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CURRENT OPINION

Non-insulin antidiabetic pharmacotherapy in patients with established cardiovascular disease: a position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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The aim of antidiabetic pharmacotherapy in patients with type 2 diabetes and cardiovascular disease

Patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (CVD) have a particularly high risk for recurrent major adverse cardiovascular events (MACE).[1] Compared with patients with CVD only, the risk for MACE increases by about 1.7-fold in those with CVD and T2DM.[1] Type 2 diabetes mellitus is a stronger risk factor for MACE than the angiographic severity of coronary heart disease (CHD).[2] Reducing the T2DM-associated risk is therefore of utmost importance. Antidiabetic pharmacotherapy reduces plasma glucose and dosing is adjusted according to HbA1c concentration. European Society of Cardiology (ESC) guidelines recommend HbA1c values <7% for patients with CVD.[3] While controlling HbA1c levels is important to prevent both microvascular disease and atherosclerosis progression, the association between HbA1c and short to mid-term cardiovascular events is less well defined. Albeit early trials showed a trend towards MACE reduction with glucose lowering agents,[4,5] recent data indicates that only specific anti-

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diabetic therapies reduce MACE,[6–9] and this effect appears to be independent of baseline HbA1c level or HbA1c reduction.[6,7] Of note, these recent outcome trials were primarily designed as non-inferiority trials to test for cardiovascular safety with subsequent hierarchical testing for superiority only. Furthermore, in most of these trials it was possible to add other glucose-lowering therapies after randomization to achieve adequate glycaemic control resulting in an imbalance of other antidiabetic therapies between intervention and control arm which may have influenced study results. This position paper will critically appraise emerging evidence regarding antidiabetic pharmacotherapy in patients with T2DM and mostly stable CVD. While patients with acute coronary syndrome (ACS) have been excluded from recent studies, the ELIXA and the EXAMINE trials specifically recruited patients post ACS.[10,11] We have critically assessed: (i) the relevance of the study population, the presence of CVD, statistical power, concomitant cardiovascular treatments, and exclusion criteria (*Table 1*, Supplementary material online, *Table S1*), (ii) the effects of antidiabetic pharmacotherapy on cardiovascular endpoints (*Figure* 1, *Table 2*, Supplementary material online, *Table S2*), and (iii) the occurrence of specific adverse effects (*Table 2*, Supplementary material online, *Table S2*).[12–15] In this article, we report relative risk reduction (RRR) for comparability of trial results and number needed to treat/harm (NNT/NNH) and absolute risk reduction (ARR) for the duration of the respective study follow-up to show the magnitude of the effect (Supplementary material online, *Table S2*). Based on current data, this article summarizes the positions of the ESC WG on Cardiovascular Pharmacotherapy on the selection of antidiabetic pharmacotherapy and potential drug combinations. The mechanisms of specific antidiabetic therapies[16] and insulin therapy (including insulin analogues) will not be discussed.

Non-insulin antidiabetic pharmacotherapy and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease—a critical appraisal of emerging clinical data

Antidiabetic pharmacotherapy with beneficial effects on primary cardiovascular outcome

The effects of the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (using two different dosages) were compared to placebo in 7020 patients with T2DM and established CVD—including 76% of patients with CHD—in the EMPA-REG OUTCOME trial.[7] Relevant exclusion criteria were ACS within 2 months and glomerular filtration rate (GFR) < 30 mL/min. The primary composite endpoint of non-fatal (excluding silent) myocardial infarction (MI), non-fatal stroke, and cardiovascular death was significantly reduced by 14% RRR in a pooled analysis of the two empagliflozin dosages during a median follow-up time of 3.1 years. This equals to an ARR from 12.1% to 10.5% (NNT = 61). The reduction in the primary endpoint was driven by a RRR of cardiovascular death by 38% (NNT = 45) with a further RRR of all-cause mortality by 32% (NNT = 39). In parallel, hospitalization for heart failure (HF) was reduced by 35% RRR corresponding to an ARR from 4.1% to 2.7% (NNT = 72). Empagliflozin therapy was associated with genital infections (NNH = 22). Recently, the results of the CANVAS Program assessing the effects of canagliflozin, another SGLT2 inhibitor, were published.[9] The CANVAS Program analysed 10 142 patients with T2DM who had a history of (66%) or were at risk for CVD from the CANVAS and CANVAS-R trial with identical main inclusion criteria but differences with regard to the study design such as the duration of follow-up (median 2.4 years) and usage of low and high dose of canagliflozin. The primary composite endpoint of non-fatal MI, non-fatal stroke, and cardiovascular death was significantly reduced by 14% RRR equalling to an ARR from 9.5% to 8.1% for a 3-year period (NNT = 72). While there was no significant reduction of all-cause mortality, a further exploratory analysis indicated an reduction of hospitalization for HF by 33% corresponding to an estimated ARR from 2.6% to 1.7% (NNT = 104). Canagliflozin therapy was associated with an increased risk of amputation (NNH = 115), low-trauma fractures ($P = 0.06$), and infections of male genitalia (NNH = 14). A pharmacovigilance analysis of the FDA confirms that the use of canagliflozin is associated with an increased risk of amputations.[17]

As highlighted by the European Medicines Agency (EMA), in elderly patients the risk of adverse effects related to volume-depletion increases with SGLT2 inhibitors, particularly with the higher dose. Furthermore, empagliflozin and canagliflozin should be interrupted in patients who are hospitalized for major surgical procedures and serious medical illness due to an increased risk of ketoacidosis.[18] Retrospective real-world data generate the hypothesis that the effect on hospitalization for HF and death might be generalizable to other SGLT2 inhibitors.[19] However, the results of ongoing randomized controlled trials with the SGLT2 inhibitors dapagliflozin (DECLARE-TIMI58, NCT01730534) and ertugliflozin (VERTIS CV, NCT01986881) are needed to prove beneficial cardiovascular effects of these SGLT2 inhibitors.

The glucagon-like peptide-1 (GLP-1) receptor agonist (RA) liraglutide given once daily subcutaneously was compared to placebo in 9340 patients with T2DM and established CVD (81%) or an age ≥ 60 years with at least one cardiovascular risk factor suggesting end organ damage, in the LEADER study.[6] The primary composite endpoint including non-fatal MI, non-fatal stroke, and cardiovascular death was significantly reduced by 13% RRR during a median follow-up of 3.8 years equalling to an ARR from 14.9% to 13.0% (NNT = 55). The reduction was driven by a 22% RRR of cardiovascular death (NNT = 79) with an additional RRR of all-cause mortality by 15% (NNT = 71). While there was no significant overall increase of adverse effects there was a significantly increased rate of drug discontinuation due to gastrointestinal symptoms (NNH = 79) and acute gallstone disease (NNH = 85). Semaglutide, another GLP-1 RA, given once weekly subcutaneously, reduced the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke by 26% RRR in the SUSTAIN-6 study in patients ($n = 3297$) with T2DM who had a history of (59%) or were at risk for CVD during a median follow-up time of 3.8 years, corresponding to an ARR from 8.9% to 6.6% (NNT = 43).[8] This lower risk was mainly driven by a RRR of non-fatal stroke by 39% (NNT = 97). Long-term glycaemic control with semaglutide in the SUSTAIN-6 trial was particularly pronounced

Table 1 Relevance of studies for patients with type 2 diabetes and established cardiovascular disease

Study	Class of drug	Drug	Power (*n* of patients with primary endpoint)	Established cardiovascular disease	Concomitant cardiovascular medication	Relevant exclusion criteria	Relevance of study
EMPA-REG OUTCOME	SGLT2 inhibitor	Empagliflozin	Adequate (772)	99%	Vast majority	Recent ACS, eGFR < 30 mL/min, medical history of cancer	Highly relevant for stable CVD
CANVAS Program		Canagliflozin	Strong (1011)	66%	Majority	Recent ACS, NYHA IV, eGFR < 30 mL/min, medical history of cancer	Highly relevant for stable CVD
LEADER	GLP-1 receptor agonist	Liraglutide	Strong (1302)	81%	Majority	Recent ACS, NYHA IV, malignant neoplasm	Highly relevant for stable CVD
SUSTAIN-6		Semaglutide	Moderate (254)	59%	Majority	Recent ACS, NYHA IV, malignant neoplasm, pancreatitis	Relevant for stable CVD
EXSCEL		Exenatide	Strong (1744)	73%	Majority	eGFR < 30 mL/min, personal or family history of medullary thyroid cancer, history of pancreatitis	Highly relevant for stable CVD
ELIXA		Lixisenatide	Adequate (805)	100% (ACS)	Vast majority	eGFR < 30 mL/min, pancreatitis, gastrointestinal disease, personal or family history of medullary thyroid cancer	Highly relevant for ACS
PROACTIVE	Thiazolidinedione	Pioglitazone	Strong (1086)	100%	Majority	Recent ACS, symptomatic heart failure, ketoacidosis	Highly relevant for stable CVD
SAVOR-TIMI 53	Dipeptidyl peptidase 4 inhibitor	Saxagliptin	Strong (1222)	79%	Majority	Recent ACS	Highly relevant for stable CVD
EXAMINE		Alogliptin	Adequate (621)	100% (ACS within the previous 15–90 days)	Vast majority	Recent ACS, NYHA IV	Highly relevant for ACS
TECOS		Sitagliptin	Strong (1690)	74%	Majority	eGFR < 30 mL/min, ketoacidosis	Highly relevant for stable CVD
UKPDS 34	Biguanide	Metformin	Moderate (139 during follow-up of > 10 years)	NR	Limited use	>65 years of age	Limited relevance for CVD
STOP-NIDDM	Alpha-glucosidase inhibitor	Acarbose (compared to sulfonylurea)	Hypothesis generating study (47)	<5%	Limited use	Any cardiovascular event within the last 6 months	Limited relevance for CVD

ACS, acute coronary syndrome; CVD, cardiovascular disease; NA, not applicable; NR, not reported.

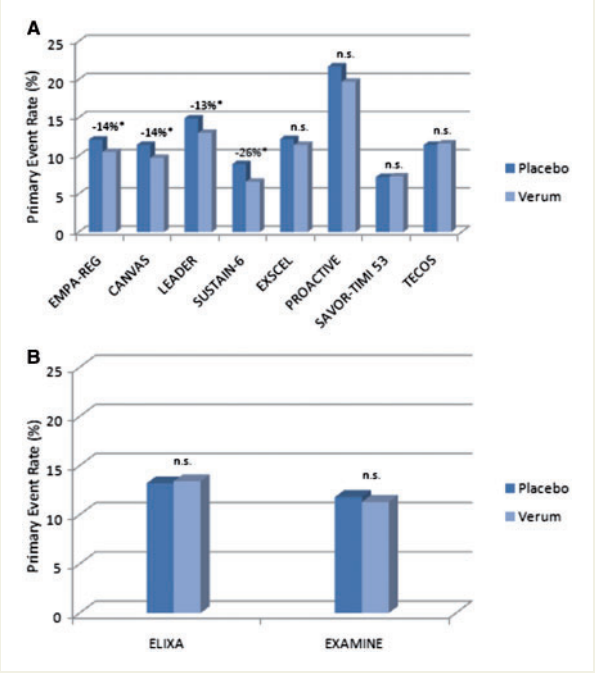

Figure 1 Primary cardiovascular composite endpoint of randomized controlled trials on non-insulin antidiabetic pharmacotherapies. (*A*) Studies with stable cardiovascular disease or patients at high risk for cardiovascular disease. (*B*) Studies with acute coronary syndrome; The bars show the event rate of the primary cardiovascular composite endpoint during the study follow-up in the intervention and control group. Numbers indicate the relative risk reduction. *$P < 0.05$.

with a dose-dependent lower HbA1c of 0.7–1.0% than in the control group after 2 years. While fewer serious adverse events and a lower rate of new or worsening nephropathy occurred with semaglutide, more patients discontinued treatment mainly because of gastrointestinal disorders (NNH = 66). Retinopathy rates were significantly higher with semaglutide (NNH = 78). In the recently published EXSCEL trial, the GLP1 RA exenatide (extended-release) given once weekly was compared to placebo in 14 752 patients with T2DM including 73% of patients with established CVD.[20] There was a non-significant trend for a reduction of the primary composite endpoint including non-fatal MI, non-fatal stroke, and cardiovascular death ($P = 0.06$). A further exploratory analysis indicated a reduction of all-cause mortality by 14% corresponding to an estimated ARR from 7.9% to 6.9% (NNT = 100). In the exenatide arm there was a higher number of thyroid papillary carcinomas ($n = 10$ vs. 4). In patients with T2DM and ACS, no benefit was observed with the GLP-1 RA lixisenatide with a shorter half-life in the ELIXA study.[10] Additionally, more patients in the lixisenatide arm stopped treatment due to gastrointestinal disorders during the follow-up of median 2.1 years (NNH = 27).

Antidiabetic pharmacotherapy with neutral effects on primary cardiovascular outcome

The thiazolidinedione pioglitazone was compared with placebo in 5238 patients with T2DM and established CVD in the PROACTIVE study.[5] The comprehensive primary endpoint including peripheral artery disease, ACS, coronary interventions, and all-cause mortality in addition to non-fatal MI and stroke was not significantly affected by pioglitazone. However, the secondary composite endpoint of all-cause mortality (in contrast to cardiovascular mortality used for the primary composite endpoint in most other trials), non-fatal MI and stroke was significantly reduced by 16% RRR corresponding to an ARR from 13.6% to 11.6% during a mean follow-up of 34.5 months (NNT = 49). Hospitalization for HF was increased with pioglitazone by 40% equalling to an absolute increase from 4.1% to 5.7% (NNH = 62). The main adverse effect was oedema without HF (NNH = 12). Moreover, in the IRIS study pioglitazone was tested in 3876 patients with insulin resistance (but without established T2DM) and ischaemic stroke or TIA within 6 months. In this study, pioglitazone decreased the primary composite endpoint of non-fatal and fatal MI as well as stroke by 24% RRR during a median follow-up time of 4.8 years equalling to an ARR from 11.8% to 9.0% (NNT = 36).[21] Pioglitazone, however, was associated with a significantly higher frequency of oedema (NNH = 9.3) and bone fractures (NNH = 53).

The dipeptidyl peptidase 4 (DPP-4) inhibitor saxagliptin was compared to placebo in the SAVOR-TIMI 53 study[22] in 16 492 patients with T2DM who had a history of (78%) or were at risk for CVD. The study showed non-inferiority (but not superiority) for saxagliptin regarding the primary composite endpoint including MI, ischaemic stroke, and cardiovascular death during a median follow-up of 2.1 years. Hospitalization for HF significantly increased by 27% equalling to an absolute increase from 2.8% to 3.5% (NNH = 140). This increased risk was limited to the first 12 months of follow-up.[23] This surprising but critical result of a secondary endpoint without a priori adjustment for multiple comparisons was not confirmed in observational studies and needs to be verified in a further randomized controlled trial. The DPP-4 inhibitor alogliptin was investigated in 5380 patients with T2DM who had a recent ACS in the EXAMINE trial.[11] The primary composite endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke showed non-inferiority but not superiority for alogliptin during a median follow-up time of 18 months. The DPP-4 inhibitor sitagliptin was investigated in 14 671 patients with T2DM and CVD in the TECOS trial during a median follow-up of 3 years.[24] Sitagliptin showed non-inferiority but not superiority with regard to the composite of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. Overall, rates of HF hospitalization were not significantly different between treatment arms in the EXAMINE and the TECOS trials. The effect of the DDP-4 inhibitor linagliptin on cardiovascular events is tested in the ongoing CAROLINA study (NCT01243424) compared to the sulfonylurea glimepiride while there is no published plan for a randomized controlled trial about the effect of the DDP-4 inhibitor vildagliptin on cardiovascular outcome.

Antidiabetic pharmacotherapy with hypothesis-generating studies with regard to a beneficial effect on cardiovascular outcomes

In a predefined sub-analysis of the UKPDS 34 study, the biguanide metformin was compared to conventional care primarily consisting of diet in 753 overweight patients (>120% ideal bodyweight) with

Table 2 Outcome for patients with type 2 diabetes and established cardiovascular disease

Study	Class of drug	Drug	Median follow-up (years)	Reduction of (NNT)			Specific adverse effects (NNH[a])	Evidence for benefit/ harm of investigational drug
				Primary composite cardiovascular endpoint	Secondary cardiovascular endpoints	All-cause mortality		
EMPA-REG OUTCOME	SGLT2 inhibitor	Empagliflozin	3.1	Yes (61)	Cardiovascular death (45), heart failure hospitalization (72)	Yes (39)	Genital infection (22), volume depletion in patients ≥75 years, ketoacidosis	Relevant benefit, particularly for patients at risk or with HF
CANVAS[a] Program		Canagliflozin	2.4	Yes (72)[a]	Heart failure hospitalization (104[a], exploratory analysis)	No	Amputation (115[a]), low-trauma fractures, male genitalia infection (14[a])	Relevant benefit at the cost of increased risk of amputations
LEADER	GLP-1 receptor agonist	Liraglutide	3.8	Yes (55)	Cardiovascular death (79)	Yes (71)	Injection site reaction with once daily sc injection (233), drug discontinuation due to nausea (79), acute gallstone disease (85)	Relevant benefit
SUSTAIN-6		Semaglutide	2.1	Yes (43)	Non-fatal stroke (97)	No	Retinopathy (78), gastrointestinal disorders (66)	Relevant benefit
EXSCEL		Exenatide	3.2	No	No	No [exploratory analysis yes (100)]	Thyroid papillary carcinomas (n = 10 vs. 4)	Non-significant trend for benefit
ELIXA		Lixisenatide	2.1	No	No	No	Gastrointestinal disorders leading to drug discontinuation (27)	No benefit
PROACTIVE	Thiazolidinedione	Pioglitazone	2.9	No	Composite endpoint of all-cause mortality, non-fatal MI and stroke (49), increase of HF hospitalization (NNH = 62)	No	Oedema wo heart failure (12)	Potential benefit, increased risk of HF hospitalization
SAVOR-TIMI 53	Dipeptidyl peptidase 4 inhibitor	Saxagliptin	2.1	No	Increase of HF hospitalization (NNH = 140)	No	Increased (but very rare) occurrence of non-fatal angioedema	No benefit, increased risk of HF hospitalization
EXAMINE		Alogliptin	2.1	No	No	No	NR	No benefit
TECOS		Sitagliptin	3.0	No	No	No	NR	No benefit
UKPDS 34	Biguanide	Metformin	10.7	Yes (11)	Non-fatal MI (16)	Yes (11)	NR	Potential cardiovascular benefit in patients wo CVD
STOP-NIDDM	Alpha-glucosidase inhibitor	Acarbose (compared to sulfonylurea)	3.3[8]	Yes (40)	Non-fatal MI (62)	NR	Premature study drug discontinuation (8)	Hypothesis generation for potential cardiovascular benefit in patients wo CVD

NNT/NNH number needed to treat/harm was calculated only for significant results with the formula 100/absolute difference of endpoint in % for the given follow-up period.
ACS, acute coronary syndrome; NR, not reported.
[a]NNTs/NNHs were calculated based on the given event rates per 1000 patient years and transformed for a follow-up of 3 years.

newly diagnosed diabetes and a mean age of 53 years.[4] Concomitant therapy consisted of antihypertensive therapy in 15%, 'more than one aspirin daily' in 1.8% and lipid lowering therapy in 0.1% of patients. The primary outcome measures included aggregates of any diabetes-related events, diabetes-related death and all-cause mortality. These endpoints were significantly reduced by 32% to 42% RRR within a long-term follow-up of median 10.7 years. With regard to cardiovascular endpoints MI was significantly reduced by 39% RRR compared to conventional therapy (but not compared to intensive therapy with sulfonylurea or insulin) equalling to an ARR from 17.8% to 11.4% (NNT = 16). There was no significant difference with regard to stroke or peripheral artery disease. As mentioned by EMA lactic acidosis is a rare but relevant complication of metformin therapy particularly in situations of hypoxia. Metformin is contraindicated in patients with severe chronic kidney disease (GFR < 30 mL/min, Supplementary material online, *Table S3*).

In the STOP-NIDDM trial, the alpha-glucosidase inhibitor acarbose was compared to placebo in 1429 patients with impaired glucose tolerance and without a cardiovascular event within the last 6 months.[25] The mean age was 55 years, with 5% of patients having a history of CVD and 21% taking cardiovascular medications. Early drug discontinuation was observed in 31% of subjects in the acarbose arm, mostly due to gastrointestinal side effects, compared to 19% in the placebo arm (NNH = 8). During a mean follow-up of 3.3 years cardiovascular events, defined as secondary endpoint, were reduced by 49% RRR in the acarbose arm equalling to an ARR from 4.7% to 2.2% (NNT = 40). While only 13 clinical cases of MI were observed there was a statistically significant RRR of 91% with acarbose (NNT = 62). Methodological aspects such as a modified intention-treat-analysis omitting the follow-up of 4.3% of originally randomized patients further limit the results of this hypothesis-generating study.

While sulfonylureas are widely used no data about their safety in patients with CVD are available. In addition they promote weight gain, and cause hypoglycaemia—mainly with first generation sulfonylureas and immediate release formulations—, the latter two adverse effects being associated with increased cardiovascular risk.[26]

Patients at risk for heart failure

The EMPA-REG OUTCOME, CANVAS Program, LEADER, SUSTAIN-6, EXSCEL, ELIXA, SAVOR-TIMI 53, EXAMINE, and TECOS study report on the proportion of patients with a diagnosis of HF at randomization which ranges from 10% in the EMPA-REG OUTCOME trial to 28% in the EXAMINE study (Supplementary material online, *Table S4*). Specific data regarding HF are limited to NYHA functional class in two studies.[6,24]

The CANVAS Program, LEADER, SUSTAIN-6, EXSCEL, ELIXA, SAVOR-TIMI 53, EXAMINE, and TECOS trial analysed whether the presence of HF affected the primary outcome but did not find any significant interaction. Heart failure hospitalization was significantly increased in the SAVOR-TIMI 53 study with saxagliptin and in the PROACTIVE study with pioglitazone. Thus, they should not be used in patients at risk for HF or with established HF. According to an analysis of the SAVOR-TIMI 53 study patients with elevated Nt-proBNP or chronic kidney disease (GFR < 60 mL/min) may be at risk for HF.[23] On the contrary, this endpoint was significantly reduced in the EMPA-REG OUTCOME study with empagliflozin and in an exploratory analysis of the CANVAS Program trial.

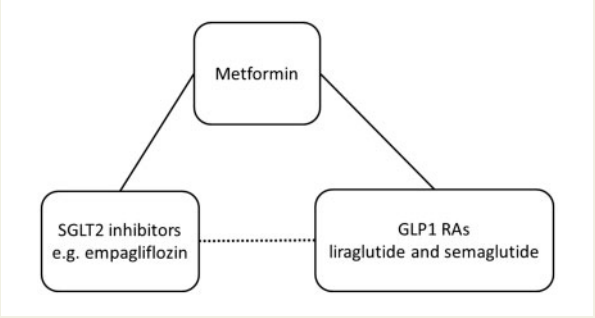

Figure 2 Positions on non-insulin antidiabetic pharmacotherapies and potential combinations in patients with type 2 diabetes and stable cardiovascular disease. The positions about the choice of antidiabetic pharmacotherapy are based on current data on reduction of cardiovascular events. SGLT2, sodium glucose cotransporter 2; GLP1, glucagon-like peptide-1; RA, receptor agonist.

Aiming at improving cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease—positions based on current trials data

In patients with T2DM and CVD, antidiabetic pharmacotherapy should be chosen based on beneficial effects on cardiovascular events in Phase III and post-marketing trials (*Figure* 2). Accordingly, EMA has recently stated that improvement of glycaemic control and reduction of cardiovascular morbidity and mortality should be major goals in the treatment of T2DM (SmPC of empagliflozin). So far, the SGLT2 inhibitors empagliflozin and canagliflozin, and the GLP-1 RAs liraglutide and semaglutide reduced cardiovascular events in adequately powered studies with contemporary concomitant cardiovascular treatment in patients with established CVD, mainly stable CHD and with the exclusion of recent ACS. For canagliflozin the net benefit is restricted by an increased rate of amputations. For semaglutide approval of EMA is pending. Hence, currently the SGLT2 inhibitor empagliflozin, and the GLP-1 RA liraglutide may be considered preferred treatment choices. So far, the 2016 European Guidelines on CVD prevention recommended that in patients with T2DM and CVD, an SGLT2 inhibitor should be considered early in the therapeutic process to reduce cardiovascular and total mortality (Class IIa recommendation).[3] In patients above 75 years of age, the use of the lower dose of empagliflozin is recommended to avoid adverse events related to volume depletion. While the power of outcome data for metformin is limited, economic reasons, ample clinical experience, and safe use in combination with other antidiabetic therapies (see Supplementary material online, *Table S5*) are reasons to continue to use this drug as first choice.

When these preferred treatments are not sufficient to achieve therapeutic goals or are contraindicated, the thiazolidinedione pioglitazone, the GLP1 RA exenatide, and DPP-4 inhibitors may be further choices due to their neutral or potentially beneficial effects on cardiovascular events in adequately powered, contemporary trials. While pioglitazone did not reduce the primary cardiovascular endpoint in the PROACTIVE trial it reduced the secondary composite endpoint of cardiovascular events.[5] Exenatide showed a non-significant

reduction of the primary composite endpoint by 9%. DPP-4 inhibitors may be considered for treatment of patients with T2DM and stable CVD based on their favourable safety profile. Contemporary trials have shown a neutral effect of the DPP-4 inhibitors saxagliptin and sitagliptin on the primary cardiovascular endpoint in patients with stable CVD or at risk for CVD. There is no evidence supporting a combination of DPP-4 inhibitors with a GLP1 RA.

Future clinical trials should pursue the possible benefit of antidiabetic pharmacotherapy on hard cardiovascular endpoints in various specified types of CVD. A reduction of HF hospitalization with the SGLT2 inhibitors empagliflozin and canagliflozin prompts *ad hoc* trials in patients with HF. While post-ACS trials with the GLP-1 RA lixisenatide and the DPP-4 inhibitor alogliptin have shown a neutral effect on the clinical outcome, further specific post-ACS trials are needed with antidiabetic drugs having shown a benefit in patients with stable CVD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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