Miles Fisher
Gerard McKay

Essentials of SGLT2 Inhibitors in Diabetes

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Biographies

Professor Miles Fisher graduated from the University of Glasgow in 1979, where he received his MD in 1988 for his thesis on 'Evidence for a Diabetic Cardiopathy.' He has been a consultant physician at Glasgow Royal Infirmary since 2001. In 2010, he was made an Honorary Professor at the University of Glasgow. He was a Vice-President (Medical) of the Royal College of Physicians and Surgeons of Glasgow from 2011 to 2014. Professor Fisher is the current President of the Scottish Society of Physicians. His interests include diabetes and the heart, hypoglycemia, and new treatments for diabetes, and he is the author or co-author of over 70 original papers, over 60 review articles, and over 40 book chapters. He was on the steering committee of the DIGAMI 2 study as the Scottish coordinator, as well as an events adjudicator for the HOPE and HOPE-TOO studies, and is currently an events adjudicator for the ACE Trial.

Professor Gerard (Gerry) McKay graduated from the University of Glasgow in 1994. He undertook specialty training in Clinical Pharmacology and Therapeutics in Newcastle upon Tyne which included specific training in diabetes and cardiovascular risk management, a one year secondment to the pharmaceutical industry and a secondment to the National Institute for Health and Clinical Excellence (NICE). He has been a Consultant Physician and Clinical Pharmacologist at Glasgow Royal Infirmary since 2007. In 2012 he was made an Honorary Clinical Associate Professor at the University of Glasgow and in 2013 a visiting Professor at the University of Strathclyde. He contributes to the provision of diabetes care

in the north east of Glasgow with a specialist interest in Type 2 diabetes and diabetic nephropathy. He is the co-editor of a major undergraduate textbook on clinical pharmacology and has published numerous papers in the field of diabetes and therapeutics.

Contents

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Chapter 1
Overview of Type 2 Diabetes

Jenna Cowan

1.1 Epidemiology and Global Disease Burden

Diabetes is a serious and escalating global health problem. The global prevalence is 8.3 % and 387 million people are currently affected [1]. Over 45 % of people with type 2 diabetes are undiagnosed and the total number affected is predicted to rise to 592 million by 2035. An additional 316 million people are estimated to have impaired glucose tolerance and many of these will progress to type 2 diabetes. For example, in the UK the prevalence of diabetes is 6.0 %, affecting 3.2 million people, while in the USA the prevalence is 12 % of the population.

The causes of this epidemic are multifactorial including aging populations, rapid cultural and social changes (e.g., increased urbanization, dietary changes), physical inactivity, and excess body weight. For example, in Scotland, over 50 % of patients with type 2 diabetes are obese and a further 30 % are overweight, indicating that weight loss should be a priority in both prevention and treatment [2]. Prevalence rates are higher in elderly patients (approximately 15 % affected), with nearly 60 % of patients with type 2 diabetes over the

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age of 65 years [2]. This has associated management challenges as elderly patients often have multiple comorbidities, increased risks of adverse drug effects and hypoglycemia, and additional health and social care support requirements.

Increasing numbers of younger obese and overweight patients are being diagnosed, which brings concerns of the long-term effects of increased risk of developing diabetes- and treatment-related complications. Complications such as renal failure and amputations are a major cause of disability, reduced quality of life, and death. Early disability in patients under 60 years of age causes loss of productivity and earning potential, affecting individuals along with their families, communities, and economies. Cardiovascular disease (CVD) is a leading cause of death in this population and 50 % of diabetes-related deaths occur in patients under 60 years of age [1].

Thus, tackling diabetes is one of the most challenging health problems of the 21st century. International Diabetes Federation data from 2014 shows the serious global impact of diabetes (Fig. 1.1). Almost 80 % of people with diabetes live in low and middle income countries, and these countries suffer a disproportionate burden in terms of prevalence, morbidity, mortality, and economic consequences. Health and social care systems are struggling to manage this burden of increasing medical and social care needs. Globally, $612 billion USD is spent annually on diabetes care, which represents 11 % of worldwide healthcare expenditure [1]. Internationally, there is a large disparity in health care spending; North America and Caribbean countries alone spend $310 billion (51 % of the total worldwide expenditure). Despite this high level of spending, these countries still have a death rate of 41 % in patients under 60 years of age. Overall, nations in the Western Pacific have the highest diabetes burden, with 138 million people affected (approximately 35 % of the global patient population) but only $101 billion USD spent (16 % global expenditure) [1].

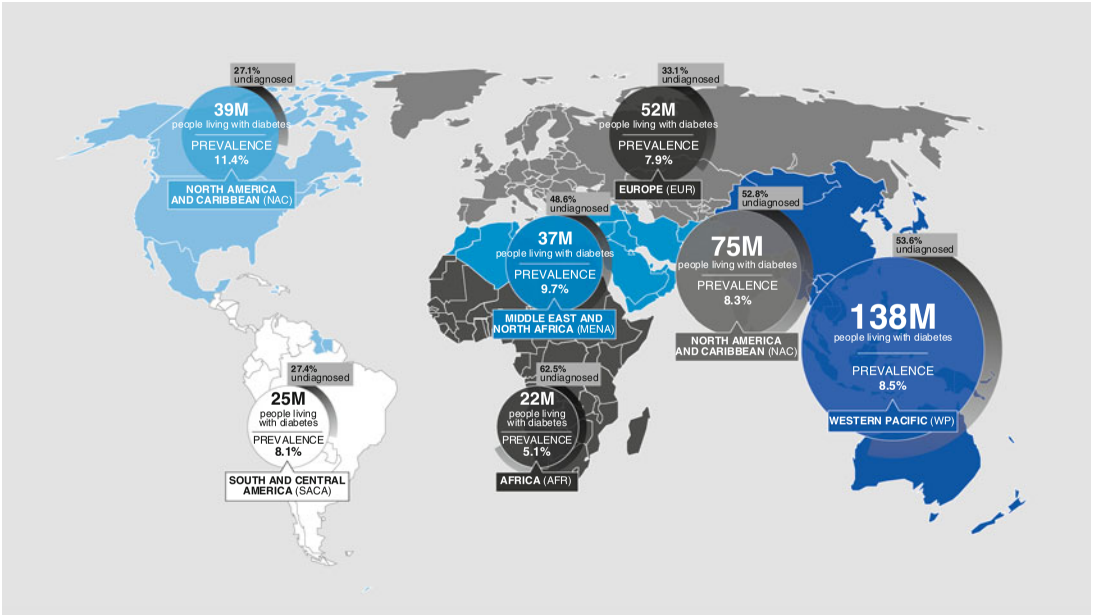

FIGURE 1.1 Global prevalence of diabetes (Reproduced with permission from the International Diabetes Federation [1] ©IDF)

1.2 Diagnostic Criteria for Diabetes

The diagnostic criteria from the World Health Organization (WHO) and the American Diabetes Association (ADA) are shown in Table 1.1 [3, 4]. Glycated hemoglobin (HbA1c) concentration of ≥48 mmol/mol (6.5 %) can be used for the diagnosis of diabetes. Patients without symptoms of hyperglycemia require two different tests (e.g., fasting plasma glucose and HbA1c) with concordant results or repeat testing on another day for confirmation.

Table 1.1 Diagnostic criteria for diabetes

	Impaired fasting glucose and impaired glucose tolerance (WHO/IDF)	**Prediabetes (ADA)**	**Diabetes mellitus (WHO/IDF and ADA)**
HbA1c (%)	–	5.7–6.4 % (39–48 mmol/mol)	≥6.5 % (48 mmol/mol)
Fasting plasma glucose (mmol/L)	6.1–6.9	5.6–6.9	≥7.0
OGTT 2-h plasma glucose (mmol/L)	7.8–11.0	7.8–11.0	≥11.1
Random glucose (mmol/L)	–	–	≥11.1 with classic symptoms

ADA American Diabetes Association, *HbA1c* glycated hemoglobin, *IDF* International Diabetes Federation, *OGTT* oral glucose tolerance test, *WHO* World Health Organization

The WHO define impaired glucose tolerance as a 2-h blood glucose between 7.8 and 11.0 mmol/L on oral glucose tolerance test (OGTT); "impaired fasting glucose" is defined as fasting plasma glucose between 6.1 and 6.9 mmol/L. ADA criteria describe a diagnosis of "prediabetes" in which glucose tolerance, fasting glucose, or both are impaired. This also includes patients with HbA1c 39–46 mmol/mol (5.7–6.4 %). These conditions are associated with increased risk of type 2 diabetes and cardiovascular disease. Figure 1.2 illustrates the natural history of impaired glucose tolerance progressing into type 2 diabetes and the mechanisms involved [5, 6]. Approximately 25 % of people will develop diabetes within 5 years and, while lifestyle interventions can reduce the risk of disease progression, there is no international consensus regarding screening and therapies for patients with prediabetes.

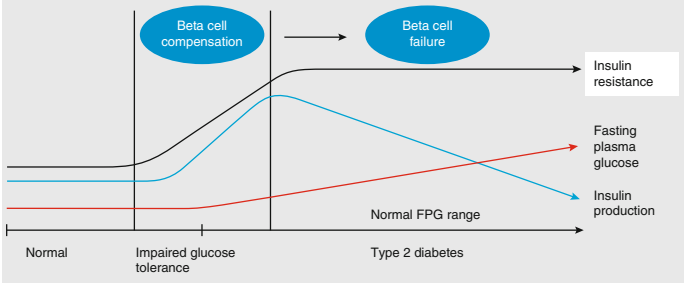

FIGURE 1.2 The natural history of type 2 diabetes. The key aspects in developing type 2 diabetes are insulin resistance, decreased insulin production, and increased blood glucose. With impaired glucose tolerance, beta cell compensation occurs, caused by loss of beta cell sensitivity to glucose and progressive beta cell failure. This contributes to delayed insulin secretion in response to oral glucose. *FPG* fasting plasma glucose (Adapted from Bailey [5] and DeFronzo and Ferrannini [6])

1.3 Glucose Homeostasis

Glucose homeostasis is normally maintained by a balance between glucose entering the bloodstream from intestinal absorption and hepatic glucose production, versus the uptake and metabolism of glucose by peripheral tissues. In the prandial state, pancreatic β-cells are stimulated to secrete insulin and glucagon secretion from alpha cells is reduced. This causes increased glucose uptake into insulin sensitive tissues namely heart, skeletal muscle, and adipose tissue. Hepatic glucose production is reduced and anabolic metabolism is promoted. In the fasting state, insulin levels are reduced and glucagon secretion is increased. Hepatic glucose production through glycogenolysis and gluconeogenesis maintains glucose levels.

The kidneys maintain homeostasis throughout by filtering and reabsorbing all glucose ensuring that no glucose is lost in the urine. 90 % of filtered glucose is reabsorbed by the high capacity sodium-glucose linked transporter 2 (SGLT2) in the convoluted segment of the proximal tubule [7]. The remaining 10 % is reabsorbed by the SGLT1 transporter in the straight arm of the descending proximal tubule.

1.4 Pathogenesis of Type 2 Diabetes

Type 2 diabetes is a complex heterogeneous disorder characterized by pancreatic β-cell dysfunction and insulin resistance. The relative contribution of each factor varies between individuals. Insulin resistance in muscle is usually the first abnormality detected [8]. Initially this signals β-cells to produce more insulin to maintain glucose homeostasis [9]. However, progressive β-cell dysfunction develops with loss of pulsatility of insulin secretion, abnormal insulin formation, loss of sensitivity to glucose stimulation, and delayed insulin secretion. β-cell loss accompanies β-cell failure and insulin production becomes inadequate, resulting in hyperglycemia. Hyperglycemia itself contributes to further β-cell dysfunction and a vicious cycle occurs. Insulin resistance is well established

when impaired glucose tolerance develops (Fig. 1.2) and further decline in β-cell function leads to the development of type 2 diabetes.

The neurohumoral feedback mechanisms between β-cells and insulin sensitive tissues (heart, skeletal muscle, and adipose tissue) are not fully understood so the precise mechanism by which insulin resistance causes β-cell failure remains unknown [9]. Obesity is a major cause of insulin resistance and is associated with inflammation of adipose tissues and excess fatty acid secretion, also known as lipotoxicity which causes β-cell dysfunction. Other pathophysiological mechanisms contributing to β-cell dysfunction are islet amyloid deposition and the lack of ability to regenerate β-cells in adults [10, 11].

Figure 1.3 illustrates the multiple pathogenic processes contributing to hyperglycemia [7]. Hepatic glucose production is increased, skeletal muscle glucose uptake is reduced, and glucagon secretion is increased. Incretins (glucagon-like

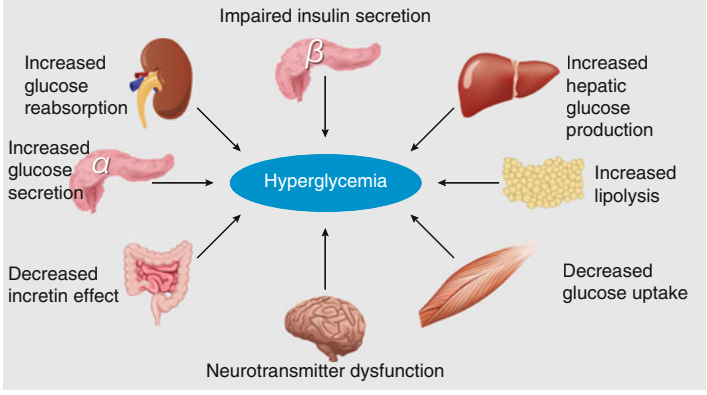

Figure 1.3 Multiple pathological features contribute to hyperglycemia in type 2 diabetes ("ominous octet" model). Skeletal muscle, liver, and pancreas, the fat cell, gastrointestinal tract, kidney, and brain all play important roles in the development of glucose intolerance in individuals with type 2 diabetes mellitus. All of these represent targets for drug therapies (available and potential drugs in development) (Adapted from DeFronzo [7])

peptide [GLP-1] and gastric inhibitory polypeptide [GIP]) are insulin secretagogues released from intestinal cells in response to feeding. In type 2 diabetes, there is impaired release of incretins, which may be a secondary process rather than primary abnormality. Additionally, in the kidneys there are increased levels of SGLT2 receptors in patients with diabetes, causing increased glucose reabsorption. Normal homeostatic control is lost as increased glucose levels are absorbed into the blood and excess glucose is excreted into the urine. Gluconeogenesis in the renal cortex may further contribute to hyperglycemia [12]. There is also evidence of central neurotransmitter dysfunction with studies showing reduced inhibition within hypothalamic appetite regulation centers [7]. Research aiming to get a better understanding of the various mechanisms causing hyperglycemia and how they interact will potentially aid the identification of suitable therapeutic targets for drug development.

1.5 Risk Factors for the Development of Diabetes

Type 2 diabetes is a heterogeneous disorder involving interaction between genetic and environmental factors. Genetic susceptibility results from complex polygenic risk factors as opposed to monogenic causes which are only responsible for 1–2 % of diabetes cases. Over 50 genetic loci have been discovered to be associated with increased risk of type 2 diabetes and most of these are linked to defects in β-cell function [9]. Approximately 40 % of patients have at least one parent with type 2 diabetes and monogenic twin studies have reported up to 90 % concordance [13, 14].

People with Asian, Pacific Islander, and Afro-Caribbean ethnicity have the highest risk of developing type 2 diabetes. The importance of environmental factors interacting with genetic factors is shown by the varying prevalence across geographical areas. For example, Pima Indians living in USA have up to a five-fold greater risk than Pima Indians living in Mexico [15].

Table 1.2 Risk factors for type 2 diabetes

Non-modifiable risk factors	Modifiable risk factors
Age >45 years	Obesity
Family history	Sedentary lifestyle
Ethnicity	Dietary factors
History of gestational diabetes	Smoking
	Previously identified glucose intolerance
	Dyslipidemia
	Hypertension

The other risk factors for type 2 diabetes are listed in Table 1.2. Excess calories and high energy diets are a central causal mechanism of obesity and type 2 diabetes. Type 2 diabetes is more prevalent in people over 65 years and aging populations are a major contributing factor to increasing prevalence of type 2 diabetes.

1.6 Clinical Features of Diabetes

Type 2 diabetes is the commonest cause of diabetes in adults. Many patients are asymptomatic at diagnosis and hyperglycemia is detected on routine or screening blood tests. The classic symptoms of hyperglycemia are polyuria, polydipsia, nocturia, blurred vision and, less frequently, weight loss. Many patients describe symptoms retrospectively following diagnosis. Glycosuria causes an osmotic diuresis and dehydration, and patients who take sugary drinks as replacement can exacerbate hyperglycemia and the osmotic diuresis. Hyperglycemia is associated with increased risks of infection and patients can present with isolated or recurrent infections, commonly urinary tract infections, genital thrush, and/or cellulitis.

Rarely patients present with hyperglycemic hyperosmolar state (HHS) characterized by severe hyperglycemia, dehydration, and reduced consciousness. This is more common in elderly patients and is often associated with sepsis, myocardial infarction, or other intercurrent illnesses. Diabetic ketoacidosis (DKA) classically occurs in type 1 diabetes but this can also occur in a small cohort of patients with type 2 diabetes with severe β-cell dysfunction. This group is called 'ketosis-prone diabetes' and it usually only occurs under certain circumstances such as severe sepsis or illness. Patients will require insulin treatment following DKA, but the clinical course is variable and in the longer term they may achieve insulin independence.

1.7 Complications of Diabetes

Chronic hyperglycemia causes microvascular and macrovascular complications which are the major cause of morbidity and mortality. The UK Prospective Diabetes Study (UKPDS) showed the importance of good glycemic control to reduce the risk of microvascular complications [16]. Several other factors including hypertension, dyslipidemia, and metabolic syndrome contribute to the risk of developing complications, and therapeutic management to reduce these factors is a priority of diabetes care. Cardiovascular disease, primarily myocardial infarction and stroke, is the most common cause of mortality in patients with diabetes.

Diabetic retinopathy is the most common complication, affecting approximately 40 % of patients and is a major cause of blindness. Cataracts are more common in diabetes and another cause of visual impairment.

Diabetic nephropathy is a leading cause of kidney failure. Onset typically starts with microalbuminuria, progressing to macroalbuminuria and decline in renal function/estimated glomerular filtration rate. Eventually, renal replacement therapy with dialysis and/or transplant may be required.

Diabetic foot disease is one of the most feared complications due to peripheral neuropathy and/or ischemia and has a high risk of amputation. Other neuropathic complications

are autonomic neuropathy (causing gastroparesis), postural hypotension, diarrhea, and erectile dysfunction.

Furthermore, there are risks of complications and adverse effects due to treatments for diabetes. Hypoglycemia is the most common and serious of these and can lead to severe episodes causing seizures, coma, or even death.

Key Points

- Type 2 diabetes is a major global health problem affecting 387 million people worldwide, and of these 45 % are undiagnosed.
- Diagnostic criteria for diabetes include measurement of random or fasting blood glucose concentrations, and/or HbA1c.
- Type 2 diabetes is a heterogeneous disorder characterized by pancreatic β-cell dysfunction and insulin resistance. The relative contribution of each factor varies between individuals.
- There are identifiable risk factors for the development of diabetes, including increased weight and reduced physical activity, aging, as well as genetic and ethnic factors.
- Diabetes is a common cause of morbidity and mortality. Microvascular complications can lead to blindness, renal failure, and amputation. Macrovascular complications can cause coronary heart disease, stroke, heart failure, and premature death.

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Chapter 2
SGLT2 Inhibitors for Treating Diabetes

Gerard McKay and Rachel Livingstone

2.1 Mode of Action and Clinical Pharmacology

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have a novel therapeutic action when compared with the many drugs available to the prescriber to treat type 2 diabetes. The pharmacological action of this drug class is in the kidneys, which play an important role in glucose homeostasis by filtering and reabsorbing glucose in the proximal tubules. On a daily basis, the kidney filters approximately 180 g of glucose. The majority of filtered plasma glucose (80–90 %) is reabsorbed in the early proximal tubule by the high capacity, low affinity SGLT2 [1]. The other 10–20 % is reabsorbed by the low capacity but high-affinity SGLT1 in the more distal portion of the proximal tubule (Fig. 2.1) [2]. This is achieved by cotransporting glucose with sodium via Na^+/K^+–adenosine triphosphatase pumps. SGLT2 is selectively expressed in the kidney, whereas SGLT1 is also expressed in the gastrointestinal tract where it has a role in the absorption of glucose and galactose [3]. In healthy individuals, virtually all glucose is reabsorbed and the urine is free from glucose.

The filtration and reabsorption of glucose are directly proportional to plasma glucose levels. In animal models of type 2 diabetes, there is increased expression of SGLT1 and

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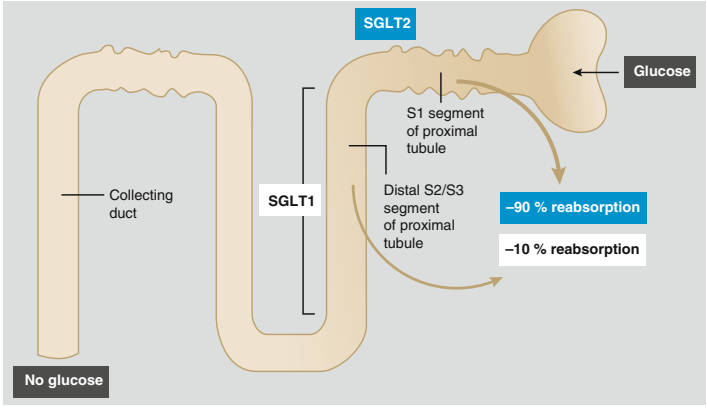

FIGURE 2.1 Normal glucose homeostasis within the kidney. In normal renal glucose homeostasis approximately 90 % of filtered glucose is reabsorbed in the proximal tubule by SGLT2. In patients with poorly controlled diabetes the renal threshold for glucose reabsorption can be exceeded resulting in glycosuria. *SGLT2* sodium-glucose cotransporter 2 (Reproduced with permission from Chao and Henry [2] ©Nature)

SGLT2 mRNA due to prolonged hyperglycemia and, therefore, enhanced activity. This causes alterations to glucose handling by the kidneys and results in the maximum threshold for glucose reabsorption to be increased, and ultimately conserves glucose and exacerbates hyperglycemia [4].

They act by inhibiting SGLT2 in the kidneys, reducing the reabsorption of glucose in the proximal convoluted tubule and increasing glucose excretion in the urine (Fig. 2.2) [2]. The glucose excreted in the urine equates to a net loss of 200–300 kcal/day and weight reduction is a favorable secondary effect. SGLT2 inhibitors have many benefits over alternative therapeutic options and act independently of pancreatic β cell function, which deteriorates over time, and therefore

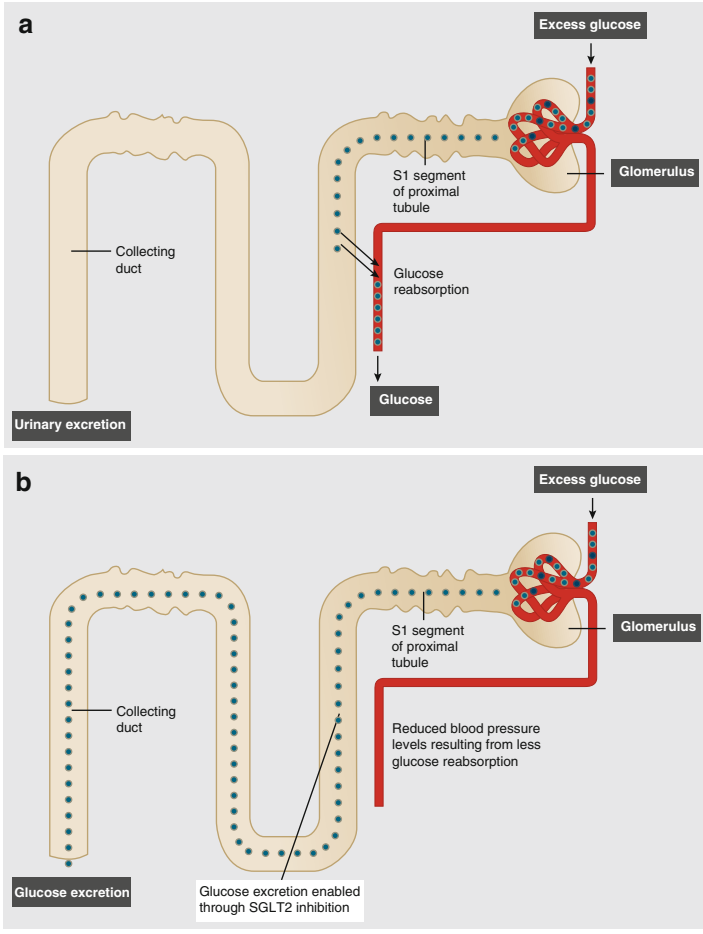

FIGURE 2.2 (**a**, **b**) Effect of SGLT2 inhibitors on glucose homeostasis. Blockade of SGLT2 allows for more of the filtered glucose to be excreted in urine increasing the glycosuria with resultant reduction in blood glucose. *SGLT2* sodium-glucose cotransporter 2 (Adapted with permission from Chao and Henry [2] ©Nature)

there should be no loss of potency with long-term use. Additionally, SGLT2 inhibition does not interfere with endogenous insulin production or endogenous glucose production in response to hypoglycemia and therefore does not increase the risk of hypoglycemia.

2.2 Drug Development and Major Clinical Trials

2.2.1 Phlorizin

Early investigations into renal glucose handling were carried out on phlorizin, which is found in the root bark of fruit trees. It is a naturally occurring competitive inhibitor of SGLT1 and SGLT2 but has greater affinity for the latter. In the 1980s, a rat model of diabetes demonstrated that phlorizin-induced glycosuria was associated with normalization of hyperglycemia without inducing hypoglycemia. Phlorizin is metabolized to phloretin in the gastrointestinal tract by glucosidase, and therefore has poor systemic bioavailability, making it unsuitable for clinical development. Research has focused on phlorizin derivatives with a c-glucoside component, which provides increased resistance to enzymatic degradation and therefore increasing systemic bioavailability.

Dapagliflozin, canagliflozin, and empagliflozin are the most studied SGLT2 inhibitors and have been developed to satisfy the efficacy and safety criteria of the Food and Drug Administration (FDA) and European Medicines Agency (EMA). In addition, ipragliflozin, luseogliflozin, and tofogliflozin are available for clinical use in Japan, where the drug approval process places less emphasis on long-term safety. There are also several newer SGLT2 inhibitors at various stages of development. Ertugliflozin has entered Phase III development for the treatment of type 2 diabetes [5]. Sotagliflozin, a combined SGLT1 and SGLT2 inhibitor, has been studied in type 1 diabetes [6].

SGLT1 is the transporter responsible for glucose and galactose absorption in the gastrointestinal tract and early studies in type 1 diabetes suggest that this approach looks promising with pivotal trials planned [7]. Phase III studies in type 2 diabetes are pending.

2.2.2 *Glycemic Effects of Dapagliflozin*

The Phase III development program for dapagliflozin included 12 studies in 6998 patients with type 2 diabetes (Fig. 2.3). In a 24-week parallel group, double-blind, placebo-controlled trial in patients with a mean HbA1c of 7–10 % ($n = 485$), dapagliflozin significantly improved glycemic control with mean HbA1c changes of –0.23, –0.58, –0.77, and –0.89 % with placebo, 2.5, 5, and 10 mg dapagliflozin, respectively [8]. In another 24-week parallel group, double-blind, placebo-controlled trial with patients on metformin ($n = 546$), dapagliflozin significantly improved glycemic control with mean HbA1c changes of –0.3 % with placebo, –0.67 % with 5 mg, –0.7 % with 10 mg [9]. The glycemic control benefit was

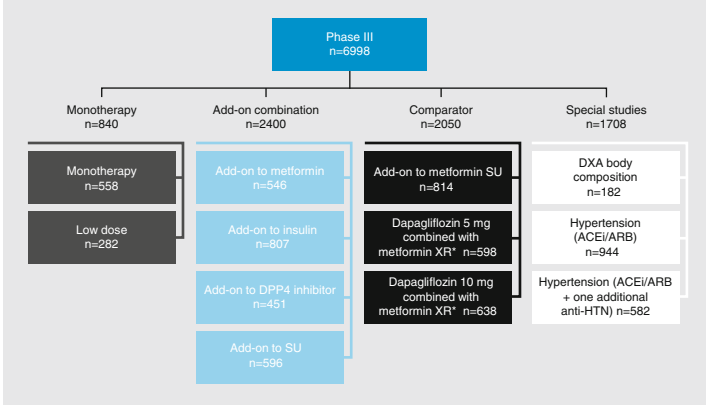

FIGURE 2.3 Dapagliflozin Phase III clinical development program. *Metformin XR is not approved or available in all countries. *DPP-4* dipeptidyl peptidase-4, *SU* sulfonylurea

sustained in patients who completed the 102-week extension study (mean HbA1c changes of +0.02, –0.48, –0.58, and –0.78 % with placebo, 2.5, 5, and 10 mg dapagliflozin) [10].

Similar improvements have been reported with dapagliflozin added on to glipizide (a sulfonylurea) and sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) [11, 12]. In a head-to-head randomized, 52-week, double-blind, active-controlled, noninferiority trial ($n = 814$) comparing dapagliflozin to glipizide, both drugs gave a significant reduction in HbA1c of 0.52 %, but did show significant differences in the secondary endpoints of weight loss and hypoglycemia [13]. Additionally, dapagliflozin has been studied as add-on to insulin in a 24-week, randomized, placebo-controlled trial followed by a 24-week extension period ($n = 808$) [14]. For the primary outcome (change in HbA1c from baseline to 24 weeks), mean HbA1c decreased from 0.79 to 0.96 % with dapagliflozin, compared to 0.39 % with placebo (mean difference, –0.4, –0.49, and –0.57 % in the 2.5, 5, and 10 mg dapagliflozin-dosing groups, respectively). Dapagliflozin has also been used in combination with modified-release metformin at 5 mg and 10 mg doses as initial treatment for type 2 diabetes when baseline HbA1c is high [15]. Two 24-week randomized trials ($n = 598$, $n = 638$) showed that the benefits of both agents were better than the individual components on HbA1c reduction (combined results showed reduction in HbA1c for dapagliflozin plus metformin XR –2.05 %, dapagliflozin alone –1.19 %, and metformin alone –1.35 %) [15]. The second study using 10 mg of dapagliflozin showed noninferiority to metformin.

2.2.3 *Glycemic Effects of Canagliflozin*

The Phase III development program for canagliflozin included ten studies in 7725 patients with diabetes (Fig. 2.4). In a 26-week, randomized, double-blind, placebo-controlled study ($n = 587$), canagliflozin at 100 mg or 300 mg significantly reduced HbA1c when compared with placebo (–0.77, –1.03,

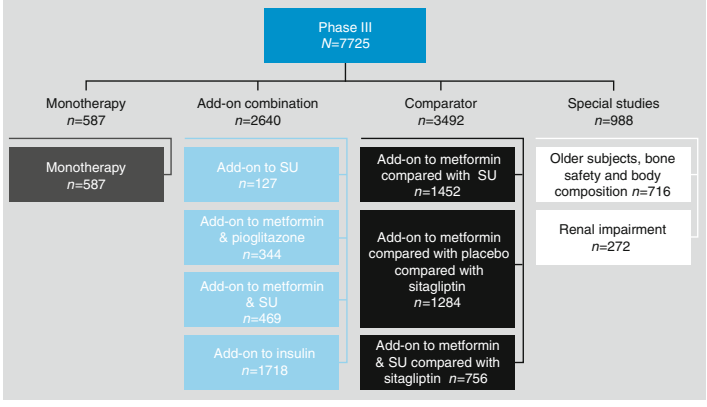

FIGURE 2.4 Canagliflozin Phase III clinical development program. *SU* sulfonylurea

and 0.14 %, respectively) [16]. In a small sub-study ($n = 127$) of the CANagliflozin cardioVascular Assessment Study (CANVAS), patients were randomized to placebo, 100 mg canagliflozin, or 300 mg canagliflozin added to a sulfonylurea [17]. At 18 weeks, placebo subtracted changes were significant at −0.74 and −0.83 % for the 100 and 300 mg doses, respectively.

In active comparator studies, canagliflozin has been added to metformin in dual therapy and compared to glimepiride and sitagliptin. In a 52-week, randomized, double-blind study ($n = 1452$), canagliflozin 100 mg was noninferior to glimepiride at lowering HbA1c (mean difference −0.01 %), and canagliflozin 300 mg was superior to glimepiride (mean difference −0.12 %) [18]. In a 26-week randomized, double-blind, four-arm, parallel group study in which patients on metformin were given placebo, sitagliptin 100 mg, or canagliflozin 100 mg or 300 mg, those given canagliflozin (100 and 300 mg) had reduced HbA1c vs. placebo (−0.79, −0.94, and −0.17 %, respectively) [19]. In a follow-up at week 52, patients given canagliflozin 100 and 300 mg demonstrated noninferiority, and canagliflozin

300 mg demonstrated superiority, to sitagliptin in lowering HbA1c (–0.73, –0.88, and –0.73 %, respectively) [19].

Two separate studies on the efficacy of canagliflozin as part of triple therapy (add-on to metformin/pioglitazone and add-on to metformin/sulfonylurea versus placebo) produced similar results, with both doses being superior to placebo, and the 300 mg dose more effective than 100 mg dose in lowering HbA1c [20, 21]. In a 52-week, randomized, double-blind, active-controlled study ($n = 756$) of subjects using stable metformin plus a sulfonylurea, canagliflozin 300 mg demonstrated noninferiority, and in a subsequent assessment superiority, to sitagliptin 100 mg (HbA1c reductions of –1.03 and –0.66 %, respectively) [22]. Canagliflozin has also been studied as add-on to insulin, with mean changes in HbA1c with canagliflozin 100 and 300 mg of –0.62 and –0.73 % at 18 weeks and –0.58 and –0.73 % at 52 weeks [23].

2.2.4 Glycemic Effects of Empagliflozin

The Phase III development program for empagliflozin included seven studies involving 5306 patients with diabetes (Fig. 2.5). In a 24-week randomized, placebo-controlled trial ($n = 899$) of empagliflozin with sitagliptin as an active comparator, the adjusted mean differences in change from baseline at week 24 were –0.74 % for empagliflozin 10 mg, –0.85 % for empagliflozin 25 mg, and –0.73 % for sitagliptin 100 mg [24]. In a 24-week, randomized, double-blind, placebo-controlled trial ($n = 637$) of empagliflozin as add-on treatment to metformin, changes from baseline in HbA1c were –0.13, –0.70, –0.77 %, with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [25].

In a double-blind, placebo-controlled study with glimepiride as an active comparator ($n = 1549$) over 52 and 104 weeks, empagliflozin was found to be noninferior. At 104 weeks, the change from baseline in HbA1c with empagliflozin vs. glimepiride was –0.11 % [26]. In a 24-week, randomized, double-blind, placebo-controlled study ($n = 666$) of empagliflozin as add-on to metformin and gliclazide, the mean changes to

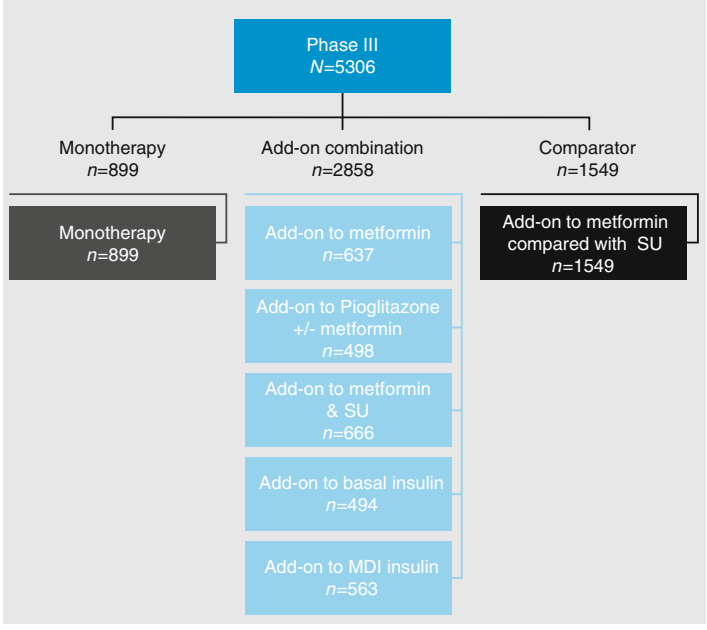

FIGURE 2.5 Empagliflozin Phase III clinical development program. *MDI* multiple daily injections, *SU* sulfonylurea

baseline HbA1c were –0.17 % for placebo, –0.82 % for 10 mg empagliflozin, and –0.77 % for 25 mg empagliflozin [27].

Dual therapy with pioglitazone and the triple combination of empagliflozin, pioglitazone, and metformin have also been shown to be effective [28]. Empagliflozin has also been shown to be beneficial when added on to insulin. In a 78-week, randomized, double-blind, placebo-controlled trial adding empagliflozin to basal insulin gave mean HbA1c changes of 0, –0.6, and –0.7 % for placebo and empagliflozin 10 and 25 mg, respectively, with a reduction in insulin dose for those given empagliflozin [29]. Additionally, in a 52-week, randomized, double-blind, placebo-controlled study looking at empagliflozin as add-on to multiple daily injections of insulin, the mean HbA1c changes were –0.81, –1.18, and –1.27 % for placebo and empagliflozin 10 and 25 mg, respectively [30].

2.2.5 *Glycemic Effects of SGLT2 Inhibitors: Where Are We Now?*

The three Phase III development programs outlined for dapagliflozin, canagliflozin, and empagliflozin have trialed on a wide range of patients with diabetes. Efficacy has been demonstrated as a monotherapy and an add-on to the older oral therapies and insulin, when compared to placebo. Only dapagliflozin has been studied in the Phase III development program as add-on to a DPP-4 inhibitor and both dapagliflozin and canagliflozin have been studied with a DPP-4 inhibitor as a comparator. There are currently no completed Phase III studies looking at their use as add-on to glucagon-like peptide-1 (GLP-1) agonists or using these agents as comparators, which is likely to represent a large target population in real-life clinical practice. Only canagliflozin is currently in the recruitment stage of a Phase III study as add-on to a GLP-1 agonist [31].

Additional uncertainty remains as to whether one SGLT2 inhibitor is better than the others at lowering blood glucose, as there have been no head-to-head Phase III clinical studies with this as the primary outcome. However, there is one small study ($n = 54$) looking at the pharmacodynamic effects of 10 mg of dapagliflozin vs. 300 mg of canagliflozin that suggested the latter had a slightly more potent effect in healthy volunteers, as measured by postprandial plasma glucose excursions, 24-h urinary glucose excretion, and renal threshold for glucose excretion [32]; how this translates into clinical practice and the management of diabetes remains unclear.

2.3 Effects of SGLT2 Inhibitors on Body Weight

Obesity and particularly visceral/abdominal obesity is associated with diabetes, insulin resistance, metabolic syndrome, and increased cardiovascular risk. Weight gain is a side effect

of insulin therapy, sulfonylureas, and thiazolidinediones, whereas metformin and DPP-4 inhibitors are weight neutral. GLP-1 agonists such as exenatide and liraglutide are associated with weight loss. Weight reduction has been a positive secondary outcome that has been consistently demonstrated in the Phase III studies of all available SGLT2 inhibitors. Mean weight changes at 24 weeks for placebo vs. dapagliflozin as initial therapy were –2.2 and –3.3 kg, respectively [8]. When added to insulin, the mean weight changes at 24 weeks for placebo vs. dapagliflozin were +0.43 and –2.04 kg (these results reflect lower insulin requirements for the active treatment group). In a 102-week study of dapagliflozin added to metformin, all doses reported sustained weight loss (–1.10 to –1.74 kg, as compared to weight gain with placebo) [10]. Similar findings have been reported for canagliflozin and empagliflozin, with weight loss in short-term studies when using them as first-line, as well as weight loss when added to drugs that are known to cause weight gain, including insulin. Weight loss benefits appear to be sustained [10].

Initial weight loss for SGLT2 inhibitors may be due to the osmotic diuretic effect of treatment. However, sustained weight loss over the subsequent weeks is a consequence of caloric loss due to glycosuria. The glucose excreted in the urine equates to net loss of 200–300 cal per day. As well as reduction in total body weight, dapagliflozin has been shown to significantly reduce waist circumference (–1.52 cm) when compared to placebo [33]. In this study, approximately two-thirds of the weight loss was attributable to reductions in fat mass. The reductions in total body weight, fat mass, and waist circumference occurred in the context of sustained and significant glycosuria, which supports the theory that this was due to caloric loss. Whole body dual-energy X-ray absorptiometry demonstrated the reduction in total body weight was due to loss in fat mass, and not loss of fluid or lean mass. It also demonstrated an initial rapid decline in weight over the first week, followed by a more gradual decline that had not plateaued at 24 weeks. This, coupled with a partial rebound in weight after discontinuation, suggests that diuresis may con-

tribute to the initial weight loss, and loss in total body fat is predominant after this. However, in a study of 86 patients with type 2 diabetes, there was evidence that weight loss did plateau as a result of increased calorie intake, as measured urinary glucose excretion did not lead to the weight loss expected [34].

2.4 Effects of SGLT Inhibitors on Blood Pressure

In patients treated with SGLT2 inhibitors, there is a demonstrable reduction in systolic blood pressure. Chronic osmotic diuresis due to glycosuria causes an increase in 24-h urine volumes of 107–400 mL, which has a favorable effect on blood pressure [35]. Dapagliflozin causes a reduction in systolic blood pressure of 2–9 mmHg with no increase in the heart rate or increase in syncopal episodes. In a pooled analysis of 12 placebo studies, treatment with 10 mg daily of dapagliflozin resulted in a reduction in systolic blood pressure of 4.4 mmHg and a reduction in diastolic blood pressure of 0.5 mmHg compared to placebo group at 24 weeks [36].

Similarly, canagliflozin had positive effects on blood pressure, and this improved with the higher dose of canagliflozin (300 mg). In a large meta-analysis looking at 27 RCTs using SGLT2s, canagliflozin was the only treatment to show a dose–response effect. At 300 mg daily of canagliflozin, there was a 5.1 mmHg improvement in systolic blood pressure compared to sitagliptin [37]. This was sustained over time.

Empagliflozin produced similar results, with a reduction in systolic blood pressure that was significant when compared to placebo. A greater reduction was seen in hypertensive patients (>140 mmHg systolic). The average reduction in systolic blood pressure was 2.6 and 3.3 mmHg with 10 and 25 mg empagliflozin, respectively. There was no associated increase in heart rate and the changes in blood pressure did not correlate with weight loss or glycemic improvement, thus indi-

cating that the antihypertensive effects of empagliflozin are independent of its ability to cause weight loss and improve glycemic control [38]. A 12 week, randomized, double-blind study ($n = 825$) showed that the adjusted difference versus placebo from baseline in mean 24-h systolic blood pressure was −3.33 and −4.16 mmHg and diastolic blood pressure was −1.36 and −1.72 mmHg for empagliflozin 10 and 25 mg, respectively [39].

2.5 Adverse Effects and Safety

SGLT2 inhibitors are well tolerated and have been used safely when prescribed as monotherapy or used in combination with other oral hypoglycemic agents or insulin therapy.

2.5.1 Hypoglycemia with SGLT2 Inhibitors

SGLT2 inhibitors have been shown to have relatively low hypoglycemic risk due to its insulin independent function. There were no major episodes of hypoglycemia documented when SGLT2 inhibitors were used as monotherapy in the Phase III development studies, and a meta-analysis has concluded that the hypoglycemic risk was similar to that associated with other agents [40]. The hypoglycemia risk is increased when these agents are used in combination with sulfonylurea or insulin therapy, in the setting of chronic kidney disease (CKD) and when treating elderly patients. For example, the combination of dapagliflozin as add-on to metformin is associated with a lower incidence of hypoglycemic events compared to glipizide in combination with metformin (4.8 % for placebo vs. 7.1–7.9 % over the dose ranges of dapagliflozin). However, these were predominantly minor in nature and did not require external assistance. Similar findings were observed with canagliflozin and empagliflozin, with a low risk when used in monotherapy, but increased risk when used in combination with insulin or sulfonylurea.

The prescribing advice with these combinations is to use a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination with an SGLT2 inhibitor.

There is a lot of interest in determining which noninsulin glucose-lowering agents are better for use in patients with type 2 diabetes during fasting (e.g., for Ramadan and other religious festivals). In a systematic review and meta-analysis, there is evidence to support the use of DPP4 inhibitors rather than sulfonylureas for reduction in hypoglycemia without a cost to diabetes control and weight [41]. There is some evidence supporting the use of the GLP-1 agonist liraglutide with SGLT2 inhibitors, but more studies are required in this patient group. Intuitively, it does seem likely that they would be safe, given that their mechanism is also non-insulin dependent.

2.5.2 Genital Infections

Diabetes itself is associated with an increased risk of genital infection and urinary tract infection (UTI), due to hyperglycemia and subsequent glycosuria. The effect of SGLT2 inhibitors is to induce hyperglycemia and, therefore, there is an associated increase in genital and UTI. Several placebo-controlled trials have reported that genital and urinary tract infections were more common with dapagliflozin when compared to placebo (genital infection 4.1–5.7 % vs. 0.9 %; UTI 3.6–5.7 % vs. 3.7 %) [34]. Similar findings were reported from pooled analyses of canagliflozin (genital infection 7.5 % vs. 1.9 % in placebo; UTI 5.1 % vs. 4.0 % placebo). The data for empagliflozin is similar for genital tract infections, but there was no statistical significance found in UTIs [35]. For dapagliflozin, canagliflozin, and empagliflozin, the frequency of genital and urinary infections were increased in females, and patients usually experienced one single episode that was mild to moderate in intensity and responded to standard treatment.

2.5.3 Volume Depletion

Approximately 375 mL of additional urine is produced daily in patents on dapagliflozin 10 mg daily. Safety analysis of dapagliflozin using data from 12 double-blind placebo-controlled trials demonstrated that volume depletion events occurred 0.6–1.2 % with dapagliflozin, compared to 0.4 % with placebo. This indicates a slightly elevated risk and emphasizes the importance of maintaining oral fluid intake [35]. The frequency of hypovolemic events in dapagliflozin-treated groups was increased in the elderly population (>75 years of age), in those with moderate renal impairment or those treated with concomitant loop diuretics. Other studies have demonstrated clinically significant increases in hematocrit, serum urea, and creatinine, with no increase in the rates of renal impairment, hypotension, or dehydration [42]. The estimated glomerular filtration rate decreased initially at treatment initiation but was shown to return to baseline by 24 weeks, and this was maintained to 102 weeks [33]. Volume depletion events occurred in 1.2 and 1.3 % of patients treated with canagliflozin 100 and 300 mg, respectively, compared to 1.1 % in placebo groups [35]. None of these events were serious and no episodes resulted in discontinuation of the study. There was no significant increase in hypovolemic events in patients treated with empagliflozin 10 or 25 mg when compared to placebo (1.4, 1.5, and 1.4 % respectively) [35].

2.5.4 Effects of SGLT2 Inhibitors on Lipids

No studies have demonstrated a significant improvement in lipid profile using dapagliflozin. Small increase in HDL cholesterol with dapagliflozin (1.8–4.4 % compared with 0.4 % placebo), and a small reduction in triglycerides (2.4–6.2 % vs. 2.1 % with placebo) have been demonstrated. However, these improvements are likely to be related to the weight loss

associated with therapy, rather than as a direct effect of dapagliflozin [35]. Significant increases in high-density lipoprotein (HDL) cholesterol were seen vs. placebo for 100 mg and 300 mg canagliflozin (difference in mean changes in HDL cholesterol of 6.6 % [$P<0.001$] and 6.1 % [$P<0.01$], respectively) [16]. There were small but nonsignificant reductions in triglycerides for both doses and small increases for all groups for non-HDL cholesterol.

2.5.5 Effects on Renal Function

There is a small drop in estimated glomerular filtration rate (eGFR) on commencing SGLT2 inhibitor treatment. The licensing indications for each drug differ. A study on dapagliflozin and placebo in patients with moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2) showed no significant difference in HbA1c results between treatment confirming that the efficacy of SGLT2 inhibitors requires adequate filtered load of glucose through renal tubules. Plasma concentrations of dapagliflozin and its metabolites are incrementally increased by declining renal function. It has been demonstrated that steady state plasma concentrations of dapagliflozin were 4, 6, and 9 % higher in individuals with mild, moderate, and severe renal impairment, respectively, when compared to normal renal function [42].

2.5.6 Fractures

Reduction in bone mineral density over 2 years in a trial of 714 elderly individuals and the finding that fractures occur more commonly than placebo and as early as 12 weeks after starting treatment resulted in the FDA issuing a warning to prescribers about this potential adverse effect [43]. The FDA is continuing to evaluate the risk of bone fractures with dapagliflozin and empagliflozin.

2.6 Ketoacidosis

There have been concerns about the risk of euglycemic ketoacidosis with SGLT2 inhibitors, resulting in both the FDA and EMA issuing warnings [44]. These warnings were based on 20 clinical cases for the FDA and 101 cases for the EMA, but it is likely that some of the cases were patients with type 1 diabetes. However, this side effect has been reported for the use of SGLT2s in both type 1 and type 2 diabetes [45]. In this case series, some of the factors that triggered ketoacidosis include insulin reductions, low caloric and fluid intake, intercurrent illness, and alcohol use. The main concern raised is that the ketoacidosis occurs in the setting of a minimally raised blood glucose or euglycemia and there may be delay in recognizing it; this should be preventable with the ability to detect significant ketonuria. In a large retrospective analysis of 17,596 participants in the CANVAS study, the estimated incidence rates are low (0.5, 0.8, and 0.2 per 1000 patient years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator) but still more than double with the SGLT2 inhibitor [46]. Therefore, this possible complication should be kept in mind, particularly when the introduction of SGLT2 results in a reduction in insulin dose. In this setting, a reduction in insulin dose should not be seen as a positive outcome in itself.

Key Points

- SGLT2 inhibitors have a novel mechanism of action in the kidney that is independent of insulin.
- The three main SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) have undergone extensive testing as part of Phase III development programs showing efficacy as monotherapy and an add-on to insulin and other oral therapies.

- The insulin independent action of SGLT2 inhibitors means that hypoglycemia is not a major side effect, as demonstrated in major clinical trials.
- SGLT2 inhibitors have been shown to consistently result in weight loss even when added to oral agents and insulin (known to promote weight gain).
- SGLT2 inhibitors have been shown to have a positive effect on blood pressure and result in changes in lipid profiles.
- The main side effects with this class are the development of genital infections.
- Other possible side effects such as euglycemic ketoacidosis and fractures are still being evaluated by the FDA.

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Chapter 3
Guidelines for the Treatment of Type 2 Diabetes Mellitus

Miles Fisher

3.1 Introduction

Evidence-based clinical practice guidelines are systematically developed statements intended to assist practitioners and patients about making and understanding care decisions for specific clinical circumstances. The evidence base should be obtained using an unbiased and transparent process of systematically reviewing and appraising published clinical research, which is then synthesized into recommendations for clinical practice. There is a hierarchy of evidence involved, from meta-analysis or systematic reviews of randomized controlled trials (RCTs), to case-controlled or cohort studies, to expert opinion. Evidence-based guidelines have largely replaced consensus statements, which typically involves a group of experts meeting and producing a series of recommendations based on the consensus of the group at that time. However, these can be prone to bias depending on the opinions of those involved in the process, and often would be based on a limited literature review which might miss key publications, especially if the results are negative.

Guidelines for the management of type 2 diabetes exist at local, national, and international levels and some examples of these are given in Table 3.1 [1–13]. These usually

M. Fisher, G. McKay, *Essentials of SGLT2 Inhibitors in Diabetes*, DOI 10.1007/978-3-319-43296-0_3,

Table 3.1 A selection of major treatment guidelines for the management of type 2 diabetes

Region	Guideline
International	International Diabetes Federation (IDF): Global Guideline for Type 2 Diabetes (2012) [1]
	American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012; 2015) [2, 3]
National	
Canada	Canadian Diabetes Association (CDA): Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (2013) [4]
England, Wales, and Northern Ireland	National Institute for Health and Care Excellence (NICE): Type 2 Diabetes in Adults: Management (2015) [5]
Scotland	Scottish Intercollegiate Guidelines Network (SIGN): Management of Diabetes (2011) [6]
USA	American College of Physicians (ACP): Oral Pharmacological Treatment of Type 2 Diabetes (2012) [7]; American Association of Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) (2015) [8]
Spain	Working Group for Consensus Documents and Clinical Guidelines of the Spanish Diabetes Society: Recommendations for the Pharmacologic Treatment of Hyperglycemia in Type 2 Diabetes. Consensus Document (2011) [9]
Germany	German National Disease Management Guideline on the Treatment of Type 2 Diabetes (2013) [10]
Japan	Japan Diabetes Society: Evidence-based Practice Guidelines for the Treatment of Diabetes in Japan (2013) [11]

Table 3.1 (continued)

Region	Guideline
India	Indian Council of Medical Research: Guidelines for Management of Type 2 Diabetes. Pharmacological Treatment of Diabetes (2005) [12]
Brazil	Brazilian Diabetes Society: Algorithm for the Treatment of Type 2 Diabetes. Position Statement (2010) [13]

include glycemic targets for HbA1c and recommendations on the therapeutic options that can be used to reach these targets. Pharmacological monotherapy is started after a period of lifestyle adjustment, including changes to the diet and increases in physical activity. Most guidelines recommend first-line therapy with metformin based on the results of the United Kingdom Prospective Diabetes Study (UKPDS) plus the slight reduction in weight that is obtained with metformin [14]. Thereafter, if targets are not met then the choice of second-line therapy varies from guideline to guideline.

3.2 International Diabetes Federation Guidelines

The 2012 International Diabetes Federation (IDF) global guideline for type 2 diabetes focuses particularly on cost, availability, and side effects of drugs [1]. The IDF guidelines recommend that metformin should be used as first-line therapy, with sulfonylureas as second-line and insulin third. More recent drug classes such as dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists are mentioned as second-line alternatives, based on the fact that the cost of these drugs is greater than

metformin and sulfonylureas because there are no generic formulations and they are not available for clinical use in every country. Sodium glucose cotransporter 2 (SGLT2) inhibitors are not included in the IDF guidelines, as no drugs in this class had been approved when the guideline was developed.

3.3 Joint American Diabetes Association and European Association for the Study of Diabetes Position Statement

In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a joint position statement on the management of hyperglycemia in patients with type 2 diabetes [2]. This was published in response to the increasing number of antidiabetic drugs being developed and was intended to be more evidence-based than previous joint statements, which had primarily been consensus reports. An important emphasis was placed on taking a patient-centered approach to making clinical decisions and aiming to provide care that is respectful of and responsive to individual patient preferences, needs, and values. Less stringent glycemic targets were suggested, depending on factors such as risks of hypoglycemia, disease duration, life expectancy, important comorbidities, and established vascular complications. Patient attitude, expected treatment efforts, resources, and support system are also to be taken into consideration (Fig. 3.1).

Considerations for the choice of glucose-lowering agent include age, weight, gender, racial, and genetic differences, as well as serious comorbidities such as coronary artery disease, heart failure, chronic kidney disease, and liver dysfunction. Again, as no SGLT2 inhibitors had been approved, they were not included as a treatment option in the 2012 ADA/EASD position statement.

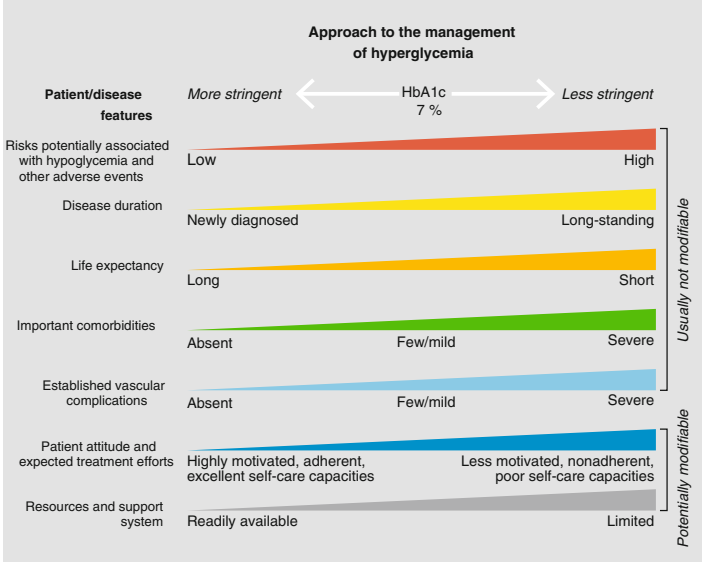

FIGURE 3.1 Depiction of the elements affecting choice of appropriate treatment to achieve glycemic targets (Reproduced with permission from Inzucchi et al. [3]; based on a figure by Ismail-Beigi et al. [15] ©American Diabetes Association)

3.3.1 Update to the Joint ADA/EASD Position Statement

The position statement was updated in 2015 to reflect new data from recent clinical trials and intended as an addendum to the 2012 full version [3]. In the update, SGLT2 inhibitors were described as a major change in antidiabetic treatment and that because the mode of action was independent of insulin action, could be used at any stage of type 2 diabetes, including when insulin secretion had waned significantly. Potential advantages of using SGLT2 inhibitors were noted and included lower risk of hypoglycemia, potential weight loss, and lowering of systolic and diastolic blood pressure, as well as potential disadvantages such as genitourinary infections, volume depletion, an increase

in low density lipoprotein (LDL) cholesterol, and a transient increase in creatinine. The cost of SGLT2 therapy was described as "high" (Table 3.2).

The ADA/EASD treatment algorithm for patients with type 2 diabetes was also updated and SGLT2 inhibitors were added as possible part of dual or triple therapy combination with metformin and either a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or insulin (Fig. 3.2). The 2015 update urges that optimal treatment must take into account comorbidities that are frequently encountered in patients with diabetes, particularly as they age. Consideration of renal status when taking an SGLT2 inhibitors is also addressed.

3.4 Country Case Study: Developing Guidelines in the UK

To illustrate the use of country-specific guidelines, the process in the United Kingdom is a particularly interesting case study. The National Institute for Health and Care Excellence (NICE), a special advisory body used to standardize and develop public health guidance, recently updated a clinical practice guideline on type 2 diabetes for use in the National Health Service (NHS) in England, Wales, and Northern Ireland [5]. This has been a controversial process, as the guideline seems to be dominated by a need to recommend generic drugs such as sulfonylureas, repaglinide, and pioglitazone, rather than considering more modern alternatives. This strong emphasis on drugs that promote weight gain, hypoglycemia, or both, is somewhat contrary to the ethos of the guideline, which is intended to promote patient-centered care.

The approach to including SGLT2 inhibitors has also been idiosyncratic. In the first draft of the guideline (published for consultation in January 2015), there was a single mention that combinations of medicines including SGLT2 inhibitors may be appropriate for some people, without defining who these people might be [16]. A reference was then made to separate health technology appraisals (HTAs) for two SGLT2 inhibitors, dapagliflozin and canagliflozin. Following critical feedback on

Table 3.2 Properties of SGLT2 inhibitors according to 2015 American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement

Class	Compounds	Cellular mechanisms	Primary physiological actions	Advantages	Disadvantages/ adverse effects	Cost
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glycosuria	No hypoglycemia Weight loss Reduces blood pressure Effective at all stages of type 2 diabetes	Genitourinary infections Polyuria Volume depletion/ hypotension/ dizziness Increases LDL cholesterol Increases creatinine (transient)	"High"

Adapted from ADA/EASD [3] © American Diabetes Association
LDL low density lipoprotein cholesterol, *SGLT2* sodium glucose cotransporter-2

FIGURE 3.2 Antihyperglycemic therapy in type 2 diabetes: general recommendations. Metformin monotherapy is added at, or soon after, diagnosis, unless there are contraindications. If the HbA1c target is not achieved after 3 months, consider one of the six treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. DPP-4i, dipeptidyl peptidase 4 inhibitors; GI, gastrointerstinal; GLP-1 RA, glucagon- like peptide 1 receptor agonist; GU, genitourinary; SGLT-2i, sodium- glucose cotransporter 2 inhibitors; SU, sulphonylureas; TZD, thiazolidinediones. *See ADA supplementary data for description of efficacy categorization. †Consider initial therapy at this stage when HbA1c is ≥9% (≥75 mmol/mol). **Consider initial therapy at this stage when blood glucose is ≥300–350 mg/dL (≥16.7–19.4 mmol/L) and/or HbA1c ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. ***Order not meant to denote any specific preference - choice dependent on variety of patient and disease-specific factors. §Usually a basal insulin (eg, NPH, glargine, detemir, degludec). (Reproduced with permission from Inzucchi et al. [3] ©American Diabetes Association)

multiple aspects of the guideline, a further draft was produced in July 2015 [17–19]. In this version, there was again a single mention of SGLT2 inhibitors in the text, with an added reference to the HTA for empagliflozin [19]. Following further consultation, the guideline was published at the end of 2015. It includes a complex algorithm for blood glucose-lowering therapy in adults with type 2 diabetes and SGLT2 inhibitors are now included (Fig. 3.3) [5]. Unfortunately, the intended effect of the revised guidelines may be to limit the use of SGLT2 inhibitors and GLP-1 receptor agonists, despite improving patient-based outcomes by reducing weight.

Guidelines in Scotland are developed by the Scottish Intercollegiate Guidelines Network (SIGN). The most recent SIGN guideline on diabetes, SIGN 116, was produced in 2010, with a minor revision in 2011 to reflect the removal of the license for rosiglitazone in Europe [6]. Like the IDF guidelines, there was no mention of SGLT2 inhibitors and these guidelines are now in need of an update.

3.5 Conclusion

Many guidelines for the treatment of type 2 diabetes either fail to mention SGLT2 inhibitors or do not give clear guidance as to when they should be used. Even the joint ADA/EASD position statement, which includes SGLT2 inhibitors as a clear therapeutic option, may require further updating to reflect the fact that empagliflozin may have preferred role in patients with coronary heart disease or heart failure (see Chap. 4). International, national, and local guidelines need revision and updating to specifically include the SGLT2 inhibitor class of drugs, which patients might benefit most, and which patients may need special consideration (e.g., patients with reduced kidney function).

Key Points

- Evidence-based clinical practice guidelines on the management of type 2 diabetes are systematically developed statements to assist practitioners and patients about health care for people with type 2 diabetes.

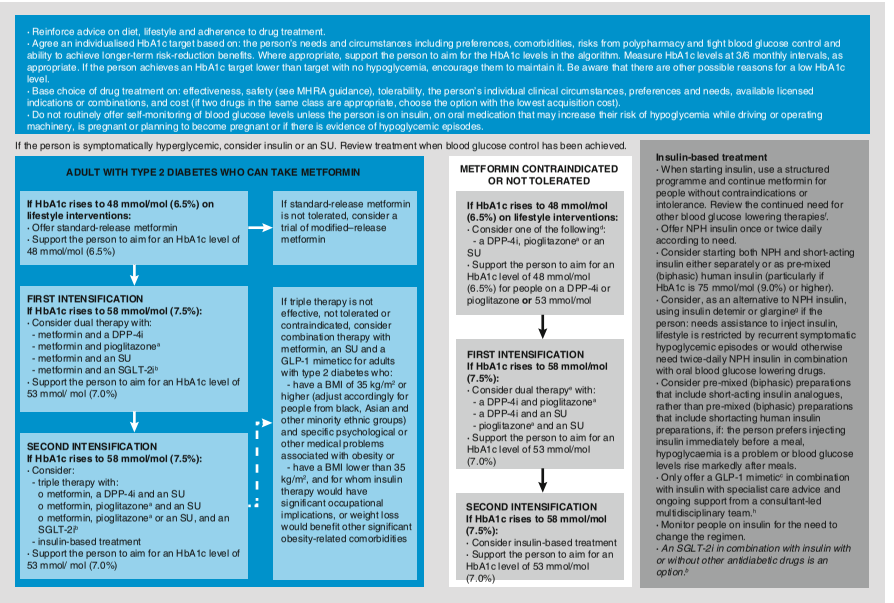

FIGURE 3.3 National Institute for Health and Care Excellence (NICE) algorithm for blood glucose-lowering therapy in adults with type 2 diabetes (UK). (**a**) When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these

conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'. (**b**) Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal. (**c**) Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months). (**d**) Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification. (**e**) Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug. (**f**) MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs. (**g**) The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication. (**h**) A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care. DPP-4i, dipeptidyl peptidase-4 inhibitor. GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2; SU, sulfonylurea. (Reproduced with permission from NICE [5] ©National Institute for Health and Care Excellence)

- Guidelines developed before 2012 do not include mention of SGLT2 inhibitors, as this class of antidiabetic drugs was not available for clinical use until dapagliflozin was launched in late 2012.
- The American Diabetes Association and the European Association for the Study of Diabetes position statement on the management of hyperglycemia in type 2 diabetes was recently updated to include SGLT2 inhibitors as a major change in treatment options since 2012.
- Additional potential advantages of modest weight loss and lowering of systolic and diastolic blood pressure are noted in the position statement, and SGLT2 inhibitors are included as possible dual and triple therapy combinations.
- Many guidelines are in need of updating based on the results of new efficacy and safety studies with SGLT2 inhibitors.

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Chapter 4
Using SGLT2 Inhibitors in Special Populations

Miles Fisher

4.1 Introduction

Type 2 diabetes is becoming a common problem in young obese people and, in some parts of the world, is as common as type 1 diabetes in teenagers and young adults. However, patients that are included in the Phase III trials of new anti-diabetic drugs tend to be middle-aged and elderly and, at this point in time, there is little information on the effects of sodium glucose cotransporter 2 (SGLT2) inhibitors in patients under 19 or over 75 years of age. Similarly, until there is much more safety data on SGLT2 inhibitors, these drugs are untested in pregnancy and gestational diabetes or in patients with serious liver disease. In pregnancy, the renal threshold for glucose reduces (i.e., glucose spills over into the urine at a lower blood glucose concentration), and so different clinical effects can be anticipated when compared to the nonpregnant population. Thus, this chapter will omit these patients and focus on the effects of SGLT2 inhibitors in four specific groups of patients where there is published information on efficacy, safety, or both. This includes:

- Patients with cardiovascular disease (CVD)
- Patients with chronic kidney disease (CKD)
- Older patients with type 2 diabetes
- Patients with type 1 diabetes

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4.2 SGLT2 Inhibitors in Patients with Cardiovascular Disease

SGLT2 inhibitors potentially have multiple effects on cardiovascular risk markers (Table 4.1) [1]. These include improved glycemia, reduced blood pressure, and reduced body weight, which are all potentially favorable effects on cardiovascular risk factors. They also cause slight but significant effects on lipids, with increases in low-density lipoprotein (LDL) cholesterol, which might potentially increase cardiovascular events.

The Food and Drug Administration (FDA) in the United States and European Medicines Evaluation Agency (EMEA) in Europe closely scrutinize the cardiovascular effects of all new treatments for type 2 diabetes. New antidiabetic drugs have to demonstrate that they are safe and do not increase the risk of cardiovascular events. Patients with higher cardiovascular risk are deliberately included in large Phase III trials of new antidiabetic drugs, and atherosclerotic events such as myocardial infarction, stroke, cardiovascular death, or hospitalization for unstable angina are blindly adjudicated. A randomized, controlled cardiovascular safety trial is usually mandated, although on most occasions the drug will be

Table 4.1 Potential effects of SGLT2 inhibitors on markers of cardiovascular risk

Potentially beneficial	Potentially harmful
Improved glycemia	Increased LDL cholesterol
Reduced blood pressure	
Reduced albuminuria	
Reduced arterial stiffness	
Reduced sympathetic nervous activity	
Reduced weight	
Reduced visceral adiposity	
Reduced oxidative stress	
Reduced uric acid	
Reduced triglycerides	
Increased HDL cholesterol	

approved on the basis of the safety in the Phase III trials before the randomized controlled trial (RCT) is completed.

4.2.1 EMPA-REG OUTCOME

EMPA-REG OUTCOME was a large cardiovascular safety study in 7020 people with type 2 diabetes and existing CVD [2]. It compared empagliflozin 10 mg, empagliflozin 25 mg, and placebo in addition to usual standards of care, and nearly half of the participants were on insulin. The first patient was enrolled in 2010 and the study was completed in 2015. Forty-seven percent (47 %) of the patients had a prior myocardial infarction, 25 % had a previous coronary artery bypass graft (CABG), 23 % had a history of stroke, 20 % had peripheral arterial disease, and 10 % had heart failure. Additionally, 26 % of the patients had a baseline eGFR (estimated glomerular filtration rate) between 30 and 60 mL/min/1.73 m^2. In other words, this was group of subjects at very high-risk of cardiovascular events.

The results were remarkable, as empagliflozin was found to be superior to placebo in reducing major adverse coronary events (defined in the study as cardiovascular death, nonfatal myocardial infarction, nonfatal stoke) and reduced total mortality by 32 % (Fig. 4.1) [3]. The effects were the same for both doses (10 and 25 mg) of empagliflozin. Significantly, hospitalization for heart failure was reduced by one-third [3]. With regard to side effects and safety, there was the expected increase in genital infections and a slight increase in urosepsis in patients treated with empagliflozin, but there was no increase in hypoglycemia, fractures, or ketoacidosis.

Several mechanisms for the cardiovascular risk benefit can be postulated, including reductions in blood pressure, weight loss, and diuresis; it seems likely that all of these mechanisms contribute, rather than it being a single factor. It will not be possible to say if this benefit is unique to empagliflozin or if this is a class effect shared with other SGLT2 inhibitors until cardiovascular safety trials with the other SGLT2 inhibitors are completed. The impressive reduction in total mortality seen with empagliflozin in the EMPA-REG OUTCOME trial will lead to a change in the management of patients who

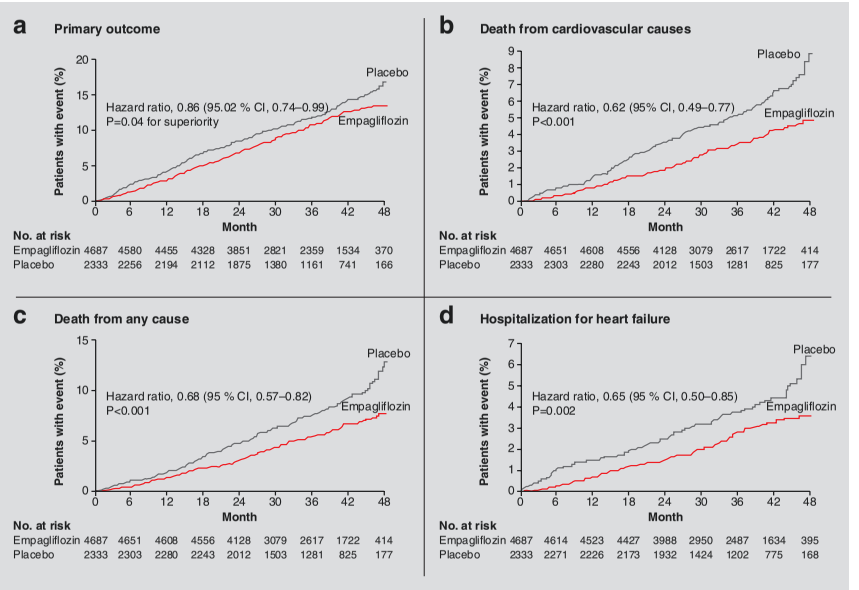

FIGURE 4.1 Cardiovascular outcomes and death compared to placebo in the EMPA-REG OUTCOME trial. Reductions in the (**a**) primary outcome, (**b**) cardiovascular death, (**c**) total mortality, and (**d**) hospitalization for heart failure with empagliflozin (Reproduced with permission from Zinman et al. [3] ©Massachusetts Medical Society)

have existing CVD and are uncontrolled on insulin therapy. Thus, initially, the increased use of empagliflozin should be focused on this challenging patient group.

4.2.2 Cardiovascular Trials with Other SGLT2 Inhibitors

Dapagliflozin was approved by the FDA and EMEA on the basis of cardiovascular safety as part of a Phase III trial program [4]. DECLARE-TIMI 58 is a large RCT comparing dapagliflozin 10 mg with placebo in around 17,000 patients aged >40 years and at high risk for cardiovascular events, with an estimated completion date of 2019. As with EMPA-REG OUTCOME, the primary outcome is a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include hospitalization for heart failure and all-cause mortality.

To approve canagliflozin, the FDA requested data from the ongoing CANVAS trial, an RCT comparing canagliflozin 100 and 300 mg with placebo in patients with either existing CVD or two or more cardiovascular risk factors [5]. Two-thirds of the patients in CANVAS have existing CVD and the double-blind study has an estimated completion date of 2017. A second RCT has been established with canagliflozin called CANVAS-R. It will recruit a similar group of patients with a primary outcome of measuring the progression of albuminuria; the cardiovascular results from CANVAS and CANVAS-R will be combined to satisfy FDA postmarketing requirements for canagliflozin.

Ertugliflozin is a newer SGLT2 inhibitor and is currently in Phase III of development. Recruitment has been completed for a cardiovascular outcomes trial comparing ertugliflozin 5 mg, 15 mg, and placebo in patients with established vascular complications. It is estimated that the trial will run for between 5 and 7 years. The cardiovascular outcome trials involving SGLT2 inhibitors are compared in Table 4.2.

Table 4.2 Cardiovascular outcomes trials with SGLT2 inhibitors

Study	Comparators	Inclusion criteria	Primary endpoint	Estimated completion
EMPA-REG OUTCOME	Empagliflozin 10 and 25 mg vs. placebo	Established CVD	CV death, non-fatal MI, non-fatal stroke	Completed 2015
CANVAS	Canagliflozin 100, 300 mg vs. placebo	Established CVD or high CV risk	CV death, non-fatal MI, non-fatal stroke	2017
DECLARE TIMI 58	Dapagliflozin 10 mg vs. placebo	High CV risk	CV death, non-fatal MI, non-fatal ischemic stroke	2019
Ertugliflozin CVOT	Ertugliflozin 5 and 15 mg vs. placebo	Established CV disease	CV death, non-fatal MI, non-fatal stroke	2020

CV cardiovascular, *CVD* cardiovascular disease, *CVOT* cardiovascular outcomes trial, *MI* myocardial infarction

4.3 SGLT2 Inhibitors in Patients with Chronic Kidney Disease

The mode of action of SGLT2 inhibitors reduces the reabsorption of glucose in the kidney, increasing glycosuria. Thus, it can be hypothesized that SGLT2 inhibitors would be less effective in reducing glycated hemoglobin (HbA1c) levels in patients who have renal impairment, where urinary glucose excretion is reduced by up to 50 %. This has been examined by performing dedicated studies in patients with CKD, and by examining all patients with CKD in the Phase III development program (e.g., as done with canagliflozin). All three of the currently available SGLT2 inhibitors have been studied in groups of patients with CKD.

Dapagliflozin (at doses of 5 and 10 mg) was compared with placebo in 252 patients with stage 3 CKD (estimated glomerular filtration rate [GFR] 30–59 mL/min/1.73 m^2) [6]. Serum creatinine increased at week 1 and then did not change after a further 2 years of treatment. This is similar to the changes in creatinine that are seen in people with normal renal function. Although blood pressure and weight both reduced with dapagliflozin, there was no significant reduction in HbA1c compared to placebo in that study [6]. Other studies analyzing dapagliflozin in patients with CKD are in progress.

Canagliflozin (100 and 300 mg) was compared with placebo in 269 patients with a subset of stage 3 CKD (eGFR 30–50 mL/min/1.73 m^2). As well as reducing weight and blood pressure, a significant reduction in HbA1c was observed at 26 weeks and at 1 year [7]. Urinary tract infections and osmotic diuresis-related adverse events were more common with canagliflozin 300 mg. Decreases in eGFR were observed with both doses of canagliflozin, and both doses reduced urine albumin–creatinine ratios vs. placebo.

THE EMPA-REG RENAL trial was a comprehensive trial of empagliflozin in patients with three different stages of CKD [8]. Empagliflozin was studied in patients with stage 2 CKD (eGFR 60–89 mL/min/1.73 m^2) comparing

empagliflozin 10 mg, 25 mg, and placebo, and in 374 patients with stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) comparing empagliflozin 25 mg and placebo. HbA1c was significantly reduced in both of these groups of patients when compared to placebo, with reductions in weight and blood pressure. A total of 74 patients with CKD stage 4 (eGFR 15–29 mL/min/1.73 m^2) were studied with empagliflozin and placebo, and in these patients empagliflozin was not effective at reducing HbA1c.

Current licensing recommends that dapagliflozin should not be used in patients with an eGFR <60 mL/min/1.73 m^2. Canagliflozin and empagliflozin can be initiated if eGFR is >60 mL/min/1.73 m^2 and can continue to be prescribed at doses of 100 mg (canagliflozin) and 10 mg (empagliflozin) until eGFR falls persistently below 45 mL/min/1.73 m^2, at which point they should be discontinued.

4.3.1 Cohort Analysis of Patients Treated with Canagliflozin

To provide further information about the effects of canagliflozin in people with CKD, data was pooled for patients with stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) from four Phase III studies [9]. This included subjects from the aforementioned canagliflozin CKD study, CANVAS, a study in older adults, and a monotherapy study [5, 7, 10, 11]. Clinically relevant reductions were seen in HbA1c, blood pressure, and body weight in patients with CKD stage 3a (eGFR 45–59 mL/min/1.73 m^2). In subjects with CKD stage 3b (eGFR 30–44 mL/min/1.73 m^2), the reduction in HbA1c was obtunded, while with the 300 mg dose, HbA1c was 0.4 % lower when compared to placebo and so of limited clinical effectiveness.

4.3.2 *Renoprotective Aspects of SGLT2 Inhibitors*

CKD is a common complication of diabetes. In people with type 1 diabetes, it is largely due to a combination of diabetic nephropathy and raised blood pressure. In people with type 2 diabetes, the pathophysiology is more complex, as vascular disease in the aorta or renal arteries and urinary tract infections can also contribute to decline in renal function.

One of the earliest changes observed in people with type 1 diabetes is hyperfiltration, where the eGFR increases. It is hypothesized that this damages the glomerulus, reducing its function, which in turn puts further strain on the remaining glomeruli. An interesting mechanistic study was performed looking at the effects of 8 weeks of open label treatment with empagliflozin 25 mg in 27 patients with type 1 diabetes and hyperfiltration (eGFR >135 mL/min/1.73 m^2) and in 13 patients with type 1 diabetes and normal renal function [12]. Empagliflozin reduced hyperfiltration in the group with baseline hyperfiltration, but no effect was seen in subjects with normal baseline function. The normalization of GFR was accompanied by reductions in effective renal plasma flow, an increase in renal vascular resistance, and reductions in plasma nitrous oxide.

The authors hypothesized that empagliflozin was affecting tubuloglomerular feedback (TGF) by blocking the reabsorption of glucose and sodium in the proximal convoluted tubule (Fig. 4.2). This increases the delivery of sodium to the macula densa in the kidney, which restores TGF by afferent vasoconstriction which, in turn, reduces renal plasma flow and hyperfiltration. The short-term reduction in hyperfiltration suggests that the long-term use of SGLT2 inhibitors might be renoprotective. This hypothesis forms the basis for the ongoing CANVAS-R and CREDENCE studies on canagliflozin.

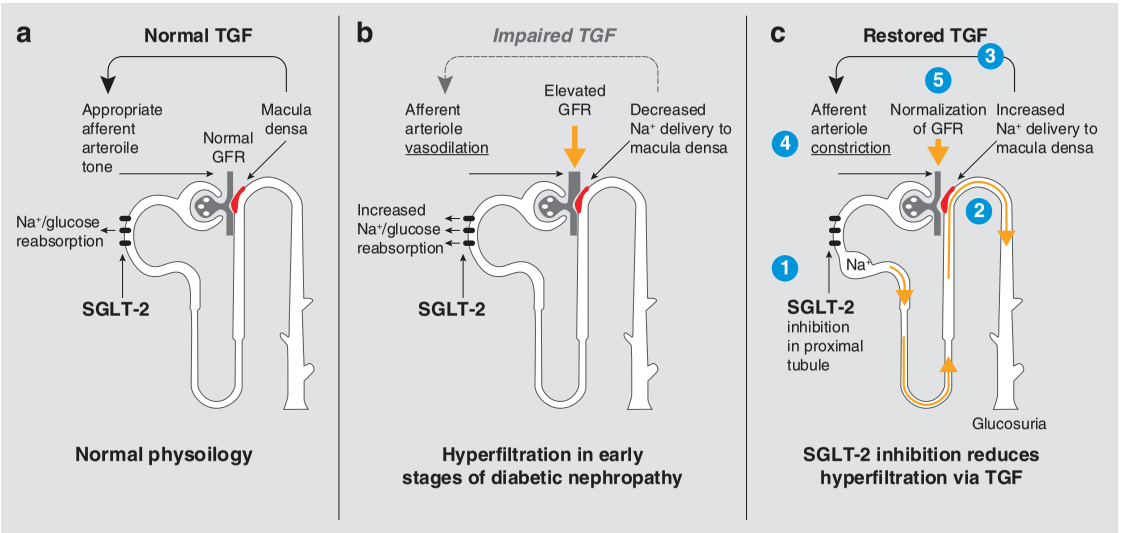

FIGURE 4.2 Postulated tubuloglomerular feedback (TGF). TGF mechanisms in (**a**) normal physiology, (**b**) early stages of diabetic nephropathy, and (**c**) after SGLT2 inhibition [10]. It is hypothesized that SGLT2 inhibition increases TGF, increases afferent arteriole tone, and reduces intraglomerular pressure. An initial reduction in eGFR is followed by stabilization and reduction in albuminuria, with the prospect of long-term renal protection (Reproduced with permission from Cherney et al. [12]. ©American Heart Association)

4.3.3 Renal Outcome Studies with SGLT2 Inhibitors

Patients with CKD are usually hypertensive and treatment with antihypertensive drugs, especially angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers, can slow the progression to end-stage renal disease (ESRD). In the short-term, eGFR increases and stabilizes, and reductions in albuminuria have been observed, which is a surrogate marker for worsening renal disease. To demonstrate conclusively, however, that SGLT2 inhibitors reduce renal outcomes requires dedicated RCTs. Analysis of renal outcomes in the EMPA-REG OUTCOME trial showed reductions in incident or worsening nephropathy and reductions of a post hoc composite renal outcome (doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease) [13].

As previously mentioned, two large studies are underway with canagliflozin in patients with different degrees of renal impairment: CANVAS-R and CREDENCE. The CANVAS-R study will examine if canagliflozin reduces either the development or progression of albuminuria. The CREDENCE trial is comparing canagliflozin 100 mg with placebo in patients with type 2 diabetes and established diabetic nephropathy, and the outcome is a composite of ESRD, doubling of serum creatinine, and renal or cardiovascular death. It is estimated that CREDENCE will be completed in 2020.

4.4 SGLT2 Inhibitors in Older Patients with Type 2 Diabetes

Although there has been an increase in the number of younger patients with type 2 diabetes, the incidence and prevalence peaks in older populations. Adverse effects of drugs tend to be more common in elderly patients and the reduction in blood pressure and potential volume depletion

that is seen with SGLT2 inhibitors may lead to problems with postural hypotension in older patients. There are two ways of obtaining this type of information during a Phase III development program. The first is to pool all of the results from the program and compare effects in older vs. younger subjects. The second method is to design a dedicated study where the inclusion criteria are for older subjects.

4.4.1 Dapagliflozin in Older Patients with Type 2 Diabetes

The glycemic efficacy and safety of dapagliflozin in elderly subjects were explored in a pooled analysis of 12 Phase IIb/III studies [14]. The glycemic effect of dapagliflozin in people over 65 years of age was slightly less than in people under 65, but this could be explained by the effects of CKD. However, hypoglycemia, volume depletion, and renal adverse events were more common in subjects over 65 years of age.

4.4.2 Canagliflozin in Older Patients with Type 2 Diabetes

Canagliflozin at doses of 100 and 300 mg has been compared to placebo in a 2-year dedicated trial in patients aged 55–80 years [10]. The average age of participants was 63 years and the expected reductions in HbA1c, weight, and blood pressure were observed. However, there was no breakdown of the results into different age bands, so this dedicated study adds little to what is already known about the efficacy and safety of canagliflozin.

A meta-analysis of four studies of patients given canagliflozin were examined according to whether subjects were less than 65 years of age or 65 years or over [15]. Improvements in HbA1c, body weight, and systolic blood pressure were consistent between younger and older patients, and there were no notable differences in the safety or tolerability profile of canagliflozin between these groups.

4.5 SGLT2 Inhibitors in Type 1 Diabetes

The mechanism of action of SGLT2 inhibitors is independent of β-cell function in the pancreas. As described in Chap. 2, SGLT2 inhibitors are effective at lowering blood glucose in patients with type 2 diabetes throughout the treatment spectrum, from initial monotherapy through to combination with insulin in patients with longstanding type 2 diabetes.

The majority of patients with type 1 diabetes have no residual β-cell function and intensive insulin therapy can be associated with substantial weight gain. It seems logical to determine whether or not SGLT2 inhibitors are of any benefit in patients with type 1 diabetes, and in particular if the use of SGLT2 inhibitors can improve glycemic control, reduce weight, or reduce insulin dosage requirements.

4.5.1 Empagliflozin in Type 1 Diabetes

To date, published studies on the use of SGLT2 inhibitors in type 1 diabetes have been of very short duration and longer studies are clearly required. An 8-week open label proof-of-concept trial with empagliflozin 25 mg that examined the effects on hyperfiltration has also reported glycemic outcomes [16]. The overall results were promising, with increases in the mean urinary excretion of glucose leading to significant reductions in HbA1c from 8.0 (64 mmol/mol) to 7.6 % (60 mmol/mol), with reductions in fasting glucose, daily insulin dose, weight, and waist circumference. Reductions were also seen in symptomatic hypoglycemia. Worryingly, however, two patients were withdrawn from the study after the early development of ketoacidosis, from which both patients fully recovered. In both of these patients, the total insulin dose was reduced by 50 % and 70 % shortly after starting empagliflozin, and this substantial reduction of insulin may have contributed to the development of ketoacidosis. The authors noted that both patients presented with plasma glucose concentrations that could be interpreted as lower than typically associated with diabetic ketoacidosis.

Empagliflozin at doses of 2.5, 10, and 25 mg was subsequently studied in a 4-week randomized, placebo-controlled trial in 75 patients with type 1 diabetes [17]. Similar overall results were obtained with increases in the 24-h excretion of glucose, and reductions in HbA1c, total daily insulin doses, weight, and symptomatic hypoglycemia compared to placebo. The basal insulin dose was kept stable for the first 7 days of treatment in this trial and no ketoacidosis was reported. As a safety measure, fasting concentrations of the ketone beta-hydroxybutyrate were measured and small increases in mean levels were observed, with high fasting levels in two subjects. The authors suggested that the mean increase reflected glucose and calorie loss and a substrate shift from glucose to lipid utilization, and noted that the doses of insulin in the two subjects with high fasting levels had been reduced by 31 and 51 %, respectively.

4.5.2 Dapaglifozin in Type 1 Diabetes

A 2-week exploratory randomized, double-blind, placebo-controlled pilot study of different doses of dapagliflozin was performed in 70 patients with type 1 diabetes [18]. The average duration of diabetes was between 16 and 22 years, and the first week of the study was performed during inpatient treatment. Glycosuria increased with dapagliflozin and decreased with placebo and, although there were trends to improvements in efficacy parameters comparing dapagliflozin with placebo, these were not statistically significant. No ketoacidosis was observed. There are several limitations to this study, including the fact that glycemic control improved in the placebo group in the inpatient setting.

4.5.3 Sotagliflozin in Type 1 Diabetes

Sotagliflozin is a drug under development that inhibits SGLT1 as well as SGLT2. As SGLT1 is involved in absorbing glucose in the intestine, inhibiting SGLT1 might reduce postprandial glucose excursions. Thirty-three patients with

type 1 diabetes were studied in a double-blind pilot study comparing sotagliflozin and placebo over 29 days [19]. Patients were on insulin pumps or multidose insulin and the outcomes were the bolus insulin dose, mean daily blood glucose (measured by continuous glucose monitoring system), and HbA1c. Bolus insulin doses were reduced with sotagliflozin, suggesting effects on postprandial glucose, mean blood glucose was reduced, and HbA1c reduced slightly. Nausea was much more common with sotagliflozin than placebo and, worryingly, two patients developed ketoacidosis on sotagliflozin. At this point in time, it is the intention of the manufacturer to further develop sotagliflozin as a treatment for type 1, as well as type 2 diabetes.

4.5.4 Future Prospects in Type 1 Diabetes

SGLT2 inhibitors are currently licensed for the treatment of type 2 diabetes, but have already been used off-label to treat patients with type 1 diabetes. Several of the case reports of ketoacidosis that have been recently described were in patients with type 1 diabetes (see Chap. 2). An 18-week trial of canagliflozin in type 1 diabetes has been completed but the results have not yet been reported. There are several ongoing clinical trials with SGLT2 inhibitors in people with type 1 diabetes, including a 52-week trial of empagliflozin, and studies of dapagliflozin in different subgroups of people with type 1 diabetes. It seems prudent to avoid the use of SGLT1 inhibitors in type 1 diabetes until these trials are completed.

Key Points

- SGLT2 inhibitors reduce HbA1c, weight, and blood pressure. A cardiovascular safety study with empagliflozin in people with existing CVD has demonstrated a significant reduction in major cardiovascular events and total mortality. It will be some time before cardiovascular outcomes studies with other SGLT2 inhibitors are completed.

- SGLT2 inhibitors are less effective at reducing HbA1c in patients with CKD. Studies are running looking at possible reductions in albuminuria and improvements in long-term renal function in patients treated with SGLT2 inhibitors.
- SGLT2 inhibitors are effective and generally well tolerated in people over 65 years of age.
- Short-term studies have shown improvements in HbA1c and weight with SGLT2 inhibitors in patients with type 1 diabetes, but an increase in diabetic ketoacidosis is a serious concern and more studies are required.

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