New European Society of Cardiology Guidelines on diabetes; prediabetes, and cardiovascular diseases - a truly strong base for the major paradigm shift in clinical practice?

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Introduction

The problem

The prevalence of diabetes mellitus (DM) continues to increase globally, and in many countries that were considered less developed until recently, its rate rose up to 10% in the general population. On the other hand, it has been also found that almost up to 50% of DM cases remain undiagnosed. Such a trend led to the alarming projections that before 2045, more than 600 million individuals would present with DM worldwide, and about the same number will develop pre-diabetes. This fact can lead to an enormous rise in the prevalence of premature cardiovascular disease (CVD) and its consequences, but at the same time, it presents an enormous public health and societal burden, also due to the effects of advancing age and comorbidities. Chronic complications in DM include macrovascular [myocardial infarction (MI), stroke, need for revascularization, and peripheral vascular disease], as well as microvascular disease (retinopathy, nephropathy, and neuropathy). It was demonstrated that individuals with one (regardless of type) microvascular complication had the CVD risk increased for 35%–40%. Increasing number of microvascular complications resulted in a stepwise increase in the composite of CV deaths, nonfatal MI, nonfatal stroke, and also in hospitalization for heart failure (HF), CV mortality, and all-cause mortality.

The release of the new guidelines

On August 30, 2019, just at the time of the beginning of the Joint Congress of the European Society of Cardiology (ESC) and the World Heart Federation in Paris, we witnessed the presentation and simultaneous publication of the new, third edition of the guidelines on the management and prevention of CVD in subjects with, and at risk of, developing DM, being prepared by the joint Task Force for diabetes, pre-diabetes, and CVD of the ESC and the European Association for the Study of Diabetes (EASD) (1). This happened exactly 6 years after the release of the previous version, issued in 2013, at the occasion of the ESC Congress in Amsterdam.

The new document in brief

The new document represents a logical evolutionary step, and it was necessary because of the enormous amount of new scientific evidence built on the foundation of recent research. It is true that for the first time in the history of Type 2 DM (T2DM), the new evidence on CV benefits come from numerous cardiovascular outcome trials (CVOT) with the use of some of the innovative drug treatment classes, and additional research findings call for at least slight modification in almost every aspect of the management of pre- and diabetic patients in clinical practice. The current guidelines document is 69 pages long (including 24 pages of introduction, appendices, and references), comprehensive enough, but practically condensed, consisting of 138 recommendations altogether (in comparison to 84 stated in the 2013 guidelines). The majority (57%) of recommendations are Class I recommendations. The level of evidence supporting these statements is also strong, with 43% of recommendations supported by the level of evidence A. Finally, despite at the time of the present guideline publication in the European Heart Jour-

nal, also a pocket version was made available by the ESC, my recommendation stays that reading the entire core document would be of an additional benefit for clinical practice.

What is new in the new guidelines?
1. Diagnostics
Diagnostics of DM

DM should be investigated using fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c). An oral glucose tolerance test (OGTT) is necessary to diagnose impaired glucose tolerance. Individuals with established CVD should be screened using HbA1c and/or fasting glucose, and an OGTT should be carried out if FPG and HbA1c are inconclusive. It is worth to emphasize especially that T2DM and pre-DM are highly common in individuals with either or both acute coronary syndrome and/or chronic coronary syndrome and are associated with a weak prognosis. Glycemic status should be systematically evaluated in all patients with coronary artery disease (CAD).

CV risk assessment reclassification

The new guidelines recommend stratification of the CV risk in patients with either pre- or established DM into moderate-, high-, and very-high risk levels rather than the binary approach according to which patients were divided into primary or secondary prevention groups. The new recommendations provide a reclassification of CV risk in patients with DM based on comorbidities and the duration of the disease, rather than just declaring them as requiring so-called primary or secondary prevention of CVD. The simplified version of the new CV risk stratification in DM patients can be summarized as follows:

- Very high risk: patients with manifest CVD, or target-organ damage, or three or more major risk factors, or an early onset DM1 with a very long duration (>20 years)
- High risk: patients with DM for >10 years, and at least one additional risk factor (but no target-organ damage)
- Moderate risk: young patients (<35 years for T1DM, or <50 years of age for T2DM), with DM duration <10 years and lack of other CV risk factors.

Additional diagnostic procedures

The electrocardiogram (ECG) recording is strongly recommended in pre-diabetes and patients with DM and hypertension or suspected CVD, and transthoracic echocardiography may be considered to test for structural heart disease. To better determine the true level of increased CV risk, they also recommend to use, as the so-called risk modifiers, the stress testing, as well as the coronary artery calcium score measurement to screen for CAD, and the ankle-brachial index (ABI) measurement for peripheral artery disease, while on the other hand, the carotid intima-media thickness measurement is not recommended any more in this sense. Routine assessment of microalbuminuria should be carried out to identify patients with DM who are at risk of developing renal dysfunction and/or CVD, while routine assessment of novel biomarkers is not recommended for CV risk stratification.

2. Management
Lifestyle change

Healthy behaviors are the mainstay of preventing CVD, and this is why also in the present guidelines the lifestyle intervention (quitting smoking, reducing calorie intake with the aim to lower excessive body weight, adopting a Mediterranean diet supplemented with olive oil and/or nuts, moderate-to-vigorous physical activity for at least 150 minutes per week, and avoiding alcohol) is highly recommended, creating a foundation of each individual's treatment, with the aim to delay/prevent the conversion from pre-DM to DM, as well as to reduce the overall CV risk. It is even more/especially encouraged in those patients with already manifested high blood pressure (BP) and/or dyslipidemia.

True paradigm shift toward earlier prescription of contemporary glucose-lowering drugs proven to be effective in CV event reduction

Intensive glycemic control may have more favorable CV effects when initiated early in the course of DM. Glucose control to target a near-normal HbA1c (<7.0% or <53 mmol/mol) will decrease the frequency and severity of microvascular complications in patients with DM. Tighter glucose control (to 6.0%–6.5% or 42–48 mmol/mol) initiated early in the course of DM in younger individuals leads to a long-term reduction in CV outcomes. Less-rigorous targets (7.5%–8.0% or 58–64 mmol/mol) should be considered in elderly patients on a case-to-case basis, and in those with severe comorbidities or advanced CVD. In contrast with the previous ESC/EASD guidelines, which firmly founded metformin as the first-line treatment in almost every patient with DM, the new guidelines document brings the biggest step toward the so-called paradigm shift, according to the leading authors of the new guidelines document. The new guidelines factually remove metformin from its place as an initial diabetes therapy for all. This effectively means that metformin stays as the first-line drug in patients with T2DM without CVD, and in patients at moderate CV risk, while in patients at high/very-high CV risk (such as those with target-organ damage or several CV risk factors, and all patients with already manifest CVD), both SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin), as well as GLP-1 RA (liraglutide, semaglutide) come into play already at the first-line, immediate decision level. Similarly, in patients currently taking metformin, an SGLT2 inhibitor or GLP-1 receptor agonist should be added to metformin in patients with atherosclerotic CVD, or in patients at high or very-high CVD risk, who have target-organ damage, or who have multiple CVD risk factors. The guidelines recommendations state that the benefits seen with GLP-1 receptor agonists are most likely derived through the reduction of arteriosclerosis-related events, while SGLT2 inhibitors seem to reduce major CV endpoints mainly related to HF.

Blood pressure targets in DM and pre-DM

Optimal BP control reduces the risk of micro- and macro-vascular complications. With the new guidelines, the BP targets are no longer recommended to be lower than 140/85 mm Hg for everyone, and individualized BP targets are now recommended. The BP goal is to target systolic BP (SBP) to 130 mm Hg in patients with DM and <130 mm Hg if tolerated (particularly for those patients at high risk of stroke or those with diabetic kidney disease), but not <120 mm Hg. In older people (aged >65 years), the SBP goal is in the range of 130–139 mm Hg. The diastolic BP (DBP) target is <80 mm Hg, but not <70 mm Hg. Up-to-date evidence strongly supports the inclusion of an angiotensin-converting enzyme inhibitor, or an angiotensin-receptor blocker. Multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium-channel blocker or diuretic, is often required for BP control, so dual therapy is recommended as the first-line treatment. The use of RAAS blockers lowers the risk of the new-onset DM in patients with pre-diabetes. As also stated below, patients with DM using antihypertensives should be encouraged to self-monitoring their BP.

Dyslipidemia in DM and pre-DM

With regard to lipid targets, the new guidelines build on the risk reclassification idea; for patients with T2DM at a moderate CV risk, the low-density lipoprotein cholesterol (LDL-C) target <2.5 mmol/L is to be achieved, for patients at a high risk, the target is <1.8 mmol/L, and for patients at a very-high CV risk, the recommended target LDL-C level now is <1.4 mmol/L. In both high- and very-high-risk patients, we should aim to reduce LDL-C levels by more than 50%. Statins, undoubtedly and repeatedly, have shown that they effectively prevent CV events and reduce CV mortality, and remain the treatment of choice in patients with T2DM, with the addition of ezetimibe, if needed, to achieve the targets. Due to the genuinely high-risk profile of patients with DM, intensive statin treatment should be used on a case-to-case basis. In patients at very high risk and a persistently higher-than-target LDL-C, despite the treatment with maximally tolerated dose of potent statin in combination with ezetimibe, or in case of statin intolerance, a PCSK9 inhibitor (evolocumab or alirocumab) is now recommended.

Other prevention treatments

Aspirin at a dose of 75–100 mg/d may still be considered for "primary" prevention in DM patients with very-high/high CV risk, when the estimated bleeding risk (needed to be assessed regularly) stays low, while it is not anymore recommended for primary prevention in patients with DM at low CV risk. Antithrombotic drugs are undoubtedly the cornerstone of the CV complications prevention in DM patients with already manifest CVD, so in patients with CAD, intensive/combined "secondary" prevention is indicated. Aspirin in combination with a reduced-dose ticagrelor may be considered for ≤3 years post-MI. In high-risk patients,

the combination of low-dose rivaroxaban and aspirin may be beneficial for longer-term prevention of CVD complications. Novel oral anticoagulants are clearly preferred over the vitamin K antagonists in DM patients with paroxysmal or persistent AF, a common comorbidity in patients with DM, and in addition to dabigatran, rivaroxaban, and apixaban, edoxaban is also introduced as one of the possible choices.

Coronary revascularization in DM and pre-DM

In comparison with the previous version, the new guidelines provide slightly modified directions on coronary revascularization, with CABG- or PCI-related recommendations based on the extent and complexity of CAD. Basically, they recommend using the same revascularization and stenting techniques in DM patients as in patients without DM. At the same time, with regard to the complexity of CAD, the new guidelines stratify the choice of revascularization a bit more in detail than the 2013 document, where the only decision-making point was attributed to the higher or lower SYNTAX score. The new document brings recommendations founded on the number and the level of the coronary vessels involved (one- or two-vessel disease, left main involvement), as well as the complexity of the pathology. Still, in multivessel CAD with high complexity, suitable coronary anatomy for revascularization, and low predicted surgical mortality, CABG is preferred over the PCI, while at the same time, such an approach is not equivocal in all cases with left main CAD.

Importance of comorbidities

The coexistence of HF represents a higher risk of all-cause death, CV death, as well as HF hospitalization in patients with DM. Guideline-based medical and device therapies are equally effective in patients with and without DM. Since renal dysfunction and hyperkalemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g., RAAS blockers) are advised. The first-line treatment of DM in HF should include metformin and SGLT2 inhibitors; SGLT2 inhibitors are recommended to lower the risk of HF hospitalization, while metformin should be considered in patients with DM and HF if eGFR >30 mL/min/1.73 m^2. Insulin and GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the HF risk and may be considered, while DPP4 inhibitor saxagliptin, and thiazolidinediones (pioglitazone and rosiglitazone) are not recommended for patients with DM and HF. Patients with DM are at higher risk of chronic critical ischemia as the first clinical manifestation of lower extremity artery disease (LEAD), supporting a regular screening with ABI measurement for early diagnosis. The management of, and indications for, different treatment strategies are similar in patients with LEAD with or without DM, although the options for revascularization may be poorer because of diffuse and distal lesions. The management of carotid artery disease is similar in patients with DM or without DM.

3. Patient-centered approach and the importance of self-care

Group-based structured education programs improve disease knowledge, glycemic control, disease management, and empowerment in patients with DM. Patient-centered care (in contrast with the historical glucocentric care) is recommended to facilitate shared control and decision making, within the context of patient priorities and goals, with the aim to help strengthen patients' capabilities for self-managing their conditions. In addition, data have emerged to implicate glucose variability in the causes of heart disease in diabetes. As well, glucose variation at night is particularly linked with hypoglycemia and deterioration in the quality of life. Guidelines now also clearly recommend self-monitoring of BP and blood glucose for patients with DM to achieve better control of these two major risk factors. It is more than obvious that optimal results cannot be achieved in the absence of medical interventions unless the patient is adherent to specific diet recommendations, physical exercise, glycemic monitoring, medication, and self-decision making.

The five most important new recommendations from 2019 guidelines (compared to the 2013 edition)

1. CV risk reclassification. Due to the acknowledgment of the CV risk continuum, the new guidelines advocate stratification of all patients into very-high, high, and moderate risk groups, while making decisions on the basis of the binary approach with primary/secondary measures is no longer recommended.

2. Glucose-lowering treatment. Metformin is no longer the first-line therapy in all patients with DM. In patients at high or very-high CV risk, the new recommendations clearly place SGLT2 inhibitors and GLP-1RA as potential primary therapy. Metformin should now be considered as the first-choice treatment in overweight patients with T2DM without CVD and in patients at moderate CV risk.

3. Lipid targets. Recommendations on lipid targets were altered to LDL-C <2.5 mmol/L for T2DM patients at moderate, to <1.8 mmol/L for those at high, and <1.4 mmol/L for those at very-high CV risk. In patients at very high risk and high LDL-C despite maximally tolerated statins plus ezetimibe, a PCSK9 inhibitor is recommended.

4. Blood pressure management. Individualized BP targets are recommended. The BP goal is to target SBP to <130 mm Hg if tolerated, but not <120 mm Hg (in older 130–139 mm Hg), and the DBP target is <80 mm Hg, but not <70 mm Hg. Preference is given to RAAS blockers over beta-blockers/diuretics.

5. Antithrombotic therapies. No aspirin is recommended for primary prevention in patients with T2DM at moderate CV risk, but it may be considered in those at very-high/high risk. Novel oral anticoagulant drugs (NOACs) are preferred over vitamin K antagonists (VKAs) VKAs for management of atrial fibrillation. Aspirin in combination with reduced-dose ticagrelor may be considered for long-term treatment post-MI, and in high-risk patients, a combination of low-dose rivaroxaban and aspirin may be beneficial in a long-term prevention of CVD complications.

Conclusion

The recently released and published ESC/EASD guidelines on diabetes, pre-diabetes, and CVDs bring us the-state-of-the-art information on how to prevent and manage the effects of diabetes on the heart and blood vessels, with a focus on new data that have emerged since the previous 2013 document. Although the document is condensed, it retained the needed comprehensiveness of many evidence-based recommendations covering the entire spectrum of issues related to the main topic.

The new guidelines document represents an important evolutionary step in understanding, teaching, and implementing the scientific evidence related to the CVD prevention, since its recommendations no longer focus on the primary and secondary prevention, but rather recommend that physicians treat patients with DM or pre-DM according to their either very-high, high, or moderate risk of CVD (see above, "Reclassification of risk").

There is no doubt that as the most revolutionary change brought by the new document will surely be the "shift of the paradigm" related to the prior than before use of some of the innovative classes of glucose-lowering drugs (SGLT2-inhibitors and GLP1-RAs) with proven efficacy in the reduction of CVD-related adverse events, as in patients at high or very high risk for CVD, the new recommendations clearly place them as primary therapy vs. metformin, which was previously and is still recommended in some of the international guidelines as the first-line therapy for all patients with DM.

In any case, despite the new evidence from some major CVOT that used these new classes of glucose-lowering drugs, the new guidelines still highlight the foundation role and highly recommend the healthy lifestyle changes with the aim to delay/prevent the conversion from pre-DM to DM, as well as to reduce the overall CV risk. In addition to blood glucose control, there are strong recommendations with the aim to ensure a consistent evidence-based management of other major CV risk factors, in front of all the tight control of BP and LDL-C, where some adjustments in recommended targets, as well as the preferred (e.g., with RAAS blocker, high-dose statin) and emerging (e.g., PCSK9 inhibitors) therapies are given. It is well known from large ran-

domized controlled trials that combined reduction in HbA1c, SBP, and lipids decreases CV events by 75%, but multifactorial treatment is still largely underused.

As a final remark, despite it is not discussed within the guidelines document itself, the author of this text would like to point to the fact that in the near future, the building of cardio-diabetes/diabetes–cardiology teams will surely become reality for a better comprehensive care in most of our patients with DM.

Reference

1. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al.; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019 Aug 31; pii: ehz486. [Epub ahead of print]