5 Things a cardiologist needs to know about diabetes

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1. Natural history of diabetes: focus on microvascular and macrovascular complications

Prevalence, risk factors, progression and impact of diabetes
The prevalence of type 2 diabetes (T2DM) is increasing: 150-200 million new cases are predicted in the next 10-15 years with the heaviest burden in less developed countries. Insulin resistance starts with weight gain and obesity, and can lead to hyperinsulinemia, hypertension, abnormal lipid levels, and altered clotting that can finally lead to T2DM. All of these factors increase cardiovascular (CV) risk in these patients.

An analysis of the Nurses’ Health Study1 showed that patients with a history of diabetes at baseline had the highest CV risk and those free of diabetes at baseline had the lowest CV risk. Interestingly, the two middle groups in this study suggested a latent period; CV risk increased by ~180% prior to the diagnosis of diabetes and increased again by ~180% after the diagnosis of diabetes. The only difference between these middle groups was the time of diabetes diagnosis, suggesting that diabetes is a progressive disease. Indeed, there is a latent period in which genetic susceptibility, environmental factors, sedentary lifestyle, obesity and inactivity contribute to an increased CV risk. Although it was initially thought that diabetes is a CVD risk equivalent, it turns out that this is not true in the early phase after diagnosis.2 This is important, because in the beginning, it is possible to alter the course and trajectory of disease, for example by improving glycemc control.

When diagnosed with diabetes at the age of 40 years, a person loses half a decade of life, with half of the adverse events being vascular events.3 If one develops diabetes at 90 years, there are fewer life years to lose. Therefore, a different therapeutic approach may apply to older patients who are more vulnerable and frail compared to younger patients, who have much more to gain in number of life years.

Macrovascular and microvascular complications and their relationship
Chronic complications in diabetes include macrovascular disease: myocardial infarction (MI), stroke, need for revascularization, and peripheral vascular disease; and microvascular disease: retinopathy, nephropathy, and neuropathy. In a large United Kingdom (UK) cohort of ~40000 individuals, the association between microvascular disease and CV events was examined.4 Individuals with 1 microvascular complication had a 35-40% increased CVD (CV death, non-fatal MI, stroke) risk, regardless of type of microvascular complication. An increase in the number of microvascular complications resulted in a stepwise increase in the composite of CV death, non-fatal MI, non-fatal stroke, and also in hospitalization for heart failure (HF), CV mortality and all-cause mortality. Thus, the prevention of microvascular disease is very important, as it is an independent risk factor for CV events. Although good control of blood pressure (BP), lipids and glucose reduces CV risk in diabetes patients, including those with microvascular complications, it is more important to prevent development of microvascular disease.

New glucose-lowering agents
It used to be assumed that lowering glucose in diabetes patients could reduce their CV risk. However, the first five trials with glucose-lowering agents did not show a reduction in the composite of CV death, non-fatal MI and stroke. A meta-analysis showed that a reduction of 0.9% in HbA1c over 4.7 years resulted in a 17% reduction in non-Fatal MI, a 15% reduction in fatal and non-fatal MI, no reduction in stroke, and no reduction in all-cause mortality.5 It is possible that undesirable effects, such as weight gain and hypoglycemia associated with older treatments may have offset some of their benefits resulting in an increase in CV events. As a consequence, it is now requested that safety of novel glucose-lowering agents is demonstrated in large trials. The therapeutic actions and CV outcomes of these new antidiabetic agents are discussed in detail in chapter 3 and 4.

Novel drug classes show a modest glucose-lowering effect. The results suggest that it matters how glucose is lowered. While lowering glucose with insulin, sulfonylureas (SU) or DPP-4 inhibitors has not resulted in CV benefit, some newer agents have additional effects and favorably affect CV death, non-fatal MI and stroke.

Microvascular disease in diabetes can be prevented by blocking the renin-angiotensin system, either with an ACE inhibitor or ARB. These drugs cause efferent arterial vasodilation, resulting in reduced glomerular pressure and slowing down of the progression of nephropathy. The SGLT2-inhibitor empagliflozin has a different mechanism
of action than ACE inhibitors and ARBs: a change in hemodynamics delivers sodium to the distal convoluted tubule, resulting in juxtamedullary apheresis and afferent vasoconstriction, which reduces the pressure on the glomerulus. In the EMPA-REG OUTCOME trial, initially a rapid decline in estimated glomerular filtration rate (eGFR) was observed, similar to that achieved with ACE inhibitors, after which eGFR levels stabilized. This is in contrast with traditional glucose-lowering therapy, which shows a steady progression and decline in eGFR.

2. HbA1c in CVD

HbA1c is a measure used in diagnosis and management of diabetes. HbA1c is glycated hemoglobin, which refers to hemoglobin bound to glucose. Measurement of HbA1c levels reflects the average glucose level of the last 2-3 months, since red blood cells survive for 8 to 12 weeks before they are renewed.

HbA1c to diagnose diabetes

To diagnose diabetes, three measurements can be performed: fasting plasma glucose (FPG), HbA1c and oral glucose tolerance test (OGTT). In the past decade, new HbA1c assays with better quality control and international standardization (to intra-assay coefficients of variation of typically less than 5%) have become available. An HbA1c assay is performed by collecting blood in EDTA, which remains stable during transportation for up to seven days. Day-to-day intra-individual variation in HbA1c is very low, making it a robust test. HbA1c can be measured anytime during the day, and fasting is not necessary. Moreover, unlike glucose testing, HbA1c is accurate after a recent event and can be done for example in the coronary care unit, when the patient is typically not fasted. As a consequence, some authorities now recommend measuring HbA1c to diagnose diabetes. Some concerns remain regarding the sensitivity of HbA1c tests in predicting DM, especially when HbA1c is <6.5%.

Diagnostic criteria now use a cut-off value of HbA1c of ≥6.5% (≥48 mmol/mol) for diagnosis of diabetes. If a patient meets this criterion, the HbA1c measurement should be repeated to confirm the finding, unless the patient has clear symptoms and FPG >11.1 mmol/L. FPG is also recommended as a first line diagnostic test. If HbA1c testing is not possible, for instance if the patient has hemoglobinopathy or abnormal red blood cell turnover (e.g. in advanced renal disease or severe anemia), FPG is recommended.

Patients are considered at high-risk for DM if their HbA1c is between 6.0% and 6.4% in the UK, and between 5.7% and 6.4% in the USA. At these values, patients should be informed about it and they should be given advice or guided to make lifestyle changes to prevent the onset of diabetes, irrespective of whether they have existing CVD.

HbA1c and micro and macrovascular complications

In a curve displaying the prevalence of retinopathy at varying levels of FPG, the point of inflection above which retinopathy starts to develop, is at 6.5-7%9, while the cut-off point in the diagnostic criteria is 7%. In a similar curve for HbA1c levels, the inflection point is around 6.5%, which concurs with the diagnostic criteria. 2-Hour glucose levels do not show a clear inflection point.10 These data show that HbA1c is a good demarcator for the risk of developing retinopathy, which defines the diagnostic criteria for diabetes, as it reflects end-organ damage. A post-hoc analysis of the ADVANCE study has shown that microvascular event risk begins above HbA1c of 6.5%11, again concurring with diagnostic criteria.

For macrovascular event risk, inflection of the curve was seen at around 7%, and the risk increased at higher HbA1c levels. In patients without known diabetes, post-load glucose is considered the best method to predict CHD. A meta-analysis has, however, shown that per 1 mmol/L higher FPG the risk ratio is 1.05, as for 1 mmol/L higher post-load glucose, while the risk ratio was 1.20 for 1% higher HbA1c.12

The evidence presented above has been implemented in the guidelines of the European Society of Cardiology (ESC) on diabetes, pre-diabetes, and CVD. These guidelines recommend that the diagnosis of diabetes is based on HbA1c and FPG combined or on an OGTT if still in doubt (class I, level B recommendation). In most clinical scenarios, HbA1c is likely to be tested, as patients have not been fasting.

Effects of lowering HbA1c

Once a patient has been diagnosed with T2DM, HbA1c can be used as a measure of diabetes control. Lowering HbA1c decreases the risk of microvascular disease such
as kidney and eye disease, and nerve disease, although this takes several years, and a modest effect is seen on macrovascular risk. Newer drugs that lower HbA1c can lower CVD beyond the effects of glycemia reduction. Mechanisms that may be involved include hemodynamic effects, effects on the vasculature, weight reduction and BP reduction. An added advantage may be that patients stop taking drugs that carry a risk of causing hypoglycemia, thereby contributing to avoiding its occurrence. The modest CV effect that can be achieved with lowering HbA1c, becomes clear when comparing observations in a study of 200 T2DM patients treated for 5 years that lowering HbA1c by 0.9% with glucose-lowering drugs prevented about 2.9 events, while lowering LDL-c by 1 mmol/L prevented about 8.2 events, and each 4 mmHg lower systolic BP prevented 12.5 CV events. Thus, statins and BP-lowering medication have a greater effect on macrovascular CV events than does glucose-lowering per se.

Glycemic targets and CVD risk
An HbA1c target of <7.0% or <53 mmol/mol is associated with a decreased frequency and severity of microvascular disease. For macrovascular disease, a specific target is less compelling, but hyperglycemia is positively associated with increased CVD risk. HbA1c of <7.0% or <53 mmol/mol may be targeted in the majority of patients, acknowledging the individual needs of the patients. When a patient has just been diagnosed and is free from significant CVD and has a long life expectancy and no other concerns, one should aim for 6.0-6.5% or 42-48 mmol/mol. By contrast, in an elderly patient with long-standing and/or complicated disease, relaxing the target to 7.5-8.0% or 58-64 mmol/mol may be wiser, given that the benefits in terms of life expectancy are less relevant.

All targets should be achieved without inducing hypoglycemia or other adverse effects. Glycemic control should be individualized in each patient, considering its effects on quality of life, adverse effects on polypharmacy and the possible inconvenience of intensified control. In each patient, the best individual compromise between glucose control and vascular risk should be searched for. Patients should be informed on the risks and benefits of intensified treatment.

In addition to hypoglycemia, which increases the risk of severe CVD events (read more in chapter 5), one should be aware of chronic kidney disease. This is common in people with diabetes, and some medications require dose adjustment or termination.

3. Key classes of antidiabetic drugs
After diagnosis of diabetes, glucose control is not the only factor that needs consideration, as CV risk and co-morbidities also require attention. The aim of therapy for T2DM is to improve glycemic control to reduce microvascular risk, and to lower macrovascular risk, mostly by control of lipids and BP. In addition, co-morbidities such as obesity, depression, fatty liver, and microvascular complications like kidney, eye and neuropathic diseases should be managed.

Multiple causes contribute to the development of T2DM
Insulin resistance and inadequate insulin production and secretion, among other problems all contribute to development of T2DM. The liver produces too much glucose, while the muscle does not receive enough of that glucose due to its insulin resistance. Often, excess adipose tissue is seen, which contributes to the proinflammatory state. And, because more glucose is filtered through the kidney, the kidney tends to adapt by reabsorbing more glucose. On the other hand, there is inadequate insulin production and often also excess production of glucagon. Moreover, there are various defects associated with the incretin effect, the microbiome is altered and there are various autonomic changes in the control of glucose regulation. As the hyperglycemia in T2DM is the result of multiple factors, bringing the glucose level down to as close to normal levels as possible, requires multiple therapies. The first approach in the management of hyperglycemia in T2DM is lifestyle improvement, through diet, exercise, health education and weight control.

Medical therapy
Metformin
Metformin is generally the preferable first-line oral antihyperglycemic agent. Metformin can counter the action of insulin resistance. Its actions are partly insulin-dependent, and partly insulin-independent. Metformin can reduce hepatic glucose production and has a modest effect in enhancing the uptake and oxidation of glucose in the
muscle. It has an important effect on the intestine, to increase the anaerobic glucose metabolism and increase glucose turnover. Advantages of metformin include that it does not cause weight gain and hypoglycemia. It tends to slightly lower basal insulin levels and it often improves the lipid profile and various vascular parameters. Metformin can cause some gastro-intestinal intolerance. When prescribing metformin, it is important to make sure that renal function is adequate. If eGFR falls below 60 mL/min/1.73m² a dose reduction should be considered, and treatment should be stopped when eGFR is below 30 mL/min/1.73m².

**Sulfonylureas**

Insulin secretion can be stimulated with sulfonylureas (SU) or meglitinides, of which the first ones are the longer acting ones, and the meglitinides the prandial insulin releasers. These agents stimulate insulin secretion by acting on the K+ ATP channel on the surface of the pancreatic β-cell. They induce weight gain and confer a risk of hypoglycemia (see table 4).

**PPAR-γ agonists**

Pioglitazone and other peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists mostly act on adipose tissue to increase adipogenesis and lipogenesis in peripheral adipose depots. In this process, by creating insulin-sensitive adipocytes, ectopic fat is taken away from other tissues. These agents increase insulin sensitivity and rebalance the glucose-fatty acid cycle. They reduce inflammation, and variable effects on lipids and reduction of some CV risk markers and events have been reported. Adipogenesis results in weight gain. The onset of action is slow, but there is no risk of hypoglycemia. Liver function should be checked, as well as NYHA risk. Fluid retention and edema can occur, and a risk of fractures and HF is associated with the use of PPAR-γ agonists.

**Incretins**

Two types of incretins exist: the oral dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) and injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs). GLP-1RAs not only enhance glucose-induced insulin secretion, but also suppress glucagon production and additionally they have neural effects to promote satiety and to delay gastric emptying. DPP-4 inhibitors prolong the life of endogenous GLP-1 to increase the incretin effect.

Altogether, these effects reduce hyperglycemia. DPP-4 inhibitors are weight neutral, while the satiety that is promoted with GLP-1RAs is helpful in achieving weight loss. Both classes do not cause hypoglycemia. Potential CV benefits have been reported with DPP-4 inhibiting therapy and GLP-1RAs. Their use may, however, lead to pancreatitis and GLP-1RA treatment may also induce nausea.

**Alpha-glucosidase inhibitors**

Alpha-glucosidase inhibitors like acarbose are able to slow down the digestion of complex carbohydrates in the intestine, which is another route to decreasing the post-prandial glucose excursion. Alpha-glucosidase inhibitors should be taken in conjunction with a diet rich in complex carbohydrates. Their advantages include that they do not cause weight gain, nor hypoglycemia. They may lower triglyceride levels. They can, however, cause gastro-intestinal disease and flatulence.

**SGLT2 inhibitors**

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, act on the kidney. These glucosuric agents are able to suppress the reabsorption of glucose from the proximal tubule. About 70-90 grams of glucose can be excreted via the urine per day, which not only reduces hyperglycemia in an insulin-independent way, but also lowers weight through the loss of calories and it may create an osmotic diuresis, which may contribute to the BP-lowering effect of SGLT2 inhibition. They do not cause hypoglycemia and have potential beneficial effects on major adverse cardiac events and possibly on the kidney, as illustrated by the effects on eGFR described above. The excreted glucose increases the risk of genital mycotic infections. Cases of diabetic ketoacidosis have been described when insulin was reduced too much. In case of pioglitazone, a risk of HF has been described, as a consequence of edema.

**Insulin**

If glycemic control cannot be achieved with each or all of the agents mentioned above, insulin therapy can be given. Insulin affects many of the defects in T2DM; it lowers hepatic glucose production, increases glucose uptake in the muscle, lowers lipolysis from adipose tissue, enhances protein anabolism and affects growth and differentiation. A disadvantage of using insulin is that it can induce hypoglycemia and that it causes weight gain. Insulin therapy should be correlated with diet and exercise.
and requires monitoring of blood glucose. Various formulations (rapid or short-acting and intermediate or long-acting) and delivery devices exist.\textsuperscript{13, 15}

Thus, multiple treatment options should be employed to get the glucose level as close to normal as possible, and should be started as soon as possible in order to defer or prevent the development of microvascular complications and to contribute to the long term reduction in macrovascular complications.

4. T2DM and CV outcomes

Since the US Food and Drug Administration (FDA) mandated demonstration of CV safety for new antihyperglycemic drugs, various trials evaluating DPP-4 inhibitors, GLP-1RAs and SGLT2 inhibitors on CV outcomes have been completed or are ongoing. Results will be briefly discussed and are summarized in table 1.

CV outcomes in DPP-4 inhibitors trials

The DPP-4 inhibitors were the first class to have completed CV safety trials: the SAVOR trial testing saxagliptin, the EXAMINE trial with alogliptin, and the TECOS trial with sitagliptin.\textsuperscript{17-19} Although the populations in these studies were slightly different, all patients were at high risk for CVD and the primary endpoint in these trials was major adverse cardiovascular events (MACE) or MACE plus. The overall results were quite consistent; HRs were (around) 1.00. The drugs showed no superiority, but demonstrated CV safety, thus complying with the FDA request.

One difference between the results of these trials was the risk for HF; a significant increase was observed with the tested drug in the SAVOR trial, the EXAMINE trial with alogliptin, and the TECOS trial with sitagliptin.\textsuperscript{17-19} Although the populations in these studies were slightly different, all patients were at high risk for CVD and the primary endpoint in these trials was major adverse cardiovascular events (MACE) or MACE plus. The overall results were quite consistent; HRs were (around) 1.00. The drugs showed no superiority, but demonstrated CV safety, thus complying with the FDA request.

More variation in results of GLP-1RAs trials

GLP-1RAs show more pharmacological differences amongst the drugs than other classes, resulting in more differences in the results of the trials testing them. The ELIXA trial on lixisenatide was done in post-ACS patients\textsuperscript{21}, the LEADER trial evaluated liraglutide\textsuperscript{22}, and the SUSTAIN-6 trial tested semaglutide, which is given once weekly.\textsuperscript{23} Both the LEADER and SUSTAIN-6 trials included patients with established CVD (80%) and patients at high-risk for CV events (20%). The EXSCEL trial tested exenatide, given once weekly, in patients with high risk for CVD.\textsuperscript{24} Thus, the study populations were fairly similar, except that in ELIXA all patients had ACS and in the other trials 70-80% of patients had a history of CVD.

The ELIXA trial showed CV safety, but no superiority for lixisenatide, in contrast to the LEADER and SUSTAIN-6 trials that showed significant reduction in the MACE endpoint. The LEADER showed a significant 14% reduction in the MACE endpoint for liraglutide, a significant reduction in CV mortality, and a non-significant reduction in MI and stroke. A 25% reduction in the MACE endpoint was observed in the SUSTAIN-6 trial for semaglutide. No significant difference was seen in CV mortality. MI was significantly reduced and stroke was also reduced, but not significantly. No superiority was observed for exenatide in the EXSCEL trial in MACE, nor were CV mortality, MI and stroke altered.

Ongoing trials with GLP-1RAs are the FREEDOM trial evaluating a subdermal infusion pump, which is inserted every 3-6 months. A smaller phase 3 trial testing this device demonstrated CV safety, but no superiority, however the details of the trials are not published yet. Other ongoing trials in high-risk populations are the REWIND trial testing dulaglutide and the HARMONY OUTCOMES trial evaluating albiglutide given once-weekly. Completion of these studies is expected in the next 1 to 2 years.

SGLT2 inhibitors and CV outcomes in trials

Two trials evaluating SGLT2 inhibitors have been completed to date: the EMPA-REG OUTCOME\textsuperscript{25} testing empagliflozin and CANVAS\textsuperscript{26} testing canagliflozin. The EMPA-REG OUTCOME exclusively included patients with a history of CVD and in the CANVAS trial about two thirds of patients had a history of CVD and one third were at risk of CV events. In the EMPA-REG OUTCOME, the primary outcome of 3-point MACE was significantly reduced by 14%, CV death was significantly reduced by 38%, non-fatal MI was non-significantly reduced and non-fatal stroke was non-significantly increased. When looking at the graphs for the incidence of CV death, over time an early separation of
curves is apparent for empagliflozin vs. placebo; already within a few months empagliflozin gives reduction in CV mortality.\textsuperscript{25} Similar results were observed for both empagliflozin doses tested (10 and 25 mg). Hospitalization for HF was significantly reduced by 35% and again an early separation of curves for empagliflozin vs. placebo was observed. Safety data in the EMPA-REG OUTCOME trial showed a small increase in genital yeast infection, both in men and women, no significant increase in volume depletion symptoms, no increase in acute kidney injury, no differences in fractures/amputations.\textsuperscript{25}

The CANVAS program, consisting of the pooled CANVAS and CANVAS-R trials, showed a 14% reduction in the primary outcome.\textsuperscript{26} The individual components, CV death, non-fatal MI and non-fatal stroke were all reduced with canagliflozin, although non-significantly because there was not enough power. A significant reduction of 33% for HF hospitalization was seen with canagliflozin. In the CANVAS program, safety data showed an increase in genital yeast infections, a significant increase of symptoms of volume depletion, a two-fold increased risk of lower limb amputations and an increase in fractures.\textsuperscript{26} Ongoing trials with SGLT2 inhibitors are the VERTIS study testing ertugliflozin in ~8000 patients at high risk for CV events, the DECLARE study evaluating dapagliflozin in ~17000 patients and the CREDENCE trial testing the effect of canagliflozin on renal outcomes.

**Effects of new drugs in the real world**

It is important to note that these studies were done primarily in patients with known CVD. In the real world, only 20% of patients with diabetes have a history of CVD.\textsuperscript{27} It will be interesting to see the results of primary prevention of CV events in patients in the real world. The finding that some new diabetes drugs give reduction in CV outcomes (canagliflozin, empagliflozin, liraglutide, semaglutide) should be translated to clinical practice: patients with diabetes and known CVD should be prescribed therapies for which there is evidence of CV benefit.

**5. Hypoglycemia in CV medicine – why worry?**

**Epidemiology of severe hypoglycemia in diabetic patients**

A recent study conducted in diabetes centers in Germany and Austria evaluated the rate of severe hypoglycemia (SH) in 29485 patients with T2DM treated with SUs.\textsuperscript{28} 2.8% of patients showed SH in their last year of SU treatment, with an adjusted SH event rate of 3.9 (3.7-4.2) events per 100 patient-years. Event rates for coma and hospitalization were 1.9 and 1.6, respectively. SH event rates were highest in patients who received SU and insulin (6.7), and lower with SU and another oral antidiabetic drug (3.1) than with SU alone (3.8). Risk for SH was particularly high in patients with impaired renal function: the event rate was 7.7 in those presenting with eGFR ≤30 mL/min/1.73m², 4.8 in those with eGFR between 30 and 60 mL/min/1.73m² and 3.9 if eGFR was >60 mL/min/1.73m². Based on the data, the authors noted that high risk of SH was associated with lack of diabetes education, older age, decreased eGFR, but also with lower BMI, suggesting that SU treatment in those patients should be considered with caution.\textsuperscript{28}

**Which diabetic patients are at risk for development of severe hypoglycemia**

The Atherosclerosis Risk in Communities (ARIC) study provided more insight into risk factors for developing SH in adults with diabetes.\textsuperscript{29} In 1206 patients from the ARIC study, 185 SH events were seen over a follow-up period

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**Table 1 | Overview of trials with new classes of antihyperglycemic drugs and CV outcomes.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Trial</th>
<th>Tested drug</th>
<th>Primary endpoint</th>
<th>CV superiority</th>
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<tr>
<td>DPP-4 inhibitors</td>
<td>SAVOR</td>
<td>Saxagliptin</td>
<td>3-point MACE</td>
<td>No</td>
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<td></td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>3-point MACE</td>
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<td></td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>4-point MACE</td>
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<tr>
<td>GLP-1Rs</td>
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<td>SGLT2 inhibitors</td>
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<td>CANVAS</td>
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<td>3-point MACE</td>
<td>Yes</td>
</tr>
</tbody>
</table>
of 15.2 years. After multivariable adjustment, important risk factors for developing SH were found, as summarized in Table 2. When individualizing diabetes care for older patients, these risk factors should be considered in hypoglycemia risk assessment. A study in 58 223 Japanese patients with T2DM also assessed associations between risk factors and SH events to elucidate potential predictors of SH. As in the American studies, age (multi-variable adjusted HR per 10 years: 1.24, 95%CI: 1.02-1.52), diabetes duration (HR: 1.58, 95%CI: 1.14-2.20) and insulin treatment (HR: 7.05, 95%CI: 4.68-10.6) were associated with a statistically significantly higher risk for SH. In this study, the risk of SH was decreased in patients who received metformin (HR: 0.53, 95%CI: 0.35-0.80), pioglitazone (HR: 0.62, 95%CI: 0.39-0.96) or a GLP-1RA (HR: 0.26, 95%CI: 0.04-1.85). In the ACCORD, ADVANCE and VADT studies, the intensive glucose control arms were associated with a significant increase of SH, as compared with standard glucose control (ACCORD: 16.2% vs. 5.1% in intensive vs standard glucose control, ADVANCE: 2.6% vs. 1.5%, VADT: 21.2% vs. 9.9%). The SH events seemed related to the use of insulin (ACCORD: final % on insulin therapy: 77% vs 55% with intensive vs standard glucose control, ADVANCE: 40% vs. 24% and VADT: 89% vs. 74%). The type of SUs used in the studies varied: glimepiride in ACCORD and VADT, and gliclazide in ADVANCE.

In the Japanese study mentioned earlier, a multivariate Cox proportional hazard model showed that SH was strongly and positively associated with the risk of CVD (adjusted HR: 3.39, 95%CI: 1.25-9.18). They also evaluated the association of SH with CVD risk in a propensity score-matched cohort of patients with similar baseline characteristics for patients with SH and those without, and found that SH was indeed strongly associated with the risk of CVD (HR: 7.31, 95%CI: 1.87-28.6). In ADVANCE, the outcome of patients with SH was quite alarming: patients with SH showed a 3-4-fold risk of all-cause death (HR: 3.27, 95%CI: 2.29-4.65) and of CVD death (HR: 3.79, 95%CI: 2.36-6.08). Similarly, in the Veteran’s VADT study, SH was a strong predictor of CV death (HR: 4.04, 95%CI: 1.45-11.28) (unpublished data). In a large retrospective study conducted at the Mayo-Clinic in 1013 diabetic patients (79% Type 1 DM [T1DM], 21% T2DM, mean age: 60.5 years and mean HbA1c: 7.3%), about 7.5% of patients reported SH. After 5 years of follow-up, patients who reported SH showed a 3.4-fold higher mortality rate as compared with those who reported no or mild hypoglycemia. In yet another study, the cumulative incidence rate of CVD events in veterans was found to be higher in those with vs. without hypoglycemia (both groups n=761, 1-year rate: 19.5% vs. 9.6%, 2-year rate: 29.10% vs. 15.9%, 3-year rate: 34.5% vs. 22.0%).

### Table 2 | Risk factors for severe hypoglycemia in adults (mean age 64 years) with diabetes, based on the ARIC study.

<table>
<thead>
<tr>
<th>Risk factor for developing severe hypoglycemia</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Years increase in age</td>
<td>1.24</td>
<td>1.07-1.43</td>
</tr>
<tr>
<td>Black race</td>
<td>1.39</td>
<td>1.02-1.88</td>
</tr>
<tr>
<td>Any insulin use vs. no medication</td>
<td>3.00</td>
<td>1.71-5.28</td>
</tr>
<tr>
<td>Oral medication only vs. no medication</td>
<td>2.20</td>
<td>1.28-3.76</td>
</tr>
<tr>
<td>Poor vs. good glycemic control</td>
<td>2.60</td>
<td>1.70-4.10</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>1.95</td>
<td>1.23-3.07</td>
</tr>
<tr>
<td>Poor cognitive function</td>
<td>1.57</td>
<td>1.33-1.84</td>
</tr>
</tbody>
</table>

### Table 3 | Associations of severe hypoglycemia and CV outcomes in adults (mean age 64 years) with diabetes, based on the ARIC study.

<table>
<thead>
<tr>
<th>Associations of severe hypoglycemia and CV outcomes</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>2.02</td>
<td>1.27-3.20</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.73</td>
<td>1.38-2.17</td>
</tr>
<tr>
<td>CV mortality</td>
<td>1.64</td>
<td>1.15-2.34</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>2.49</td>
<td>1.46-4.24</td>
</tr>
</tbody>
</table>

Associations of severe hypoglycemia with CV events and all-cause and CV mortality

Another analysis of the ARIC study data revealed that the 3-year cumulative incidence of CHD after an SH event was 10% and of mortality was 28.3%. Adjusted analyses revealed the increased risks of CV outcomes as shown in Table 3. Hypoglycemia was not associated with stroke, HF, atrial fibrillation or non-CV and non-cancer mortality.
Although the increased incidence of SH in the ORIGIN trial in patients treated with insulin glargine as compared with controls (6.3% vs 1.8%) was not considered a big problem at the time of presentation of the results, study data were published later that showed that SH was significantly associated with increased risks of CV death or nonfatal MI or stroke (HR: 1.59, 95%CI: 1.24-2.03), total mortality (HR: 1.75, 95%CI: 1.39-2.19), CV death (HR: 1.71, 95%CI: 1.27-2.30) and arrhythmic death (HR: 1.77, 95%CI: 1.17-2.68). Interestingly enough, the relative risk of CV outcomes with hypoglycemia was lower with insulin glargine-based glucose-lowering therapy than with standard glycemic control with metformin and SU. Thus, the ORIGIN results would have been very different if patients in the control group had received different antidiabetic drugs that do not induce hypoglycemia.36

UK Observational data show that both in patients with T1DM and T2DM, those who experienced hypoglycemia had a higher risk of experiencing CV events and all-cause mortality, irrespective of whether patients had a history of CVD.37 A retrospective cohort study evaluated the risk of stroke, CHD, congestive HF and mortality in 46135 patients with CKD (of whom 85% had diabetes) who had two or more SH events. The risks of all these conditions were greatly increased in those with at least two SH events: stroke HR: 11.6, CHD HR: 9.4, congestive HF HR: 11.2 and mortality HR: 33.0.38

Very recently, the DEVOTE study39 randomized 7637 patients with T2DM to insulin degludec or insulin glargine. SH occurred less frequent in the degludec than in the glargine group (4.9% vs. 6.2%, OR: 0.73, P<0.001 for superiority). The risk of all-cause mortality and CV death was significantly higher in patients who had vs. who did not have SH (HR: 2.51, 95%CI: 1.79-3.50 and HR: 2.14, 95%CI: 1.37-3.31, respectively). The risk of death was highest in the short term after SH (e.g. HR: 4.20, 95%CI: 1.35-13.09 at 15 days after the SH event), and declined over time but remained statistically significantly elevated throughout the study.39

Pathophysiological CV consequences of hypoglycemia
Hypoglycemia induces abnormalities in blood coagulation, hyperactivation of platelets, neutrophil activation and an increase of factor VIII. Endothelial dysfunction also takes place, which reduces vasodilation. Finally, there is an increase in inflammation, as reflected by increased levels of C-reactive protein, vascular endothelial growth factor and interleukin-6. These processes, together with the sympathoadrenal response with increased level of epinephrine that lead to rhythm abnormalities and hemodynamic changes, may explain why hypoglycemia is harmful for patients with established CVD.31, 40

**Strategies to avoid severe hypoglycemia in the treatment of diabetic patients**
The question then rises whether the link between hypoglycemia and CV risk or mortality is causal or merely a correlation. In some cases a causal link between SH and acute death indeed seems likely, for instance in case of the ‘dead-in-bed-syndrome’. The two-fold increased risk of sudden death in patients with T2DM after MI could also be linked to SH. Moreover, the ADVANCE study has shown that diabetic patients with SH have a higher vulnerability for all-cause and CVD mortality as well as for severe vascular complications.

Irrespective of whether the association is causal; preventive strategies to avoid SH are mandatory. This is particularly important in high risk situations of patients with T2DM, including long duration of diabetes, presence of macrovascular complications, acute MI/stroke, impaired renal function (CKD), coronary revascularization, admission to intensive care unit, in case of unawareness to hypoglycemia and finally at high age with hypovigilance.

**Table 4 | Glucose-lowering drugs and the risk of hypoglycemia.**

<table>
<thead>
<tr>
<th>Glucose-lowering drugs NOT associated with hypoglycemia</th>
<th>Glucose-lowering drugs associated with hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Insulin</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>GLP-1RAs</td>
<td>Glinides</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td></td>
</tr>
<tr>
<td>Acarbose/miglitol</td>
<td></td>
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<tr>
<td>SGLT2-inhibitors</td>
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</tbody>
</table>

A recent review41 discusses strategies to avoid SH in older patients with T2DM. It states that the heterogeneity of older patients must be considered and a need exists to individualize all therapeutic strategies based on specific factors that predict benefits and risks, including the functional and cognitive status and the burden of co-morbidities. Nowadays, a number of glucose-lowering drugs are available that are not associated with
hypoglycemia (summarized in table 4). These agents are the preferred therapies in elderly patients with impaired kidney function who are at increased risk for SH, in order to avoid the risk of CV events and mortality associated with SH.

References


19. White WB, Cannon CP, H 中文内容不完整，无法提供自然语言的文本表示。