Current management of diabetes and cardiovascular risk in primary care

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Abstract

- Type 2 diabetes (T2DM) is a growing global problem.
- T2DM is usually a progressive disease that starts with impaired glucose tolerance (IGT, or pre-diabetes), which may lead insulin resistance (IR), and the accumulation of complications over time. T2DM is associated with an increased risk of a range of cardiovascular diseases (CVD) and is recognized as a cardiovascular (CV) mortality risk factor.
- Traditionally, the focus of T2DM treatment was on lowering glycated haemoglobin (HbA1c).
- Whilst lowering glucose has been shown to decrease microvascular complications, lowering HbA1c with older therapies, with the exception of metformin, does not improve mortality or vascular risk. However, some newer anti-diabetes medications have demonstrated significant CV benefits, namely the sodium-glucose cotransporter-2 (SGLT2) inhibitors, and some GLP-1 receptor agonists (GLP-1RAs). These new findings offer the potential a more comprehensive treatment approach in T2DM management, which addresses both hyperglycaemia and the associated risk of CV morbidity and mortality.
- All of these aspects will be discussed in more detail in this practical guidance document, which aims to guide general practitioners (GPs) and other primary care physicians on how to manage vascular disease in T2DM patients in primary care.

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Introduction

Type 2 diabetes (T2DM) is a growing global problem. The International Diabetes Federation (IDF) Diabetes Atlas 8th Edition 2017 estimates the rising prevalence, with dramatic increases as high as 156% by 2045 predicted for Africa, and although anticipated rises in other regions are lower, an overall increase of 48% has been suggested in many countries worldwide (1).

T2DM is an often progressive disease that starts with impaired glucose tolerance (IGT, or pre-diabetes) and can progress to insulin resistance (IR), with accumulation of complications over time. T2DM is associated with microvascular complications such as retinopathy, neuropathy and nephropathy. Moreover, individuals with T2DM are at increased risk of a range of cardiovascular diseases (CVD), such as peripheral arterial disease, ischaemic stroke, angina, myocardial infarction (MI) and heart failure (HF)(2). Moreover, diabetes is recognized as a cardiovascular (CV) mortality risk factor (3, 4). Cardiovascular disease is now the main cause of premature death for patients with T2DM and drives much of the very high costs of caring for patients.

Glucose regulation and expanding the scope of diabetes management based on new evidence

Traditionally, the focus of T2DM treatment was on lowering glycated haemoglobin (HbA1c), with oral medications, such as metformin, sulphonylureas (SU), and biguanides, or insulin. While these traditional treatments decrease microvascular complications such as retinopathy, lowering HbA1c with older therapies had not been shown to improve CV mortality. More intensive glucose-lowering strategies have also been evaluated with older therapies, some of which even showed harmful effects. Lowering HbA1c with longstanding treatments have yielded conflicting results, but most strategies, with the exception of metformin and insulin, did not reduce the CV risk associated with T2DM, possibly because multiple processes contribute to the increased CV risk seen in T2DM (5).

The anti-diabetes drug class of glitazones have been developed in the past decades. They became a subject of concern when rosiglitazone, a commonly prescribed diabetes drug, was found to be associated with an increase in the risk of MI and possibly of CV death (6). This led the United States Food and Drug Administration (FDA) to issue guidance for industry, stating that industry should demonstrate that any new therapies will not result in an unacceptable increase in CV risk (7). This has led to many CV outcomes studies designed to demonstrate non-inferiority of novel anti-diabetes drugs as compared to currently available therapies, rather than superiority.

However, some CV outcomes studies of newer T2DM treatments have demonstrated CV benefits for patients with established CVD, namely with the sodium-glucose cotransporter-2 (SGLT2) inhibitors empagliflozin, canagliflozin, and dapagliflozin (8-11) and the GLP-1 receptor agonists (GLP-1RAs) liraglutide and semaglutide (12-14). These new findings pave the way for a new, more comprehensive treatment approach in T2DM management, which addresses both hyperglycaemia and the associated risk of CV morbidity and mortality. All of these aspects will be discussed in more detail in this document.

Multiple CVD risk and risk assessment

Though this guidance document focuses on management of diabetes and the associated CV risk, it is important to stress that for most patients a comprehensive risk factor management approach, or modifying all elevated risk factors simultaneously, is needed to help lower risk of a CVD event. Dyslipidaemia (EPCCS Guidance document for primary care is available on IPCCS.org), high blood pressure (BP), hyperglycaemia and unhealthy lifestyle all contribute to CV risk, and national and international guidelines (15) consider the management options for all of these domains. For diabetes, the decision of which patients have sufficient CVD risk to warrant treatment is not based upon formal risk assessment, since most guidelines short-cut to assuming patients with diabetes are already at high enough risk to warrant full CVD prevention interventions.

This document aims to guide general practitioners (GPs) and other primary care physicians on how to manage vascular disease in T2DM patients in primary care. This document is based on the summary evidence for vascular disease in T2DM and its management presented during the 2018 European Primary Care Cardiovascular Society (EPCCS) Annual CV Summit, and the discussion thereafter among primary care physicians from all across Europe. It provides a brief scientific background and practical guidance, focussing on challenges faced in clinical reality.

Take home messages

Lowering HbA1c with traditional therapies decreases microvascular complications, but has not been shown to improve CV mortality substantially.

Some CV outcomes studies of newer T2DM treatments have demonstrated significant CV benefits, allowing a T2DM management approach that addresses both hyperglycaemia and the associated risk of CV morbidity and mortality.

Most guidelines short-cut to assuming patients with diabetes are already at higher enough risk to warrant full CVD prevention interventions, rather than recommending formal risk assessment.

Progression of pre-diabetes to type 2 diabetes: diagnosis

Pre-diabetes

Prediabetes is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or a glycated haemoglobin (HbA1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications. Not all individuals with prediabetes will necessarily progress along the continuum of dysglycaemia to develop diabetes (16).

Since plasma glucose levels normally fluctuate, IGT is assessed with an oral glucose tolerance test (OGTT: IGT when 2-hour post-load plasma glucose [2hPG] is ≥7.8 and <11.1 mmol/L (or ≥140 and <200 mg/dL). For a standardised OGTT, it is performed in the morning after an overnight fast (8-14 hours). Blood samples should be drawn before and 120 minutes after the patient starts drinking 75 grams glucose dissolved in 250-300 mL water, over the course of 5 minutes (17). The European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD)Diabetes Guidelines recommend that an OGTT is used for diagnosing IGT (class I level B) (17).

Progression from pre-diabetes to T2DM

Unhealthy dietary habits and a sedentary lifestyle importantly contribute to development of T2DM, thus progression from pre-diabetes to diabetes. Randomised controlled trial evidence has demonstrated that lifestyle modification, based on modest weight loss and increased physical activity, can prevent or delay progression to T2DM in high-risk individuals with IGT (summarised in reference (18)). Thus, once IGT is established or a high risk for T2DM is acknowledged, appropriate lifestyle counselling should be provided. The IMAGE toolkit has been developed with the aim to prevent T2DM, and includes practical advice for healthcare personnel (19).

Type 2 diabetes mellitus

T2DM is characterized by insulin resistance (IR) combined with beta-cell failure, associated with obesity (typically abdominal) and a sedentary lifestyle. In the early stages of T2DM, IR and an impaired first-phase insulin secretion causing post-prandial hyperglycaemia are seen. Later, the second-phase insulin response deteriorates and hyperglycaemia persists in the fasting state (20, 21). While T2DM typically developed after middle age, a trend is on-going towards a younger age of onset due to increasing obesity in young people.

It is important to note that T2DM usually does not cause specific symptoms for several years, and it is estimated that about half of the cases are undiagnosed. To date, population screening of blood glucose to assess CV risk is not recommended, due to lack of sufficient evidence that early detection and treatment of T2DM can improve prognosis of the related CVD. Hence, screening should be targeted at high-risk individuals (17).

While the World Health Organization (WHO) diagnostic criteria for diabetes are based on fasting plasma glucose (FPG) and 2hPG concentrations, the American Diabetes Association (ADA) recommends use of glycated haemoglobin A1c (HbA1c) fasting glycaemia, before recommending OGTT. Both methods have advantages and disadvantages, and are the subject of some debate (17, 22). The ESC/EASD Diabetes Guidelines recommend basing the diagnosis of diabetes on HbA1c and FPG combined in venous plasma (HbA1c of >6.5% [48 mmol/L] and an FPG of >6.5 mmol/L (117 mg/dL), or on an OGTT if still in doubt (class I level B recommendation). Moreover, it is recommended that screening for potential T2DM in people with CVD is initiated with HbA1c and FPG and that an OGTT is added if the other two tests are inconclusive (class I level A)(17).

Take home messages

Pre-diabetes refers to impaired glucose tolerance. The ESC/EASD Guidelines recommend that an OGTT is used for diagnosing IGT.

In individuals with IGT or at high risk of T2DM, appropriate lifestyle counselling should be provided. Healthy diet, modest weight loss and increased physical activity can prevent or delay progression to T2DM.

T2DM is characterized by insulin resistance, but does not cause symptoms for several years. Diagnosis is based on HbA1c and FPG combined.

Type 2 diabetes-related CV risk

Risk of microvascular and macrovascular complications
In T2DM, both microvascular and macrovascular complications are recognised. Microvascular complications include retinopathy, nephropathy and neuropathy. Macrovascular complications refer to MI, stroke, need for revascularization and peripheral vascular disease.

It has been demonstrated that the prevalence of diabetes-specific retinopathy starts to increase at HbA1c of 6.5% (23). Similarly, a post-hoc analysis of the ADVANCE trial showed that microvascular event risk became evident above HbA1c of 6.5%, with each 1% higher HbA1c level correlating to 40% higher risk of a microvascular event (24). Thus, HbA1c is a good demarcator for the risk of developing this type of end-organ damage.

Persons with T2DM show a higher risk of several CVD presentations than do individuals without T2DM, with significant hazard ratios (HRs) of around 1.4-1.7 for initial presentation of stable angina, unstable angina, non-fatal MI, unheralded coronary death (death with the primary cause certified as coronary heart disease (CHD), and no prior history of CVD), HF, transient ischaemic attack and ischaemic stroke. The risk of presentation with peripheral arterial disease shows an HR of 2.98 for those with T2DM (2). Moreover, diabetes has been reported to be a CV mortality risk factor, to a similar degree as seen in persons without diabetes but who suffered an MI (3). An analysis of CHD mortality rate by diabetes status in individuals at least 65 years old, demonstrated that the risk was highest in T2DM patients treated with insulin (HR: 2.75, 95%CI: 1.95-3.87), and somewhat lower in T2DM patients using oral hypoglycaemic agents (HR: 2.47, 95%CI: 1.89-3.24), both groups showing a significantly elevated risk compared to non-diabetes individuals (4).

The relationship between microvascular and macrovascular disease has been examined in a large United Kingdom (UK) cohort of about 40,000 individuals with T2DM (25). Persons with one microvascular complication, irrespective of which kind, showed a 35-40% higher risk of CVD (CV death, non-fatal MI, stroke), as compared with those without microvascular disease. More microvascular complications resulted in a stepwise increase in the composite of CV death, non-fatal MI, non-fatal stroke, and also in hospitalization for HF, CV mortality and all-cause mortality (25). Thus, the presence of microvascular complications in T2DM can be regarded as an independent predictor of CV events.

Risk assessment
In T2DM, developing generally applicable risk scores is difficult due to multiple confounding factors that play a role, associated with ethnicity, cultural differences, metabolic and inflammatory markers, and, importantly, because CAD and stroke scores are different (26). A meta-analysis reviewed 17 risk scores that were specifically developed for populations with diabetes. The meta-analysis found little evidence to suggest that DM-specific risk scores provided a more accurate estimate of CVD risk than non-diabetes specific scores (27). These risk scores tend to show good results in the population they were developed in, but external validation is needed before they can be extrapolated to other populations (17).

The 2013 ESC Guidelines on diabetes, pre-diabetes and CVD therefore state the importance of managing patients with diabetes according to evidence-based, target-driven approaches, tailored to the individual patient's need (17). The 2016 Joint European Society guidelines on CVD prevention recommended that patients with DM and at least one other CV risk factor or target organ damage should be considered to be at very high risk. All other patients with T2DM should be considered at high risk (15).

Take home messages

HbA1c is a good biomarker for the risk of developing microvascular complications, with this risk becoming evident above HbA1c of 6.5%.

Risk of several CVD presentations is higher in those with vs. those without T2DM and diabetes is a CV mortality risk factor.

The presence of microvascular complications in T2DM is an independent risk factor for macrovascular CV events.

Patients with DM and at least one other CV risk factor or target organ damage should be considered at very high risk. All other patients with T2DM should be considered at high risk.

Therapeutic considerations

Anticipated effects of hypoglycaemic treatment

Compelling evidence from randomised controlled trials has demonstrated that tight glycaemic control can reduce microvascular complications of T2DM (28-30). The effect of tight glycaemic control on macrovascular disorders is less clear. While hyperglycaemia is associated with increased CV risk in a dose-dependent manner, recent randomised controlled trials have failed to demonstrate a clear benefit on CV risk of improving glycaemia (31-33). A small, but favourable effect on CVD may become apparent after many years (34, 35). However, the presence of multiple comorbidities in long-standing T2DM and the complex risk phenotype that develops in the context of insulin resistance likely explain why controlling HbA1c does not tackle the CV risk sufficiently.

The Steno-2 Study demonstrated that multifactorial intervention (lowering lipid levels and BP, plus use of aspirin) had beneficial effects with respect to vascular complications and mortality (36). More recently, the ASCEND study results suggested that the benefit of using aspirin 100 mg for primary prevention in T2DM patients is not evident, as a reduction in non-fatal vascular events was seen, but at the cost of increased risk of major bleeding, and no reduction in CVD death was noted in the aspirin arm as compared with placebo (37).

Finding an optimal risk-benefit balance

The first trial to examine the impact of HbA1c lowering on CV outcomes in T2DM patients was the UK Prospective Diabetes Study (UKPDS (29, 34), in which intensive therapy was compared with standard therapy. A reduction in microvascular events (retinopathy and nephropathy) was seen with intensive therapy when HbA1c levels were 7.0% compared to the standard group with levels of 7.9%, but macrovascular events and mortality were unchanged (29, 34).

The ACCORD (31), ADVANCE (32), VADT (33) trials followed, and showed mixed results with overall no benefit on CVD with glucose lowering. ACCORD even showed an increase in mortality in those in the intensive therapy group (HbA1c: 6.4%) as compared with those on standard therapy (HbA1c: 7.5%)(31). These data complicate the evidence base on the need for strict control of HbA1c levels, at least in some more elderly patients. The studies raise concerns that rapid achievement of strict control, or the therapies used in the trials, may produce more harm than benefit in some individuals, especially in those patients with longer diabetes duration and co-morbidities due to increased risk of hypoglycaemic episodes.

Finding a good risk-benefit balance is important when choosing the intensity of HbA1c-lowering strategy. The rationale behind a good risk-benefit balance in diabetes is changing from “Treat to target” to ”Treat to benefit”, and should be based on the evaluation of efficacy and adherence, safety and the balance between the positive impact over the risk of worsening of the condition and over CV mortality.
In T2DM, early glycaemic control is key to long-term reduction in complications, which is known as the legacy effect. A good legacy effect was shown in the UKPDS follow-up study, in which early, strict glycaemic control reduced the long-term risk of both microvascular and macrovascular complications (34). An adverse legacy effect is, however, also possible, when glycaemic control is achieved late in the disease, after a long period of poor control; then the long-term risk of macrovascular complications is not improved (33). Indeed, in VADT, the long-standing, preceding hyperglycaemia accounted for the high rate of complications at baseline (38).

Ideal treatment for T2DM

The many factors that contribute to increased CV risk in T2DM include hyperinsulinaemia, insulin resistance, hyperglycaemia leading to advanced glycation end-products, hypertension, lipidaemia and thrombosis. Nowadays, inflammation and the microbiome can be added to the list of processes involved (5). Consequently, therapy for T2DM ideally targets all or most of these processes.

Moreover, an ideal drug for T2DM should also be safe, efficacious and well-tolerated, provide durable control, give a low risk of hypoglycaemia, should be weight neutral or induce weight loss, and should reduce complications and improve mortality in the long term (39, 40).

New anti-diabetes agents and CV outcomes

As mentioned above, many CV outcomes trials (CVOT) for new anti-diabetes drugs have been or are being conducted to assess whether the novel drugs are safe with respect to CV risk, thus they are set up to test for non-inferiority rather than superiority. The primary endpoint in these trials is three- or four-point MACE (major adverse cardiovascular events); a composite of CV mortality, non-fatal MI and non-fatal stroke, and in case of four-point MACE unstable angina/acute coronary syndrome or hospitalization for HF is added.

In short, CVOT have been done for dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1RAs and SGLT2 inhibitors:

- For DPP-4 inhibitors, three trials have been published that showed a neutral CV effect with sitagliptin in TECOS (41), linagliptin in CARMELINA (42), saxagliptin in SAVOR-TIMI 53 (43), and alogliptin in EXAMINE (44), although in the latter two studies, an increase in HF outcomes was observed.

- The GLP-1RAs liraglutide and semaglutide not only demonstrated non-inferiority, but also superiority for MACE, in the LEADER (12) and SUSTAIN-6 trials (13), respectively. The GLP-1RA exenatide showed CV safety, but did not show CV superiority in the EXSCEL trial (45). similarly, the ELIXA trial showed CV safety, but no superiority for lixisenatide (46). (Reviewed in reference (47)).

- Treatment with the SGLT2 inhibitors empagliflozin and canagliflozin resulted in a decrease in MACE, as demonstrated in the EMPA-REG OUTCOME (8) and CANVAS (9) trials, respectively. Moreover, both empagliflozin and canagliflozin yielded a reduction in HF endpoints, something that had not been seen with the other drug classes (11). The SGLT2 inhibitor dapagliflozin did not affect the rate of MACE, in a generally lower CV risk population, but did lower the rate of the combined CV death and hospitalization for HF endpoint in the DECLARE TIMI-58 trial (10).

Regarding safety, it can be said that, while each of the novel classes is associated with different specific side effects, they share a 'similar' safety profile, although more peripheral amputations were seen in the canagliflozin arm of the CANVAS trial and diabetic keto-acidosis is a rare adverse event seen with SGLT2s. The new drug classes are relatively easy to handle in clinical practice, although most GLP-1RAs are currently administered via injection (once daily for liraglutide, once weekly for semaglutide and exenatide) (48). An oral formulation of semaglutide is currently in late stage clinical development.

These recent insights facilitate a new approach in management of T2DM and the accompanying CV risk, towards a more holistic approach in which diabetes is seen as a state of enhanced CV risk that is the target of therapy, rather than only hyperglycaemia.

Take home messages

Tight glycaemic control can reduce microvascular complications of T2DM, but does not lower CV risk sufficiently. Rapid and strict HbA1c control can do harm in some individuals.

Multifactorial intervention, comprising of lowering lipid levels and BP, and possibly use of aspirin, has been shown to reduce vascular complications and mortality.

CV outcome trials have shown CV benefit upon treatment with GLP-1RAs or SGLT2 inhibitors. Specific benefits vary among the drug classes and individual agents.

Diabetes should be considered a state of enhanced CV risk that should be targeted with therapy, as opposed to only treating hyperglycaemia.

Management options for hyperglycaemia and CV risk

Non-pharmacological control of hyperglycaemia

The ADA and the EASD have jointly published a scientific statement that advocates lifestyle management as a first measure for the prevention and/or management of T2DM. As mentioned above, a healthy lifestyle is paramount to preventing progression from IGT to diabetes (and it can even reverse IGT). A healthy lifestyle includes healthy eating, physical activity, maintaining a healthy weight and cessation of smoking (40).

Diet

The 2013 ESC Diabetes Guidelines (17) summarise available evidence and use recommendations of the EASD Diabetes and Nutrition Study Group (49). In brief, overall it is acknowledged that several dietary patterns can be adopted, with the notion that an appropriate intake of total energy is more important, along with consumption of a diet in which fruits, vegetables, wholegrain cereals and low-fat protein sources predominate, than the precise proportion of total energy provided by the major macronutrients. Salt intake should be restricted (17). Specific recommendations on distributions of macronutrients are given, based on the EASD Diabetes and Nutrition Study Group (49).

Physical activity

Physical activity is important in the prevention of the development of T2DM in subjects with IGT, as well as for glycaemic control and related CVD complications. Aerobic and resistance training improve insulin action and plasma glucose, and positively impact on BP, lipids and other CV risk factors. Regular exercise is necessary for the benefit to last (17). A combination of aerobic and resistance training yields better improvement of glycaemic control than either training type alone (50). In prospective cohort studies, exercise has also been shown to be associated with improvement in CV outcomes, and both CV and overall mortality in T2DM patients and in patients with IGT (47, 51, 52).

Smoking

Since smoking increases the risk of T2DM (53), CVD and premature death (54), it should be avoided. Stopping smoking decreases the risk of CVD. Persons with DM who smoke should be offered a structured smoking cessation programme, including pharmacological support (17).

Weight loss

Most European people with T2DM are obese, and weight control has therefore been considered a central component of improving lifestyle. Unfortunately, it is challenging to achieve CV benefits with weight control interventions. The Look AHEAD (Action for Health in Diabetes) trial assessed the effects of long-term weight loss on glycaemia and prevention of CVD events in T2DM. After one year, patients who followed the intensive lifestyle intervention showed on average 8.6% weight loss, significantly lower HbA1c, and a reduction in several CVD risk factors. These benefits were sustained after four years. However, no difference in CVD events was seen between the intensive intervention group and the control group, and the trial was stopped for reasons of futility (55, 56). In very obese subjects, bariatric surgery can result in long-term weight loss and it has been shown to lower the rate of incident T2DM and mortality (57).

Of note, the cluster-randomised Diabetes Remission Clinical Trial (DiRECT) trial demonstrated that in individuals with T2DM of up to 6 years' duration, diabetes can be reversed by weight loss, achieved with an evidence-based structured weight management programme, delivered in a community setting by routine primary care staff (58). The intervention was an initial phase of total diet replacement with low energy formula diet (about 830 kcal/day, 59% carbohydrate, 13% fat, 26% protein, 2% fibre), followed by structured food reintroduction and an on-going programme with monthly visits for long-term weight loss maintenance. Almost half (46%) of participants in the intervention group showed remission of diabetes after 12 months, as compared with 4% in the control group (OR: 19.7, 95%CI: 7.8-49.8)(58). The DiRECT cohort will be followed up for at least four years.

Traditional oral anti-diabetes drugs

As laid out, anti-diabetes therapy should be aimed at improving glycaemic control to reduce microvascular risk, as well as reducing macrovascular risk, thus it should also encompass control of lipids and BP. In addition, comorbidities such as obesity, depression, fatty liver should be managed. A brief overview of currently available therapy to manage T2DM will follow. Table 1 shows a summary of agents that do and do not cause hypoglycaemia.

Metformin

Metformin is considered the first-line oral antiglycaemic therapy. It counters the action of insulin resistance, with partly insulin-dependent and partly insulin-independent action. Metformin can reduce hepatic glucose production and modestly enhances uptake and oxidation of glucose in the muscle. In the intestine, metformin increases the anaerobic glucose metabolism and increases glucose turnover (59).

In the UKPDS trial, about 10 years of use of metformin seemed to reduce the risk of CV mortality, especially

in obese patients (30). Metformin does not cause weight gain and hypoglycaemia. It often slightly lowers basal insulin levels and improves the lipid profile and various vascular parameters. Metformin treatment may be associated with gastro-intestinal intolerance. Renal function needs to be adequate (minimal estimate glomerular filtration rate [eGFR]: 30 mL/min/1.73m^2, possibly with a dose reduction if eGFR falls below 60 mL/min/1.73m^2) (59).

Sulphonylureas

Sulphonylureas (SU) stimulate insulin secretion. Prandial insulin releasers and longer acting versions exist. First generation SU include chlorpropamide, tolazamide and tolbutamide. Data on SU is scarcer, but tolbutamide has been associated with increased CV mortality compared with diet alone or diet plus insulin, already in the 70s (60). Second-generation SU are gliclazide, glipizide, glimepiride and glyburide.

Little is known about their effect on CV outcomes, but glimepiride is currently being investigated in CAROLINA, in the comparison with the DPP-4 inhibitor linagliptin. SU induce weight gain and confer a risk of hypoglycaemia (59).

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors like acarbose slow down digestion of complex carbohydrates in the intestine, which can decreased the post-prandial glucose excursion. They should be taken in conjunction with a diet rich in complex carbohydrates.

In the ACE-trial, no benefit or harm with respect to CVD was seen upon treatment with acarbose in patients with impaired glucose tolerance (61). Alpha-glucosidase inhibitors do not cause weight gain, nor hypoglycaemia, and they may lower triglyceride levels. Disadvantages include that they can induce gastro-intestinal disease and flatulence (59).

PPAR-γ agonists

Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists like pioglitazone and rosiglitazone mostly act on adipose tissue to increase adipogenesis and lipogenesis in peripheral adipose depots. Insulin-sensitive adipocytes are created in this process, which takes ectopic fat away from other tissues. PPAR-γ agonists increase insulin sensitivity and rebalance the glucose-fatty acid cycle.

The case of rosiglitazone has been discussed already; its use is not favoured because of the observed increase in risk of MI and possibly CV death (6). Pioglitazone did not show an improvement in the primary endpoint in the PROactive trial, but a secondary endpoint suggested that three years of treatment with pioglitazone may reduce the risk of all-cause mortality, non-fatal MI and stroke in patients with T2DM and macrovascular disease. In addition, a subgroup analysis suggested that pioglitazone for about three years in T2DM patients with a previous stroke may experience fewer recurrent fatal or non-fatal stroke (62). The IRIS trial later found that about five years of treatment with pioglitazone in patients with pre-diabetes and a history of stroke or transient ischaemic attack may reduce the risk of a future stroke or MI (63).

PPAR-γ agonists can decrease inflammation and various effects on lipids and CV risk markers have been reported. A disadvantage is that adipogenesis results in weight gain. While the onset of action is slow, there is no risk of hypoglycaemia. Liver function should be checked, as well as development of symptoms of HF. Fluid retention and oedema may occur, and a risk of fractures is reported (59).

Table 1 | Anti-diabetes drugs and the risk of hypoglycaemia

Agents NOT associated with hypoglycaemia	Agents associated with hypoglycaemia
Metformin	Insulin
Alpha-glucosidase inhibitors	Sulphonylureas
PPAR-γ agonists	
DPP-4 inhibitors	
GLP-1 receptor agonists	
SGLT2 inhibitors	

Novel anti-diabetes drugs

DPP-4 inhibitors

The oral DPP-4 inhibitors (or gliptins) are one type of incretins. DPP-4 inhibitors prolong the life of endogenous GLP-1 to increase the incretin effect. This effect functions to control postprandial glucose excursions, by stimulating insulin secretion from the pancreatic beta-cells, in response to oral glucose ingestion. DPP-4 inhibitors do not cause hypoglycaemia and are weight neutral (59).

DPP-4 inhibitors are subject to the FDA requirement to demonstrate CV safety. Sitagliptin has been shown to

be neutral with regard to CV risk in the TECOS trial (41). Saxagliptin was also shown to be safe with regard to CV outcomes in SAVOR-TIMI 53, except that a higher risk of hospitalization for HF was found (43). Alogliptin also did not increase the rate of MACE in the EXAMINE trial. Alogliptin was associated with an increased risk of HF-related admissions (44).

Linagliptin is a selective DPP-4 inhibitor that was evaluated in the CARMELINA trial, for its effect on CV outcomes and kidney outcomes in patients with T2DM at high risk of CV and kidney events. As compared with placebo, linagliptin was found to be non-inferior when added to usual care with regard to major CV events over a median of 2.2 years (42). The CAROLINA trial is on-going to study the effect of treatment with linagliptin on CV outcomes compared with treatment with glimepiride in patients with T2DM (64).

GLP-1 receptor agonists

The injectable GLP-1RAs also belong to the incretin class. They enhance glucose-induced insulin secretion, and suppress glucagon production. Moreover, they reduce appetite by binding to GLP-1 receptors in the brain and they delay gastric emptying. Thus, GLP-1RA can help reduce weight. They do not cause hypoglycaemia.

Both liraglutide in the LEADER trial (12) and semaglutide in the SUSTAIN 6 (13), added to standard care in patients with T2DM at high CV risk were shown to not only be safe in terms of CV outcomes, but also to reduce the rate of CV events.

Liraglutide was tested in patients with T2DM and high CV risk, compared to placebo added to standard of care (9340 patients were randomised), over a median follow-up duration of 3.8 years. The primary composite outcome of first occurrence of death from CV causes, nonfatal MI or nonfatal stroke occurred in 13% of patients in the liraglutide group, as compared with in 14.9% of the placebo group (HR: 0.87, 95%CI: 0.78-0.97, P<0.001 for non-inferiority, P=0.01 for superiority). Fewer patients died from CV causes after treatment with liraglutide (4.7% vs. 6.0%, HR: 0.78, 95%CI: 0.66-0.93, P=0.007). Death from any cause occurred less frequently in the liraglutide group than in the placebo group (8.2% vs. 9.6%, HR: 0.85; 95%CI: 0.74-0.97; P=0.02) (12).

Semaglutide was evaluated against placebo, added to standard care, in 3297 patients with T2DM and high CV risk. The primary composite outcome was the same as for liraglutide, and occurred in 6.6% of patients treated with semaglutide and in 8.9% of patients on placebo (HR: 0.74, 95%CI: 0.58-0.95, P<0.001 for non-inferiority, P=0.02 for superiority). Nonfatal MI occurred in 2.9% vs. 3.9% of patients in the respective treatment arms (HR: 0.74, 95%CI: 0.51-1.08, P=0.12) and stroke in 1.6% vs. 2.7%, respectively (HR: 0.61, 95%CI: 0.38-0.99, P=0.04).

The CVOT testing of lixisenatide, ELIXA, demonstrated non-inferiority, but lixisenatide did not significantly alter CV risk (46). Exenatide once weekly was also found to be CV neutral in EXSCEL (45). Albiglutide was found to be superior to placebo with respect to MACE in patients with T2DM and CVD (65). Albiglutide was withdrawn from the market. REWIND is a CVOT that evaluates the GLP-1RAs dulaglutide but has not published yet.

SGLT2 inhibitors

SGLT2 inhibitors suppress reabsorption of glucose from the proximal tubule in the kidney. About 70-90 grams of glucose can be excreted via the urine per day. This reduces hyperglycaemia, but also lowers weight through the loss of calories. Moreover, it may create osmotic diuresis, which possibly contributes to the BP-lowering effect of SGLT2 inhibition. SGLT2 inhibitors do not cause hypoglycaemia and may beneficially affect kidney function. The urinary glucose excretion increases the risk of genital mycotic infections (59).

Both empagliflozin in EMPA-REG OUTCOMES (8) and canagliflozin in CANVAS (9) are associated with significant reductions in MACE (both 14% reduction). Empagliflozin was evaluated in 7020 patients with T2DM and established CVD, and compared against placebo, over a median observation time of 3.1 years. The primary composite outcome was death from CV causes, nonfatal MI or nonfatal stroke, and occurred in 10.5% of patients randomised to empagliflozin and in 12.1% on placebo (HR: 0.86, 95%CI: 0.74-0.99, P=0.04 for superiority). Empagliflozin showed a relative risk reduction of 35% in hospitalisation for HF (2.7% vs. 4.1%), a 38% relative risk reduction in death from CV causes (3.7% vs. 5.9%) and of 32% for death from any cause (5.7% vs. 8.3%) (8).

Canagliflozin was compared with placebo in 10,142 participants with T2DM and high CV risk, who were followed for a mean of 188.2 weeks. The primary composite outcome was death from CV causes, nonfatal

MI or nonfatal stroke, which occurred less frequently in patients randomised to canagliflozin than with placebo (26.9 vs. 31.5 events per 1000 patient-years, HR: 0.86, 95%CI: 0.75-0.97, P<0.001 for non-inferiority, P=0.02 for superiority). The endpoint of fatal or hospitalised HF was reduced by 30% upon treatment with canagliflozin. A subgroup analysis based on those with or without a history of HF at baseline, suggested that those with HF at baseline benefitted more from canagliflozin in terms of reduction of CV death or hospitalized HF (66). In CANVAS, an increase in the rate of amputations and fractures in toes was observed (6.3% vs. 3.4% participants per 1000 patient-years, HR: 1.97, 95%CI: 1.41 to 2.75), which was not confirmed in EMPA-REG OUTCOME.

The results of the DECLARE TIMI-58 trial evaluating the SGLT2 inhibitor dapagliflozin have recently been published (64). The DECLARE TIMI-58 was different from both EMPA-REG OUTCOMES and CANVAS, in that it included about two-thirds of patients without atherosclerotic disease, thus a lower risk population. In the overall population, followed for a median of 4.2 years, dapagliflozin did not result in a lower rate of MACE, as compared with placebo (8.8% vs. 9.4%, HR: 0.93, 95%CI: 0.84-1.03, P=0.17). The co-primary endpoint of CV death or hospitalization for HF was, however, significantly reduced upon treatment with dapagliflozin (4.9% vs. 5.8%, HR: 0.83, 95%CI: 0.73-0.95, P=0.005). The latter outcome reflected a lower rate of hospitalization for HF (HR: 0.73, 95%CI: 0.61-0.88), and there was no between-group difference in CV death (HR: 0.98, 95%CI: 0.82-1.17)(10).

Simultaneously with the publication of the DECLARE TIMI-58 results, the authors published a systematic review and meta-analysis of all three CVOTs evaluating SGLT2 inhibitors, totalling data on over 34,000 patients, of whom 60.2% had established ASCVD (67). Overall, treatment with SGTL2 inhibition reduced MACE by 11% (HR; 0.89, 95%CI: 0.83-0.96, P=0.0014). A reduction of 23% of the risk of CV death or hospitalisation for HF was observed with SGLT2 inhibitors (HR: 0.77, 95%CI: 0.71-0.84, P<0.0001), both in patients with and without atherosclerotic disease and in those with and without a history of HF at baseline. Interestingly, when stratifying into primary and secondary prevention cohorts, CV benefit was only seen in patients with ASCVD (HR: 0.86, 95%CI: 0.80-0.93) and not in those without (HR: 1.00, 95%CI: 0.87-1.16, P-interaction: 0.0501). SGLT2 inhibition was found to reduce the risk of progression of renal disease by 45% (HR: 0.55, 95%CI: 0.48-0.64, P<0.0001)(67).

Remaining questions and future opportunities

It is important to note that many CVOTs were done primarily in patients with known CVD. In daily clinical practice, only about 20% of T2DM patients have a history of CVD. It is unknown whether the agents give similar results in primary prevention, although the DECLARE TIMI-58 trial, which was not shown to reduce MACE, included two thirds of patients who did not have established CVD. A recently published meta-analysis on the effects of SGLT2 inhibition suggests that SGTL2 inhibitors do not affect atherosclerotic MACE in individuals without existing ASCVD, while the effects on reducing hospitalization for HF are robust regardless of existing ASCVD (67). Moreover, it is unknown whether these new agents can be used in people with pre-diabetes to prevent the development to diabetes. So far, the best option to prevent diabetes is by lifestyle modification and metformin might be an option, but it is uncertain whether it will give CV benefit.

There is an indication to use these agents in kidney disease patients and trials with renal failure patients are currently on-going. It is important to pay attention to eGFR levels to identify high-risk patients that could benefit from therapy with these new agents.

Another area in which these agents could be used is obesity, as treatment with some of these agents results in weight loss. Liraglutide 3.0 mg has been approved for use in obese individuals. In a phase II trial, semaglutide has recently been evaluated in obese, non-diabetic individuals, and doses of at least 0.2 mg per day were shown to result in dose-dependent reductions in body weight loss, as compared with placebo, and as compared with liraglutide 3.0 mg (68).

Table 2 lists remaining questions regarding the management of T2DM that warrant further research.

Take home messages

Lifestyle management is the first measure for the prevention and/or management of T2DM (healthy eating, sufficient and regular physical activity and cessation of smoking).

Diabetes can be reversed by weight loss, achieved with an evidence-based structured weight management programme delivered in primary care.

Metformin is the first-line oral antiglycaemic therapy. It does not cause weight gain and hypoglycaemia, and it may reduce the risk of CV mortality, especially in obese patients.

Additional oral antiglycaemic therapies include SU, alpha-glucosidase inhibitors and PPAR-γ agonists. While SU and PPAR-γ agonists cause weight gain, alpha-glucosidase inhibitors do not. Of these three classes, only SU confer a risk of hypoglycaemia.

Weight: Of the novel anti-diabetes agents, DPP-4 inhibitors are weight neutral, while GLP-1RAs and SGLT2 inhibitors induce weight loss.

Hypoglycaemia: The incretins DPP-4 inhibitors and the injectable GLP-1RAs do not cause hypoglycaemia, and neither do SGLT2 inhibitors.

CV safety/benefit: CV safety has been demonstrated for the DPP-4 inhibitor sitagliptin and linagliptin, while saxagliptin or alogliptin were associated with a higher risk of hospitalization for HF.
GLP-1RAs liraglutide, semaglutide and albiglutide are safe and reduce the rate of CV events, while lixisenatide and exenatide were CV neutral. The SGLT2 inhibitors empagliflozin and canagliflozin have been shown to lower the rate of MACE, with specific benefit for HF endpoints. Dapagliflozin, tested in a lower risk population, did not lower MACE, but did reduce hospitalisation for HF.

In primary prevention patients, SGLT2 inhibitors do not appear to lower MACE, but they do lower hospitalisation for HF in this group.

Suggested mechanisms of new anti-diabetes agents

One of the suggested mechanisms underlying the CV benefit seen with SGLT2 inhibitors and some members in the GLP-1RA class are less volume in the circulation due to osmotic processes. Moreover, an increase in ketones has been hypothesised to play a role, as a result of a switch towards this source of energy, when the level of sugar in the blood available as a fuel drops. Ketones are suggested to have a beneficial effect on the cardiac muscle. Other possibilities include implications on calcium, sodium and potassium levels (48). The rapid separation of the event curves in the SGLT2 inhibitor trials and the benefit on HF outcomes suggests a volume effect. The GLP-1RAs needed longer time to show a CV benefit, indicative of an effect on atherogenic processes.

Take home messages

The mechanisms underlying the CV benefit may involve reduced circulatory volume, especially considering the rapid effect seen with SGLT2 inhibitors. The benefit seen with GLP-1RAs takes longer to become apparent, indicative of impact on atherogenic processes.

Recommendations and guidelines

The ADA Standards of Medical Care in Diabetes 2018 (69) recommend tailoring therapy to the individual patient, balancing harms and benefits. The document contains a flow chart on how to manage T2DM patients. The guidance is based on HbA1c levels, and the guidelines suggest that the choice for additional therapy, next to lifestyle management and metformin, should depend on the characteristics of the individual patient. Giving individualized treatment also means that glycaemic objectives must be differentiated not only on the basis of the patient's clinical characteristics, but also on the basis of the therapy used. (70). These recommendations are concordant with what is written in the ESC/EASD 2013 Guidelines (17).

Late 2018, the European (EASD) and American (ADA) Diabetes Associations jointly published a Consensus Report. This report contained expert opinion on pharmacotherapy, namely that in patients with clinical CVD, an SGLT2 inhibitor or a GLP1RA with proven CV benefit is recommended (71). The 2019 Standards of Medical Care in Diabetes published by ADA has been updated to align with the ADA-EASD consensus report. It now included the recommendation that, for most patients who need the greater efficacy that comes with injectable treatment, a GLP-1RA should be the first choice, ahead of insulin (72, 73).

Based on current evidence, T2DM patients with established CVD should receive metformin therapy, combined with additional therapy that has demonstrated

to give CVD benefit. For example, patients with ischemic heart disease and stroke might be prescribed GLP-1RAs and patients with HF could use SGLT2 inhibitors. Formal recommendations in European guidelines for this tailored approach are awaited – the consensus statements are guidance recommendations whilst the formal evidence synthesis methods used in the guideline documents are awaited. New ESC Guidelines on the management of T2DM are expected in late 2019. Treatment options are summarised in figure 1.

Take home messages

T2DM patients with established CVD should receive lifestyle management and metformin therapy, combined with additional therapy with demonstrated CVD benefit in a relevant patient population.

Challenges faced in clinical reality

Personalized approach

Current data suggest that certain diabetes patient groups may benefit more from the new anti-diabetes agents; for example the effect of canagliflozin on the risk of CV death or hospitalised HF was greater in those with a history of HF at baseline (9). Especially in patients with low CVD risk, treatment on top of metformin should be chosen based on the best benefit-risk-ratio, both considering short- and long-term effects of therapy. Various treatment options are available, but certainties on their effects are scarce in these subjects, also because of lack of head-to-head comparison studies. In addition, treatment objectives may differ between patients, further increasing the need for a more personalised therapeutic approach in T2DM.

Data analysis of large databases can be used to identify patients who will benefit most from specific therapy. Interestingly, cluster analysis of six variables in adult-onset diabetes patients resulted in the identification of five subgroups with predictive value for future complications: severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes. These subgroups were based on the following characteristics: glutamate decarboxylase antibodies (GADA), age at diagnosis, body-mass-index (BMI), HbA1c, β-cell function, insulin resistance (74). These results suggest that a more precise stratification of new onset diabetes is possible and clinically useful. Moreover, it can provide information about underlying disease mechanisms. This stratification can be used in trials to better characterise patients, which will allow better individualisation of treatments in the future, according to risk of complications.

Take home messages

T2DM management should be personalised, balancing benefits and risks, taking individual treatment objectives into account, and specific benefits of new anti-diabetes agents in subgroups of patients

Using six variables, five subgroups of adults with new-onset diabetes have been identified with predictive value for future complications

Table 2 | Areas for more research

What order should be used for the introduction of additional diabetes medications? Most guidance is based on opinion or simple cost containment grounds
Should we screen for diabetes? If so, how?
What is the best training for general practitioners? Diabetes is complex and yet most patients are managed by GPs in the community. Training is needed on managing pre-diabetes, diabetes, treatment triage, initiating insulin, patient education.

When (pre-)diabetes is suspected

Diagnosis of pre-diabetes:
- OGTT: IGT if 2h-PG is ≥7.8 and <11.1 mmol/L (or ≥140 and <200 mg/dL)

Diagnosis of T2DM:
- HbA1c of >6.5% [48 mmol/L] and FPG of >6.5 mmol/L (117 mg/dL)
  If still in doubt: perform OGTT

When diagnosis of pre-diabetes or T2DM is established

Comrehensive risk factor management approach:
- Consider lipid lowering and blood pressure lowering

Lifestyle management:
- Healthy eating, maintain a healthy weight, adequate physical activity, smoking cessation

Pharmacological treatment options in case of T2DM:

Traditional pharmacotherapy:

	Lower macrovascular risk?	Effect on weight	Cause hypoglycaemia	Remarks
Metformin *First-line*	✓ modestly	No weight gain	No	eGFR: >30 mL/min/1.73m^2 (reduce dose if eGFR <60)
Sulphonylureas	✗	Induce weight gain	⬆ risk	
Alpha-glucosidase inhibitors	✗	No weight gain	No	Should be taken with diet rich in complex carbohydrates.
PPAR-γ agonists	✗	Induce weight gain	No	Check liver function and symptoms of heart failure.

Novel classes pharmacotherapy:

	Lower macrovascular risk?	Effect on weight	Cause hypoglycaemia	Remarks
DPP-4 inhibitors	✗	No weight gain	No	Some ⬆ risk of HF outcomes
GLP-1RAs	✓ (not all GLP-1RAs)	Help reduce weight	No	Some members of class lower MACE, possibly act on atherogenesis
SGLT2 inhibitors	✓	Induce weight loss	No	Specific benefit for HF outcomes. Lower MACE only if ixisting CVD.

Figure 1 l Flowchart with management options for (pre-)diabetes and associated CV risk
OGGTT: Oral glucose tolerance test; impaired glucose tolerance; 2hPG: 2-hour post-load plasma glucose; HbA1c: glycated haemoglobin A1c; FPG: fasting plasma glucose

BOX 1 | Take home messages

INTRODUCTION

- Lowering HbA1c with traditional therapies decreases microvascular complications, but has not been shown to improve CV mortality substantially.
- Some CV outcomes studies of newer T2DM treatments have demonstrated significant CV benefits, allowing a T2DM management approach that addresses both hyperglycaemia and the associated risk of CV morbidity and mortality.
- Most guidelines short-cut to assuming patients with diabetes are already at higher enough risk to warrant full CVD prevention interventions, rather than recommending formal risk assessment.

PROGRESSION OF PRE-DIABETES TO TYPE 2 DIABETES: DIAGNOSIS

- Pre-diabetes refers to impaired glucose tolerance. The ESC/EASD Guidelines recommend that an OGTT is used for diagnosing IGT.
- In individuals with IGT or at high risk of T2DM, appropriate lifestyle counselling on should be provided. Healthy diet, modest weight loss and increased physical activity can prevent or delay progression to T2DM.
- T2DM is characterized by insulin resistance, but does not cause symptoms for several years. Diagnosis is based on HbA1c and FPG combined.

TYPE 2 DIABETES-RELATED RISK

- HbA1c is a good biomarker for the risk of developing microvascular complications, with this risk becoming evident above HbA1c of 6.5%.
- Risk of several CVD presentations is higher in those with vs. those without T2DM and diabetes is a CV mortality risk factor.
- The presence of microvascular complications in T2DM is an independent risk factor for macrovascular CV events.
- Patients with DM and at least one other CV risk factor or target organ damage should be considered at very high risk. All other patients with T2DM should be considered at high risk.

THERAPEUTIC CONSIDERATIONS

- Tight glycaemic control can reduce microvascular complications of T2DM, but does not lower CV risk sufficiently. Rapid and strict HbA1c control can do harm in some individuals.
- Multifactorial intervention, comprising of lowering lipid levels and BP, and use of aspirin, has been shown to reduce vascular complications and mortality.
- CV outcome trials have shown CV benefit upon treatment with GLP-1RAs or SGLT2 inhibitors. Specific benefits vary among the drug classes and individual agents.
- Diabetes should be considered a state of enhanced CV risk that should be targeted with therapy, as opposed to only treating hyperglycaemia.

BOX 1 | Take home messages - continued

MANAGEMENT OPTIONS FOR HYPERGLYCAEMIA AND CV RISK

- Lifestyle management is the first measure for the prevention and/or management of T2DM (healthy eating, sufficient and regular physical activity and cessation of smoking).
- Diabetes can be reversed by weight loss, achieved with an evidence-based structured weight management programme delivered in primary care.
- Metformin is the first-line oral antiglycaemic therapy. It does not cause weight gain and hypoglycaemia, and it may reduce the risk of CV mortality, especially in obese patients.
- Additional oral antiglycaemic therapies include SU, alpha-glucosidase inhibitors and PPAR-γ agonists. While SU and PPAR-γ agonists cause weight gain, alpha-glucosidase inhibitors do not. Of these three classes, only SU confer a risk of hypoglycaemia.
- **Weight:** Of the novel anti-diabetes agents, DPP-4 inhibitors are weight neutral, while GLP-1RAs and SGLT2 inhibitors induce weight loss.
- **Hypoglycaemia:** The incretins DPP-4 inhibitors and the injectable GLP-1RAs do not cause hypoglycaemia, and neither do SGLT2 inhibitors.
- **CV safety/benefit:** CV safety has been demonstrated for the DPP-4 inhibitor sitagliptin and linagliptin, while saxagliptin or alogliptin were associated with a higher risk of hospitalization for HF. GLP-1RAs liraglutide, semaglutide and albiglutide are safe and reduce the rate of CV events, while lixisenatide and exenatide were CV neutral. The SGLT2 inhibitors empagliflozin and canagliflozin have been shown to lower the rate of MACE, with specific benefit for HF endpoints. Dapagliflozin, tested in a lower risk population, did not lower MACE, but did reduce hospitalisation for HF. In primary prevention patients, SGLT2 inhibitors do not appear to lower MACE, but they do lower hospitalisation for HF in this group.

SUGGESTED MECHANISMS OF NEW ANTI-DIABETES AGENTS

- The mechanisms underlying the CV benefit may involve reduced circulatory volume, especially considering the rapid effect seen with SGLT2 inhibitors. The benefit seen with GLP-1RAs takes longer to become apparent, indicative of impact on atherogenic processes.

RECOMMENDATIONS AND GUIDELINES

- T2DM patients with established CVD should receive lifestyle management and metformin therapy, combined with additional therapy with demonstrated CVD benefit in a relevant patient population.

CHALLENGES FACED IN CLINICAL REALITY

- T2DM management should be personalised, balancing benefits and risks, taking individual treatment objectives into account, and specific benefits of new anti-diabetes agents in subgroups of patients
- Using six variables, five subgroups of adults with new-onset diabetes have been identified with predictive value for future complications.

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