Adv Exp Med Biol - Advances in Internal Medicine (2020) 4: 129–152
https://doi.org/10.1007/5584_2020_514
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Published online: 8 April 2020

Glycaemic Control and Vascular Complications in Diabetes Mellitus Type 2

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Abstract

Diabetes mellitus is constantly increasing worldwide. Vascular complications are the most common in the setting of long-standing disease, claiming the greatest burden in terms of morbidity and mortality. Glucotoxicity is involved in vascular damage through different metabolic pathways, such as production of advanced glycation end-products, activation of protein kinase C, polyol pathway activation and production of reactive oxygen species. Vascular complications can be classified according to the calibre of the vessels involved as microvascular (such as diabetic retinopathy, nephropathy and neuropathy) or macrovascular (such as cerebrovascular, coronary and peripheral artery disease). Previous studies showed that the severity of vascular complications depends on duration and degree of hyperglycaemia and, as consequence, early trials were designed to prove that intensive glucose control could reduce the number of vascular events. Unfortunately, results were not as satisfactory as expected. Trials showed good results in reducing incidence of microvascular complications but coronary heart diseases, strokes and peripheral artery diseases were not affected despite optimal glycemia control. In 2008, after the demonstration that rosiglitazone increases cardiovascular risk, FDA demanded stricter rules for marketing glucose-lowering drugs, marking the beginning of cardiovascular outcome trials, whose function is to demonstrate the cardiovascular safety of anti-diabetic drugs. The introduction of new molecules led to a change in diabetes treatment, as some new glucose-lowering drugs showed not only to be safe but also to ensure cardiovascular benefit to diabetic patients. Empaglifozin, a sodium-glucose cotransporter 2 inhibitor, was the first molecule to show impressing results, followed on by glucagon-like peptide 1 receptor agonists, such as liraglutide. A combination of anti-atherogenic effects and hemodynamic improvements are likely explanations of the observed reduction in cardiovascular events and mortality. These evidences have opened a completely new era in the field of glucose-lowering drugs and of diabetes treatment in particular with respect to vascular complications.

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Keywords

Atherosclerosis · Cardiovascular complications · CVOT · Diabetes · Glycaemic control · Nephropathy · Neuropathy · Peripheral artery disease

1 Introduction

During last years, prevalence of diabetes mellitus (DM) has risen considerably both in developed and developing countries. The high number of patients involved and the significant impact on prognosis determined by its complications make diabetes a key health priority from a global point of view.

It is however important to notice that, thanks to the spread of preventive strategies, the incidence of clinically diagnosed DM has remained stable or even dropped in the majority of populations studied since 2006 (Magliano et al. 2019). On the other hand, the prevalence of DM is constantly increasing and the cases of patients with DM are expected to rise from 9.1% of the population in 2014, to 13.8% in 2030 and 17.9% in 2060 (Lin et al. 2018). The aging of population and the high incidence of obesity and metabolic syndrome are major causes of the increase in DM prevalence. These projections have been done using statistical models mainly applied to the USA population but projections from other high-income countries are similar.

Vascular complications are by far the most common complication in the setting of long-standing diabetes, representing the most important determinant of morbidity and mortality (Tseng 2004). Atherosclerosis in different body districts, both micro and macrovascular, is the reason for reduced life expectancy and poor quality of life owing to its functional consequences.

2 Pathophysiology and Molecular Mechanism at the Basis of Vascular Insult in Diabetes

The origin of vascular complications in type 1 and type 2 DM is certainly multifactorial but persistently elevated glycemia seems to be the key mediator in organ injury through a mechanism called glucotoxicity.

Glucotoxicity refers to the structural and functional damage occurring both in beta pancreatic cells and in target tissues of insulin. It is caused by chronic elevation of glycemia levels leading to disruption of normal cellular mechanisms involved in carbohydrate management and to build-up of toxic metabolic by-products. These alterations represent a double-edged sword as from one side they cause a reduction in insulin secretion from affected beta cells and from the other side they cause reduction in insulin action at peripheral level, inducing the so-called insulin resistance.

Many different metabolic pathways are involved in the development of the vascular insult at the basis of long-term diabetic injuries (Kumar et al. 2010; Rask-Madsen and King 2013). It is important to notice that some pathogenic mechanisms are preferentially active in one organ but generally they are responsible for the development of vascular complications in more than one district.

1. Production of AGEs (Advanced Glycation End-products). AGEs are produced by means of non-enzymatic reaction between di-carbonyl compounds derived from glucose (such as methylglyoxal, glyoxal, and 3-deoxyglucone) and the amino-groups derived from intra and extracellular proteins. Their formation is followed by the interaction with specific receptors, called RAGEs (Receptor of Advanced Glycation End-products) whose activation leads to a chain of metabolic cellular consequences enhancing tissue injury. The RAGEs are found on inflammatory cells and smooth muscle cells of blood vessels. The detrimental effects depend on the release of inflammatory cytokines, the activation of fibroblasts for the deposition of extracellular matrix, the entrapment of certain molecules in the media of arterial vessels (such as LDL particles), the production of reactive oxygen species (ROS) and the increased procoagulant activity of endothelial cells: the final net result is the acceleration of atherosclerosis and a predisposition to atherothrombosis.

2. Activation of Protein Kinase C (PKC) pathway. The numerous glycotic intermediates derived by the constant state of hyperglycaemia can activate PKC signalling pathway. One of the main downstream effects consists in the increased production of Vascular Endothelial Growth Factor (VEGF), responsible for example for the retinal neovascularization which is a typical feature of diabetic retinopathy. Another well studied consequence is the increased release of Tissue Growth Factor (TGF)-beta which is a potent stimulator for fibroblast release of extracellular matrix. The increased deposition of interstitial material is at the base of vascular fibrosis in all body districts, ranging from large-sized blood vessels to nephroangiosclerosis at glomerular level.
3. Polyol pathway activation. Cellular glucose uptake may be significantly increased because of the high extracellular concentration. The excess of glucose may be shunted to the polyol pathway (also known as sorbitol pathway). Glucose is converted to sorbitol and eventually to fructose in a reaction produced by aldose reductase that uses NADPH as a cofactor. When the polyol pathway is highly active the intracellular storage of NADPH is rapidly depleted with detrimental consequences. NADPH is involved by glutathione-reductase enzyme in a reaction whose aim is to regenerate reduced glutathione (GSH), which is one of the main anti-oxidant molecules at cellular level. When intracellular NADPH level drops, also the level of GSH is reduced because it cannot be regenerated. In this setting the cell loses its primary antioxidant protection from oxidative stress becoming susceptible to multiple injuries. This seems to be the primary mechanism of neuron damage leading to peripheral diabetic neuropathy.
4. Oxidative stress. Oxidative stress at cellular level is multifactorial and depends primarily on the activation of AGE-related intracellular pathways, the depletion of NADPH and GSH storage, the increased production of ROS and free radicals. Oxidative damage may lead to a change in cellular phenotype increasing LDL-R on endothelial cells and promoting the establishment of a procoagulant state in blood vessels.
5. Hexosamine pathway. The presence of elevated glucose concentration inside the cell may lead to the shift of this molecule in unusual pathways such as the hexosamine pathway. The products of this pathway may lead to endoplasmic reticulum stress which can cause altered transcription of molecules involved in accelerated atherosclerosis and insulin resistance.

In the end, hypertension and dyslipidaemia are frequently present in diabetic patients, as well as other cardiovascular (CV) risk factors. Their co-existence not only adds other mechanisms of vascular damage but also enhances the diabetic specific detrimental effects. Endothelial dysfunction is a central and well known final pathophysiological element common to the various factors described above (Avogaro et al. 2011; De Vriese et al. 2000; Hadi and Suwaidi 2007).

3 Classification of Vascular Complications

Atherosclerosis in the context of DM can affect all vascular districts and it is the central pathological mechanism at the basis of vascular complications. Importantly, the risk of developing vascular complication depends on both the severity and the duration of hyperglycaemia, similarly to what happens with LDL exposure (Ference et al. 2018). Patients with long-standing elevation of blood sugar and higher level of glycemia are the ones that will present with earlier, more severe and more diffuse forms of vascular complications.

Vascular complications are conventionally classified as microangiopathies, involving small-sized blood vessels (such as arterioles and capillaries) and macroangiopathies, involving medium and large-sized blood vessels (such as

aorta, coronary arteries, lower limb vessels and cerebral vessels) (Kumar et al. 2010). Therefore, according to the size and location of the blood vessels involved authors generally recognize the following:

- microvascular complications: retinopathy, nephropathy, neuropathy;
- macrovascular complications: coronary artery disease, cerebrovascular disease, peripheral artery disease.

3.1 Diabetic Retinopathy

Diabetic retinopathy is probably the most common microvascular complication. It is responsible for as many as 10000 new cases of blindness every year in the USA (Fong et al. 2004). The main mechanism involved in the pathogenesis seems to be the production of AGEs, the increase in local production of VEGF and oxidative stress due to ROS. It is generally classified as non-proliferative (background) retinopathy and proliferative retinopathy. Non-proliferative (background) retinopathy consists of small haemorrhages, referred to as "dot haemorrhages", in the middle layer of the retina, whose margins are characterized by the presence of hard exudates formed by lipid deposition. Microaneurisms are very common together with retinal oedema resulting from fluid extravasation. Proliferative retinopathy is characterized by florid neoangiogenesis with the formation of new blood vessels sprouting in a disorganized manner on the surface of the retina. The new vessels are clearly visible as white areas called "cotton wool spots". Vitreous haemorrhage and retinal detachment are two complications of long-standing retinopathy leading to abrupt or progressive blindness.

3.2 Diabetic Nephropathy

Diabetic nephropathy is one of the leading causes of renal failure and end-stage renal disease (ESRD) requiring dialysis and its incidence is on the rise due to the high prevalence of diabetes worldwide. It is defined as the presence of overt proteinuria >500 mg in 24 h in the context of DM without other specific causes. It is usually preceded by a long period of microalbuminuria, consisting in albuminuria of 30–300 mg in 24 h. Microalbuminuria signals the presence of an underlying glomerular damage that can be reversed in case of optimal glycaemic and blood pressure control. The onset of overt proteinuria on the other hand, indicates an irreversible damage. Seven percent of type 2 diabetic patients presents with nephropathy at the time of diagnosis. It occurs in up to 12% of patients with type 1 diabetes mellitus by 7 years, and in 25% of patients with type 2 DM by 10 years after the diagnosis (Adler et al. 2003). The origin of diabetic nephropathy stems from a combination of metabolic and hemodynamic alterations contributing to alteration of podocytes function, increasing basement membrane thickening, reduction of filtration rate and reduced tubular function (Cao and Cooper 2011). Pathological changes observable in histological kidney specimen are the presence of thickened glomerular basement membrane, mesangial nodules distorting glomerular architecture (called Kimmelsteil-Wilson nodules), thickening of arteriolar medial wall, capillary microaneurysm formation and progressive extension of interstitial fibrosis. Aggressive treatment consisting in glycaemic control and antihypertensive strategies using ACE-inhibitors and angiotensin-receptor blockers can prevent progression toward further damage and delay the need for dialysis.

It is worth to mention a form of diabetes-related nephropathy named non-proteinuric diabetic kidney disease: a variable proportion of patients (around 35–40%) presents with advanced renal impairment (eGFR <60 mL/mq) in the absence of proteinuria or albuminuria (microalbuminuria <300 mg/g) (Robles et al. 2015). This entity is associated with a higher incidence of cardiovascular diseases. However, it is not yet clear the underlying pathological mechanisms and the risk of progression toward end-stage renal disease.

3.3 Diabetic Neuropathy

Diabetic neuropathy has been defined by the American Diabetes Association (ADA) as the presence of symptoms and signs of peripheral nerve dysfunction in the setting of diabetes after the exclusion of other causes. Both vascular and non-vascular abnormalities have been advocated in the establishment of nerve injury. Histological findings show that several pathological changes occur in nerve structure, such as basement membrane thickening and pericyte loss. Notably, there is evidence of reduced density of capillaries, resulting in attenuated perfusion and eventually endoneurial hypoxia. Finally, this contributes to the axonal thickening and loss of neurons seen in most advanced forms of neuropathy (Tavakoli et al. 2008). Polyol accumulation and oxidative stress seem to be the two most important contributors for nerve damage. Many forms of neuropathy can occur, including sensory, motor and autonomic neuropathies. They can be focal or multifocal. It is important to recognize neuropathies as early as possible because of the significant morbidity and mortality they are associated with. Eighty percent of amputations occurs after foot ulceration or injury secondary to peripheral neuropathy and impaired healing due to lower limb perfusion defects (Boulton et al. 2005). Chronic sensorimotor distal symmetric neuropathy is the most common form, presenting with burning tingling sensation at the extremities that is worse at night. Some patients present with hypoesthesia and numbness and they are the ones at higher risk for foot ulceration. Pure sensory neuropathy is rare. Mononeuropathy have sudden onset and can involve every nerve, even though the most common are ulnar, radial and median. Autonomic neuropathy can manifest with gastroparesis, constipation or diarrhoea, erectile dysfunction, bladder dysfunction, orthostatic hypotension; moreover, it affects patient perception of anginal pain, leading to the high incidence of silent ischemia reported in diabetic patients (Maser et al. 2003).

3.4 Coronary Artery Disease

Coronary artery disease has been linked to diabetes mellitus in many studies starting from the Framingham study (Kannel and McGee 1979). DM increases the risk of myocardial infarction more than any other risk factor (except for cigarette smoking) and coronary artery disease is the most common macrovascular complication registered (Anand et al. 2008). From a pathological point of view, DM promotes atheroma formation in coronary arteries and at the same time the constant state of hyperglycaemia promotes a procoagulant state favouring the occurrence of thrombotic events. Notably, from an anatomical point of view, coronary artery lesions tend to be more diffuse and more distal relative to lesions observed in non-diabetic patients (Morgan et al. 2004). Even though the classical lesions concern epicardial vessels, it is important to recognize the role of coronary microvascular dysfunction in diabetes (also known as diabetic coronary microangiopathy) as a large number of diabetic patients with normal epicardial vessels shows reduced coronary flow reserve (Kibel et al. 2017). These patients tend to be symptomatic, have a worse prognosis and tend to progress to overt CAD.

The CV risk in diabetic population is much higher than in normal population and specifically the risk of CV events in many cases is equivalent to the risk of non-diabetic patients who have a history of previous myocardial infarction (Haffner et al. 1998). Therefore, the European Society of Cardiology (ESC), the European Association for the Study of Diabetes (EASD) and ADA consider diabetic patients mainly at high and very-high risk (in particular for this case it is evident how diabetes is considered a sort of coronary artery disease equivalent rather than a simple risk factor) (Buse et al. 2007; Piepoli et al. 2016; Mach et al. 2019). Moreover, the consequences of a myocardial infarction are more pronounced in patients suffering diabetes, whose incidence of cardiovascular death or stroke after a cardiovascular event is higher than in general population (Wallentin et al. 2009). Despite persistently higher rate of coronary

artery disease, the rate of mortality has dropped significantly in last two decades (Roger et al. 2012). This improvement is likely the consequence of effective medical treatment and early revascularization strategies. However, the prevalence of DM is increasing over time and patients are living longer: therefore, the overall burden of CAD attributable to DM will rise over time, making strategies to mitigate the risk of CAD in diabetics a fundamental goal for the future (Fox et al. 2007).

3.5 Cerebrovascular Disease

Stroke incidence is elevated in diabetic population claiming a high cost in terms of morbidity and mortality. Patients with type 2 DM have a 150–400% higher risk of stroke relative to non-diabetic population. As for coronary artery disease, DM itself worsen the outcome of stroke as the severity of the cerebrovascular events tend to be higher and the risk of vascular dementia and recurrences are higher as well (Beckman et al. 2002).

3.6 Peripheral Artery Disease

Diabetes is strongly related to peripheral artery disease. The risk of developing PAD is two- to four-fold increased in diabetes mellitus relative to non-diabetic patients. As for other complications the duration and severity of hyperglycaemia influence the extent and severity of PAD. Notably, as observed in coronary arteries, lesions are more diffuse and more distal relative to patients who are not affected by diabetes. Around 20–30% of patients with diabetes have prevalent PAD described as ankle-brachial index (ABI) below <0.9 (Marso and Hiatt 2006). Most patients are asymptomatic and only 20% show symptoms. Importantly, one fourth of patients with PAD demonstrates progression of symptoms over 5 years and a rate of amputation of around 4%. It is important to stress out that diabetes does not only affect large-calibre peripheral vessels, but it affects distal arterioles as well (the so-called peripheral microangiopathy). This form of distal arteriopathy is thought to be the pathogenetic mechanism at the base of pigmented pretibial patches, necrobiosis lipoidica and erysipelas-like erythema observed in diabetic patients.

4 Efficacy of Glycaemic Control on Coronary Artery Disease

As already mentioned, the elevation of blood sugar strictly correlates with severity of vascular complications. Therefore, a reasonable target to reduce these complications would be the reduction of glycemia. On one hand, many studies have shown how reaching the target of a better glycaemic control can reduce the number of microvascular complications. On the contrary, the evidence regarding the effect of glycaemic control on macrovascular complications has been more controversial.

Coronary artery disease is the most common macrovascular complication in the setting of diabetes, being elevated blood glucose and high glycated haemoglobin (HbA1c) two major well-known risk factors. From this ground, it may seem logical that strategies able to decrease blood glucose could be the mainstem in prevention of cardiovascular events in diabetic population. However, the relationship between glucose-lowering therapies and cardiovascular outcome is not straightforward, as shown by many studies where the reduction of glycaemic parameters did not clearly associate with a reduction of patient cardiovascular events. Since patient outcomes could not be easily predicted by the effect of interventions on surrogate measures, this discrepancy called into question the possible CV benefits of glucose-lowering strategies. Nowadays, a new era of glucose-lowering therapies has been opened by the use of some glucose-lowering drugs (GLDs), such as empaglifozin and liraglutide. These drugs have been demonstrated to impact significantly on CV mortality as shown by the cardiovascular outcome trials. The study of their effects, that extend well beyond the simple

reduction of glycemia, could shed light on the "common soil" from where DM and coronary heart disease stem from (Stern 1995).

4.1 Relationship Between Hyperglycaemia and Cardiovascular Outcome

Most studies have established a strong relationship between cardiovascular risk and blood glucose level (measured by means of different parameters, such as fasting glucose, 2-h glucose during oral glucose tolerance test and HbA1c). The relationship reported by the studies is usually linear and continuous with a progressive increase in CV events as glycaemic parameters are increasing.

In the Study of Norfolk, 10232 patients from UK were followed up for 6–8 years showing a linear correlation between the level of HbA1c and CV disease and CV mortality (Khaw et al. 2004). The risk was lower in patient with HbA1c <5% and increased continuously with the elevation of HbA1c: each percentage point of HbA1c over 5% corresponded to a rise in CV relative risk of 20%. Most of the events occurred in patients with moderately elevated HbA1c suggesting that the reduction of HbA1c could be beneficial for CV protection. The Atherosclerosis Risk in Communities (ARIC) study conducted in a US population of adults without prior history of diabetes, showed similar linear trend between CV disease and HbA1c (Selvin et al. 2010). Relative to patients with normal HbA1c values (<5.5%), CV events increased by 23% in those with HbA1c 5.5–6%, by 78% in those with HbA1c 6–6.5% and by 95% in those with HbA1c >6.5%. Similarly, in a diabetic patient population, the United Kingdom Prospective Diabetes Study (UKPDS-35) (Stratton et al. 2000) found that each 1% increase in HbA1c was associated with a 14% relative risk increase for myocardial infarction. On the other side, every 1% decrease in HbA1c was associated with clinically important reductions in the incidence of diabetes-related death (<21%; p-value <0.0001), myocardial infarction (<14%; p-value <0.0001), microvascular complications (<37%; p-value <0.0001) and peripheral vascular disease (<43%; p-value <0.0001).

The metanalysis of Selvin et al. published in 2004 put together data from all the available observational studies to estimate the association between glycated haemoglobin and cardiovascular events (Selvin et al. 2004). In type 2 diabetes mellitus, there was an increase in relative risk of 18% every 1% point of glycated haemoglobin. This result confirmed the evidences already observed in the single studies.

To be noticed from UKPDS-35 study it appears not to be a lower limit beyond which reductions in HbA1c cease to be of benefit in terms of reduction of CV events and other diabetes-related endpoints. However, the concept "the lower HbA1c the better" cannot be applied in clinical practice because at lower goals of HbA1c the threat of hypoglycemia stands up.

While these initial studies conveyed the message that the lower HbA1c the better for the patient outcome, the UK General Practice Research Database (GPRD) was one of the first study showing that lowering glycemia too much could have harmful consequences (Currie et al. 2010). 27965 patients with type 2 DM whose oral therapy was intensified to oral combinational therapy and 20005 whose oral therapy was intensified adding insulin were followed for 4.5 years monitoring for CV events and mortality. The pattern of risk was U-shaped with an increased number of events at lower and higher HbA1c levels. The same point was confirmed by the results coming from the Kaiser Permanente North Carolina Register (Huang et al. 2011). Data from 71092 patients with diabetes mellitus type 2 were analysed to evaluate the association between HbA1c and CV events and mortality. The authors showed a U-shaped relationship between HbA1c level and mortality with higher risk in those with HbA1c below 6% and over 10%. Again, a third study (Colayco et al. 2011) showed similar results with a U-shaped relationship with increased number of events when HbA1c level was lower than <6% and higher

than >8%. All in all, the results of the aforementioned studies added a little more piece to a complex puzzle. In fact, they showed that achievement of low glycemia confers protection from CV events but very low levels of glycemia may result in increased harm, probably due to severe complications of hypoglycaemia.

From these premises glycemia reduction appeared to be the key point to obtain a significant reduction in cardiovascular events, but evidences from later studies were not as satisfactory as expected.

4.2 Hypoglycemia and the Possible Explanation of the U-Shaped Mortality Curve

If a strict control of glycemia can have positive prognostic impact on patients, the drawback of excessive glycemia control is an increase in patient mortality. One of the proposed explanations is the higher incidence of hypoglycaemia that is a dreadful complication of intensive glucose-lowering strategies. Hypoglycemia is associated to a higher number of falls, fall-related fractures, cardiovascular events, poor quality of life, dementia and higher number of deaths. The proposed mechanism by which hypoglycaemia could increase mortality seems to be linked to the feedback mechanism that is triggered by overactivation of the sympathetic autonomic nervous system. Acute hypoglycaemia stimulates the release of epinephrine which subsequently increases cardiac rate and contractility, induces easier platelet aggregation, worsens vasoconstriction and afterload, heightens cardiac muscle excitability and arrhythmia risk, exacerbates myocardial oxygen consumption leading to ischemia. Moreover, hypoglycaemia may induce hypokalemia as result of potassium shift from extracellular space to intracellular space, leading to worrisome prolongation of QT interval.

4.3 Intensive Versus Conventional Glucose-Lowering Strategies

The first randomized clinical trials were developed to test whether interventions aimed at reducing glycemia were able to reduce micro and macrovascular complications and mortality in population with overt DM. An intensive glucose control group versus a conventional group was usually set to study the effect of the interventions (see Table 1 for summary).

The first landmark trial was the Diabetes Control and Complications Trial (DCCT) published in 1993 showing that intensive glycaemic control reduced the incidence of microvascular

Table 1 Summary of the most important trials comparing intensive versus conventional glycaemic control in type 2 diabetes mellitus

Trials	Population	Follow-up (Years)	Effect on microvascular complications	Effect on macrovascular complications	Effect on mortality
UKPDS (1998)	T2DM N = 3867	11.0	Reduced microvascular endpoints	No difference	No difference
ACCORD (2008)	T2DM N = 10251	3.5	Reduce retinopathy, nephropathy, neuropathy	No difference	Increased
ADVANCE (2008)	T2DM N = 11140	5.5	Reduced nephropathy	No difference	No difference
VADT (2009)	T2DM N = 1791	5.6	Reduced progression of albuminuria	No difference	No difference

Primary endpoints. UKPDS: an aggregate endpoint of any diabetes-related complications. ACCORD: a composite of non-fatal myocardial infarction, non-fatal stroke, and fatal myocardial infarction and stroke. ADVANCE: combined microvascular and macrovascular disease. VADT: time to occurrence of a composite of major cardiovascular events. See text for details

complications in patients affected by type 1 DM (Diabetes Control and Complications Trial Research Group et al. 1993).

Later in 1999, the United Kingdom Prospective Study (UKPDS-33) was targeting patients with type 2 DM (UK Prospective Diabetes Study (UKPDS) Group 1998a). 3867 patients diagnosed with DM type 2 were randomized to receive intensive treatment with sulfonylureas or with insulin versus conventional therapy plus diet alone. Patients were assessed for 10 years follow-up. At the end of follow-up period, the HbA1c in conventional group was 7.9% while in intensive group was 7.0%. The result showed that intensive group had significantly lower incidence (−12%, p-value = 0.03) of diabetes-related complications (micro, macrovascular and metabolic) relative to conventional group. However, there was non-significant reduction of diabetes-related death (−10%, p-value = 0.34) and non-significant reduction in overall mortality (−6%, p-value = 0.44). Moreover, the reduction of diabetes-related complication was dependent on a 25% reduction of microvascular complications (p-value = 0.0099) while the overall risk reduction for MI in the two groups was only of borderline significance (p-value = 0.052). A significant reduction in macrovascular complications was reached only in a subgroup of obese patients treated with metformin (UK Prospective Diabetes Study (UKPDS) Group 1998b). The conclusion drawn was that an intensive glucose-lowering strategy reduces diabetes-related complications but does not change the overall survival of patients. Furthermore, the reduction of diabetes-related complications was mainly the result of the decrease of microvascular complications in a group of naïve patients, while macrovascular complications were reduced only in a subset of overweight patients. It is interesting to notice that in a 10-year post-trial monitoring study of UKPDS, conducted on patients who survived after the end of the study, a sustained modest effect in reduction of diabetes-related complications in the intensive group control was still present (even if there was no more difference in glycated haemoglobins) (Holman et al. 2008). Moreover, a significant risk reduction in terms of myocardial infarction (15%, p = 0.005) and mortality (27%; p = 0.002) emerged in the intensive group, probably suggesting the need for a longer time to evaluate an effect on atherosclerotic outcomes.

One of the lessons learned from this trial is that when a strict glycemia control was initiated early in the history of diabetes and with low CV risk the effect was a longstanding cardiovascular benefit that was not observed for the same degree of glycemia control in older patients with years of uncontrolled diabetes. This protection coming from early diabetes control is thought to come from tissue "metabolic memory". The term metabolic memory refers to the idea that exposure to high levels of glucose for long time is "remembered" by the tissues in terms of damage, because of epigenetic and metabolic long-term effects. Immediate intensive treatment reducing not only the degree of hyperglycemia but also the duration of tissue exposure has protective effects that are maintained for years.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) 10251 patients were randomised to intensive control over conventional control (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). The trial was stopped prematurely after 3.5 years because of higher mortality rate in the intensive arm; the rate of serious hypoglycaemia requiring medical treatment was three-fold higher than in conventional group (10.5% Vs 3.5%).

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial 11140 patients were randomised to intensive versus conventional control (ADVANCE Collaborative Group et al. 2008). After 5 years there was a reduction in the primary endpoint (composite of micro and macrovascular complications) but there was no significant effect on MI, suggesting the contribution was mainly from the reduction of the microvascular complications, similarly to the UKPDS trial.

The Veteran Affairs Diabetes Trial (VADT) confirmed the lack of benefit of intensive glucose lowering strategies on major cardiovascular

events (Duckworth et al. 2009). 1791 US veterans with type 2 DM were randomly assigned to the intensive and conventional treatment group. There was no significant difference in terms of composite outcomes and cardiovascular endpoints.

In this scenario, it is important to remember the STENO-2 trial published in 2008 because it presents similarities but substantial differences from previous studies (Gæde et al. 2008). The trial enrolled 160 patients presenting with diabetes type 2 and microalbuminuria. Patients were followed-up for a median time of 7.8 years showing net beneficial effect on vascular complications and mortality. The key innovation relative to previous studies was the randomization to multifactorial intensive treatment of risk factors, including stricter glycemia control, blood pressure control, aspirin and statin. Patients were randomized to either intensive or conventional control arms: intensive therapy was associated with a lower risk of CV death (HR 0.43; 95% CI, 0.19–0.94; $P = 0.04$) and of cardiovascular events (HR 0.41; 95% CI, 0.25–0.67; $P < 0.001$). Despite positive results, it is not clear if the beneficial effect was simply determined by glycemia control or by the combined reduction of multiple risk factors. It is surely an important trial in defining that combinational control can truly gain CV benefit but it did not clarify if glycemia control alone could impact on CV events.

The net result of these trials is that intensive glucose control failed to improve cardiovascular outcome despite the strong relationship established between glycemia and cardiovascular events. These disappointing results could be explained by several considerations. First of all, glycemia is probably a weaker risk factor for CAD compared to LDL-cholesterol. Cholesterol decrease of 1 mg/dL obtains a relative risk reduction (RRR) of 23% in the incidence of myocardial infarction (Silverman et al. 2016). The expectations of early DM trials were largely based on assumption that glycemia reduction could lead to a similar impact. On a population level based on the data from UKPDS, fewer people should be treated with strict BP control (NNT 23) rather than intensive blood glucose control (NNT 46) to prevent one MI (Vijan and Hayward 2003). In the same way, cholesterol control in primary (NNT 34) and secondary (NNT 13) prevention seems more effective than intensive glucose lowering (Vijan et al. 2004). Secondly, adverse effects secondary to glycemia lowering may counterbalance potential benefits. As shown before, hypoglycaemia is a dreadful complication of intensive control and mortality has been shown to be increased in trials where glycaemic target was set too low. Thirdly, the use of glucose-lowering strategies in advanced diabetes may result useless because the disease and atherosclerosis could be too advanced. Lastly, the effects on macrovascular complications with some drugs may be evident only on the long-term (maybe because of the lack of specific anti-atherogenic effects) and some trials may be too short to adequately observe them.

It should be noted that the aim of these previous studies was to demonstrate the effect of glucose reduction on a certain outcome irrespective of the pharmacological strategy adopted: in most trials combination of various drugs had to be used to control glycemia and there was no particular advantage of one strategy over the other. These early glucose lowering trials were not designed to test the effects on outcomes of a specific drugs but to evaluate the efficacy of a stricter or lenient control of glycemia targets irrespective of the strategy that was used. The lessons learned from these early trials was that most drugs have a significant impact on diabetes mellitus onset and control but scarcely have an effect on cardiovascular events, that are the ones claiming the highest number of deaths in diabetic population.

4.4 Previous Evidences from Early Trials Concerning Specific Drug Classes

When trials started to focus on specific glucose-lowering molecules some of them showed cardiovascular positive effects.

Biguanide drug class is well-represented by metformin, that works reducing hepatic glucose

production and promoting peripheral insulin sensitivity, without inducing hypoglycaemia. Numerous observational studies and clinical trials have demonstrated CV benefits in terms of reduction of micro-macrovascular complications and CV-related mortality. In the HOME trial (Hyperinsulinemia: the Outcome of its Metabolic Effect) patients treated with metformin demonstrated a 40% reduction of endpoints (a composite of both micro and macrovascular events) (Kooy et al. 2009). In SPREAD-DIMCAD, metformin is compared with glipizide showing that metformin-treated patients have a 46% reduction of CV events (HR 0.54; 95% CI 0.30–0.90; p-value<0.026) (Hong et al. 2013). Therefore, metformin is one of the earliest drugs to show CV benefit. These evidences support the use of metformin as first-line agents in most patients, as recently confirmed by latest guidelines (Cosentino et al. 2019).

For sulfonylureas evidences are conflicting. Sulfonylureas are the oldest oral agents in the treatment of hyperglycemia. As insulin secretagogues they favour insulin secretion, being effective in reducing glycemia at expenses of a significant risk of hypoglycaemia and weight gain. An early warning concerning safety comes from a study in 1970 (UGDP), in which tolbutamide-treated patients showed increased CV mortality (University Group Diabetes Program 1976). However, later studies which compared different treatment arms containing sulfonylureas, found no difference in the CV events. After 50 years of studies, whether sulfonylureas are associated with adverse events is still debatable.

Intestinal alfa-glucosidase inhibitors act inhibiting carbohydrate breakdown in intestine reducing absorption after meals. In STOP-NIDDM, 1429 participants with glucose intolerance were randomised to receive acarbose or placebo. The acarbose allowed to delay the onset of DM in people with glucose intolerance (Chiasson et al. 2002). After 3 years of follow-up the trial reported 49% RRR in CV events with an incredible 91% reduction of MIs. From this evidence, ACE trial was devised to observe the real impact of acarbose on CV outcome (Holman et al. 2017). The trial enrolled 6522 participants over 176 Centres in China. It did not reduce the risk of major CV events but did reduce the incidence of DM.

Thiazolidinediones lower glucose by activating the nuclear transcription factor peroxisome proliferator-activated receptor gamma (also known as PPR-gamma agonists). The two major drugs, pioglitazone and rosiglitazone, despite the efficacy raised concerns about safety. In PRO-ACTIVE 5238 patients with previous CV disease were treated with pioglitazone or placebo. After a median follow-up of 2.9 years, pioglitazone showed a significant benefit on secondary endpoints (death for all-causes, MI and stroke) that has been reduced by 16% (HR 0.84; 95% CI 0.72–0.98, p-value = 0.027) (Dormandy et al. 2005). However there has been an increased risk of heart failure in the intervention group (16% versus 11.5%). The use of rosiglitazone has been investigated by numerous observational studies however only one trial, the RECORD trial, investigated the action of rosiglitazone on CV endpoints. 4447 diabetic patients with inadequately controlled hyperglycaemia were treated with rosiglitazone showing no difference in the primary end-point (CV hospitalization or CV death) among the groups (Home et al. 2009). Notably, the risk of heart failure was increased approximately two-fold with rosiglitazone and this opened the path for further assessments due to concerns related to safety. In 2007, Nissen et al. published a metanalysis which demonstrated an increased risk of MI and mortality with the use of rosiglitazone (Nissen and Wolski 2007). This paper will be a turning point in the history of anti-diabetic drugs for the consequences generated.

4.5 The Cardiovascular Outcome Trials (CVOTs) in the Era of Novel Glucose-Lowering Drugs

4.5.1 History and Concepts Behind CVOTs in Diabetes

Previous studies were heterogeneous in design and the main outcome was the demonstration of the efficacy in controlling glucose-related

parameters. This paradigm however changed in 2007 when Nissen et al. raised great concerns regarding possible unexpected CV risks of anti-hyperglycaemic medications (Nissen and Wolski 2007). The meta-analysis showed a significant 43% increase in MI and 64% increase in CV mortality with the use of rosiglitazone. After rosiglitazone experience, in 2008 Food and Drug Administration (U.S. Food and Drug Administration 2008) mandated that every GLD should be demonstrated not only efficacious in reducing glycaemic level but also safe from a CV point of view. Guidelines for drug acceptance now require randomized double-blinded placebo-control trials to assess drug safety, that is to say non-inferiority relative to placebo. The drugs now need to be tested against placebo on top of background therapy. The primary outcomes are combined in 3-points MACE that are similar for all trials and include CV mortality, non-fatal MI and non-fatal stroke. Some studies use 4-points MACE adding hospitalization for unstable angina as one of the primary endpoints. Secondary outcomes variably include all-cause mortality, hospitalization for heart failure and renal outcome. Median follow-up should be at least of 2 years. FDA specifies that non-inferiority is defined with the upper bound of 95% CI for the risk ratio of CV events being <1.3. An upper 95% CI >1.8 would require further pre-marketing trials for approval. Agents showing CI <1.8 but >1.3 requires a large post-marketing CV outcome trial to define risk (U.S. Food and Drug Administration 2018). As the main task of these randomized studies is to assess the prognostic impact of GLDs on cardiovascular endpoints they are called CardioVascular Outcome Trials (CVOTs).

It is important to emphasize that the studies were indeed not designed to assess superiority. They were designed to be sure anti-diabetic drugs were not harmful from a cardiovascular point of view. However, something unexpected happened when the results from EMPA-REG trial first came out. The astonishing results nourished the idea that some antidiabetic medications may not only be safe but may even reduce the risk of cardiovascular diseases in a subset of population at high risk for cardiovascular events. From that moment on a special attention has been focused on these new drugs, especially when different pharmacological classes yielded similar results. Therefore, most recent trials are now powered enough to estimate superiority relative to placebo (upper bound of 95% CI for risk ratio of CV events <1.0) in case non-inferiority (upper bound 95% CI for risk ratio of CV events <1.3) is demonstrated.

At the present time, encouragingly, all the completed trials have reached the non-inferiority standard for the primary cardiovascular end-point relative to placebo, demonstrating reassuring cardiovascular safety. Notably, six trials demonstrated superiority over placebo providing evidence of cardiovascular benefit in addition to safety (EMPA-REG OUTCOME for empaglifozin, CANVAS for canaglifozin, LEADER for liraglutide, SUSTAIN-6 for semaglutide, Harmony Outcomes for albiglutide and REWIND for dulaglutide). These evidences open a completely new era in the field of GLDs.

The following sections describe the main trials and results concerning the most important pharmacological classes (see Table 2 for summary).

4.5.2 Dipeptidyl-Peptidase-4 Inhibitors (DPP-4i)

After demonstration of the increased risk of mortality due to hypoglycaemic events in ACCORD trial, dipeptidyl-peptidase-4 inhibitors (DPP-4i) were launched on the market. DDP4 is an enzyme involved in degradation of incretins, like GLP-1, the molecules that favour insulin release. Inhibitors act stopping the action of DPP-4, increasing the systemic level of incretins, mainly GLP-1. Since incretin action results in a glucose-balanced insulin release, the risk of hypoglycaemia with this class of drug is therefore very low.

DPP-4i have minimal adverse effects (most common being nasopharyngitis, headache, and upper respiratory infections). Differently from GLP-1 receptor agonists, they do not slow GI motility and have weight neutral effect, which is still beneficial for most patients with type 2 DM. DPP-4i primarily target the postprandial plasma

Table 2 Summary table of the main cardiovascular outcome trials (CVOTs)

Trials *Year*	Active treatment	Patients *Features; number*	Endpoints	Follow-up *Years*	Outcome *HR (95% CI); p-value*	Superiority *Yes or No*	Details
Dipeptidyl-peptidase-4 inhibitors (DPP-4i)							
SAVOR-TIMI 53 (2013)	Saxagliptin	T2DM + CVD or high CVR N = 16492	3-MACE	2.1	1.00 (0.89–1.12); p = 0.99	No	Increase HF hospitalization
EXAMINE (2013)	Alogliptin	T2DM + ACS N = 5380	3-MACE	1.5	0.96 (≤1.16); p = 0.32	No	No increase in HF
TECOS (2015)	Sitagliptin	T2DM + CVD N = 14671	4-MACE	3.0	0.98 (0.89–1.08); p = 0.65	No	No increase in HF
CARMELINA (2018)	Linagliptin	T2DM + high CVR or renal risk N = 6979	3-MACE	2.2	1.02 (0.89–1.17); p < 0001	No	No increase in HF
Glucagon-like peptide 1 receptor agonist (GLP-1 RA)							
ELIXA (2015)	Lixisenatide	T2DM + ACS N = 6068	4-MACE	2.1	1.02 (0.89–1.17); p = 0.81	No	/
LEADER (2016)	Liraglutide	T2DM + CVD or high CVR N = 9340	3-MACE	3.8	0.87 (0.78–0.97); p = 0.01	Yes	Reduction of CV death
SUSTAIN-6 (2016)	Semaglutide	T2DM + CVD, renal disease or high CVR N = 2735	3-MACE	1.9	0.74 (0.58 to 0.95); p < 0.001	Yes	Reduction of stroke
EXSCEL (2017)	Exenatide	T2DM +/− CVD N = 14752	4-MACE	3.2	0.91 (0.83–1.00) p < 0.001	No	/
Harmony outcomes (2018)	Albiglutide	T2DM + CVD N = 9463	3-MACE	1.6	0.78 (0.68–0.90); p < 0.0001	Yes	Reduction of MI
REWIND (2019)	Dulaglutide	T2DM + CVD or high CVR N = 9622	3-MACE	5.4	0.88 (0.79–0.99); p = 0.026	Yes	Reduction of stroke
Sodium-glucose linked transporter 2 inhibitors (SGLT-2i)							
EMPA-REG outcome (2015)	Empaglifozin	T2DM + CVD N = 7020	3-MACE	3.1	0.86 (0.74–0.99; p = 0.0382)	Yes	Reduced HF hospitalization
CANVAS (2017)	Canaglifozin	T2DM + high CVR N = 10142	3-MACE	2.4	0.86 (0.75–0.97); p = 0.02	Yes	Reduced HF hospitalization Increased risk of amputation

(continued)

Table 2 (continued)

Trials *Year*	Active treatment	Patients *Features; number*	Endpoints	Follow-up *Years*	Outcome *HR (95% CI); p-value*	Superiority *Yes or No*	Details
DECLARE-TIMI 58 (2018)	Dapaglifozin	T2DM + CVD or high CVR N = 17160	3-MACE	4.2	0.93 (0.84–1.03); p = 0.17	No	Reduced HF hospitalization
Insulin							
ORIGIN (2012)	Glargine	T2DM, IGT + high CVR N = 12537	3-MACE	6.2	1.02 (0.94–1.11); p = 0.63	No	/
DEVOTE (2017)	Degludec	T2DM + CVD, renal disease or high CVR N = 7637	3-MACE	1.9	0.91 (0.78–1.06); p < 0.001	No	/

CVD cardiovascular disease, *CVR* cardiovascular risk, *T2DM* type 2 diabetes mellitus, *ACS* acute coronary syndrome, *IGT* impaired glucose tolerance, *3-MACE* Composite of CV death and nonfatal MI or stroke, *4-MACE* Composite of CV death and nonfatal MI or stroke or hospitalization for UA. See text for details

glucose, and have less impact in reducing HbA1c relative to other drug classes, such as GLP-1 agonists.

Four main drugs are recognized in this class: saxagliptin, alogliptin, sitagliptin and linagliptin.

In the study SAVOR-TIMI 53, 16492 patients were treated with saxagliptin or placebo in addition to conventional therapy (Scirica et al. 2013). Enrolled patients with DM type 2 presented with history of CV diseases (85%) or high CV risk profile. Median follow-up was 2.1 years. No significant differences in outcome were observed for primary endpoints. The safety of the drug was therefore confirmed. However, a significant increase in hospitalization for heart failure was observed, even though the data were not confirmed by further analysis.

Alogliptin was tested against placebo in EXAMINE trial, conducted on 5380 patients with DM type 2 and recent acute coronary syndrome (White et al. 2011). The drug showed CV safety with no increase in risk of MACE.

In TECOS study, 14671 patients with type 2 DM and high CV risk were treated with sitagliptin for a median follow-up period of 3 years (Green et al. 2015). The trial showed no increase in risk for 3-points MACE and for hospitalization for heart failure. Glycaemic control was similar in the two arms.

In CARMELINA, linagliptin was tested on 6979 patients with DM type 2 and high CV risk resulting to be non-inferior relative to usual care (Rosenstock et al. 2019). No increased risk of heart failure was observed.

DPP-4i clearly showed to have cardiovascular safety but no one of them demonstrated cardiovascular benefit. One explanation may be that trials were designed to test for non-inferiority and not adequately powered to evidence superiority. Additionally, it is possible that the increase in incretins generated by DPP-4i acts simply on the reduction of glycemia without a direct CV influence. Notably, DPP-4i should be used cautiously in patients with history of heart failure, due to unclear evidence.

4.5.3 Sodium-Glucose Linked Transporter-2 Inhibitors (SGLT-2i)

Sodium glucose cotransporters-2 are located at the level of the proximal convoluted tubules and are involved in the combined reabsorption of glucose and sodium, being responsible for the 90% of glucose reabsorption of the kidney. Their inhibition leads to significant glycosuria helping in normalization of glycemia. General infections seem to be the most common adverse effect of this class of drug, particularly urinary tract infections due to the induced osmotic diuresis.

Three main drugs are recognized in this class: empaglifozin, canaglifozin, dapaglifozin.

In EMPA-REG OUTCOME trial, 7020 patients with diabetes mellitus type 2 and history of CV disease were treated with empaglifozin versus conventional therapy for a median follow-up of 3.1 years (Zinman et al. 2015). Patients randomized to empaglifozin showed a significant reduction of primary endpoint with a reduction of 14% of risk of 3-points MACE (HR 0.86; p-value = 0.04 for superiority). Moreover, treatment group showed a 38% decrease in CV death (HR 0.62; p-value<0.001), a 32% decrease in all-cause mortality (HR 0.68; p-value<0.001) and a 35% reduction of hospitalization for heart failure (HR 0.65; p-value = 0.002). Following these astonishing results, empaglifozin was the first drugs to demonstrate CV benefit, ensuring a significant reduction of CV events. Interestingly, the reduction of CV mortality was already evident at only 15 weeks from randomization and depended largely on reduction of heart failure numbers, while myocardial infarction incidence was largely unaffected (5.4% in placebo group vs 4.8% in treatment group). These results cannot be explained by the only modest decrease in HbA1c (−0.24% relative to conventional treatment) and suggest beneficial CV effect beyond glucose lowering.

Similar results were presented for canaglifozin. In CANVAS trial, canaglifozin showed a reduction of 14% of primary endpoint (HR 0.86; p-value<0.01 for non-inferiority and

p-value<0.02 for superiority) confirming the CV benefit already demonstrated by empaglifozin (Neal et al. 2017). Furthermore, the risk of hospitalization was significantly reduced relative to placebo (HR 0.67). To be noted, there was concern regarding an increased risk of amputation in canaglifozin arm (HR 1.97).

The lastly published SGLT-2i trial is the DECLARE-TIMI 58 (Wiviott et al. 2019). 17160 patients were randomized to dapaglifozin or placebo for a median follow-up of 4.2 years. In primary safety outcome analysis, dapaglifozin met the criteria for non-inferiority. Differently from the previous two drugs, dapaglifozin did not demonstrate superiority with improved CV benefit. However, it did result in reduction of heart failure hospitalization and death (HR 0.83; p-value = 0.005).

Despite dapaglifozin did not result in reduced primary endpoint, empaglifozin and canaglifozin demonstrated strong CV benefit with marked and rapid reduction of CV death and hospitalization for HF. Notably, all three SGLT-2i tested have demonstrated improvements in renal endpoints.

4.5.4 Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA)

GLP-1 is an incretin produced by intestinal cells in response to glucose concentration rise. It acts on GLP-1 receptors exposed on the surface of pancreatic cells, favouring insulin release and inhibiting glucagon secretion. Moreover, GLP-1 slows gastric emptying and increases satiety acting on intestinal and gastric receptors. GLP-1 RA mimic the structure of GLP-1 in order to obtain receptor activation and stimulate physiological responses. GLP-1 RA are administered in concentrations that are 6–10 times greater than endogenous levels. This causes significant slowing of GI motility leading to nausea and sometimes vomiting, that are the two most common side effects. Subsequently, weight loss is a frequently observed adverse event under treatment with GLP-1 RA, being beneficial for overweight or obese patients. GLP-1 receptor agonists target fasting plasma glucose as well as postprandial one. This is the reason why a higher HbA1c lowering effect is observed with GLP-1 RA relative to other agents such as DPP-4i.

Six main drugs are recognized in this class: liraglutide, lixisenatide, exenatide, semaglutide, dulaglutide, albiglutide.

In ELIXA trial, 6068 patients were randomized to lixisenatide or conventional therapy, showing no differences in MACE (HR 1.02; p < 0.001 for non-inferiority), confirming its CV safety (Marso et al. 2016a).

LEADER trial was conducted on 9340 patients with DM type 2 and previous CV disease, randomized to receive liraglutide or placebo plus conventional therapy for a median follow-up of 3.8 years. Liraglutide showed a significant reduction of 13% in primary endpoint (HR 0.87; p-value = 0.01 for superiority), with a reduction of 22% of CV death and 13% of all-cause mortality (Marso et al. 2016b). There was a non-significant reduction of MI and stroke. Notably, the survival curves begin to diverge after 12 months, suggesting that liraglutide effect requires more time to become evident from a CV point of view and this may be related to the presence of an anti-atherosclerotic action.

In EXSCEL trial, 10782 patients were randomized to receive exenatide or placebo for a median follow-up of 3.2 years (Mentz et al. 2018). The exenatide treatment demonstrated a reduction of primary endpoint that was significant for CV safety but not for CV benefit (HR 0.91; p-value<0.001 for non-inferiority; p-value = 0.06 for superiority).

SUSTAIN-6 trial was conducted on 3297 patients randomized to receive either semaglutide or conventional therapy plus placebo for a median follow-up of 2.1 years (Marso et al. 2016a). Semaglutide demonstrated 26% reduction in primary endpoint (HR 0.74; p-value = 0.02 for superiority), showing clear CV benefit. This result was mainly driven by the reduction 39% in fatal stroke.

In Harmony Outcomes trial, albiglutide versus placebo was tested in 9463 patients (Hernandez et al. 2018). It reduced by 22% the 3-points

MACE combined endpoint (HR 0.78; p-value<0.0001 for non-inferiority; p-value = 0.0006 for superiority). This result was mainly driven by a significant reduction of 25% in myocardial infarction.

In REWIND trial, dulaglutide showed once again the great potential of GLP-1 RA (Gerstein et al. 2019). 9901 patients with DM type 2 and high CV risk were randomized to receive dulaglutide or placebo. After a median follow-up of 5.4 years, dulaglutide group showed a significantly lower number of MACE (HR 0.88; p-value = 0.026), mainly dependent on the reduction of the number of non-fatal stroke.

All GLP-1 RA demonstrated CV safety. Additionally, liraglutide, semaglutide, albiglutide and dulaglutide proved their CV benefit reducing CV events.

4.5.5 Insulin

Novel insulin molecules tested in CVOTs are Glargine and Degludec molecules. ORIGIN trial evaluated the use of long-acting basal insulin Glargine against placebo in 12537 patients with pre-diabetes and overt DM type 2 (ORIGIN Trial Investigators et al. 2012). The trial found no significant reduction in two co-primary outcomes, major cardiovascular events and major cardiovascular events plus revascularization and heart failure. DEVOTE trial tested Degludec insulin against Glargin insulin in head-to-head trial showing no differences in outcome (Marso et al. 2017).

4.5.6 Effects on CV Risk Beyond Simple Glycaemic Control

In the end, two classes of drugs (SGLT-2i and GLP-1 RA) demonstrated to provide cardiovascular benefit in diabetic patients, significantly reducing CV events. Their peculiarity is the ability to ensure a reduction of CV events with only a modest decrease in glycated haemoglobin relative to conventional therapy. The understanding of their cardioprotective mechanism is still incomplete and the explanation of their effect is not straightforward as they exert heterogeneous modifications at different levels going beyond simple glycemia control. Here a short and concise overview of the main pathophysiologic mechanisms at the basis of their effect.

SGLT-2 inhibition reduce CV outcome by means of a combination of hemodynamic and metabolic positive effects (Sattar et al. 2016, 2017). SGLT-2i prevent reabsorption of glucose from the proximal convoluted tubule inducing osmotic diuresis due to increased glycosuria and natriuria. Interestingly, reduction of CV events was limited to patients with T2DM and established atherosclerotic cardiovascular disease in secondary prevention, whereas reduction of HF and progression of renal disease occurred even in primary prevention in patients without history of CV disease or HF. Five main mechanisms seem to be involved in CV benefits:

- Modulation of traditional risk factors. SGLT2-2i causes loss of body weight, reduction of HbA1c, reduction in systolic blood pressure and diastolic BP.
- Reduction on LV loading conditions. SGLT2-2i causes a significant reduction on plasma volume due to osmotic diuresis reducing preload, LV filling pressure and afterload. The effect is greater relative to diuretics because of selective interstitial volume reduction shown by this class of drugs (Verma and McMurray 2018).
- Reverse cardiac remodelling. The positive effect on cardiac filling pressure may help in reducing LV mass due to reduction of LV wall stress according to Laplace's law (Verma et al. 2019).
- Improvement of cardiac energetics. SGLT2-2i favour the increase of ketone bodies due to a generalized state of starvation derived from glucose depletion. Locally, at heart muscle levels they promote the use of ketone bodies and fatty acid oxidation as main energy source (Garcia-Ropero et al. 2019). Being the metabolic pathway more favourable in terms of ATP production this improves myocardial work performance.

– Inhibition of Na+/H+ exchanger. SGLT2-2i act as ionic exchanger inhibiting the Na+/H+ exchange present on cardiomyocyte surface (Uthman et al. 2018). This causes a drop in sodium and calcium intracellularly and an increase in calcium in sarcoplasmic reticulum leading to improvement in cardiac contractility and mechanics.

Summarizing, the osmotic diuresis favours a decrease in intravascular volume with a drop in blood pressure and peripheral decongestion. These changes significantly reduce the cardiac stressors (both preload and afterload), improving myocardial oxygen supply and decreasing left ventricular stretch that is thought to be an important trigger for arrhythmias and remodelling. Additionally, SGLT2-2i improves myocardial performance thanks to the use of alternative energy sources, such as ketone bodies and fatty acid oxidation, and increasing sarcoplasmic calcium level that favours cardiac contractility. Moreover, renal dysfunction is slowed thanks to the improvement of hemodynamic conditions and the reversal of the maladaptive tubulo-glomerular feedback. Putting all these mechanisms together, they generate the observed positive effect in reducing CV events, HF and renal disease progression.

As already described, GLP-1 receptor agonists stimulate receptors exposed on pancreatic beta cells, gastric and intestinal cells mimicking the action of endogenous GLP-1. Even though the biochemical action is well-known, it is not yet clear how GLP-1 RA may help in reducing CV events. In line with the evidence that the relative benefit over CV mortality appears later after treatment initiation (compared with SGLT-2i), most experts believe that GLP-1 RA action is, at least in part, an anti-atherothrombotic effect, derived from modulation of endothelial function, anti-inflammatory properties and anti-atherosclerotic actions.

Interestingly, despite the common biochemical pathways, DPP-4i and GLP-1 RA did not show the same results. If GLP-1 RA showed positive effect in terms of superiority in the context of coronary artery disease, DPP-4i appeared to be neutral. One possible explanation is that DPP-4i are involved in degradation of incretins and their action can potentiate additional peptides that are shown to have adverse CV effects due to the involvement in inflammation and fibrosis (Packer 2018).

In contrast to SGLT-2i that showed their protective effect reducing the incidence of heart failure, it is important to underline that GLP-1 RA are neutral in this context. One possible explanation is that GLP-1 receptors are localized in sino-atrial node as well. The use of GLP-1 RA cause an increase in heart rate (6–10 bpm for long-acting agents and 3–4 bpm for short-acting agents) (Lorenz et al. 2017). This has been advocated as a possible reason for neutral effect on HF events. However, despite the raised concern, currently there is no evidence of harm derived from this slight increase in heart rate.

Five main mechanisms are involved in CV benefits:

– Modulation of risk factors. GLP-1 RA cause significant reduction in blood pressure, body weight, HbA1c and lipid status. As already discussed this drug class causes significant weight reduction as it slows gastric motion leading to an increased sense of satiety and sometimes to vomiting.
– Modulation of endothelial cells. GLP-1 RA are involved in modulation of endothelial function. This action is obtained thanks the reduction of expression of ICAM-1 and VCAM-1 on endothelial cells, reducing leukocyte translocation (Liu et al. 2009).
– Anti-atherosclerotic and anti-inflammatory action. GLP-1 RA reduce release of pro-inflammatory cytokines reducing local inflammation responsible for plaque formation, expansion and vulnerability (Liu et al. 2009).

– Reduction of pro-thrombotic state. GLP-1 RA reduce coagulation cascade activation, by decreasing PAI-1 release (Liu et al. 2009), and platelet aggregation, reducing expression of platelet surface receptors (Cameron-Vendrig et al. 2016).
– Direct action on heart. GLP-1 could directly protect the heart against ischemic injuries via pro-survival signalling pathways activated by specific kinases, such as PKA, PI3K, p42/44 (Bose et al. 2005).

All things considered, a combination of anti-atherogenic effects and hemodynamic improvements are likely explanations of the reduction of CV events and mortality observed in patients treated with these two classes of drugs.

5 Efficacy of Glycaemic Control on Other Vascular Complications

No prospective trials have been performed to assess whether optimal glycaemic control could reduce the incidence of peripheral artery disease. Similarly, looking to the past studies, no drug has been proven effective in significantly reduce the rate of stroke and coronary artery disease in diabetics, even with intensive glycaemic control. This scenario has changed with the arrival on the market of novel GLDs.

One of the problems reported in the past – and still present nowadays in the context of CVOTs – is the lack of peripheral artery disease among the clinical endpoint under evaluation. No data at hand are present to evaluate the efficacy of novel GLDs in reducing PAD events and progression. To be notice the warning raised for canaglifozin because of the increased risk of limb amputation with the use of this drug.

Stroke is instead well represented by MACEs in all trials. SGLT-2i does not affect the incidence of stroke in any of the trials. On the other hand, GLP-1 agonists are the only drugs among novel GLDs reducing stroke incidence. In REWIND, dulaglutide treatment arm showed a significantly lower number of total stroke relative to placebo (3.2% vs 4.1%; HR 0.76; 95% CI 0.62–9.94; p-value 0.010) (Gerstein et al. 2019). Similarly, in SUSTAIN-6 trial semaglutide showed a significant reduction in the risk of stroke (1.6% vs 2.7%; HR 0.61; 95% CI 0.38–0.99; p-value 0.04) (Marso et al. 2016a).

As discussed previously, renal function was already improved by intensive glycemia control as patients in treatment arms with stricter control were associated with reduced progression toward CKD and reduction of proteinuria. New GLDs have shown further nephroprotective effect improving renal outcomes. In DPP-4i experience, saxagliptin significantly reduced microalbuminuria (Scirica et al. 2013), but other DPP-4i did not report similar effects on renal function or albuminuria. In LEADER trial, liraglutide group showed a reduction of the composite renal endpoint (new-onset macro-albuminuria, persistent doubling of creatinine, ESRD or death due to renal disease) that was mainly dependent on reduction in macro-albuminuria (HR 0.74, 95% CI 0.60–0.91) (Mann et al. 2017). In the SUSTAIN-6, semaglutide showed similar effect. In ELIXA trial, lixisenatide-treated patients showed lower levels of microalbuminuria compared with placebo (Marso et al. 2016a). All in all, GLP-1 RA demonstrated ability in reduction of albuminuria but clear evidence in reduction of worsening renal function is missing. SGLT-2i are the class of novel GLDs that obtained the best results in terms of improvement of renal function. Canaglifozin showed a 27% reduction in progression of albuminuria and a reduction of the composite renal endpoints (HR 0.53; 95% CI 0.33–0.84), consisting of 40% reduction in eGFR, renal replacement therapy or death from acute kidney injury (Neal et al. 2017). Similarly, empaglifozin demonstrated to decrease the incidence of progression to macro-albuminuria,

Table 3 Summary of recent ESC guidelines 2019 recommendations concerning use of GLDs in diabetic patients according to CV profile

Recommendations	Class of recommendation	Level of evidence
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death	I	B
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death	I	B
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.	IIa	C
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities	IIa	C
Thiazolidinediones are not recommended in patients with HF	III	A
Saxagliptin is not recommended in patients with T2DM and a high risk of HF	III	B

GLDs glucose lowering drugs, *CV* cardiovascular

doubling of serum creatinine, initiation of renal replacement therapy and death from renal disease (HR 0.61; 95% CI 0.53–0.70) (Wanner et al. 2016). Recently, also patients treated with dapaglifozin showed significant a reduction of renal endpoints, namely 40% decrease in eGFR, ESRD and renal death (HR 0.53; 95% CI 0.43–0.66) (Wiviott et al. 2019).

All these evidences clearly show that new GLDs move diabetes treatment well beyond simple glycemia control.

6 Conclusions and Guidelines Recommendations

After years of disappointing results about the effects of glycaemic control on CV hard endpoints, data from several CVOTs suggest that clear benefits in terms of CV outcomes can be obtained using some of the novel GLDs in patients with already established CVD or in patients at high/very high risk of CV disease. These new evidences have been received and incorporated in recently published 2019 ESC guidelines on diabetes and CV diseases (see Table 3 for reference) (Cosentino et al. 2019). The strongest recommendations concern mainly SGLT-2 inhibitors (empaglifozin, canaglifozin and dapaglifozin) and GLP-1 RA (liraglutide, semaglutide and dulaglutide). In both cases they are recommended as first line anti-diabetic agents in patients with type 2 DM and with CVD or high CV risk profile to reduce CV events (class I, level A) and to reduce mortality (class I, level B). In case of patients with no history of CV events and moderate-to-low CV risk profile they are recommended on top of metformin whether the HbA1c target is not reached.

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