

Commentary**Clinical Implications of Cardiovascular Outcome Trials in Type 2 Diabetes: From DCCT to EMPA-REG**

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ABSTRACT

Cardiovascular disease is a major threat to people with diabetes. Attempts have long been made to lower cardiovascular risk by means of glucose-lowering treatment. Initially, it seemed that was an option, but subsequent trials could not verify the original observations and there was concern that some glucose-lowering drugs can actually cause cardiovascular harm. This led medical product agencies in the United States and Europe to require major outcomes trials before accepting new glucose-lowering drugs. The least requirement was noninferiority compared with existing treatment modalities. A large number of such trials have been performed or are ongoing, including >100,000 patients. The drug classes investigated are basal insulin, glucagon-like peptide-1 agonists, dipeptidyl peptidase 4 inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. This commentary discusses these trials and their outcomes, the reasons why several of them ended with neutral results (noninferiority), and that the likelihood for showing cardiovascular benefit was minor or even nonexistent. The surprising and highly rewarding impact of the SGLT2 inhibitor empagliflozin is described and potential mechanisms for cardiovascular benefits are discussed. (*Clin Ther.* 2016;38:1279–1287) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: diabetes, glucose-lowering drugs, clinical trials, prognosis, cardiovascular events.

GLUCOSE LOWERING AND VASCULAR BENEFITS

In 1929 and 1931, Levine¹ and Cruickshank² had already hypothesized that the link between coronary artery disease and diabetes was hyperglycemia. The association between high blood glucose and cardiovascular disease has since been confirmed in several populations.^{3–5} A frequently used example is based on the UK Prospective Diabetes Study (UKPDS). It was reported that each 1% reduction in updated mean HbA1c related to a 37% decrease in microvascular complications, a 14% decrease in fatal and nonfatal myocardial infarction, a 12% decrease in fatal and nonfatal stroke, and a 16% decrease in heart failure during a mean period of follow-up of 10 years.⁶ Although there might be other factors contributing to the relationship between cardiovascular disease and diabetes, the hyperglycemia concept gained much attention and many trials tested the hypothesis that glucose normalization should prevent vascular injury. A glucocentric approach led many trials of new glucose-lowering compounds to focus entirely on the glucose-lowering capacity rather than on cardiovascular outcomes as well.

The very first trial to show vascular benefits by means of glucose lowering was the Diabetes Control and Complications Trial (DCCT) study⁷ and its prolonged follow-up DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC).⁸ These studies investigating insulin treatment in patient with type 1 diabetes revealed that a 2% reduction of HbA1c decreased the microvascular complication retinopathy by 66% (95% CI, 62%–85%; $P < 0.001$) and a



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composite end point of cardiovascular death and nonfatal myocardial infarction or stroke by 57% (95% CI, 12%–79%; $P < 0.02$) during follow-up periods of 9 and 21 years, respectively. It should be noted that this, the first and still unopposed observation of cardiovascular benefits by means of tight, insulin-based, glycemic control, did not appear until 1993.

The pioneering study in patients with type 2 diabetes was the UKPDS in which patients with newly detected type 2 diabetes experienced a 25% (95% CI, 7%–40%; $P < 0.0099$) reduction in microvascular complications and a significant reduction in myocardial infarction, with a 0.9% decrease in HbA1c based on insulin-providing therapy.⁹ Likewise, intensified glycemic control by means of metformin reduced the risk for myocardial infarction.¹⁰ Another promising trial, Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), revealed that pioglitazone reduced the secondary end point of the study, a composite of death and nonfatal myocardial infarction or stroke (hazard ratio [HR] = 0.84; 95% CI, 0.72–0.98; $P = 0.027$), while a small reduction of the primary end point, also including leg amputation and revascularizations, did not reach statistical significance.¹¹ It may be summarized that until then it seemed as if the hypothesis that tight glycemic control had a positive impact on macrovascular disease had been verified. More doubts were raised after the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) trials.^{12–14} ACCORD¹² was prematurely stopped due to a somewhat increased cardiovascular mortality in the intensively managed study arm (HR = 1.27; 95% CI, 0.99–1.63; $P = 0.07$). In a meta-analysis by Ray et al¹⁵ of the by then 5 major glucose-lowering trials (UKPDS, PROACTIVE, ADVANCE, ACCORD, and VADT), a mean reduction of HbA1c by 0.9% between patients randomized to intensive compared with conventional glucose-lowering treatment did not impact all-cause mortality (odds ratio [OR] = 1.02; 95% CI, 0.87–1.19), and nonfatal myocardial infarction was reduced by 17% (OR = 0.83; 95% CI, 0.75–0.93).

The contrast between the initially beneficial and subsequently neutral, or in some aspects negative, outcome of tight glycemic control caused a lot of debate. An important difference between UKPDS and subsequent studies was the lack of effective lipid- and blood pressure-lowering drugs at the time of UKPDS.⁹ The

subsequent glucose-lowering trials investigated patients on efficient blood pressure and lipid-lowering therapy, which might have made the impact of glucose-lowering less apparent. Another explanation for the disappointing results might relate to the side effects of glucose-lowering compounds (Table I) used in high dosages alone or in variety of combinations.¹⁶

SAFETY OF GLUCOSE-LOWERING DRUG

Concerns about the safety profile of glucose-lowering drugs took off after a report by Nissen and Wolski¹⁷ on a meta-analysis of rosiglitazone and cardiovascular events. According to their report, there was a 43% increased risk for myocardial infarction and a 64% increased risk for death by cardiovascular reasons when rosiglitazone was compared with a several other glucose-lowering drugs, including metformin, sulfonylureas, and insulin. Although this meta-analysis was questioned for, among other reasons, the inclusion of several small studies not reasonably representative for the study of cardiovascular outcomes, it caused considerable debate

Table I. Potential side effects of various glucose-lowering drugs.

Potential Side Effect	Pharmacological Agent
Weight gain	Sulfonylureas, glinides, thiazolidinediones, insulin
Gastrointestinal	Biguanides, α -glucosidase inhibitors
Hypoglycemia	Sulfonylureas, glinides, Insulin
Lactic acidosis	Biguanides, SGLT-2 inhibitors
B-12 deficiency	Biguanides
Kidney dysfunction	Biguanides
Urinary tract infection	SGLT-2 inhibitors
Hepatic dysfunction	Glinides, thiazolidinediones, biguanides
Pancreatitis	DPP4 inhibitors, GLP1 agonists
Fractures	Thiazolidinediones
Cardiovascular	Thiazolidinediones

DPP4 = dipeptidyl peptidase 4; GLP1 = glucagon-like peptide-1; SGLT-2 = Sodium-glucose cotransporter-2.

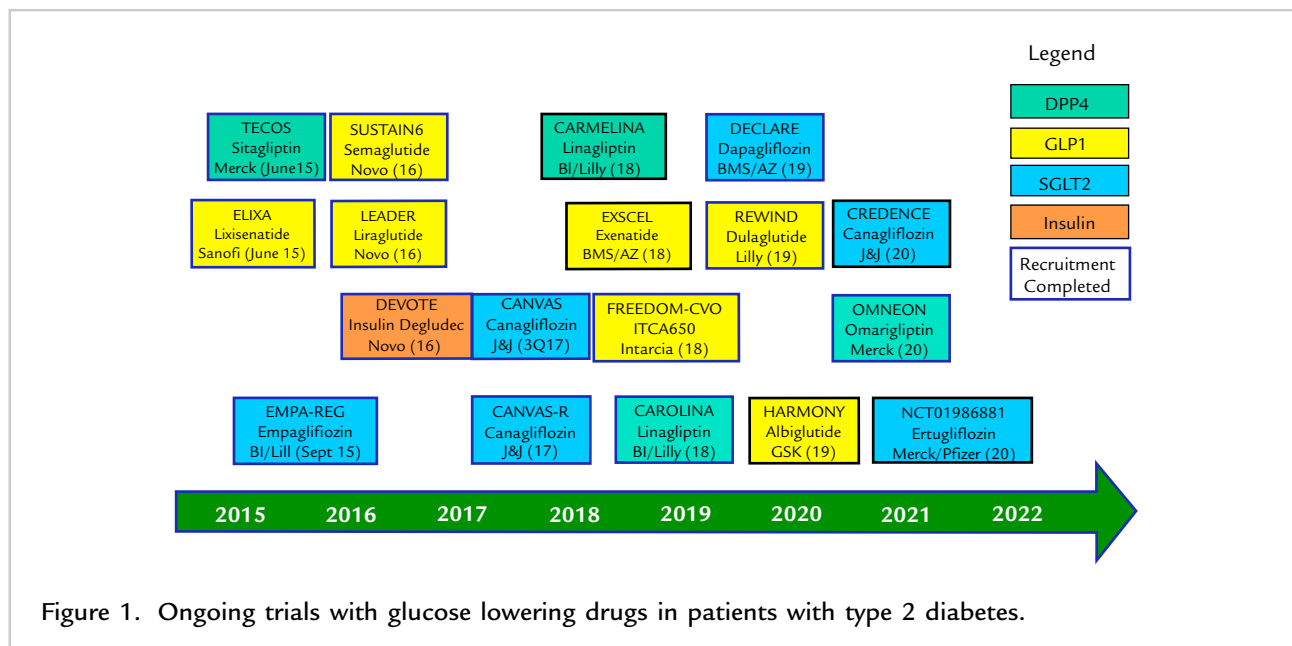


Figure 1. Ongoing trials with glucose lowering drugs in patients with type 2 diabetes.

and worry. It must also be seen as a driving force when the US Food and Drug Administration in December 2008 recommended “Manufacturers developing new drugs in biologics for type 2 diabetes to provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack,” which was subsequently adopted by the European Medicines Agency. As illustrated in Figure 1, the recommendation resulted in a large number of clinical trials of new glucose-lowering drugs, including basal insulin, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, and SGLT-2 inhibitors. Some of these trials have been completed and will be commented on, while others are ongoing. As reported by Holman et al,¹⁸ the cumulative number of patients in these glucose-lowering trials is huge, approaching 115,000 in 2016 and the costs are considerable.

CONTEMPORARY GLUCOSE-LOWERING TRIALS

A summary of important characteristics of the completed trials, Outcome Reduction With Initial Glargine Intervention (ORIGIN),¹⁹ Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR),²⁰ Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE),²¹ Trial to Evaluate

Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS),²² and Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)²³ is presented in Table II. The first trial was ORIGIN,¹⁹ comparing insulin glargine with conventional glucose-lowering treatment in patients with type 2 diabetes, impaired glucose intolerance, and impaired fasting glucose at high vascular risk. The hypothesis that early institution of basal insulin would improve the prognosis could not be confirmed. The next trial to report was SAVOR,²⁰ which studied the impact of saxagliptin added to ongoing treatment in patients with type 2 diabetes at high cardiovascular risk. The incidence of cardiovascular death, nonfatal myocardial infarction, or stroke was more or less superimposed between the saxagliptin and placebo groups. A surprising and much-debated finding was that hospitalization for heart failure was observed in 3.5% of patients randomized to received saxagliptin compared with 2.8% in those allocated to placebo (HR = 1.27; 95% CI, 1.07–1.51; $P = 0.007$). No obvious explanation was actually presented and it might have been a result of chance due to multiple comparisons. EXAMINE²¹ compared alogliptin and placebo added to ongoing therapy in patients with a recent myocardial infarction or unstable angina. There was no difference in cardiovascular death, nonfatal myocardial infarction, or stroke between the study groups. A reassuring finding was the lack of any indication of an increase

Table II. Cardiovascular outcome trials with glucose-lowering drugs (see text for further explanation).

Trial	Treatment Active/Comparator	Patient Type, n	Primary End Point	Median Follow-Up, y	HbA1c by the End of Trial, %	Outcome, HR (95% CI)	Remarks
ORIGIN ²⁵	Insulin glargine/ conventional	T2DM, IFG, IGT + high CV risk, 12,537	Composite of CV death and nonfatal MI or stroke	6.2	Insulin 6.2 Control 6.5	No difference 1.02 (0.94–1.11)	—
SAVOR ²⁶	Saxagliptin/placebo	T2DM + high CV risk, 16,492	Composite of CV death and nonfatal MI or stroke	2.1	Saxagliptin 7.7 Placebo 7.9	No difference 1.00 (0.89-1.12)	Increase in HF hospitalizations in the saxagliptin group
EXAMINE ²⁷	Alogliptin/placebo	T2DM + recent MI/UA, 5380	Composite of CV death and nonfatal MI or stroke	1.5	Alogliptin 7.7 Placebo 8.0	No difference 0.96 (–1.16)	No increase in HF
TECOS ²⁸	Sitagliptin/ placebo	T2DM + CVD, 14,671	Composite of CV death and nonfatal MI or stroke or hospitalization for UA	3.0	Sitagliptin 7.1 Placebo 7.4	No difference 0.98 (0.89–1.08)	No increase in HF
ELIXA ²⁹	Lixisenatide/placebo	T2DM + ACS, 6068	Composite of CV death and nonfatal MI or stroke or hospitalization for UA	2.1	Lixisenatide 7.4 Placebo 7.6	No difference 1.02 (0.89–1.17)	No increase in HF

CV = cardiovascular; CVD = cardiovascular disease; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXAMINE = Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome; HR = hazard ratio; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; MI = myocardial infarction; ORIGIN = Outcome Reduction With Initial Glargine Intervention; SAVOR = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; T2DM = type 2 diabetes mellitus; TECOS = Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin; UA = unstable angina.

in heart failure hospitalizations among alogliptin-treated patients (3.1% vs 2.9%). Sitagliptin or placebo was added to ongoing treatment in TECOS,²² addressing patients with type 2 diabetes and cardiovascular disease. There was no impact on the composite end point of cardiovascular death, nonfatal myocardial infarction and stroke, or hospitalization for unstable angina. In addition, there was no increase in hospitalizations for heart failure in the sitagliptin compared with the placebo group (7.3% vs 7.2%). One study, SAVOR, exploring saxagliptin, found an increase in heart failure hospitalizations, while 2 others, EXAMINE (alogliptin) and TECOS (sitagliptin), did not reveal any signs of such risk. Whether this can be taken as a safety signal for gliptins as a class of drugs or if it should be looked at individually for each of the studied gliptins is a matter for debate. It should be remembered that the molecules of available gliptins are quite different from each other. An FDA safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. As a result, FDA is adding new warnings to the drug labels about this safety issue.

The glucagon-like peptide-1 agonist lixisenatide was studied in the ELIXA trial,²³ recruiting patients with type 2 diabetes and a recent acute coronary syndrome. Lixisenatide did not impact cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina and there were no signs of increased heart failure hospitalizations.

REASONS FOR THE LACK OF IMPACT OF GLUCOSE LOWERING

Why then did the idea that tight glycemic control should have a beneficial impact on cardiovascular outcome not work? There may be several contributing explanations, as listed in [Table III](#). Of primary importance is, of course, that the epidemiologic observation that cardiovascular events increase with increasing blood glucose does not necessarily mean that lowering glucose will impact the outcome. It has to be verified in prospective, randomized trials. In addition, the contemporary glucose-lowering trials have some shortcomings. First, type 2 diabetes is a considerably more complex disease than is expressed by hyperglycemia only. Insulin resistance, dyslipidemia, oxidative stress, inflammatory activation, endothelial

Table III. Potential explanations to the neutral results in contemporary glucose-lowering trials.

Short periods of follow-up
End points may need revision
Resource demanding and costly
Study populations with cardiovascular damage
Long-term benefits and risks not elucidated
Few head-to-head comparisons with available drugs
Firm end points needed, surrogate markers insufficient
Market and regulatory driven rather than academic research

dysfunction, and hypercoagulability are all components in this metabolic disease, in several respects different from type 1 diabetes, which relates to lack of insulin production. The authors behind the STENO 2 trial, which found a considerable impact on morbidity and mortality in type 2 diabetes by intensive, multifactorial treatment, applied the UKDPS risk score in an attempt to explain individual contributions by different treatments.²⁴ They noted that lipid reduction explained about 73%, blood pressure 11%, and HbA1c reduction 13% of the beneficial impact. As discussed by Laakso and Kuusisto,²⁵ cardiovascular disease starts to develop many years before blood glucose reaches the cutoff point defined as diagnostic for type 2 diabetes. Many trials were initiated several years after the diagnosis of type 2 diabetes, a time that might be too late to impact at least macrovascular injuries. This concept gets support from a meta-analysis by Turnbull et al,²⁶ which found that an early start (<5 years from onset of diabetes) in the absence of macro- and microvascular disease manifestations favors more-intensive glucose control than treatment starting later and in patients who already have developed signs of vascular damage. One may in fact want to see studies performed on patients with impaired glucose intolerance that, at least in patients who have suffered an acute myocardial syndrome, seem to have a dismal prognostic impact similar to newly detected diabetes.²⁷ Another drawback may be that end points like myocardial infarction and stroke, frequent end points for many years, are less relevant today than before, due to the improved

prognosis after a myocardial infarction. Sha et al²⁸ reported that the first manifestation of cardiovascular disease in people with diabetes is frequently peripheral artery disease, heart failure, and unstable angina pectoris, with myocardial infarction and stroke following first thereafter. Future trials should therefore reconsider which composite end point to be applied. Finally, ORIGIN, SAVOR, TECOS, EXAMINE, and ELIXA all added the new glucose-lowering drug to already existing, conventional treatment and permitted adjustment of the glucose-lowering therapy in the comparator arm. As can be seen in [Table II](#), glycemic control expressed as HbA1c was fairly similar in the actively treated and control arms. These trials should be considered more as studies of cardiovascular safety, as none showed inferiority regarding such outcomes compared with conventional treatment. This was usually the intention even if some studies claimed that they meant to show superiority from a cardiovascular standpoint, a difficult or impossible target considering too-short periods of follow-up and a lack of a head-to-head comparison between different types of drugs. It may be claimed that many of these trials were driven by market and regulatory reasons rather than an academic interest. In summary, it can be said that if any of the studied drugs had shown cardiovascular benefit, it must have been an expression of an independent, “pleiotropic” effect and not of the glucose lowering per se.

NEW IDEAS AND HOPES: THE EMPA-REG OUTCOME TRIAL

The prognosis for patients with diabetes compared with those without remains worse, especially if complicated by cardiovascular disease. An example is a follow-up during a mean period of 2.5 years of consecutive patients with no previous revascularization ($n = 58,891$; mean age 67 years; diabetes 19%) included in the Swedish Coronary Angiography Angioplasty Registry (SCAAR). The adjusted risk for combined cardiovascular events (first of all-cause mortality, myocardial infarction, stroke, and heart failure) was higher in patients on insulin (HR = 1.63; 95% CI, 1.55–1.72), oral treatment (HR = 1.23; 95% CI, 1.15–1.31) and diet alone (HR = 1.21; 95% CI, 1.12–1.29) compared with patients without diabetes.²⁹ Another example is a report from the Swedish Heart Failure Registry following patients with ($n = 8809$) and without ($n = 27,465$) type 2 diabetes and heart failure

during a median time of 1.9 years.³⁰ Diabetes was a strong predictor of mortality, somewhat stronger in women (OR = 1.72; 95% CI, 1.53–1.94) than in men (OR = 1.47; 95% CI, 1.34–1.61). These findings from recent reports on patients in all-day care make it highly relevant to ask whether there is any light on the horizon for impacting cardiovascular outcomes in patients with diabetes who, despite contemporary treatment possibilities, are in a compromised position. Such hope was seen in the presentation of the randomized, prospective EMPA-REG outcome trial in which the SGLT-2 inhibitor empagliflozin reduced the composite outcome of cardiovascular death or nonfatal myocardial infarction or stroke by 24% (HR = 0.86; 95% CI, 0.74–0.99; $P = 0.0382$) in a population of people with type 2 diabetes and established cardiovascular disease, of whom 4675 were randomized to receive empagliflozin and 2333 to receive placebo.^{31,32} Of the individual components in the composite end points, it was cardiovascular death that was reduced during a median follow-up of 3.1 years. The main driver was a substantial reduction in heart failure hospitalizations (HR = 0.65; 95% CI, 0.50–0.85; $P = 0.0017$). As expected from an SGLT-2 inhibitor, empagliflozin induced a modest reduction in HbA1c (–0.24%, compared with placebo) by the end of the study and small reductions in weight, waist circumference, and blood pressure were also seen.

In an in-depth analysis of the heart failure outcomes in EMPA-REG, Fitchett et al³³ reported on consistent effects of empagliflozin across various subgroups, including patients with and without heart failure at the time of randomization and on different treatment of diabetes and heart failure, including those on angiotensin receptor and beta blockers. In addition, hospitalization for, or death from, heart failure was improved in the group receiving empagliflozin (HR = 0.66; 95% CI, 0.59–0.79; $P < 0.001$). The number of patients needed to treat to prevent 1 heart failure hospitalization or cardiovascular death was estimated to be 35 over 3 years.

In an accompanying editorial,³⁴ it was emphasized that the beneficial impact of empagliflozin on heart failure hospitalizations was already visible within a period of 15 weeks, which is a very rapid onset of action. Although the exact pathophysiologic mechanisms behind these favorable effects cannot be determined by data presented in the EMPA-REG outcome trial, they cannot reasonably relate to the

modest glucose-, blood pressure-, and weight-lowering effects seen in the empagliflozin-treated patients. Similarly rapid onsets of action in heart failure trials have, to the best of our knowledge, only been seen with the use of angiotensin-converting enzyme inhibitors³⁵ and aldosterone antagonists,³⁶ drugs that interfere with neuroendocrine activation due to congestive heart failure. A more plausible, however still speculative, explanation for the EMPA-REG outcome effects, taking the rapid onset of action into account, may be a decrease in volume load related to osmotic diuresis and increased sodium excretion, possibly in combination with reduced arterial stiffness. Experimental studies provide some support for these assumptions, but these findings must be confirmed in a clinical setting.

CLINICAL IMPLICATIONS

The findings in the EMPA-REG trial were partially unexpected, indeed surprising, and truly beneficial regarding the impact on mortality and heart failure morbidity. The results will certainly be considered not only by those who want to study the impact of SGLT-2 inhibition further, and to understand the mechanisms of action, but also by those asked to produce management guidelines and by practicing physicians. Even while awaiting results from ongoing trials (Figure 1) before a definite position of this class of glucose-lowering drugs can be firmly established, one must answer some questions that will certainly arise. There are, however, already some issues in need of contemplation. Some of them will be commented on from a primarily cardiology perspective.

SGLT-2 inhibitors are available for prescription. The patient population studied in the EMPA-REG outcome trial had established cardiovascular disease in addition to diabetes. It can be foreseen that practice guidelines will soon include empagliflozin as a suitable treatment modality for these patients who are rather common and who have a notoriously compromised prognosis. At the moment, it seems reasonable to prescribe empagliflozin after careful consideration of any contraindications and keeping in mind that those on diuretics might be sensitive to volume depletion and that ketoacidosis has been described with the use of SGLT-2 inhibitors. Even if this is a very rare complication, the patients need to be informed about signs in this direction and those who might be

particularly vulnerable not exposed. When choosing an SGLT-2 inhibitor, it should be kept in mind that the results achieved with empagliflozin have so far not been reported with any other SGLT-2 inhibitor.

Cardiovascular benefits have so far not been reported in patients with type 2 diabetes at high risk for, but not yet established, cardiovascular disease manifestations. A more general recommendation on the use of SGLT-2 inhibitor as a tool to protect against cardiovascular events must therefore await the results of ongoing clinical trials (Figure 1). These trials have, in addition to patients with established cardiovascular disease, also recruited people with diabetes and multiple cardiovascular risk factors but not yet established cardiovascular disease. Some of them do also address renal outcomes. Additional information will be available within a time frame of 1–2 years.

SGLT-2 inhibitors are an approved option for glucose lowering according to present guidelines. It is reasonable to include them as interesting and promising pharmacologic tools when standard glucose-lowering drugs fail to bring a patient to recommended glycemic targets. The mechanisms behind the most interesting features of empagliflozin, and hopefully other SGLT-2 inhibitors, seems, however, to be related to effects other than their glucose-lowering capabilities (see the section “New ideas and hopes – the EMPA-REG Outcome trial” for further information). It is therefore, reasonable, at the moment, to consider price differences between the SGLT-2 inhibitors and other glucose-lowering drugs when glycemic control is the main reason for a prescription.

FUTURE RESEARCH

Further research is highly demanded to improve the understanding of the benefits. There is a need for mechanistic trials in small but carefully and repeatedly examined patients, randomly assigned to receive empagliflozin or placebo, utilizing modern imaging technology, including echocardiography and cardiac magnetic resonance imaging for the study of left ventricular performance, myocardial blood flow reserve, myocardial extracellular fibrosis, and arterial elasticity in patients with type 2 diabetes and heart failure. Such investigations are under way.

Besides mechanistic trials to understand pathophysiology and to open new indications for SGLT-2

inhibitors, the results of the EMPA-REG trial open the field for outcome trials in heart failure patients with glucose perturbations known and newly detected. A group of particular interest would be those with heart failure of ischemic origin. In such trials, one may even consider patients without previously recognized glucose perturbations, which are common among patients with heart failure.^{37–39} Careful screening for hidden impaired glucose tolerance or type 2 diabetes should precede randomization to the study drug or placebo and the outcome serve as a basis for stratifying patients with and without dysglycemia to obtain balanced study groups.

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