is recommended that:

- The level 2 stroke center team includes a dedicated individual, preferably a stroke nurse or a stroke fellow, with the responsibility of data recording and database management.
- All technical and clinical data of AISI procedures, patient outcomes, and follow-up must be entered into an electronic database either locally or (preferably) nationally or internationally.
- The center shall establish target time metrics for all cases in accordance with the most recent requirements by international standards. Cases that exceed their chosen metrics should trigger an internal process for quality improvement.[17]
- The database should be regularly audited. At a minimum, process metrics such as time from arrival to intravenous tissue plasminogen activator, to start of angiography, and to recanalization, as well as overall recanalization rates, are to be reviewed and compared against reasonable published benchmarks.
- The center provides routine continuing education (suggested minimum of 8 hours per year) related to cerebrovascular disease and stroke for all core members of the center, as designated by the medical director.
- All cases of symptomatic intracranial hemorrhage shall be reviewed. For the purposes of this document, we broadly define symptomatic intracranial hemorrhage as the presence of new intracranial hemorrhage on post-treatment brain imaging, with clinical deterioration that is potentially attributable to the hemorrhage.
- Standardized care pathways should be implemented with clinical practice guidelines, order sets, and other tools to ensure consistent care delivery and minimize practice variability. This should apply to providers and nursing and ancillary staff. These pathways should be developed by the multidisciplinary AAFITN, ANZSNR, ASNR, CSNR, ESMINT, ESNR, ESO, JSNET, SFNR, SILAN, SNIS, SVIN, WSO, and WFITN leadership of the center and reflect evidence-based practice.

Community and emergency medical services outreach

Outstanding stroke care starts not in the hospital but in the field. Increasingly, operators will likely promote selection of the most appropriate destination for suspected ELVO patients based on distance to a center from the field.[19] Such a mechanism should decrease time to treatment. As such, the level 2 center should interface with local emergency medical services (EMS) in order to coordinate care in the prehospital arena.

Specifically, we feel there are some key items in this area.

- Representatives of the center shall work with local and regional EMS officials to ensure they are aware of the system's capabilities, as well as which patients (based on the region's chosen severity scale) are appropriate for direct field triage to the level 2 or 1 centers.
- Additionally, some patients may be distant from the level 2 (or 1) and present to a level 3 center. The level 2 center should work with these local centers to assist in identification of suspected or confirmed ELVO patients and facilitate rapid transfer as part of a 'hub and spoke' model of care. However, if a level 1 center is available in a similar transfer time, it is preferable that interfacility transfers are directed to the highest level facility.
- A mechanism should exist for providing feedback to the EMS and referring non-thrombectomy centers to highlight which aspects of care went well and identify areas for improvement. This would be similar to quality assessment work done on patients presenting directly to the level 2 and 1 centers.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

David S Liebeskind http://orcid.org/0000-0002-5109-8736

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