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Research Article

SGLT-2 Inhibitors: Drug Selection by Means of the System of Objectified Judgement Analysis Method

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Abstract

Objectives: The increasing number of antidiabetic drugs makes it almost impossible to have sufficient knowledge of each individual medicine and device, especially for general practitioners.

Reducing the number of different antidiabetics based on rational criteria, allows physicians and pharmacists to build experience with a more limited set of medicines and to optimise patient information.

Methods: In this study SGLTs are compared by means of the SOJA method.

The following selection criteria were applied: ease of use, available dosage forms, clinical efficacy, documented effects on clinical endpoints, safety, tolerability, drug interactions and documentation.

Results: Some differences in scores were found between canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. Ertugliflozin showed the lowest score, mostly because of its more limited clinical evidence and documentation. Empagliflozin and dapagliflozin showed the highest scores. These medicines are well documented concerning clinical endpoints, including heart failure and safety.

Acquisition cost was not taken into account, because this varies with time. In practice acquisition cost is of course an important selection criterion, especially because there are no major differences between the medicines from a clinical perspective. Exclusion of this criterion also makes this comparison more internationally applicable.

Conclusions: Empagliflozin and dapagliflozin showed the highest scores, mainly because of their documented effects on clinically relevant endpoints and safety.

Keywords: Dapagliflozin; Empagliflozin; SOJA Method

Introduction

Diabetes

The prevalence of type 2 diabetes in Europe is at least 2-3% and increases significantly in patients over 70 years of age.

Microvascular [retinopathy, nephropathy and neuropathy] and macrovascular complications such as ischemic heart disease, cerebrovascular accident and peripheral arterial vascular disease frequently occur. Microvascular complications are probably due primarily to hyperglycemia, while macrovascular complications are more related to the interaction between hyperglycemia, insulin resistance, dyslipidemia and hypertension [1,2].

The UK Prospective Diabetes Study [UKPDS] has been studying various aspects of the natural course and treatment of type 2 diabetes mellitus since the 1970s.

In one of the investigations [UKPDS 29], the incidence of CVA was investigated. The average study duration was 7.9 years. CVA was seen in 2.6% of patients. The main risk factors were age, male sex and hypertension [3]. The major risk factors for developing coronary heart disease were elevated LDL cholesterol, decreased HDL cholesterol, elevated triglycerides, elevated systolic blood pressure, elevated HbA1c, increased fasting blood glucose and smoking [4].

For the treatment of type 2 diabetes mellitus, a number of oral agents are available with different mechanisms of action: sulfonylurea derivatives and meglitinides [increase of insulin secretion through the pancreas], metformin [primarily inhibition of hepatic glucose production and partially inhibited glucose uptake in peripheral tissues] ,aAlpha-glucosidase inhibitors [delayed absorption of intestinal monosaccharides] and thiazolidinediones [reduction of insulin resistance and enhancement of insulin effects on glucose metabolism] [1,2,5-12]. DPP-4 inhibitors, GLP inhibitors and SGLT-2 inhibitors were introduced more recently.

The differences between the various modes of action, side effects, demonstrated effect on clinically relevant endpoints, drug interactions, price and documentation are significant, which necessitates weighted weighing of pros and cons of the various medicines.

Sodium-glucose cotransporter-2 [SGLT2] inhibitors are the newest class of oral antihyperglycemic agents available for the treatment of diabetes mellitus type 2. SGLT2 inhibitors act by reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release. Other benefits may include favorable effects on blood pressure and weight.

This article focuses on drug selection within this class of medicines, using the SOJA method.

Methodology

The System of Objectified Judgement Analysis [SOJA] method is a model for rational drug selection. The relevant selection criteria for a certain group of drugs are defined and judged by a panel of experts and each selection criterion is given a relative weight. The more important that a selection criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the score of the ideal drug for all selection criteria. The drugs with the highest total score are most suitable for formulary inclusion [13].

After the authors had weighted the criteria, Medline and the Cochrane database were searched and references from review articles obtained. A request was sent to all companies to submit all articles on their medicine that they considered relevant for the matrix. It was explicitly stated that the project was not supported by any pharmaceutical companies.

The evaluation of criteria in the SOJA method is highly standardised in order to promote unbiased judgement of drugs from various pharmacotherapeutic categories based on clinically relevant criteria. There will of course always be room for debate whether or not the correct scoring system was used for each criterion and judgement may be arbitrary for most, if not all, criteria. This is the case with any method used to quantify properties of drugs. The SOJA method is intended as a tool for rational drug decision making, forcing clinicians and pharmacists to include all relevant aspects of a certain group of drugs, thereby preventing formulary decisions being based on only one or two criteria. Besides this, possible "hidden criteria" are excluded from the decision making process. The outcome of this study should be seen as the basis for discussions within formulary committees and not as an absolute truth.

This analysis is limited to the subpopulation of overweight patients. This subpopulation comprises 85% of the total type 2 diabetes population. In these patients, insulin resistance plays an important role, as opposed to patients without obesity.

This analysis focuses on the SGLT-2 inhibitors:

- Canagliflozin [Invokana]
- Dapagliflozin [Forxiga]
- Empagliflozin [Jardiance]
- Ertugliflozin [Steglatro]

Selection criteria

The following selection criteria are applied

Criterion	Relative weight
Ease of use	50
Available dosage forms	50
Efficacy	200
Documented effects on clinically relevant endpoints	250
Safety	200
Tolerability	100
Interactions	50
Documentation	100
Total	1000

Table a

Ease of use

This criterion contains 2 subcriteria:

- Dosage frequency: 80%
- Applicability in renal function impairment : 20%.

Dosage frequency

Dosage frequency plays an important role in patient compliance. Compliance is not usually a problem in patients taking the drugs once or twice daily, but decreases considerably in the event that 3-4 dosages are to be taken daily. The method of evaluation of this criterion corresponded with that of all of the other SOJA scores.

Frequency	Score
Once daily	100%
One to two times daily	90%
Twice daily	80%
Two to three times daily	60%
Three times daily	40%
Four times daily	10%

Table b

Applicability in renal function impairment

This was scored as follows:

	Score
No need to stop existing treatment in case of decreased renal function	100%
Stopping at eGFR < 30 ml/min	75%
Stopping at eGFR < 45 ml/min	50%
Stopping at eGFR < 60 ml/min	25%
Contra-indicated	0%

Table c

Applicability

Availability of different forms of administration

This was scored as follows:

	Score
One strength only	20%
Two or more strengths	40%
Combination tablet with one other class of antidiabetics	+20%
Combination tablet with two other classes of antidiabetics	+40%
Combination tablet with three or more other classes of antidiabetics	+60%

Table d

Clinical efficacy

Clinical efficacy is by definition a very important selection criterion for each group of drugs. The relative efficacy of the various [classes of] medicines used for maintenance treatment of diabetes mellitus was determined using [preferably double-blind] randomised comparative studies between these drugs in the first instance.

If these studies were not available, results from randomised placebo-controlled studies or [double-blind or open-label] studies with other medicines included in this analysis were also taken into consideration.

There is a large number of placebo controlled and directly comparative clinical trials conducted with SGLT-2 inhibitors. [references available on request from the authors] Intensive treatment

of type 2 diabetes mellitus, regardless of the chosen agent, leads to a significant improvement of "surrogate markers" such as HbA1c [14].

Glycemic control [HbA1c, fasting glucose levels]

HbA1c is an important "marker" for the risk of microvascular complications. In this article HbA1c is expressed as %. HbA1c is also expressed as mmol/mol. Seven % equals 53 mmol/mol, and every % point counts for 11 mmol/mol, so 8% equals 64 mmol/mol and so on. The maintenance of HbA1c below 7% was found to be associated with a reduced incidence of microvascular complications, whereas they occur more frequently at HbA1c values above 10% [15,16]. In an analysis of the effects of HbA1c on the incidence of diabetes complications, UKPDS 35), every 1% reduction in HbA1c showed a 21% reduction in total diabetes complications, 21% diabetes-related mortality, 14% reduction of myocardial infarction and 37% of microvascular complications [17]. In the UKPDS 47 study, a relationship was found between HbA1c [<6.3 or> 7.6%] and fatal or non-fatal myocardial infarction, but not with CVA [18]. In the more recent UKPDS 66 study, a relationship between HbA1c and the subsequent occurrence of fatal myocardial infarction or fatal CVA [19] was found.

Determining HbA1c is a better "parameter" for chronic blood glucose control than the fasting blood glucose measurements, which are snapshots [20].

It is important that the results of direct comparisons between two or more agents are used in the analysis of the effects of the blood glucose lowering agents. The results of placebo-controlled research cannot be used to make statements about the mutual effectiveness of the various medicines. The effects on HbA1c depend on the baseline HbA1c [higher reduction at higher baseline] and the history of the use of blood glucose lowering agents prior to the study [stronger reduction in "naive" patients] [1,2,21,22].

Effects on insulin resistance

Type 2 diabetes mellitus is a heterogeneous condition characterized by abnormalities in the beta cells of the pancreas and in peripheral tissues, such as skeletal muscle and fat tissue. At least three metabolic disorders play a role in the development of hyperglycemia in patients with type 2 diabetes mellitus: decreased insulin secretion in response to glucose, increased glucose production in the liver and a reduced insulin-dependent glucose uptake in peripheral tissues [23-26]. The last two abnormalities are defined as insulin resistance. Insulin resistance can be treated by enhancing insulin activity, increasing glucose consumption in peripheral tissues, reducing gluconeogenesis and glycogenolysis in the liver and reducing lipolysis in the fat cells. Insulin resistance occurs in the first phase of the disease and can contribute to the progression of the disease and depletion of the beta cells. Insight into the importance of insulin resistance and insulin resistance syndrome [dyslipidemia, increased chance of intravenous clotting, endothelial dysfunction and hypertension] has grown [1,23,27] in recent years, and insulin resistance is now believed to play a central role in developing Name macrovascular complications of type 2 diabetes mellitus. Medicines that can reduce insulin resistance work, to some extent, causal [23,24].

Of these effects only effects on HbA1c [70% of relative weight] and insulin resistance [30% of relative weight] were scored.

Documented effects of clinically relevant endpoints

The following effects were taken into consideration:

- Effect on macrovascular complications [myocardial infarction, stroke, peripheral vascular disease or acute death].
- Effects on microvascular complications [neuropathy, retinopathy, nephropathy].

This was scored as follows:

Safety

Rare, dangerous side effects

The extent and the severity of adverse effects is another important selection criterion for drugs. A distinction was made between

	Macrovascular complications	Neuropathy	Retinopathy	Nephropathy	Score
Max score	60%	10%	10%	20%	100%

Table e

"minor" side effects, such as gastrointestinal disturbances or skin reactions, occurring in clinical trials [scored under tolerability] and severe or even life-threatening adverse reactions observed with large scale use of the drugs.

Tolerability

The extent and the severity of adverse effects is another important selection criterion for drugs. A distinction was made between "minor" side effects, such as gastrointestinal disturbances or skin reactions, occurring in clinical trials and severe or even life-threatening adverse reactions observed with large scale use of the drugs [scored under safety]. The evaluation of the "minor" adverse effects was based on results of double blind comparative clinical studies.

Drug interactions

This criterion is of importance in formulary decision making as the majority of patients treated with diabetes will take other medications as well. Drug interactions may result in an increased or reduced clinical efficacy of the antidiabetic medicine in question or in a reduction of the clinical efficacy of the other drug, with which the interaction occurs. Interactions may also give rise to increased toxicity of one or both compounds. The more frequent these interactions occur and the more serious the consequences are, the lower the score for the drug in question.

Documentation

The first two sub criteria are indicative of the overall clinical documentation of the drugs in randomised controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies leave no doubt about the clinical efficacy and safety of this drug in the studied population. The latter two criteria are indicative of the overall clinical experience with the drug. These sub criteria may introduce a bias to the advantage of older drugs, but this is done intentionally. The safety of a newly introduced drug cannot be guaranteed from the results of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions [e.g. patients with diminished renal function] were excluded. Both the number of patients that has been treated on a worldwide basis and the period that a certain drug has been available are of importance, as it may take time until adverse reactions occur.

The method of evaluation of this criterion was identical to that of all of the other SOJA scores. The score includes the following aspects:

- The number of comparative studies: 25%
- The number of patients in these studies :25%
- The number of years on the market: 25%
- The number of patient days worldwide: 25%

The number of comparative studies

Five percent of the maximum score was assigned for each study of a specific drug. As a result, the score for 20 studies is 100%.

The number of patients in these studies

For every 10 patients participating in these studies 1% of the maximum score was assigned. As a result, the score for 1000 patients is 100%.

The number of years on the market

Every year a certain drug has been on the market represents 10% of the score. If a drug has been on the market for at least 10 years, the score is 100%.

Number of patient days worldwide

Everyone million patient days of experience represents 1% of the score. If the number of patient days of experience exceeds 100 million, the score is 100%.

Results

Ease of use

Dosage frequency

The score for dosage frequency is expressed below.

	Dosage frequency	Score	Renal function	Score	
Canagliflozin	1 x daily	80%	Not needed	20%	100%
Dapagliflozin	1 x daily	80%	<45 ml/min	10%	90%
Empagliflozin	1 x daily	80%	<45 ml/min	10%	90%
Ertugliflozin	1 x daily	80%	<45 ml/min	10%	90%

Table f

User-friendly dosage forms

No user-friendly dosage forms, such as liquid or dispersible formulations are available for any compound.

Food intake

All medicines can be combined with food. In order to achieve optimal therapeutic efficacy, the intake is recommended just before or during the meal.

Applicability

Availability of different forms of administration

This resulted in the following score.

	Strengths	Subscore (max 40%)	Combination with other antidiabetics	Sub-score (max 60%)	Total Score
Canagliflozin	100 mg, 300 mg	40%	Metformin	20%	60%
Dapagliflozin	5 mg, 10 mg	40%	Metformin	20%	60%
Empa-gliflozin	10 mg, 25 mg,	40%	Metformin	20%	60%
Ertugliflozin	5 mg, 10 mg	40%	Metformin Sitagliptin	40%	80%

Table g

The combination of sitagliptin and ertugliflozin is available on the market, but is not reimbursed by health insurance companies in the Netherlands.

Clinical efficacy

It should be stressed that patient education is an important aspect of the treatment of diabetes mellitus type 2: losing weight [by diet and exercise] is very important in reducing insulin resistance.

Effects on HbA1c

One meta-analysis studied the effects of SGLT-s inhibitors on HbA1c. The mean decrease was 0.69% compared with placebo, with canagliflozin showing the highest decrease [0.85%]. The evidence was considered to be low quality, because of variability and evidence of publication bias [28]. Another meta-analysis also showed a slightly higher effect [difference 0.10 - 0.20%] on HbA1c for canagliflozin compared to dapagliflozin and empagliflozin [29].

Another meta-analysis compared studies with ertugliflozin to other SGLT-2 inhibitors. The high dose of ertugliflozin [15 mg] was significantly [but slightly] more effective concerning effects on HbA1c than dapagliflozin 10 mg or empagliflozin 25 mg [30].

Empagliflozin showed comparable effect on HbA1c, with a mean decrease of 0.62% compared to placebo in a meta-analysis of 15 randomised studies [31]. Another meta-analysis showed a HbA1c decrease of 0.57% for 10 mg and 0.65% for 25 mg empagliflozin. Empagliflozin 10 mg was as effective as linagliptin, sitagliptin and glimepiride in direct comparative studies, whereas the 25 mg was significantly more effective than these pooled comparators, with a 0.13% stronger reduction in HbA1c [32].

DPP4 inhibitors and SGLT-2 inhibitors showed similar effects on HbA1c when added to metformin plus sulfonylurea [33].

A meta-analysis showed that DPP4 inhibitors, SGLT-2 inhibitors, thiazolidinediones and sulfonylurea resulted in similar HbA1c reduction when added to metformin, ranging from 0.5 to 1.0% in various studies [34].

Insulin sensitivity

Few studies have been published regarding the effects of SGLT-2 inhibitors on insulin sensitivity. A positive effect on insulin sensitivity was seen in 2 clinical studies [35,36]. A positive effect is to be expected because of the weight loss induced by SGLT-2 inhibitors [37-51]. This was scored as follows.

	HbA1c	Insulin Resistance	Score
Max score	70%	30%	100%
Canagliflozin	35%	20%	55%
Dapagliflozin	35%	20%	55%
Empagliflozin	35%	20%	55%
Ertugliflozin	35%	20%	55%

Table h

Other effects

Effects on lipids profile

Dyslipidemia occurs in 40 - 50% of patients with type 2 diabetes mellitus. The main features are elevated triglycerides, decreased

HDL and normal to slightly elevated LDL cholesterol [52,53]. The UKPDS 66 study showed no relationship between the LDL/HDL ratio and the subsequent occurrence of fatal myocardial infarction or fatal CVA [12]. In the UKPDS 59 study, a relationship was found between HDL cholesterol and the occurrence of peripheral vascular disease. Any reduction of HDL with 0.1 mmol/l showed an increase of 22% risk [54].

The 10-year risk of coronary heart disease was 21% in patients with diabetes mellitus type 2 [55].

A beneficial effect on the lipid spectrum of blood glucose lowering agents is important, but in practice the vast majority of patients will need a statin to achieve optimal lipid control.

There is still no clarity about the relevance of these observations. There are no indications for relevant differences between the various compounds regarding effects on lipids.

SGLT-2 inhibitors

SGLT-2 inhibitors showed limited effects on cholesterol metabolism in clinical studies [40,42,50,56-60].

Effects on blood pressure

SGLT-2 inhibitors resulted in a decrease in systolic and diastolic blood pressure in a range of clinical and database studies [61-76]. There are no indications for relevant differences between the various compounds regarding effects on blood pressure.

Documented effects of clinically relevant endpoints

Both diabetes and high age are important risk factors for death to cardiovascular complications. Coronary heart disease is the major cause of death in type 2 diabetes patients [55]. The cardiovascular risk profile of diabetes patients is similar to that of non-diabetes individuals who are 15 years of age [77].

It is always checked whether it has been demonstrated that a significant reduction in morbidity or mortality relative to placebo or other drugs is achieved. If this is demonstrated, the size of the effect is also included in the score. In addition, it is included in the score whether it is an effect in an overall diabetes population or in a specific group, such as primary and secondary treatment, obesity, etc.

The relationship between blood glucose control and effect on macrovascular complications is complex. In a systematic review, a decreased incidence was found of non-fatal heart disease, RR 0.80 as well as the overall incidence of cardiovascular complications, RR 0.90 for intensive control over standard treatment, but not for the other endpoints, such as CVA or Cardiovascular mortality [78].

SGLT-2 inhibitors

The primary purpose of the cardiovascular safety studies is to demonstrate that the SGLT2 inhibitors are non-inferior to placebo in terms of cardiovascular morbidity and mortality. Non-inferiority means that the SGLT2 inhibitor does not cause more cardiovascular morbidity and mortality than placebo. In case the SGLT2 inhibitor was non-inferior to placebo, researchers checked whether the substance is superior. This should be included prospectively in the study protocols. Superior in this case means that the SGLT2 inhibitor causes less cardiovascular morbidity and mortality than placebo. All studies were conducted in patients at high risk for cardiovascular morbidity and mortality.

10,142 patients participated in the CANVAS and CANVAS-R study with canagliflozin. Patients had a history of cardiovascular disease or at least 2 risk factors for cardiovascular disease. The median duration of follow-up was 2.4 years [79].

The DECLARE-TIMI 53 study on dapagliflozin involved 17,160 patients. The patients had an atherosclerotic disorder in the history, or multiple risk factors for atherosclerotic disorders. The median follow-up was 4.2 years [80].

7,020 patients participated in the EMPA-REG OUTCOME study on empagliflozin. The patients had a history of cardiovascular disease. The median duration of follow-up was 3.1 years [81].

8246 patients participated in the Vertis CV trial with ertugliflozin. The patients had diabetes and atherosclerotic cardiovascular disease. The median duration of follow-up was 3.5 years [82].

The SGLT2 inhibitors studied were non-inferior to placebo and therefore cardiovascular safe. Canagliflozin and empagliflozin were also superior to placebo. These medicines caused less cardiovascular morbidity and mortality than placebo.

Canagliflozin

The effects of canagliflozin were investigated in the Canvas program, integrating data from two trials with over 10,000 patients with diabetes and high cardiovascular risk. The primary endpoint was death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. This endpoint occurred in 26.9 patients per 1,000 patient years with canagliflozin and in 31.5 patients per 1,000 patient years with placebo. The difference was statistically significant: HR = 0.86; 95% CI = 0.75 to 0.97. There was no significant reduction on any individual components of the primary endpoint, any hospitalization, hospitalisation due to heart failure [79].

The NNT was 224 for 2.4 years [79].

Although the primary endpoint occurred less frequently with canagliflozin, no significant reduction of cardiovascular mortality [HR 0.87, 95% CI 0.72-1.06] or death from any cause was observed [HR 0.89, 95% CI 0.74-1.01] [79].

Dapagliflozin

The DECLARE-TIMI 53 study on dapagliflozin had 2 primary end points. The primary safety outcome was a composite of major adverse cardiovascular events [MACE], defined as cardiovascular death, non-fatal myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite [≥40% decrease in estimated glomerular filtration rate to < 60 ml per minute per 1.73m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes] and death from any cause. Dapagliflozin showed non-inferiority compared to placebo, but superiority could not be demonstrated. This first endpoint occurred in 8.8% of patients with dapagliflozin and 9.5% of patients with placebo. The difference was not statistically significant: HR = 0.93; 95% CI = 0.84 to 1.03 [80].

The second primary endpoint was a combination of cardiovascular death and hospital admissions due to heart failure. This endpoint occurred in 4.9% of patients with dapagliflozin and 5.8% of patients with placebo. The difference was statistically significant: HR = 0.83; 95% CI = 0.73 to 0.95. The significance was due to the effect on hospital admissions due to heart failure 2.5% vs 3.3%]. The cardiovascular mortality was not significantly different [2.9% in both groups] [80].

The DAPA-HF study investigated the effects of dapagliflozin 10 mg once daily and placebo in 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin [at a dose of 10 mg once daily] or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure [hospitalization or an urgent visit resulting in intravenous therapy for heart failure] or cardiovascular death.

Over a median of 18.2 months, the primary outcome occurred in 16.3% of patients [16.3%] in the dapagliflozin group and in 21.2%] in the placebo group [HR 0.74; 95% CI, 0.65 to 0.85; P < 0.001].

A first worsening heart failure event occurred in 10.0% of patients in the dapagliflozin group and in 13.7% of patients in the placebo group [HR, 0.70; 95% CI, 0.59 to 0.83]. Death from cardiovascular causes occurred in 9.6% and 11.5% of patients, respectively [HR 0.82; 95% CI, 0.69 to 0.98]; and death from any course was seen in 11.6% and 13.9%], respectively [HR, 0.83; 95% CI 0.71 to 0.97] [83].

In an analysis of the DAPA-HF study effects on heart failure in patients with diabetes were similar to those in patients without diabetes [84].

Empagliflozin

The effects of empagliflozin on cardiovascular morbidity and mortality were investigated in the double-blind Empa-reg study. The study involved over 7,000 patients, with a median observation time of 3.1 years. The primary composite endpoint was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary endpoint was observed in 10.5% of patients treated with empagliflozin and in 12.1% in the placebo group [HR 0.86, 95% CI 0.74-0.99]. The incidence of death from cardiovascular causes and all-cause mortality was significantly lower for empagliflozin: 2.7% vs 4.1%, [38% relative risk reduction] and 5.7% and 8.3% [32% relative risk reduction]. The incidence of hospitalisation for heart failure was significantly lower for empagliflozin: 2.7% vs 4.1%, 35% relative risk reduction [81].

The NNT was 63 for 3.1 years [81].

A meta-analysis [based on the above studies] confirmed the positive effects of SGLT-2 inhibitors on cardiovascular endpoints [85].

One meta-analysis [including data from the above study] confirmed positive effects on MACE [86].

No positive effects on the incidence of cerebrovascular events were observed in the Empa-reg study [87]. A significant reduction of heart failure was observed for empagliflozin compared to placebo [88]. This was confirmed in another study [89].

The Emperor reduced trial assigned 3730 patients with class II-IV heart failure and an ejection fraction of 40% or less to receive empagliflozin [10 mg once daily] or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

During a median of 16 months, a primary outcome event occurred in 19.4% of patients in the empagliflozin group and in 24.7% of patients in the placebo group [HR 0.75; 95% CI 0.65 to 0.86; P < 0.001]. The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group [HR, 0.70; 95% CI, 0.58 to 0.85; P < 0.001] [89].

It should be noted that the cost of prevention of one serious cardiovascular event with canagliflozin or empagliflozin is high [about 80,000 euro per event] [90] and that the results are only valid in high risk patients. The cost of preventing one event in a more general diabetes type 2 population would be considerably higher than that.

Ertugliflozin

In the Vertis CV trial, patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomized to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events [a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke]. The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 11.9% of patients in the ertugliflozin group and in 11.9% in the placebo group as well [hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P < 0.001 for noninferiority]. Death from cardiovascular causes or hospitalization for heart failure occurred in 8.1% in the ertugliflozin group 9.1% in the placebo group [hazard ratio, 0.88; 95.8% CI,0.75 to 1.03; P = 0.11 for superiority]. The hazard ratio for death from cardiovascular causes was 0.92 [95.8% CI, 0.77 to 1.11], and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 [95.8% CI, 0.63 to 1.04]. Amputations were performed in 2.0% who received the 5-mg dose of ertugliflozin and in 2.1% who received the 15-mg dose, as compared with 45 patients 1.6% who received placebo [82].

Observational studies

The observational CVD-Real Nordic study investigated the effects of SGLT-2 inhibitors [94% dapagliflozin] compared SGLT-2 inhibitors with DPP-4 inhibitors regarding association with MACE, hospital events for heart failure, atrial fibrillation and severe hypoglycaemia in a real world setting in diabetes 2 patients. The incidence of all-cause mortality HR 0.44, 95% CI 0.33-0.60], was significantly lower for SGLT-2 inhibitors. The total follow-up was over 38,000 patient years [in about a 1:3 ratio for SGLT-2 and DPP-4 inhibitors]. The incidence of MACE [HR 0.79, 95% CI 0.67-0.94] and hospital events for heart failure HR 0.62, 95% CI 0.50-0.77] was significantly lower for SGLT-2 inhibitors. No significant differences were observed on other endpoints [91].

The same study group investigated cardiovascular morbidity and mortality of SGLT-2 inhibitors versus other glucose lowering drugs. The incidence of cardiovascular mortality HR 0.53, 95% CI 0.40-0.71], was significantly lower for SGLT-2 inhibitors. No significant differences were observed on other morbidity endpoints. The incidence of MACE [HR 0.78, 95% CI 0.69-0.87] and hospitalisation for heart failure HR 0.70, 95% CI 0.61-0.81] was significantly lower for SGLT-2 inhibitors. No significant differences were observed on other morbidity endpoints [92].

Effects on microvascular complications

Neuropathy

Foot problems occur frequently as a complication of diabetes, especially in the elderly. Both vascular and neurological factors

play a role. The prevalence of diabetic neuropathy in patients over 60 years may be above 50%. Diabetic neuropathy is a dreaded complication of type 2 diabetes mellitus, which can manifest itself in paresthesia, burning sensation or decreased pain sensation, especially in the feet. This can lead to ulceration, infection and gangrene or amputation of the feet [2].

The UKPDS 33 study showed no significant differences between the intensive and conventional treatment on individual endpoints related to diabetic neuropathy, such as amputation.

No specific studies using SGLT-2 inhibitors were performed.

Retinopathy

Diabetic retinopathy is the main cause of blindness. Older patients with diabetes also have an increased risk of other eye disorders, such as glaucoma, cataracts and macular degeneration. Regular eye control is very important [2].

No specific studies using SGLT-2 inhibitors were performed.

Nephropathy

The first indication of diabetic nephropathy is microalbuminuria, followed by proteinuria. Diabetic nephropathy is one of the most important indications for hemodialysis [2]. Various drugs, including angiotensin II antagonists and ACE inhibitors, may reduce renal impairment in patients with type 2 diabetes mellitus.

Nephropathy is a major complication of diabetes mellitus. About 25% of type 2 diabetes mellitus patients develop microalbuminuria within 10 years and approximately 5% of patients develop macro albuminuria. Only a relatively small proportion [0.8%] exhibits increased serum creatinine or undergoes renal function replacement therapy. In particular, the last group showed a significant increase in mortality [93].

Canagliflozin had a more favourable effect on UACR compared to glimepiride [94]. The effects of canagliflozin were investigated in the Canvas program, integrating data from two trials with over 10,000 patients with diabetes and high cardiovascular risk. The primary endpoint was death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The effects on renal events were investigated as well. Progression of albuminuria occurred significantly less frequent with canagliflozin compared to placebo: 8.94 vs 12.87 events per 100 patient years [HR 0.73, 95% CI 0.67-0.79] [79].

The CREDENCE study on canagliflozin involved 4,401 patients with chronic kidney damage [30 to 90 ml/min/1.73 m2 eGFR] with severe albuminuria. The primary endpoint was a combination of end-stage renal failure, doubling of serum creatinine that persisted for longer than 30 days, and renal or cardiovascular death. Patients were followed for an average of 2.62 years [Can50]. The CREDENCE study was stopped prematurely when an interim analysis showed that canagliflozin achieved a significant result at the primary endpoint compared to placebo. The primary composite endpoint had occurred in 245 of the 2,202 patients with canagliflozin and in 340 of the 2,199 patients with placebo. This means that 22 patients must be treated with canagliflozin instead of placebo for 2.5 years to prevent 1 case of end-stage renal failure, doubling of serum creatinine, renal or cardiovascular death [95].

The DAPA-CKD study randomised 4304 participants with an estimated GFR of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of 200 to 5000 to dapagliflozin 10 mg or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

The study was stopped prematurely because of the observed difference in efficacy between the groups., a primary outcome event occurred in 9,2% of participants in the dapagliflozin group and in 14.5% in the placebo group [HR 0.61; 95% CI 0.51 to 0.72; P < 0.001], over a median of 2.4 years. The number needed to treat to prevent one primary outcome event was 19 [95% CI, 15 to 27]]. The HR for the composite of a sustained decline in the estimated GFR of at least 50%, ESRD, or death from renal causes was 0.56 [95% CI, 0.45 to 0.68; P < 0.001]. Death occurred in 101 participants [4.7%] in the dapagliflozin group and 146 participants [6.8%] in the placebo group [HR, 0.69; 95% CI, 0.53 to 0.88; P = 0.004]. The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes [96].

Empagliflozin has demonstrated a decreased UACR compared to placebo in the large scale EMPA-REG OUTCOME study. This decrease was more pronounced in patients with existing macroalbuminuria [32%] or microalbuminuria [25%] than in subjects with normoalbuminuria [7%]. The likelihood of an improvement in albuminuria was significantly greater in the empagliflozin groups compared to placebo [97].

In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. Incident or worsening nephropathy occurred in 12.7% in the empagliflozin group and in 18.8% in the placebo group [hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70; P < 0.001]. Doubling of the serum creatinine level occurred in 1.5% in the empagliflozin group and in 2.6% in the placebo group, a significant relative risk reduction of 44%. There was no significant between-group difference in the rate of incident albuminuria [98].

The Emperor reduced trial assigned 3730 patients with class II-IV heart failure and an ejection fraction of 40% or less to receive empagliflozin [10 mg once daily] or placebo, in addition to recommended therapy. The second secondary outcome was the rate of the decline in the estimated GFR during double-blind treatment. The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group [-0.55 vs. -2.28 ml per minute per 1.73 m2 of body-surface area per year, P < 0.001], and empagliflozin-treated patients had a lower risk of serious renal outcomes [89].

A recent meta-analysis including studies with empagliflozin [EMPA-REG OUTCOME], canagliflozin [CANVAS Program and CREDENCE], and dapagliflozin [DECLARE-TIMI 58]. involved 38 723 participants. SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease [RR 0·67, 95% CI 0·52-0·86, p = 0·0019], the effect was consistent across studies. SGLT2 inhibitors also reduced end-stage kidney disease [0·65, 0·53-0·81, P < 0·0001], and acute kidney injury [0·75, 0·66-0·85, P < 0·0001], with consistent benefits across studies [99].

No significant difference in renal effects was observed between ertugliflozin and placebo in the Vertis CV study, although a trend towards positive effects was observed [82].

These results should be interpreted with caution: HbA1c and blood pressure were significantly lower in the intention to treat analyses and provided no comment of per protocol analysis, which is mandatory to claim non inferiority in these trials and which has to be shown before moving to superiority analyses. It's unclear if the differences in renal disease markers would be secondary to these management differences or to the study drug itself [taking into account low adherence to assigned treatment in these studies].

	Macrovascular complications	Neuropathy	Retinopathy	Nephropathy	Score
Max score	60%	10%	10%	20%	100%
Canagliflozin	36%	5%	5%	20%	66%
Dapagliflozin	43%	5%	5%	20%	73%
Empagliflozin	46%	5%	5%	20%	76%
Ertugliflozin	24%	5%	5%	10%	44%

Table i

This was scored as follows

Discussion

Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin do not cause more cardiovascular morbidity and mortality than placebo in patients with a high cardiovascular risk. No studies are available regarding patients without high cardiovascular risk. The results of the endpoint studies cannot be compared directly, because of differences in the patient population. Some studies were performed in patients with existing cardiovascular disease, whereas other studies also included patients at high risk of developing cardiovascular disease, but without existing disease.

Canagliflozin, dapagliflozin and empagliflozin cause less cardiovascular morbidity and mortality than placebo in patients with a high cardiovascular risk. This has not been demonstrated for ertugliflozin. For empagliflozin, 63 people must be treated for 3.1 years to prevent 1 case of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. For canagliflozin this is 224 patients for 2.4 years. This was not established for dapagliflozin, because significance was not reached in the DECLARE-TIMI 53 study, which also included patients without existing cardiovascular disease.

Canagliflozin and empagliflozin are awarded 36% [60% of the available 60% for this sub criterion].

Dapagliflozin is awarded 33% [55% of the available 60% for this sub criterion], because one of the primary endpoints was not reached [in a different patient population].

Ertugliflozin is awarded 24% [40% of the available 60% for this sub criterion].

Dapagliflozin and empagliflozin are awarded 10% extra because of the documented effects in patients with heart failure: 43% and 46%, respectively for CV effects.

Safety

Fractures

Canagliflozin showed a decrease in BMD and an increased incidence of fractures [100,101], whereas no effect on the incidence of fractures was seen in dapagliflozin or empagliflozin [102-108].

Several meta-analyses have studied the relationship between SGLT-2 inhibitors as a group and fractures. None of these studies found a significant increase in fractures compared to placebo or other oral antidiabetics [109-111]. Most studies were however of short duration.

Hypoglycaemia

The incidence of hypoglycaemia during monotherapy with SGLT-2 inhibitors is low. An increased risk of hypoglycaemia compared to placebo was found when these drugs are combined with insulin or sulfonylureas [95-108,112-114]. A pooled analysis of studies with empaglifozin did not show an increased incidence of hypoglycaemia in combination with insulin or sulfonylureas [115].

Volume depletion

The incidence of all adverse reactions related to volume depletion [such as postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope] was similar for SGLT-2 inhibitor and for placebo or other oral antidiabetics. The incidence was increased in patients with high risk, such as a history of cardiovascular disease, impaired renal function or age > 75 years [10-108,116,117].

Genital mycotic infections

Vulvovaginal candidiasis and balanitis are observed 3 times more frequently during use of SGLT-2 inhibitors than with placebo. Between 0.5% and 1% of patients discontinued treatment because of these complaints [105-108,112,113,117,118].

Amputation

The FDA has issued warnings of increased leg and foot amputation risk be added to canagliflozin drug labelling. The risk associated with other SGLT2 inhibitors was uncertain. One meta-analysis investigated the risk of amputation in 14 clinical trials. SGLT2 inhibitors as a group were not associated with an increased risk of diabetic foot syndrome compared with placebo: OR 1.05, 95% CI: 0.58-1.89. SGLT-2 inhibitors as a class were not significantly associated with amputation risk [OR 1.40, 95% CI:0.81-2.41], but canagliflozin showed an increased incidence of amputation in participants using canagliflozin [OR 1.89, 95% CI: 1.37-2.60], compared with oral antidiabetics or placebo. Empagliflozin did not show an increased incidence of amputation [119].

In ongoing, long-term clinical studies of canagliflozin in type 2

diabetes patients with cardiovascular disease [CVD] or at high risk for CVD, an increase in cases of lower limb amputation [primarily of the toe] has been observed in patients treated with canagliflozin [SPC Invokana]. This was confirmed in the Canvas study: 0.63 versus 0.34 amputations per 100 patient years [79]. As an underlying mechanism has not been established, risk factors, apart from general risk factors for amputation are unknown [SPC Invokana]. It is unclear whether this applies to the other SGLT-2 inhibitors as well [SPC Forxiga, Jardiance]. The large scale EMPA-REG study did not present data indicating an increased risk for empagliflozin.

A large US database study, investigating 142 800 new users of canagliflozin, 110 897 new users of other SGLT- 2 inhibitors and 460 885 new users of non-SGLT-2 antidiabetics], showed no increased risk of amputation for canagliflozin. The estimate for lower limb amputation with canagliflozin vs non-SGLT-2 antidiabetics was 0.75 [95% CI, 0.40-1.41] in the on-treatment analysis and 1.01 [95% CI, 0.93-1.10] in the intent-to-treat analysis [120].

Increased creatinine

An increase in serum creatinine has been found for dapagliflozin [SPC Forxiga]. The Canvas trial showed a possible positive effect of canagliflozin in the progression of albuminuria [HR 0.73; IC95% 0.67- 0.79] and in a composite outcome [glomerular filtration rate, the need for renal transplant and renal related death; HR 0.60; IC95% 0.47- 0.77] [79].

Cancer risk

The available evidence from short-term RCTs did not indicate a significantly increased risk of overall cancer among individuals with type 2 diabetes using SGLT2 inhibitors. Most studies were however of short duration [121].

Infections

A meta-analysis showed that SGLT-2 inhibitors increased the risk of genital infections compared to placebo [RR 3.37, 95% CI 2.89-3.93] and active comparator [RR 3.89, 95% CI 3.14-4.82]. The risk of urinary tract infection was not increased with SGLT-2 inhibitors as a group, compared to placebo or active comparators. Dapagliflozin 10 mg daily was associated with a significantly increased risk of UTI compared to placebo [RR 1.33, 95% CI 1.10-1.61] [122].

One meta-analysis showed that canagliflozin, dapagliflozin and empagliflozin were associated with a higher risk of genital infections than placebo, with ORs ranging from 3.21 [95% CI 2.08-4.93] for dapagliflozin 2.5 mg to 5.23 [95% CI 3.86-7.09] for canagliflozin 300 mg [123].

Other adverse events

Fournier's gangrene

Post-marketing cases of necrotising fasciitis of the perineum, [also known as Fournier's gangrene], have been reported in female and male patients taking SGLT-2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's 6 gangrene is suspected, all SGLT-2 inhibitors should be discontinued and prompt treatment [including antibiotics and surgical debridement] should be instituted] [105-108].

Ketoacidosis

Rare cases of diabetic ketoacidosis [DKA], including life-threatening and fatal cases, have been reported in clinical trials and post-marketing in patients treated with SGLT-2 inhibitors, and cases have been reported in clinical trials with the SGLT-2 inhibitors. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l [250 mg/dl]. It is not known if DKA is more likely to occur with higher doses of SGLT-2 inhibitors. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with SGLT-2 inhibitors should be discontinued immediately [105-108].

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with SGLT-2 inhibitors may be restarted when the ketone values are normal and the patient's condition has stabilised. Before initiating therapy with SGLT-2 inhibitors, factors in the patient history that may predispose to ketoacidosis should be considered. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve [e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults [LADA] or patients with a history of pancreatitis], patients with conditions

that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients. Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved [105-108].

Ketoacidosis and Fournier's gangrene are rarely observed during treatment with SGLT-2 inhibitors. There are no indications of relevant differences between the medicines in this effect.

Dapagliflozin, empagliflozin and ertugliflozin are awarded 70% for safety.

The incidence of amputations may be higher for canagliflozin. This medicine is awarded 60%.

Tolerability

Frequent, non-serious adverse effects

SGLT-2 inhibitors are also usually well tolerated, with an incidence of adverse events comparable to placebo [116-123], with the exception of a higher incidence of genital infections [124].

One meta-analysis included studies comparing canagliflozin 100 mg and 300 mg to sitagliptin. No differences were found in the incidence of adverse events, serious adverse events, discontinuation, urinary tract infections and hypoglycaemia. The only significant difference between both medicines was the higher incidence of genital mycotic infections, which was higher for canaglifozin 100 mg [RR 4.32]. The risk was significantly increased in both men and women [125].

Canagliflozin showed a higher incidence of osmotic diuresis related adverse events compared to placebo in a meta-analysis of monotherapy [Meta 35] and a higher incidence of pollakiuria in combination with other oral antidiabetics compared with placebo [126].

Empagliflozin showed a higher incidence of genital infections compared to placebo in a meta-analysis of 15 randomised studies [127].

All SGLT-2 inhibitors are awarded 70%.

Drug interactions

Few clinically relevant interactions have been found for SGLT-2 inhibitors.

Pharmacodynamic interactions may occur with diuretics, resulting in additional volume depletion and hypotension.

Rifampicin decreases the AUC of SGLT-2 inhibitors: 51% reduction for canagliflozin, 22% for dapagliflozin, 35% for empagliflozin and 39% for ertugliflozin [105-108,127].

Clinically insignificant increases in the AUC of digoxin and simvastatin [less than 20%] have been described in combination with SGLT-2 inhibitors [105-108].

All SGLT-2 inhibitors are awarded 75%.

Documentation

The documentation is summarized below. The documentation included only double-blind studies with at least 25 patients per treatment arm and a study duration of at least 4 weeks.

SOJA score

The SOJA score is presented in the Table below.

	Studies	Patients	Years	Patient years (million)	Score
Canagliflozin	>20	>1000	8	>100	95%
Dapagliflozin	>20	>1000	9	>100	97%
Empagliflozin	>20	>1000	7	>100	92%
Ertugliflozin	7	>1000	4	>100	68%

Table j: Overview of documentation

Applied methodology

Drug selection was performed by means of the SOJA method, which is a well-established rational and transparent way of selecting medicines [or in this case inhalation devices] within a therapeutic class from a formulary perspective. The evaluation of the criteria in the SOJA method is highly standardized in order to promote unbiased judgement of drugs from various pharmacological categories based on clinically relevant criteria. Of course, there is potential debate on the correct scoring system with respect to

	Weight	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Ease of use	50	50	45	45	45
Available dosage forms	50	30	30	30	40
Efficacy	200	138	138	138	138
Documented effects on clinically relevant endpoints	250	165	182	190	110
Safety	200	120	140	140	140
Tolerability	100	140	140	140	140
Interactions	50	38	38	38	38
Documentation	100	95	97	92	68
Total	1000	776	810	813	719

Table k

each criterion and individual decisions are highly subjective. This is the case with any method used to quantify properties of drugs. The SOJA method is intended as a tool for rational drug decision making, enabling clinicians and pharmacists to include all relevant aspects of a certain group of drugs, thereby preventing formulary decisions being based on only one or two criteria. Besides this, possible "hidden criteria" [such as personal financial interest] are excluded from the decision making process. The outcome of this study should be seen as the basis for discussions within formulary committees and not as the absolute truth.

Outcomes

Relatively limited differences in score are seen between the SGLT-2 inhibitors [about 12% between the highest and lowest score]. Of course, the present scoring is based on the weights assigned by the authors. The essence of the SOJA method is that users of the method may assign their own relative weight to each selection criterion. This interactive program is available on the internet: www.tablet.sojaonline.nl. Other relative weights will of course affect the relative scores for the medicines.

It should be stressed that one single SGLT-2 inhibitor may not be suitable for all patients. All SGLT-2 inhibitors have minor differences regarding advantages and disadvantages, but these may be more pronounced in individual patients.

The relatively high scores for empagliflozin and dapagliflozin are caused by a favourable score for the criteria documented effects on clinical endpoints [including effects on heart failure] and safety. Canaglilozin also scores well, but this drug has a slightly lower score for safety and no studies on effects on heart failure are available.

Strength and limitations of the methodology

Selection criteria

Of course, other selection criteria could be applied as well. We did not include Contra-indications and Warnings and Precautions in the matrix. There were no relevant differences between the SGLT-2 antagonists in this respect. Differences in the incidence of bleeding or drug interactions were accounted for in the current selection criteria.

Variability of the AUC is a standard criterion for SOJA. Its relevance for SGLT-2 antagonists is unclear. That is why a low weight was assigned to this criterion. When one considers this criterion to be completely irrelevant, a zero weight can be given to this criterion in the interactive program.

Clinical efficacy and safety are the most important selection criteria for all groups of medicines. Unfortunately these criteria are difficult to score for SGLT-2 inhibitors because of the lack of direct comparative studies and differences in patient populations, study design and applied endpoints. Meta-analyses and registry data may be of value in the judgement of efficacy and safety. All data sources have specific strengths and weaknesses.

Acquisition cost was not included as a selection criterion to

make the score internationally applicable. The present matrix can be used as a pre-selection tool of the most suitable SGLT-2 inhibitors from a quality point of view. Because prices may different institutions and in different healthcare systems, individual procurement procedures should lead to a selection of the best options.

Judgement of properties of SGLT-2 inhibitors

Double-blind comparative studies are the most important source of information of the determination of clinical efficacy and tolerability. These studies usually have limitations in the selection of patients and a limited duration of the study. No direct comparative studies are available, which makes it possible to reliably evaluate the SGLT-2 inhibitors on the most important selection criteria, clinical efficacy, documented effects on clinically relevant endpoints and safety. This score should therefore be considered as preliminary. On the other hand, it seems quite unlikely that large scale direct comparative studies with more than 2 SGLT-2 inhibitors will be published in the near future, so we will have to deal with indirect comparisons. An analysis of the landmark studies with SGLT-2 inhibitors showed a positive effect on mortality for empagliflozin in patients with existing atherosclerotic cardiovascular disease [HR 0.62, 95% CI 0.49-0.77], whereas this was not documented for the other SGLT-2 inhibitors [128].

Because of the lack of direct comparative studies, the results of meta-analyses and registries were also taken into consideration. These kinds of studies also have limitations. The quality of meta-analyses is as good as the quality of the studies which are included. Patient populations may be quite different for patients treated with the individual SGLT-2 inhibitors in registry studies.

Formulary choices versus decisions in treatment of individual patients

It should be stated that formulary selection is a different process than decision making in individual patients. Selection criteria like variability in AUC, number of approved indications and documentation are typical criteria that may be relevant from a formulary perspective, but not for the selection of an SGLT-2 inhibitor in individual patients.

The above described differences in properties of SGLT-2 inhibitors may lead to drug and dosage choices based on the specific situation of the patient, such as comedication [risk of interactions], comorbidity, renal function impairment and individual tolerability.

Conclusions

We found limited differences in the scores of the available SGLT-2 inhibitors. Empagliflozin and dapagliflozin showed the highest

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