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2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

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Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Primary Care, Council on Hypertension.

Working Groups: Aorta and Peripheral Vascular Diseases, Cardiovascular Surgery, Thrombosis.

Recommendations for multifactorial management of patients with diabetes

Recommendations	Class[a]	Level[b]
A multifactorial approach to DM management with treatment targets, as listed in *Table 9*, should be considered in patients with DM and CVD.[238,239,245–248]	IIa	B

CVD = cardiovascular disease; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

Gaps in the evidence

- The optimal strategy for multifactorial treatment in primary and secondary intervention has not been established.
- Sex differences have not been evaluated in the setting of multifactorial intervention.

7 Management of coronary artery disease

Key messages

- T2DM and pre-DM are common in individuals with ACS and chronic coronary syndromes (CCS), and are associated with an impaired prognosis.
- Glycaemic status should be systematically evaluated in all patients with CAD.
- Intensive glycaemic control may have more favourable CV effects when initiated early in the course of DM.
- Empagliflozin, canagliflozin, and dapagliflozin reduce CV events in patients with DM and CVD, or in those who are at very high/high CV risk.
- Liraglutide, semglutide and dulaglutide reduce CV events in patients with DM and CVD, or who are at very high/high CV risk.
- Intensive secondary prevention is indicated in patients with DM and CAD.
- Antiplatelet drugs are the cornerstone of secondary CV prevention.
- In high-risk patients, the combination of low-dose rivaroxaban and aspirin may be beneficial for CAD.
- Aspirin plus reduced-dose ticagrelor may be considered for ≤3 years post-MI.
- Antithrombotic treatment for revascularization does not differ according to DM status.
- In patients with DM and multivessel CAD, suitable coronary anatomy for revascularization, and low predicted surgical mortality, coronary artery bypass graft (CABG) is superior to percutaneous coronary intervention (PCI).

7.1 Medical treatment

Glucose abnormalities are common in patients with acute and stable CAD, and are associated with a poor prognosis.[16,18,249] Approximately 20–30% of patients with CAD have known DM, and of the remainder, up to 70% have newly detected DM or IGT when investigated with an OGTT.[9,250,251] Patients with CAD, without known glucose abnormalities, should have their glycaemic state evaluated as outlined in *sections 4* and *5*.

It is important to acknowledge that recommendations for the secondary prevention of CAD in patients with DM are mostly based on evidence from subgroup analyses of trials that enrolled patients with and without DM.[72] Because of the higher CV event rates consistently observed in patients with DM, the absolute benefit often appears amplified while the relative benefit remains similar.[238,247] General recommendations for patients with CCS and ACS are outlined in other ESC Guidelines.[252–255]

There is evidence that improved glycaemic control defers the onset, reduces the progression, and (in some circumstances) may partially reverse markers of microvascular complications in patients with DM. Accordingly, early, effective, and sustained glycaemic control is advocated in all DM guidelines to mitigate the risks of hyperglycaemia. Achieving this without detriment and with benefit to the CV system is an important challenge, particularly when selecting glucose-lowering therapies to suit the individual. Key clinical trials that delineate the effects of glucose-lowering therapies on CV outcomes are considered below.

7.1.1 Effects of intensified glucose control

7.1.1.1 UKPDS

In UKPDS, 5102 patients with newly diagnosed drug-naïve DM were randomly assigned to intensive glucose control with a sulfonylurea or insulin, or to management with diet alone, for a median 10.7 years. Although a clear reduction in microvascular complications was evident, the reduction in MI was marginal at 16% (P=0.052).[145] In the study extension phase, the risk reduction in MI remained at 15%, which became significant as the number of cases increased.[149] Furthermore, the beneficial effects persisted for any DM-related endpoint, including death from any cause, which was reduced by 13%. Of note, this study was performed when modern aspects of multifactorial management (lipid lowering and BP) were unavailable.

7.1.1.2 ACCORD, ADVANCE, and VADT

Three trials reported the CV effects of more-intensive vs. standard glucose control in patients with DM at high CV risk.[138,256–258] They included >23 000 patients treated for 3–5 years and showed no CVD benefit from intensified glucose control. ACCORD was terminated after a mean follow-up of 3.5 years because of higher mortality in the intensive arm (14/1000 vs. 11/1000 patient deaths/year), which was pronounced in those with multiple CVRFs and driven mainly by CV mortality. A further analysis found that individuals with poor glycaemic control within the intensive arm accounted for the excess CV mortality.[259]

7.1.1.3 DIGAMI 1 and 2

DIGAMI 1[260] reported that insulin-based intensified glycaemic control reduced mortality in patients with DM and acute MI (mortality

after 3.4 years was 33% in the insulin group vs. 44% in the control group; P=0.011).[261] The effect of intensified glycaemic control remained 8 years after randomization, increasing survival by 2.3 years.[262] These results were not reproduced in DIGAMI 2, which was stopped prematurely due to slow recruitment of patients.[263] In pooled data, an insulin–glucose infusion did not reduce mortality in acute MI and DM.[264] If it is felt necessary to improve glycaemic control in patients with ACS, this should be carried out cognisant of the risk of hypoglycaemia, which is associated with poor outcomes in patients with CAD.[265,266] The strategy of metabolic modulation by glucose-insulin-potassium, to stabilize the cardiomyocyte and improve energy production, regardless of the presence of DM, has been tested in several RCTs without a consistent effect on morbidity or mortality.[267,268]

In patients undergoing cardiac surgery, glucose control should be considered.[269] Observational data in patients undergoing CABG suggest that the use of continuous insulin infusion achieving moderately tight glycaemic control is associated with lower mortality, and fewer major complications, than tighter or more lenient glycaemic control.[270] In the CABG stratum in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, long-term insulin-providing treatment was associated with more CV events than insulin-sensitization medications.[271]

The glycaemic targets for people with CAD, and the preferred classes of drugs for DM, are outlined in *section 6.2* and below.

7.1.2 Glucose-lowering agents: new evidence from cardiovascular outcome trials

7.1.2.1 Established oral glucose-lowering drugs

The CV effects of long-established oral glucose-lowering drugs have not been evaluated in large RCTs, as with more recent drugs.

7.1.2.1.1 Metformin. In a nested study of 753 patients in UKPDS comparing conventional therapy with metformin, metformin reduced MI by 39%, coronary death by 50%, and stroke by 41% over a median period of 10.7 years in newly diagnosed overweight patients with T2DM without previous CVD.[146] Metformin also reduced MI and increased survival when the study was extended for a further 8–10 years of intensified therapy, including the use of other drugs.[149] Observational and database studies provide supporting evidence that long-term use of metformin improves CV prognosis.[272,273] Still, there have been no large-scale randomized CV outcome trials (CVOTs) designed to assess the effect of metformin on CV events.

7.1.2.1.2 Sulfonylureas and meglinides. CV risk reduction with a sulfonylurea is more effective than modest lifestyle interventions alone, but is less effective than metformin.[145,146,274–276] Sulfonylureas carry the risk of hypoglycaemia and, since the 1960s, there has been an ongoing debate on the CV safety of sulfonylureas. However, the CAROLINA (CARdiovascular Outcome Study of LINAgliptin Versus Glimepiride in Type 2 Diabetes) study, comparing the DPP4 inhibitor linagliptin vs. the sulfonylurea glimiperide, showed comparable CV safety of both drugs in patients with T2DM over 6.2 years.[277] Nateglinide did not reduce major CV events in the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, a 5 year prospective study of IGT and CVD, or high CV risk.[278]

7.1.2.1.3 Alpha-glucosidase inhibitor. Acarbose did not alter MACE in patients with IGT and CVD during the large, 5 year, prospective ACE trial.[129]

7.1.2.1.4 Thiazolidinediones. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) of pioglitazone was a neutral trial for its composite primary outcome (HR 0.90, 95% CI 0.80–1.02; *P*=0.095).[279] Because of this, reported secondary outcomes should be viewed as hypothesis generating only. These included a nominally significant reduction of the secondary composite endpoint by 16% (HR 0.84, 95% CI 0.72–0.98; *P*=0.027),[279] and the risk of subsequent MI and recurrent stroke by 16 and 47%, respectively,[280,281] with a reduction in the risk of recurrent stroke in non-DM.[282] The occurrence of HF was significantly higher with pioglitazone than with placebo in the PROactive trial, but without increased mortality.[283] The Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT)—a large, randomized, but unblinded comparison of pioglitazone vs. sulfonylurea as add-on to metformin—was stopped prematurely because of futility. The composite endpoint and the individual components of the composite endpoint were similar in the two groups.[284] In the IRIS trial of insulin-resistant subjects without DM, pioglitazone reduced the combined endpoint of recurrent stroke and MI by 24% vs. placebo over a median follow-up of 4.8 years.[282] Following a meta-analysis of CV events with the thiazolidinedione rosiglitazone,[285] the regulatory landscape for DM drugs underwent a major change in 2008,[286] after which all future DM drugs were required to demonstrate designated margins of CV safety to achieve or maintain regulatory approval. This led to an increase in trials to assess CV outcomes with these therapies,[287,288] most of which were designed to confirm non-inferiority of the experimental therapy vs. placebo added to background antihyperglycaemic treatment.

7.1.2.1.5 Insulin. In the ORIGIN trial, 12 537 people (mean age 63.5 years) at high CVD risk—with IFG, IGT, or DM—were randomized to long-acting insulin glargine [targeting an FPG level of 5.3 mmol/L (≤95 mg/dL)] or standard care. After a median follow-up of 6.2 years, the rates of CV outcomes were similar in the two groups.[289] In DEVOTE, a double-blind comparison of ultra-long-acting degludec o.d. (*n*=3818) with insulin glargine U100 (*n*=3819) for 1.8 years in patients with DM at high CV risk found no significant differences in MACE (composite of CV death, non-fatal MI, or non-fatal stroke).[290] A significant reduction in the frequency of hypoglycaemia was observed in the degludec arm. [290]

7.1.2.2 Newer oral glucose-lowering drugs

7.1.2.2.1 Dipeptidyl peptidase-4 inhibitors. Five large prospective trials in T2DM populations with different CV risk (*Table 10*) that assessed the CV effects of DPP4 inhibitors have reported to date: saxagliptin [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–thrombolysis in myocardial infarction 53 (SAVOR-TIMI 53)][291] alogliptin [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)],[292] sitagliptin [Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)],[293] and linagliptin [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes

Mellitus [CARMELINA][294] and CAROLINA[277]). Four of these trials confirmed statistical non-inferiority vs. placebo (which included alternative glucose-lowering medication to achieve glycaemic equipoise) for the primary composite CV outcome examined. However, none of the DPP4 inhibitors were associated with significant CV benefits in their trial populations, which comprised patients with a long history of DM and CVD, or clustered CVD risk factors. In the SAVOR-TIMI 53 trial, saxagliptin was associated with an increase in risk of hospitalization for HF,[291] compared with a numerical, non-significant increase with alogliptin in EXAMINE,[292] and no HF signal with sitagliptin in TECOS[293] and with linagliptin in CARMELINA.[294,295] Subgroup analyses of SAVOR-TIMI 53 suggested that high baseline NT-proBNP, pre-existing HF, or CKD conferred a greater risk of hospitalization for HF in saxagliptin-treated subjects.[296] Only the CAROLINA study compared linagliptin vs. glimiperide as an active comparator and showed comparable CV safety of both drugs.[277]

7.1.2.2.2 Glucagon-like peptide-1 receptor agonists. Seven CVOTs have examined the effects of GLP1-RAs on CV events in patients with DM and high CV risk. In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, lixisenatide 10 or 20 μg o.d. was non-inferior to placebo, but did not significantly affect a four-point MACE (three-point MACE plus hospitalization for unstable angina) in patients with DM post-ACS.[297] In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study of a DM population in whom 73% had experienced a previous CV event, exenatide 2 mg once weekly showed non-inferiority vs. placebo and a numerical, but non-significant, 14% reduction of the primary three-point MACE.[158] The intention-to-treat analysis revealed a significant reduction in all-cause death by exenatide of 14% (P=0.016), but this result has to be considered exploratory given the hierarchical statistical testing. However, in the subgroup with known CVD, those treated with exenatide demonstrated a 10% relative risk reduction for MACE (HR 0.90, 95% CI, 0.816−0.999; nominal P=0.047).

In the LEADER trial, 9340 patients with DM at high CV risk (81% with previous CVD) were randomized to liraglutide 0.6 - 1.8 mg o.d. vs. placebo as add-on to other glucose-lowering drugs. All patients had a long history of DM and CVRFs that were well controlled. After a follow-up of 3.1 years, liraglutide significantly reduced the composite three-point primary endpoint (CV death, non-fatal MI, or non-fatal stroke) by 13%. In addition, liraglutide significantly reduced CV death and total death by 22 and 15%, respectively, and produced a non-significant numerical reduction in non-fatal MI and non-fatal stroke.[176] Pre-specified secondary analyses showed lower rates of development and progression of CKD with liraglutide compared with placebo.[298] The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was a phase III pre-approval study in which a smaller population of 3297 patients with DM and high CV risk (73% with CVD) were randomized to semaglutide 0.5−1.0 mg once weekly vs. placebo. After 2.1 years, semaglutide significantly reduced the three-point MACE by 26%, an effect driven mainly by a 39% significant reduction of non-fatal stroke. Moreover, semaglutide led to a non-significant numerical reduction of non-fatal MI. Semaglutide also reduced the secondary endpoint of new or worsening nephropathy.[299] The Peptide Innovation for Early Diabetes Treatment (PIONEER)-6 trial, also a phase III pre-approval CVOT, examined the effect of oral semaglutide o.d. (target dose 14 mg) vs. placebo on CV outcomes in patients with T2DM and high CV risk. Non-inferiority for CV safety of oral semaglutide was confirmed with an HR of 0.79 (P < 0.001) in favour of oral semaglutide compared with placebo over a median follow-up of 16 months. Moreover, semaglutide significantly reduced the risk for CV death [15 (0.9%) events with oral semaglutide vs. 30 (1.9%) events with placebo, HR 0.49, P=0.03] and all-cause death [23 (1.4%) events in the semaglutide vs. 45 (2.8%) events in the placebo group, HR 0.51, P=0.008].[300] However, albeit low in absolute numbers, there was a significant increase in retinopathy complications, including vitreous haemorrhage, blindness, or requirement for intravitreal agent or photocoagulation, the implications of which require further study. In the Albiglutide and CV outcomes in patients with type 2 DM and CVD (Harmony Outcomes) trial, once weekly albiglutide, a no-longer marketed GLP1-RA, led to a significant 22% reduction of three-point MACE compared with placebo in patients with DM and manifest CVD. In addition, albiglutide significantly reduced MI by 25%.[301] A recent meta-analysis of five of these trials suggests that GLP-RAs reduce three-point MACE by 12% (HR 0.88, 95% CI 0.84−0.94; P < 0.001).[302] The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial assessed the effect of once weekly subcutaneous dulaglutide (1.5 mg) vs. placebo on three-point MACE in 9901 subjects with T2DM, who had either a previous CV event or CVRFs. During a median follow-up of 5.4 years, the primary composite outcome occurred in 594 (12.0%) participants in the dulaglutide group and in 663 (13.4%) participants in the placebo group (HR 0.88, 95% CI 0.79−0·99; P=0.026).[303]

Although the mechanisms through which some of these GLP-RAs reduced CV outcomes have not been established, their long half-lives may be contributing to their CV benefits. In addition, GLP1-RAs improve several CV parameters, including a small reduction in SBP and weight loss, and have direct vascular and cardiac effects that may contribute to the results.[304] The gradual divergence of the event curves in the trials suggests that the CV benefit is mediated by a reduction in atherosclerosis-related events.

7.1.2.2.3 Sodium-glucose co-transporter 2 inhibitors. Four CVOTs with SGLT2 inhibitors [Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients−Removing Excess Glucose (EMPA-REG OUTCOME), the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction (DECLARE-TIMI 58), and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial] have been published. In EMPA-REG OUTCOME, 7020 patients with DM of long duration (57% >10 years)

and CVD were randomized to empagliflozin 10 or 25 mg o.d., or placebo; patients were followed for a mean of 3.1 years.[305] The patient population was well treated with good management of risk factors (mean BP 135/77 mmHg and mean LDL-C 2.2 mmol/L). Empagliflozin significantly reduced the risk of the three-point composite primary outcome (CV death, non-fatal MI, or non-fatal stroke) by 14% compared with placebo. This reduction was driven mainly by a highly significant 38% reduction in CV death ($P < 0.0001$), with separation of the empagliflozin and placebo arms evident as early as 2 months into the trial. There was a non-significant 13% reduction of non-fatal MI ($P=0.30$) and a non-significant 24% increased risk of non-fatal stroke.[306] In a secondary analysis, empagliflozin was associated with a 35% reduction in hospitalization for HF ($P < 0.002$), with separation of the empagliflozin and placebo groups evident almost immediately after treatment initiation, suggesting a very early effect on HF risk. Empagliflozin also reduced overall mortality by 32% ($P < 0.0001$), a highly significant effect, translating into a number needed to treat of 39 over 3 years to prevent one death. These findings were consistent in all subgroups. Additional analyses from EMPA-REG OUTCOME revealed that the CV benefit was gained by those with and without HF at baseline, the latter comprising ~10% of the study cohort.[307]

The CANVAS Program integrated data from two RCTs (CANVAS and CANVAS-R), in which 10 142 patients with DM at high CV risk were randomized to canagliflozin 100−300 mg o.d. vs. placebo.[308] After 3.1 years, canagliflozin significantly reduced a composite three-point MACE by 14% ($P=0.02$), but did not significantly alter CV death or overall death.[309] Similar to the findings in EMPA-REG OUTCOME, canaglifozin significantly reduced HF hospitalization. However, canagliflozin led to an unexplained increased incidence in lower limb fractures and amputations (albeit low numbers), a finding that was not replicated in a recent large cohort study.[310]

DECLARE−TIMI 58 examined the effect of 10 mg dapagliflozin o.d. vs. placebo in 17 160 patients with DM and CVD, or multiple CVRFs, among them 10 186 without atherosclerotic CVD.[311] After a median follow-up of 4.2 years, dapagliflozin met the pre-specified criterion for non-inferiority for the composite three-point MACE compared with placebo. In the two primary efficacy analyses, dapaglifozin did not significantly reduce MACE, but resulted in a lower rate of the combined endpoint of CV death or HF hospitalization (4.9 vs. 5.8%; HR 0.83, 95% CI 0.73 - 0.95; $P=0.005$). This was driven by a lower rate of HF hospitalizations (HR 0.73, 95% CI 0.61 - 0.88), but no between-group difference in CV death (HR 0.98, 95% CI 0.82 - 1.17). The benefit of dapagliflozin with respect to CV death or HF hospitalization was similar in the subgroup with CVD, as well as those with multiple risk factors only. A meta-analysis of the three trials suggested consistent benefits on reducing the composite of HF hospitalization or CV death, as well as on the progression of kidney disease, regardless of existing atherosclerotic CVD or a history of HF, while the reduction in MACE was only apparent in patients with established CVD.[312] The CREDENCE trial[313] randomized 4401 patients with T2DM and albuminuric CKD (eGFR 30 to <90 mL/min/1.73 m^2) to canagliflozin or placebo, and showed a relative reduction of the primary renal outcome of 30% by canagliflozin after a median follow-up of 2.6 years. In addition, canagliflozin significantly reduced the pre-specified secondary CV outcomes of three-point MACE (HR 0.80, 95% CI 0.67 - 0.95; $P=0.01$) and hospitalization for HF (HR 0.61, 95% CI 0.47−0.80; $P < 0.001$) compared with placebo in this very high-CV risk group of patients (see *section 11*).[313]

The CV benefits of SGLT2 inhibitors are mostly unrelated to the extent of glucose lowering and occur too early to be the result of weight reduction. The rapid separation of placebo and active arms in the four studies in terms of reduction in HF hospitalizations indicates that the beneficial effects achieved in these trials are more likely the result of a reduction in HF-associated events. They could involve effects on haemodynamic parameters, such as reduced plasma volume, direct effects on cardiac metabolism and function, or other CV effects.[314−317]

7.1.2.3 Implications of recent cardiovascular outcome trials

For the first time in the history of DM, we have data from several CVOTs that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The results obtained from these trials, using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE), strongly suggest that these drugs should be recommended in patients with T2DM with prevalent CVD or very high/high CV risk, such as those with target-organ damage or several CVRFs (see *Table 7*), whether they are treatment naïve or already on metformin. In addition, based on the mortality benefits seen in LEADER and EMPA-REG OUTCOME, liraglutide is recommended in patients with prevalent CVD or very high/high CV risk, and empagliflozin is recommended in patients with prevalent CVD, to reduce the risk of death. The recommendation for empagliflozin is supported by a recent meta-analysis which found high heterogeneity between CVOTs in mortality reduction.[312] The benefits seen with GLP1-RAs are most likely derived through the reduction of arteriosclerosis-related events, whereas SGLT2 inhibitors seem to reduce HF-related endpoints. Thus, SGLT2 inhibitors are potentially of particular benefit in patients who exhibit a high risk for HF. In subjects with newly diagnosed T2DM without CVD and at moderate risk, the results of UKPDS suggest a beneficial effect of metformin in primary prevention. Although the trial-based evidence for metformin monotherapy from UKPDS is not as strong as with the novel drugs tested in recent CVOTs, it is supported by extensive observations from everyday clinical practice. In the recent CVOTs, a majority of patients received metformin before and concurrently with the newer drug under test. However, because metformin was similarly present in the active and placebo groups, it is unlikely to explain the beneficial effects of the newer drugs under test. Thus, the choice of drug to reduce CV events in patients with T2DM should be prioritized based on the presence of CVD and CV risk (*Figure 3*).

Table 10 Patient characteristics of cardiovascular safety studies with glucose-lowering agents[a]

	SGLT2 inhibitors				GLP1-RAs							DPP4 inhibitors				
Trial	**EMPA-REG OUTCOME**[306]	**CANVAS**[309]	**DECLARE–TIMI 58**[311]	**CREDENCE**[313]	**ELIXA**[297]	**LEADER**[176]	**SUSTAIN-6**[299]	**EXSCEL**[158]	**Harmony Outcomes**[301]	**REWIND**[303]	**PIONEER 6**[300]	**SAVOR–TIMI 53**[291]	**EXAMINE**[292]	**TECOS**[293]	**CARMELINA**[294]	**CAROLINA**[277]
Baseline	**Empagliflozin vs. placebo**	**Canagliflozin vs. placebo**	**Dapagliflozin vs. placebo**	**Canaglifozin vs. placebo**	**Lixisenatide vs. placebo**	**Liraglutide vs. placebo**	**Semaglutide vs. placebo**	**Exenatide vs. placebo**	**Albiglutide vs. placebo**	**Dulaglutide vs. placebo**	**Oral Semaglutide vs. placebo**	**Saxagliptin vs. placebo**	**Alogliptin vs. placebo**	**Sitagliptin vs. placebo**	**Linagliptin vs. placebo**	**Linagliptin vs. glimiperide**
n	7020	10 142	17160	4401	6068	9340	3297	14 752	9463	9901	3182	16 492	5400	14 671	6979	6033
Age (years)	63	63	63	63	60	64	64	62	64	66	66	65	61	66	65	64
DM (years)	57% >10	13.5	11.8	15.8	9.3	12.8	13.9	12.0	14.1	10.5	14.9	10	7.2	9.4	14.7	6.2
Body mass index (kg/m^2)	30.6	32.0	32.1	31.3	30.1	32.5	32.8	31.8	32	32.3	32.3	31	29	30	31.3	30.1
Insulin (%)	48	50	~40	65	39	44	58	46	60	24	61	41	30	23	58	0
HbA1c (%)	8.1	8.2	8.3	8.3	7.7	8.7	8.7	8.0	8.7	7.2	8.2	8.0	8.0	7.3	7.9	7.2
Previous CVD (%)	99	65	40	50.4	100	~81	~83	73	100	31	35	78	100	100	57	42
CV risk inclusion criteria	**MI, CHD, CVD, or PVD**	**MI, CHD, CVD, or PVD**	**CVD or at least one CVRF**	**CKD**	**ACS <180 days**	**Age ≥50 years and CVD,[b] or CKD, or age ≥60 years and at least one CVRF**		**CHD, CVD, or PVD27% no previous CV event**	**MI, CHD, CVD, or PVD**	**Age ≥50 years and CVD or CVRFs**	**Age ≥50 years and CVD, or CKD, or age ≥60 years and CVRFs**	**Age ≥40 years and CVD (CHD, CVD, or PVD), or age ≥55 years and at least one CVRF**	**ACS <90 days**	**CHD, CVD, or PVD**	**CVD and/or CKD**	**CVD or evidence of vascular-related end-organ damage, or age ≥70 years, or at least two CVRFs**
Hypertension (%)	94	89	89	96.8	76	92	92	90	86	93	94	81	83	86	95	90
Follow-up (years)	3.1	2.4	4.5	2.6	2.1	3.8	2.1	3.2	1.6	5.4	1.3	2.1	1.5	2.8	2.2	6.3

ACS = acute coronary syndromes; CANVAS = Canagliflozin Cardiovascular Assessment Study; CARMELINA = Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; CAROLINA = Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; CHD = coronary heart disease; CKD = chronic kidney disease > stage 3; CREDENCE = Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial; CV = cardiovascular; CVD = cardiovascular disease; CVRF = cardiovascular risk factor; DECLARE–TIMI 58 = Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction 58 trial; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; GLP1-RA = glucagon-like peptide-1 receptor agonist; Harmony Outcomes = Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; HbA1c = haemoglobin A1c; HF = heart failure (New York Heart Association class II or III); LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI = myocardial infarction; PIONEER 6 = A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; PVD = peripheral vascular disease; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53; SGLT2 = sodium-glucose co-transporter 2; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Follow-up is median years.

[a]Modified after.[318]

[b]CVD in LEADER and SUSTAIN-6 included CHD, CVD, PVD and HF.

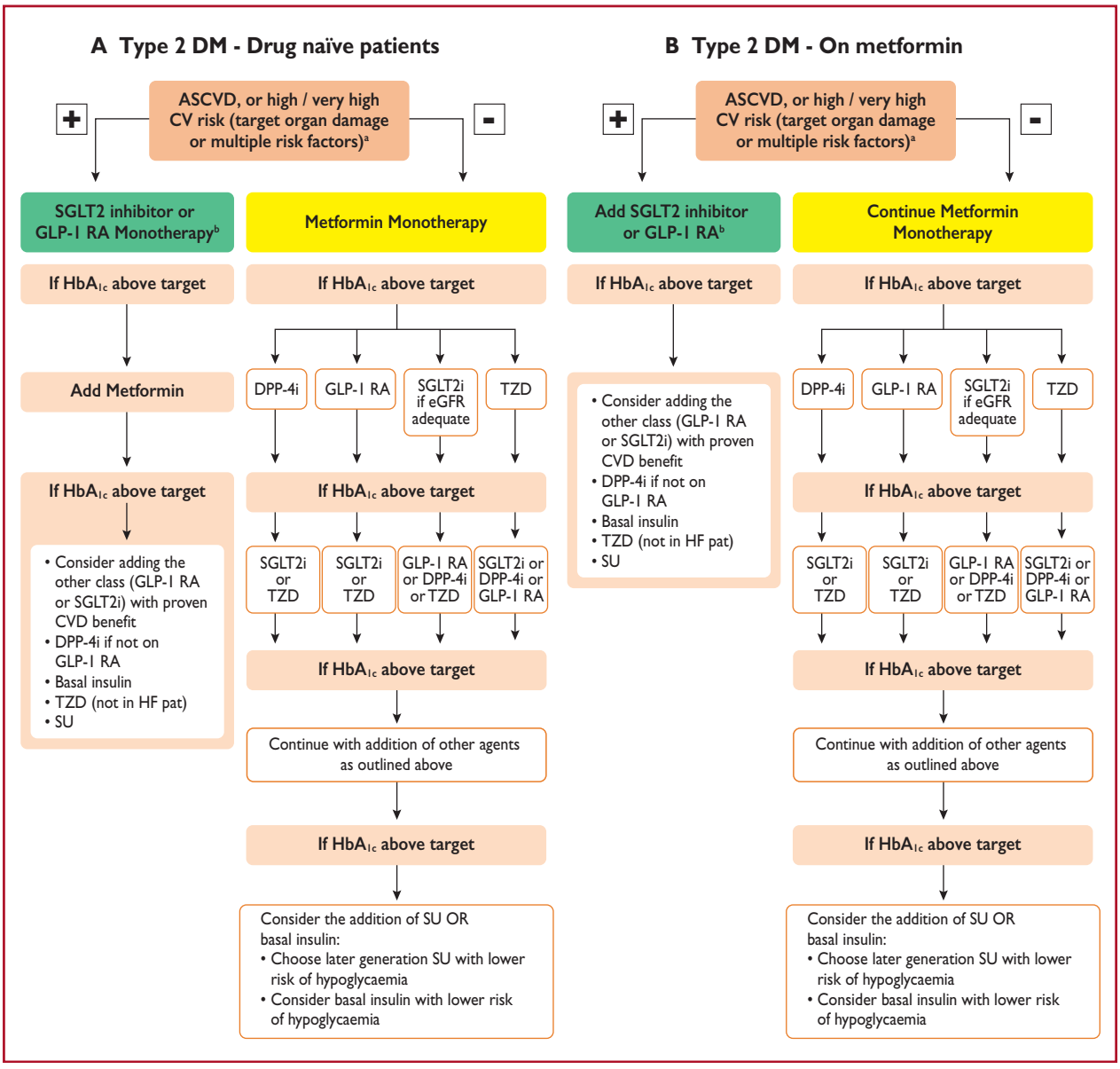

Figure 3 Treatment algorithm in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease, or high/very high CV risk Treatment algorithms for (*A*) drug-naïve and (*B*) metformin-treated patients with diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease: CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonist; HbA1c = haemoglobin A1c; HF = heart failure; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SU = sulphonylureas; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione. [a]See *Table 7*. [b]Use drugs with proven CVD benefit.

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

ACS = acute coronary syndromes; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; GLP1-RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]See *Table* 7.