Kardiovaskularna sigurnost oralnih antidijabetika

Cardiovascular Safety of Oral Antidiabetic Drugs

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SAŽETAK: Hrvatska pripada skupini europskih zemalja s visokim kardiovaskularnim rizikom i rastućom prevalencijom šećerne bolesti tipa 2 (DMT2). Prema podatcima Nacionalnog registra osoba sa šećernom bolešću (CroDiab registar), u Hrvatskoj je 2014. godine bilo evidentirano ukupno 254 296 osoba oboljelih od dijabetesa starijih od 18 godina (7,9 %). DMT2 je, uz hipertenziju i hiperlipidemiju, jedan od vodećih čimbenika kardiovaskularnog rizika. Glavne regulatorne agencije za lijekove, potaknute štetnim kardiovaskularnim učincima rosiglitazona u RECORD studiji i kasnijim metaanalizama, zahtijevaju za sve antidijabetike kliničke pokuse o utjecaju na kardiovaskularne ishode i dokaze o sigurnosti. U procjeni učinka antidijabetika na kardiovaskularni rizik važna je gornja granična vrijednost dvostranog intervala pouzdanosti od 95 % (95 % CI) za procijenjeni omjer rizika. Svi antidijabetici s gornjom granicom omjera rizika ≥ 1,3 zahtijevaju dodatne sigurnosne provjere. Kardiovaskularna sigurnost oralnih antidijabetika posebno je važna u bolesnika sa zatajivanjem srca. S obzirom na veliki broj antidijabetika na tržištu, odluka o optimalnom liječenju DMT2 treba ovisiti o svim individualnim karakteristikama bolesnika i procijenjenom kardiovaskularnom riziku.

SUMMARY: Croatia belongs to a group of European countries with a high cardiovascular risk and growing prevalence of diabetes mellitus type 2 (DMT2). According to data of the National Diabetes Registry (CroDiab registry), a total of 254,296 individuals aged >18 suffering from diabetes were registered in 2014 (7.9%). Along with hypertension and hyperlipidemia, DMT2 is one of the leading cardiovascular risk factors. Prompted by adverse cardiovascular effects of rosiglitazone, demonstrated in the RECORD study and subsequent meta-analyses, the main drug regulatory agencies require clinical trials of the effect on cardiovascular outcomes and safety evidence for all antidiabetic drugs. On assessing the effects of antidiabetic drugs on cardiovascular risk, the two-sided confidence interval upper borderline value of 95% (95% CI) is highly relevant for the estimated risk ratio. Additional safety testing is required for all antidiabetic drugs with the risk ratio upper limit ≥1.3. Cardiovascular safety of oral antidiabetic drugs is of special importance in patients with heart failure. Considering the great number of antidiabetic drugs on the market, decision on optimal DMT2 therapy should be made in dependence of specific characteristics of each individual patient and cardiovascular risk assessment.

KLJUČNE RIJEČI: šećerna bolest, oralni antidijabetici, kardiovaskularne bolesti.

KEYWORDS: diabetes mellitus, oral antidiabetic drugs, cardiovascular diseases.

Uvod

Šećerna bolest (dijabetes melitus, DM) metabolička je bolest s osnovnim obilježjem kronične hiperglikemije zbog oštećene inzulinske sekrecije ili aktivnosti. Postoje četiri glavne etiološke kategorije dijabetesa: šećerna bolest tip 1 (DMT1), šećerna bolest tip 2 (DMT2), gestacijski dijabetes

Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia due to impaired insulin secretion or activity. There are four etiologic categories of diabetes mellitus, as follows: diabetes mellitus type 1 (DMT1); diabetes mellitus type 2 (DMT2); gestational diabetes; and

te druge specifične vrste šećerne bolesti. Velika većina ili oko 95 % bolesnika ima DMT2. Dijagnoza se postavlja mjerenjem glukoze natašte, dva sata nakon obroka te određivanjem glikoziliranog hemoglobina A1c (HbA1c).

DMT2 je, uz arterijsku hipertenziju i hiperlipidemiju, jedan od vodećih čimbenika kardiovaskularnog rizika. Velika je metaanaliza utvrdila da prisutnost DMT2, neovisno o drugim čimbenicima rizika udvostručuje rizik od koronarne bolesti srca, infarkta miokarda, ishemijskoga moždanog udara i kardiovaskularne smrti uzrokovane različitim vaskularnim događajima[1]. Dok kontrola čimbenika rizika kao što su hipertenzija i hiperlipidemija te antiagregacijsko liječenje u DMT2 smanjuje rizik od makrovaskularnih komplikacija, a dobra kontrola "glukotrijade" (ciljni HbA1c < 6,5 %, glikemija natašte < 6,6 mmol/L, postprandijalna glikemija < 7,8 mmol/L) ima povoljan učinak na mikrovaskularne komplikacije[2], učinci strože kontrole glikemije na makrovaskularne komplikacije u postojećim studijama (UKPDS, VADT, ACCORD, ADVANCE) bili su proturječni[3-6]. Iako je u nekim ispitivanjima stroža kontrola glikemije djelovala povoljno na makrovaskularne komplikacije, u ACCORD studiji povećala je smrtnost.

Potaknuti štetnim kardiovaskularnim učinicima rosiglitazona u RECORD studiji i kasnijim metaanalizama[7-9], Američka *Food and Drug Administration* (FDA) od 2008. i europska *European Medicines Agency* (EMA) od 2012. godine zahtijevaju za sve nove antidijabetike, osim povoljnoga hipoglikemijskog djelovanja, odgovarajuće kliničke pokuse o utjecaju na kardiovaskularne ishode (engl. *CV Outcome Trial*, CVOT) i dokaze o sigurnosti (**slika 1**)[10]. Procjena utjecaja na KV rizik temelji se na rezultatima kliničkih ispitivanja faze 2 i 3 za sve antidijabetike u razvoju, kao i one koji su već na tržištu. U ocjeni učinka lijeka na kardiovaskularni rizik važna je gornja granična vrijednost dvostranog intervala pouzdanosti od 95 % (95 % CI) za procijenjeni omjer rizika. Pri gornjoj graničnoj vrijednosti < 1,3 lijek se smatra sigurnim i može biti odobren bez dodatnih provjera sigurnosti. Ako je gornja granična vrijednost omjera rizika > 1,8, lijek ne može biti odobren i potrebno je provesti veliko ispitivanje sigurnosti (CVOT). Antidijabetici s gornjom granicom omjera rizika između 1,3 i 1,8 mogu dobiti odobrenje za stavljanje na

other specific DM types. DMT2 accounts for the great majority of DM patients (95%). Diagnosis of DM is made by measuring fasting blood glucose, 2-h postprandial blood glucose and glycated hemoglobin A1c (HbA1c) determination.

Along with arterial hypertension and hyperlipidemia, DMT2 is one of the leading cardiovascular risk factors. A large meta-analysis found the presence of DMT2, independently of other risk factors, to double the risk of coronary heart disease, myocardial infarction, ischemic stroke and cardiovascular death caused by various vascular events[1]. While efficient control of risk factors such as hypertension and hyperlipidemia, as well as antiaggregation therapy in DMT2 reduces the risk of macrovascular complications, and good control of the 'glucotriad' (target HbA1c <6.5%, fasting glycemia <6.6 mmol/L and postprandial glycemia <7.8 mmol/L) has favorable effect on microvascular complications[2], the effects of tight glycemic control on macrovascular complications reported from different studies are controversial (UKPDS, VADT, ACCORD and ADVANCE)[3-6]. In some studies, tight glycemic control had favorable influence on macrovascular complications, whereas in the ACCORD study it increased mortality.

Prompted by the adverse effects of rosiglitazone in the RECORD study and subsequent meta-analyses[7-9], the US Food and Drug Administration (FDA) since 2008 and European Medicines Agency (EMA) since 2012 require, besides beneficial hypoglycemic action, appropriate clinical cardiovascular outcome trials (CVOT) and safety evidence for all antidiabetic drugs (**Figure 1**)[10]. Assessment of the effect on cardiovascular risk is based on the results of phase 2 and 3 clinical trials for all developing antidiabetic drugs, as well as for those already on the market. On assessing the effects of antidiabetic drugs on cardiovascular risk, the two-sided confidence interval upper borderline value of 95% (95% CI) is highly relevant for the estimated risk ratio. At the upper borderline value <1.3, the drug is considered safe and can be registered without additional safety testing. If the upper borderline value of risk ratio is >1.8, the drug cannot be registered and requires additional large safety testing (CVOT). Antidiabetic drugs with the risk ratio upper borderline limit between 1.3 and 1.8 can be registered, but appropriately designed and statistically powered postmarketing trial must

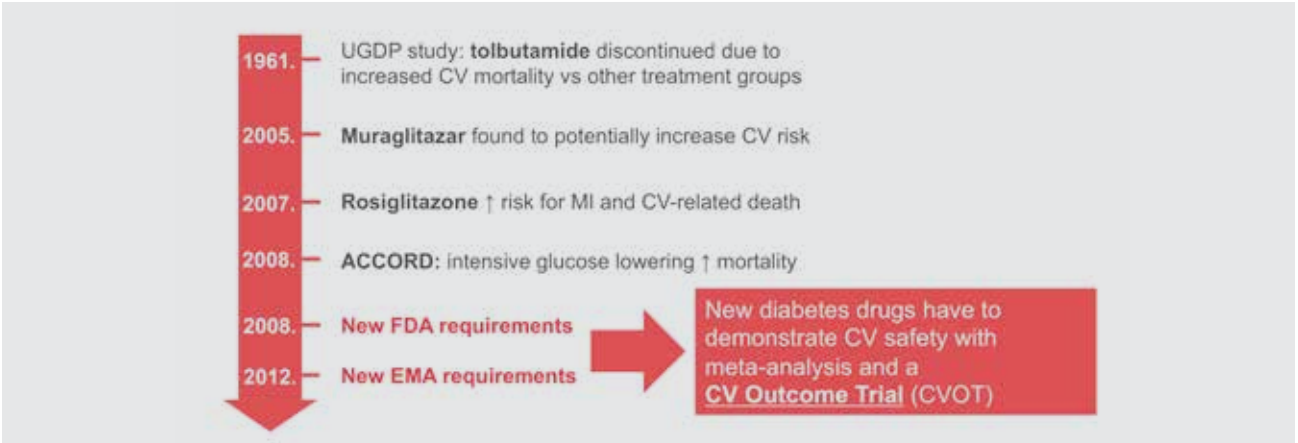

FIGURE 1. Adverse cardiovascular events led regulators to require demonstration of cardiovascular safety for new glucose-lowering drugs.

CV = cardiovascular; MI = myocardial infarction

tržište, ali nakon stavljanja u promet treba provesti ispitivanje odgovarajućeg dizajna i statističke snage kako bi se dokazala gornja granična vrijednost omjera rizika < 1,3[10].

Šećerna bolest i zatajivanje srca

Kardiovaskularna sigurnost oralnih antidijabetika posebno je važna u bolesnika sa zatajivanjem srca (ZS). Hrvatska pripada skupini europskih zemalja s visokim kardiovaskularnim rizikom i rastućom prevalencijom DMT2. Prevalencija ZS-a u općoj europskoj i hrvatskoj populaciji jest oko 2 %, a oko 0,4 % opće populacije, uz ZS, ima i DMT2[11,12]. Prema podatcima Nacionalnog registra osoba sa šećernom bolešću (CroDiab registar), u Hrvatskoj je 2014. godine evidentirano ukupno 254 296 osoba oboljelih od DM-a starijih od 18 godina, odnosno 7,9 %[13]. Ranija su istraživanja pokazala, međutim, da čak 40 % oboljelih nema postavljenu dijagnozu pa se procjenjuje da čak 400 000 osoba u Hrvatskoj boluje od DM-a, odnosno svaka deseta odrasla osoba. Prevalencija DM-a mnogo je viša u simptomatskih bolesnika sa ZS-om (12 – 30 %), a u hospitaliziranih čak do 40 %[14,15]. Novih epidemioloških istraživanja i sigurnih podataka o prevalenciji i incidenciji ZS-a u nas nema, a posebno nedostaju podatci o ZS-u u DMT2[16]. Iz prethodno navedenih relevantnih europskih epidemioloških podataka moguće je s približnom sigurnošću ekstrapolirati takve podatke za Hrvatsku. S obzirom na ukupan broj od 4,3 milijuna stanovnika, uz predmnijevanu prevalenciju ZS-a od 2 %, u Hrvatskoj bi oko 86 000 osoba imalo ZS. Uz prevalenciju ZS-a i DMT2 od oko 0,4 %, oba bi stanja bila prisutna u oko 17 200 osoba. U oko 250 000 dijabetičara tipa 2 u Hrvatskoj vjerojatna je prevalencija ZS-a oko 8 % ili četiri puta veća nego u općoj populaciji.

Zatajivanje srca odgovorno je za smanjenje kvalitete života i invalidnost, ima visok pobol i smrtnost, a može ga uzrokovati svaka bolest koja oštećuje građu i funkciju srca[11,12,16,17]. ZS i DMT2 često su prisutni istodobno i imaju nepovoljan međusobni utjecaj na prirodni tijek obaju stanja. Snažni čimbenici rizika za ZS, koronarna bolest srca i arterijska hipertenzija, imaju visoku prevalenciju u dijabetičara. Hiperglikemija sama po sebi štetno utječe na miokard povećavajući rizik od njegove disfunkcije. Dijabetička kardiomiopatija, pojam koji označuje poseban klinički entitet, uključuje brojne patofiziološke mehanizme oštećenja miokarda u DMT2: nakupljanje krajnjih produkata glikozilacije, oksidativni stres, upalnu reakciju, poremećen intracelularni metabolizam kalcija, promjene u ekspresiji mikroRNK, promociju aterosklerotskih promjena i razvoj koronarne bolesti srca. U suprotnome smjeru, sama prisutnost ZS-a povećava rizik od nastanka dijabetesa zbog hipersimpatičkog tonusa, hipoperfuzije i kongestije gušterače i jetre, inzulinske rezistencije i smanjene tjelesne aktivnosti[2,18].

Metformin

Liječenje metforminom preuhranjenih dijabetičara tipa 2 tijekom 10 godina nakon poznate *United Kingdom Prospective Diabetes Study* (UKPDS) znatno je smanjilo sve o dijabetesu ovisne nepovoljne ishode, i to za 21 % (p = 0,01), infarkt miokarda za 33 % (p = 0,005) i ukupnu smrtnost za 27 % (p = 0,002)[3,19,20]. Ovakvo uvjerljivo smanjenje kardiovaskularnih

be conducted to demonstrate the risk ratio upper borderline limit <1.3[10].

Diabetes Mellitus and Heart Failure

Cardiovascular safety of oral antidiabetic drugs is of particular importance in patients with heart failure. Croatia belongs to a group of European countries with a high cardiovascular risk and increasing prevalence of DMT2. The prevalence of heart failure in the general population of Europe and Croatia has been estimated to 2%, while 0.4% of the general population suffer from both heart failure and DMT2[11,12]. According to data of the National Diabetes Registry (CroDiab registry), a total of 254,296 individuals aged >18 suffering from diabetes were registered in 2014, yielding a prevalence of 7.9%[13]. However, previous studies have shown that even 40% of those suffering from DM have not been diagnosed with the disease, thus it is estimated that as many as 400,000 individuals or every tenth adult in Croatia have DM. The prevalence of DM is significantly higher in symptomatic patients with heart failure (12%-30%), in hospitalized patients increasing up to 40%[14,15]. There are no recent epidemiological studies or reliable data on the prevalence and incidence of heart failure in Croatia; in particular, data on heart failure in DMT2 are lacking[16]. The relevant European epidemiological study reports mentioned above can quite certainly be extrapolated to Croatia. With the 4.3 million population and presuming a 2% prevalence of heart failure, about 86,000 individuals would suffer heart failure in Croatia. With the prevalence of both heart failure and DMT2 of 0.4%, both conditions would be present in about 17,200 individuals. The likely prevalence of heart failure in 250,000 DMT2 patients in Croatia is 8% or fourfold that recorded in the general population.

Heart failure is responsible for impaired quality of life and disability, is associated with high morbidity and mortality, and can be induced by any disease causing damage to the heart structure and function[11,12,16,17]. Heart failure and DMT2 are frequently found as comorbidities and exert unfavorable mutual effect on the natural course of both conditions. Coronary heart disease and arterial hypertension as potent risk factors for heart failure have a high prevalence in diabetic patients. Hyperglycemia per se has adverse effect on myocardium, increasing the risk of myocardial dysfunction. Diabetic cardiomyopathy, a term denoting a specific clinical entity, includes numerous pathophysiological mechanisms of myocardial damage in DMT2, e.g., accumulation of advanced glycation end products, oxidative stress, inflammatory reaction, impaired intracellular calcium metabolism, altered microRNA expression, atherosclerotic lesion promotion, and development of coronary heart disease. And vice versa, the very presence of heart failure increases the risk of diabetes development due to hypersympathetic tone, pancreas and liver hypoperfusion and congestion, insulin resistance, and reduced physical activity[2,18].

Metformin

Metformin therapy of overweight DMT2 patients for 10 years after the well-known United Kingdom Prospective Diabetes Study (UKPDS) significantly reduced all diabetes dependent adverse outcomes by 21% (p=0.01), myocardial infarction by 33% (p=0.005) and overall mortality by 27% (p=0.002)[3,19,20]. Such a notable reduction of

događaja pozicioniralo je metformin kao prvi lijek izbora u preuhranjenih dijabetičara tipa 2. Velikom je metaanalizom potvrđen povoljan učinak metformina na kardiovaskularne događaje i smrtnost, posebno u dugotrajnom liječenju i u mlađih bolesnika[21]. Pritom je upozoreno na moguće nepovoljne učinke kombinacije metformina i preparata sulfonilureje.

Metformin je prije smatran kontraindiciranim u ZS-u zbog straha od laktične acidoze, no poslije je pokazao smanjenje ukupne smrtnosti, svih hospitalizacija i neželjenih događaja[22,23]. U usporednoj studiji s drugim oralnim hipoglikemicima i inzulinom, metformin je u monoterapiji smanjio smrtnost za 35 %, u kombiniranoj terapiji za 28 %, dok su ostali lijekovi bez metformina imali neutralan učinak[24]. Osim smanjenja hiperglikemije, metformin djeluje povoljno na dislipidemiju, smanjuje agregaciju trombocita, aktivnost inhibitora aktivatora plazminogena-1 (PAI-1), endotelnu disfunkciju i kroničnu vaskularnu upalu[25]. U posebnom istraživanju Masoudi *i sur.* pokazali su da je učestalost laktične acidoze u bolesnika koji uzimaju metformin bila manja (2,3 %) nego u kontrolnoj skupini (2,6 %)[26]. U sustavnoj Cochrane analizi 347 prospektivnih, komparativnih i opservacijskih kohortnih studija, učestalost laktične acidoze u bolesnika liječenih metforminom bila je 4,3/100 000 bolesnika, a u nemetforminskoj skupini 5,4/100 000[27]. Rizik od laktične acidoze raste u bolesnika s oštećenom bubrežnom funkcijom i eGFR-om < 50, a kod eGFR-a < 30 metformin treba izbjegavati. U dijabetičara s eGFR-om 30 – 50 metformin se može rabiti uz pojačan oprez, a terapijska odluka ovisi o svim individualnim osobinama bolesnika[28].

Preparati sulfonilureje i meglitinidi

Preparati sulfonilureje i analozi sulfonilureje (meglitinidi) najstarija su skupina oralnih antihiperglikemika. Blokirajući na ATP osjetljive kalijske kanale na beta-stanicama Langerhansovih otoka, potiču sekreciju inzulina te se stoga nazivaju i inzulinskim sekretagogima. Čine drugu liniju liječenja DMT2 kada monoterapijom metforminom, glitazonima, DPP-4 inhibitorima ili GLP-1 analozima nije postignuta zadovoljavajuća kontrola glukotrijade. U monoterapiji se primjenjuju u slučaju kontraindikacija za druge antidijabetike.

Njihova kardiovaskularna sigurnost, još od objave rezultata poznate *University Group Diabetes Programme* (UGDP) studije[29], u kojoj su dijabetičari liječeni adekvatnom prehranom i tolbutamidom imali povećan kardiovaskularni rizik u usporedbi s bolesnicima liječenima samo dijetom, predmet je rasprava već dugi niz godina, a postojeće, uglavnom retrospektivne kohortne studije, rezultirale su kontradiktornim podatcima. U velikoj UKPDS studiji[3] nije zabilježen povećan kardiovaskularni rizik, dok je zaključak drugih studija bio suprotan. Zaključeno je da, osim učinka skupine, postoje razlike u djelovanju pojedinih lijekova. Povećanje kardiovaskularnog rizika moguća je posljedica antivazodilatacijskoga djelovanja zbog blokade na ATP osjetljivih kalijskih kanala na koronarnim arterijama te proaritmijskog djelovanja na miokard. Rezultati studija na modelima animalnog miokarda utvrdili su da u uvjetima ishemije glibenklamid povećava rizik od ekstrasistolije, tahiaritmije i fibrilacije, dok gliklazid djeluje protektivno u bazalnim i ishemičnim uvjetima[30-32]. Retrospektivna kohortna studija provedena na 5631 di-

cardiovascular events made metformin the first drug of choice in overweight DMT2 patients. A large meta-analysis confirmed the favorable effect of metformin on cardiovascular events and mortality, in particular in long-term therapy and in younger patients[21]. However, caution was warranted due to the possible adverse effects of a combination of metformin and sulfonylurea agents.

Earlier, metformin was considered to be contraindicated in heart failure for fear from lactic acidosis, but later it showed reduction in total mortality, number of hospitalizations and adverse events[22,23]. In a comparator study with other oral hypoglycemic drugs and insulin, metformin as monotherapy reduced mortality by 35% and in combined therapy by 28%, whereas other drugs without metformin had neutral effects[24]. Besides decreasing hyperglycemia, metformin acts favorably on dyslipidemia and reduces platelet aggregation, plasminogen activator inhibitor-1 (PAI-1) activity, endothelial dysfunction and chronic vascular inflammation[25]. In their specific study, Masoudi et al. demonstrated lower prevalence of lactic acidosis in patients on metformin as compared with control group (2.3% vs. 2.6%)[26]. In a systematic Cochrane analysis of 347 prospective comparator and observational cohort studies, the prevalence of lactic acidosis in metformin treated patients was 4.3/100,000 patients versus 5.4/100,000 patients in the non-metformin group[27]. The risk of lactic acidosis is increased in patients with impaired renal function and estimated glomerular filtration rate (eGFR) <50, and metformin should be avoided at eGFR <30. In diabetic patients with eGFR 30-50, metformin should be used with caution, and decision on therapy depends on other characteristics of each individual patient[28].

Sulfonylureas and meglitinides

Sulfonylureas and sulfonylurea analogues (meglitinides) are the oldest group of oral antihyperglycemics. These agents stimulate insulin secretion by blocking the adenosine triphosphate (ATP) sensitive potassium channels on the islands of Langerhans β cells and therefore are called insulin secretagogues. They represent the second line of DMT2 treatment when monotherapy with metformin, glitazones, dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) analogues fails to produce satisfactory glucotriad control. These agents are administered as monotherapy in case of contraindications to other antidiabetic drugs.

Cardiovascular safety of these agents has been a subject of debate for years now, i.e. since the publication of the results of the known University Group Diabetes Programme (UGDP) study[29], in which a higher cardiovascular risk was recorded in diabetic patients treated with appropriate diet and tolbutamide as compared with those treated with diet alone. Later generally retrospective cohort studies have reported contradictory results. In the large UKPDS trial[3], no increase was recorded in cardiovascular risk, whereas an opposite conclusion has been reported from some other studies. It has been concluded that besides the effect of the group of drugs, there are differences in the action of particular drugs. The cardiovascular risk increase may be consequential to the anti-vasodilatory action due to blocking the ATP sensitive potassium channels on coronary arteries and the proarrhythmic action on the myocardium. Studies performed on animal myocardium models found glibenclamide to increase the risk of extrasystole, tachyarrhythmia and fibrillation in ischemic condi-

jabetičaru utvrdila je godišnju incidenciju zatajivanja srca od 4,4/100 dijabetičara liječenih preparatima sulfonilureje, u usporedbi s 3,3/100 dijabetičara liječenih metforminom, a rizik je bio ovisan o dozi (HR 1,38, 95 % CI 1,20 – 1,60)[33]. Prema opservacijskoj studiji u dijabetičara na kombiniranoj terapiji inzulinskim sekretagogima i metforminom, smrtnost je bila veća u skupini liječenoj glibenklamidom u odnosu prema skupinama liječenima repaglinidom, gliklazidom i glimepiridom[34]. Slične je rezultate dala i studija provedena na 107 806 dijabetičara, u kojoj je u skupinama liječenima glimepiridom, glipizidom, glibenklazidom ili tolbutamidom ukupna smrtnost bila veća negoli u bolesnika liječenih metforminom, dok se rezultati za gliklazid i repaglinid nisu statistički značajno razlikovali od skupine liječene metforminom[35]. Zbog nedostatka u dizajnu nekih od navedenih studija, nije jasno je li povećani kardiovaskularni rizik posljedica djelovanja preparata sulfonilureje ili je posrijedi bio protektivni učinak metformina[36,37].

Tijazolidindioni

Aktivacijom PPARγ receptora (engl. *peroxisome proliferator-activated receptor γ*) tijazolidindioni (TZD) (PPARγ agonisti) povećavaju inzulinsku osjetljivost skeletnih mišića i smanjuju jetrenu produkciju glukoze. Time povoljno djeluju na regulaciju glikemije, posebno u pretilih dijabetičara tipa 2[38]. Sami ne povećavaju rizik od hipoglikemije i imaju trajniji učinak od metformina i preparata sulfonilureje[39]. Nepovoljna okolnost kod TZD-a jest njihov "aldosteronski" učinak u distalnim i sabirnim bubrežnim kanalićima, gdje izazivaju reapsorpciju natrija i vode, povećavajući rizik od pojave edema i manifestnog ZS-a u dijabetičara s asimptomatskom disfunkcijom lijeve klijetke[2,24]. Metaanalize kliničkih ispitivanja rosiglitazona utvrdile su povećan rizik od svih makrovaskularnih događaja, posebno infarkta miokarda, u usporedbi s različitim komparatorima[8,9]. Rosiglitazon je u RECORD studiji znatno povećavao rizik od nefatalnog i fatalnog ZS-a, u *intent-to-treat* analizi za 110 % (p < 0,001), a u *per protocol + 30 days* analizi za 91 % (p = 0,013)[7]. EMA je stoga suspendirala rosiglitazon s europskoga tržišta, dok je na američkom tržištu upotreba rosiglitazona dopuštena pod određenim uvjetima.

Nasuprot rosiglitazonu, pioglitazon je pokazao povoljne učinke na prevenciju kardiovaskularnih događaja. U PROactive studiji pioglitazon je, u usporedbi s placebom, u visokorizičnih dijabetičara s makrovaskularnom bolešću smanjio kombinirani sekundarni ishod (ukupnu smrtnost, infarkt miokarda i moždani udar) za 16 % (p = 0,027)[40]. Znatno je smanjen i rizik u više pojedinačnih sekundarnih ishoda: od ponovnog moždanog udara za 47 % (p = 0,008), od ponovnoga akutnog koronarnog sindroma za 37 % (p = 0,035) i od ponovnog infarkta miokarda za 28 % (p < 0,045)[41,42]. U meta-analizi kardiovaskularnog rizika od TZD-a pioglitazon je, različito i suprotno od rosiglitazona, smanjivao rizik od svih makrovaskularnih događaja i infarkta miokarda, u usporedbi s komparatorima[9,43]. I FDA metaanaliza kliničkih ispitivanja pioglitazona pokazala je takav pozitivan učinak lijeka na smanjenje kardiovaskularnih događaja[44]. Zbog povećanog rizika od pojave edema i ZS-a pioglitazon u Europi nije dopušten u bolesnika sa ZS-om NYHA I. – IV. stupnja, a u SAD-u u NYHA III. – IV. stupnja. Povoljna je okolnost činjenica da u studijama pioglitazona nije bila riječ o fatalnom zatajivanju srca, dakle potions, whereas gliclazide had protective action in baseline and ischemic conditions[30-32]. A retrospective cohort study including 5631 diabetic patients found an annual incidence of heart failure of 4.4/100 diabetic patients treated with sulfonylureas versus 3.3/100 diabetic patients on metformin; the risk was dose dependent [hazard ratio (HR) 1.38; 95% confidence interval (CI) 1.20-1.60][33]. According to the observational study in diabetic patients on combined therapy with insulin secretagogues and metformin, mortality was higher in the glibenclamide group as compared with the groups on repaglinide, gliclazide or glimepiride[34]. Similar results have also been reported from a study in 107,806 diabetic patients, where total mortality was higher in the groups treated with glimepiride, glipizide, glibenclamide or tolbutamide as compared with those on metformin, but there was no statistically significant difference for gliclazide and repaglinide groups in comparison with metformin group[35]. As some of these studies suffered from certain drawbacks in design, it is not clear whether the increased cardiovascular risk was a consequence of sulfonylurea action or there was a protective effect of metformin[36,37].

Thiazolidinediones

Thiazolidinediones (TZD, PPARγ agonists) increase insulin sensitivity of skeletal muscle and reduce hepatic glucose production through activation of the peroxisome proliferator-activated receptor γ (PPARγ), thus acting favorably on glycemic regulation, in obese DMT2 patients in particular[38]. These agents do not increase the risk of hypoglycemia and have longer action than metformin and sulfonylureas[39]. An unfavorable property of TZD is their 'aldosterone' effect in distal and collecting tubules of the kidney, where they cause sodium and water reabsorption, thus increasing the risk of edema and manifest heart failure in diabetic patients with asymptomatic left ventricular dysfunction[2,24]. Meta-analyses of clinical trials with rosiglitazone found an increased risk of all macrovascular events, myocardial infarction in particular, in comparison with various comparators[8,9]. In the RECORD study, rosiglitazone increased the risk of nonfatal and fatal heart failure significantly, i.e. in the intent-to-treat analysis by 110% (p<0.001) and in the per-protocol + 30 days analysis by 91% (p=0.013)[7]. Therefore, EMA suspended rosiglitazone from the European market, whereas on the US market the use of rosiglitazone is approved under a special prescription program.

In contrast to rosiglitazone, pioglitazone showed beneficial effects on preventing cardiovascular events. In the PROactive study, pioglitazone in comparison with placebo reduced the combined secondary outcome (total mortality, myocardial infarction and stroke) in high-risk diabetic patients with macrovascular disease by 16% (p=0.027)[40]. The risk of several isolated secondary outcomes was also reduced significantly, as follows: stroke by 47% (p=0.008); recurrent acute coronary syndrome by 37% (p=0.035); and myocardial reinfarction by 28% (p<0.045)[41,42]. In a meta-analysis of the cardiovascular risk of TZD, unlike rosiglitazone, pioglitazone reduced the risk of all macrovascular events and myocardial infarction in comparison with comparators[43]. The FDA meta-analysis of clinical trials of pioglitazone also demonstrated the beneficial effect of this drug on cardiovascular event reduction[44]. Due to the increased risk of edema and heart failure, pioglitazone is not allowed for use in patients with NYHA grade I-IV heart failure in Europe and in those with NYHA grade III-IV in the USA. In favor of pioglitazone, it should

većanju smrtnosti, te da se pojava edema mogla dobro kontrolirati diuretskom terapijom. Osim u PROactive studiji, pozitivni terapijski učinci pioglitazona opisani su i u nekoliko manjih kliničkih ispitivanja sa surogatnim ciljevima. U QUARTET studiji monoterapija pioglitazonom bila je superiorna u odnosu prema terapiji gliklazidom po boljoj regulaciji glikemije natašte, rjeđoj pojavi hipoglikemije te povoljnijem učinku na trigliceride, HDL kolesterol i omjer ukupni kolesterol/HDL[45]. U CHICAGO studiji pioglitazon je prevenirao progresiju karotidne ateroskleroze mjerenu IMT-om (engl. *intima/media thickness*), ali ne i komparator glimepirid[46]. Slično antiaterosklerotsko djelovanje pioglitazona u prevenciji koronarne ateroskleroze, u usporedbi s glimepiridom, nađeno je i u PERISCOPE studiji, u kojoj je progresija koronarnih plakova analizirana IVUS-om (engl. *intravascular ultrasound*)[47]. Iako je bila riječ o manjim studijama sa surogatnim ciljevima, ukupni rezultati svih kliničkih ispitivanja pioglitazona potvrđuju važno mjesto lijeka u liječenju dijabetičara tipa 2, posebno preuhranjenih, u kojih periferna inzulinska rezistencija ima važnu patofiziološku ulogu[48]. Fiksna kombinacija metformin-pioglitazon u takvih je bolesnika odličan terapijski izbor, osim u bolesnika sa znatno oštećenom bubrežnom funkcijom i ZS-om NYHA I. – IV. stupnja.

Inhibitori dipeptidil-peptidaze 4 (DPP-4 inihibitori)

Riječ je o novijoj skupini antidijabetika koji smanjuju razinu glukoze u krvi inaktivacijom enzima dipeptidil-peptidaze 4. Inhibicija tog enzima smanjuje razgradnju inkretina, što povećava izlučivanje inzulina, smanjuje lučenje glukagona i usporuje pražnjenje želudca. DPP-4 inhibitori djeluju povoljno na têk, imaju neutralan učinak na tjelesnu težinu i sami ne izazivaju hipoglikemiju. Prvi lijek iz skupine DPP-4 inhibitora jest sitagliptin, a ostali su lijekovi iz skupine vildagliptin, linagliptin, omarigliptin i alogliptin, od kojih su neki još u fazama razvoja ili istraživanja[49]. Kardiovaskularni učinci DPP-4 inhibitora u visokorizičnih dijabetičara tipa 2 istraženi su u trima velikim randomiziranim studijama (alogliptin u EXAMINE, saxagliptin u SAVOR-TIMI 53 i sitagliptin u TECOS), a nekoliko je sličnih velikih studija u tijeku (linagliptin u CAROLINA i CARMELINA, omarigliptin u MK-3102-015 AM1 i MK-3102-018) (**slika 2**)[49-52]. U velikom, dobro dizajniranom, placebom kontroliranom EXAMINE istraživanju, alogliptin nije povećavao rizik od velikih kardiovaskularnih događaja u dijabetičara tipa 2 s nedavno preboljelim akutnim koronarnim sindromom (AKS < 90 dana od randomizacije). Opisan je trend smanjenja kardiovaskularne smrtnosti, ali nije bio statistički značajan[49-51]. Rezultati EXAMINE, SAVOR-TIMI 53 i TECOS potvrđuju kardiovaskularnu sigurnost DPP-4 inhibitora, koji ni u jednoj od spomenutih triju studija nisu niti smanjivali niti povećavali učestalost velikih kardiovaskularnih događaja (engl. *major cardiovascular events*, MACE)[49].

Ipak, u SAVOR-TIMI 53 istraživanju u skupini liječenoj saxagliptinom opisan je neočekivan znatan porast hospitalizacija zbog ZS-a od 27 % (p = 0,007)[52]. Nedavna metaanaliza nije našla razlike u MACE i ukupnoj smrtnosti usporedbom DPP-4 inhibitora s placebom, ali je učestalost ZS-a zbog liječenja DPP-4 inhibitorima bila 16 % veća (p = 0,04)[53]. Na sličan porast ZS-a upozorila je i jedna druga metaanaliza kardiovaskularne si-

be noted that those pioglitazone studies did not involve fatal heart failure, i.e. there was no mortality increase, while the occurrence of edema could be well controlled by diuretic therapy. Besides the PROactive study, favorable therapeutic effects of pioglitazone have also been reported from a number of small clinical trials with surrogate endpoints. In the QUARTET study, pioglitazone monotherapy proved superior to gliclazide in regulating fasting glycemia, less frequent hypoglycemia and better effect on triglycerides, high density lipoprotein (HDL) cholesterol and total cholesterol/HDL cholesterol ratio[45]. In the CHICAGO study, pioglitazone, but not the comparator glimepiride, prevented progression of carotid atherosclerosis as measured by the intima/media thickness (IMT)[46]. A similar anti atherosclerotic action of pioglitazone in comparison with glimepiride in the prevention of coronary atherosclerosis was found in the PERISCOPE study, in which the progression of coronary plaques was analyzed by intravascular ultrasound (IVUS)[47]. Although these were small trials with surrogate endpoints, the overall results of all clinical trials of pioglitazone have confirmed the importance of this agent in the management of DMT2 patients, those overweight in particular, where peripheral insulin resistance has a major pathophysiological role[48]. A fixed combination of metformin and pioglitazone is an excellent therapeutic choice in these patients, with the exception of those with seriously damaged renal function and NYHA grade I-IV heart failure.

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

These are a newer group of antidiabetic drugs that decrease the level of blood glucose by inactivating the dipeptidyl peptidase-4 (DPP-4) enzyme. Inhibition of this enzyme reduces incretin breakdown, thus increasing insulin secretion, decreasing glucagon secretion and slowing down gastric emptying. DPP-4 inhibitors act favorably on appetite, have neutral effect on body weight, and do not cause hypoglycemia. The first drug from the group of DPP-4 inhibitors is sitagliptin, and the others are vildagliptin, linagliptin, omarigliptin and alogliptin, some of these still in the phase of development or research[49]. Cardiovascular effects of DPP-4 inhibitors in high-risk DMT2 patients have been investigated in three large randomized studies (alogliptin in EXAMINE, saxagliptin in SAVOR-TIMI 53, and sitagliptin in TECOS), while a number of similar studies are just being under way (linagliptin in CAROLINA and CARMELINA, and omarigliptin in MK-3102-015 AMI and MK-3102-018) (**Figure 2**)[49-52]. In the large, well designed, placebo-controlled EXAMINE study, alogliptin did not increase the risk of major adverse cardiovascular events (MACE) in DMT2 patients with recent acute coronary syndrome (<90 days of randomization). A decreasing trend of cardiovascular mortality is described, however, without reaching statistical significance[49-51]. Results of the EXAMINE, SAVOR-TIMI 53 and TECOS studies confirm cardiovascular safety of DPP-4 inhibitors, which neither reduced nor increased the prevalence of MACE in these three studies[49].

However, in the SAVOR-TIMI 53 study, an unexpected and significant 27% (p=0.007) increase in the rate of hospitalizations for heart failure was recorded in the group of patients on saxagliptin[52]. A recent meta-analysis found no differences in MACE and total mortality between DPP-4 inhibitors and placebo but the prevalence of heart failure was by 16% greater (p=0.04) in the group of patients on DPP-4 inhibitors[53]. Another meta-analysis of cardiovascular safety of DPP-4 inhibitors has also pointed to a comparable increase in the

gurnosti DPP-4 inhibitora[54]. U EXAMINE ispitivanju u skupini liječenoj alogliptinom trend porasta hospitalizacija zbog ZS-a od 19 % nije bio značajan (p = NS)[51], a kasnija *post-hoc* analiza nije našla razlike između alogliptina i placeba u kombiniranom ishodu hospitalizacija zbog zatajivanja srca i kardiovaskularnoj smrtnosti[55]. Sitagliptin u TECOS studiji nije povećavao ZS, a ovakvu razliku u učestalosti ZS-a u usporedbi s drugim ispitivanjima DPP-4 inhibitora moguće je objasniti razlikama u osobinama uključenih ispitanika, ostaloj terapiji, definiciji i registraciji ZS-a, intrinzičnim farmakološkim razlikama među različitim DPP-4 inhibitorima ili mogućoj čistoj slučajnosti[56].

U svakom slučaju, apsolutni je rizik od ZS-a kod DPP-4 inhibitora nizak, povezan i s drugim često rabljenim lijekovima (derivatima sulfonilureje i tijazolidindionima) te još uvijek kontroverzan. Rezultati velikih randomiziranih studija u tijeku (CAROLINA, CARMELINA, MK-3102-015 AM1, MK-3102-018) i budućih kliničkih istraživanja sigurno će pridonijeti još boljem razumijevanju kardiovaskularnih učinaka i sigurnosti DPP-4 inhibitora[49].

SGLT2 inhibitori (gliflozini)

SGLT2 inhibitori (engl. *subtype 2 sodium-glucose transport (SGLT-2) inhibitors*) relativno su nova skupina oralnih antihiperglikemika i nema mnogo podataka o njihovoj kardiovaskularnoj sigurnosti. SGLT2 je transmembranski protein koji obavlja o natriju ovisnu reapsorpciju glukoze i odgovoran je za oko 90 % ukupne reapsorpcije glukoze u proksimalnom bubrežnom tubulu. Njegovom inhibicijom navedena skupina lijekova potiče bubrežnu ekskreciju glukoze i na taj način smanjuje hiperglikemiju, povećava poželjni ukupni kalorijski deficit, potiče osmotsku diurezu i snizuje arterijski tlak, smanjujući time kardiovaskularni rizik. Učinkovitost SGLT2 inhibitora ispitivana je u nekoliko studija. U CANTATA-SU studiji na 1452 dijabetičara kojima metforminom nije postignuta zadovoljavajuća regulacija glikemije (prosječna vrijednost HbA1c 7,8 %), uspoređivana je učinkovitost dodanog kanagliflozina u dozi od 100 mg ili 300 mg s glimepiridom (prosječna doza 5,6 mg). Redukcija HbA1c u obje skupine s kanagliflozinom bila je slična s glimepiridom, nešto bolja u liječenih većom dozom kanagliflozina (0,81 % ili 0,82 %, odnosno 0,93 %). Uočen je povoljan učinak kanagliflozina na smanjenje tjelesne težine (-4,2 do -4,4 kg) u usporedbi s glimepiridom (+0,8 kg), ali uz veću učestalost gljivičnih infekcija spolnih organa[57]. U metaanalizi koja je uključivala podatke 2313 dijabetičara, od toga 1332 na antihipertenzivnoj terapiji, u usporedbi s placebom kanagliflozin je u dozi od 100 mg prosječno smanjio sistolički tlak za 4,3 mmHg, a u dozi od 300 mg za 5,0 mmHg. Odgovarajuće sniženje dijastoličkoga tlaka iznosilo je 2,5 i 2,4 mmHg (0,6 mmHg na placebu). Veće sniženje arterijskoga tlaka postignuto je u skupini hipertoničara negoli u normotenzivnih dijabetičara[58].

U EMPA-REG OUTCOME studiji analizirana je kardiovaskularna sigurnost empagliflozina tijekom prosječno 3,1 godine liječenja. Primarni složeni ishod sastojao se od kardiovaskularne smrtnosti, nefatalnog infarkta miokarda i moždanog udara. Empagliflozin je bio superioran u usporebi s placebom u smanjenju primarnog ishoda (10,5 % prema 12,1 %, HR 0,86% CI 0,74-0,99, p = 0,0382). U analizi pojedinačnih ishoda empa-

rate of heart failure[54]. In the EXAMINE study, the 19% increase in hospitalizations for heart failure recorded in the group of patients on alogliptin was not statistically significant (p=NS) and subsequent post-hoc analysis revealed no difference between alogliptin and placebo in the combined endpoint of hospitalization for heart failure and cardiovascular mortality[55]. In the TECOS study, sitagliptin did not increase the rate of heart failure; this variation from other studies with DPP-4 inhibitors in the prevalence of heart failure could be explained by differences in the characteristics of study populations, other therapies, definition and recording of heart failure, intrinsic pharmacological differences among particular DPP-4 inhibitors, or just as mere coincidence[56].

Anyway, the absolute risk of heart failure with DPP-4 is low, associated with other frequently taken drugs (sulfonylurea derivatives and thiazolidinediones) and still a controversial issue. Results of the large randomized studies that are under way (CAROLINA, CARMELINA, MK-3102-015 AMI and MK-3102-018) and future clinical trials will certainly contribute to better understanding of the cardiovascular effects and safety of DPP-4 inhibitors[49].

Subtype 2 Sodium-Glucose Transport (SGLT-2) Inhibitors (Gliflozines)

Subtype 2 sodium-glucose transport (SGLT-2) inhibitors are a relatively novel group of oral antihyperglycemics, so as yet there are little data on their cardiovascular safety. SGLT-2 is a transmembrane protein performing sodium dependent glucose reabsorption and is responsible for about 90% of overall glucose reabsorption in proximal renal tubule. This new group of drugs stimulate renal excretion of glucose by inhibiting this protein activity, thus reducing hyperglycemia, increasing desirable total calorie deficit, stimulating osmotic diuresis and lowering arterial pressure, thus eventually reducing the cardiovascular risk. The efficacy of SGLT-2 inhibitors has been investigated in a number of studies. In the CANTATA-SU study, which included 1452 diabetic patients that failed to achieve satisfactory glycemia control on metformin (mean HbA1c 7.8%), the efficacy of add-on canagliflozin in a dose of 100 mg or 300 mg was compared with glimepiride (mean dose 5.6 mg). In both canagliflozin groups, HbA1c reduction was similar to that recorded with glimepiride, and was somewhat better in the group on a higher dose of canagliflozin (0.81% and 0.82%, respectively, vs. 0.93%). Canagliflozin had a beneficial effect on weight loss (-4.2 to -4.4 kg) as compared with glimepiride (+0.8 kg), but with a higher prevalence of genital fungal infections[57]. According to a meta-analysis that included data on 2313 diabetic patients, 1332 of them on antihypertensive therapy, canagliflozin in doses of 100 mg and 300 mg decreased systolic blood pressure by a mean of 4.3 mm Hg and 5.0 mm Hg, respectively, in comparison with placebo. The respective diastolic blood pressure decrease was 2.5 mm Hg and 2.4 mm Hg versus 0.6 mm Hg on placebo. Greater arterial pressure decrease was recorded in the group of hypertensive than in normotensive diabetic patients[58].

The EMPA-REG OUTCOME study assessed cardiovascular safety of empagliflozin during a mean 3.1-year treatment. The primary composite endpoint consisted of cardiovascular mortality, nonfatal myocardial infarction and stroke. Empagliflozin was superior to placebo in primary outcome reduction [10.5% vs. 12.1%; hazard ratio (HR) 0.86; 95% confidence interval (CI) 0.74-

gliflozin je znatno smanjio kardiovaskularnu smrtnost za 38 % (p < 0,0001), hospitalizacije zbog zatajivanja srca za 35 % (p = 0,0017) i ukupnu smrtnost za 32 % (p < 0,0001)[59].

Metaanaliza 21 studije faze 2b i 3 istraživala je utjecaj dapagliflozina na MACE. Nakon stratifikacije bolesnika prema dodatnim čimbenicima rizika za MACE, zaključeno je da dapaglifozin ne povećava rizik od MACE u skupini dijabetičara bez dodatno povećanog kardiovaskularnog rizika (HR 0,77, CI 0,54 – 1,10) ni u skupini bolesnika s dodatno povećanim kardiovaskularnim rizikom (HR 0,80, CI 0,52 – 1,22)[59].

U tijeku je nekoliko studija o kardiovaskularnoj sigurnosti i učinkovitosti SGLT2 inihibitora (REFORM, CANVAS, CREDENCE, DECLARE-TIMI 58) (**slika 2**.)[61-64].

Moguće nuspojave gliflozina jesu hipoglikemija, češće u populaciji dijabetičara liječenih kombinacijom gliflozina i preparata sulfonilureje ili inzulinom, pogoršanje bubrežne funkcije, ortostatska hipotenzija i genitourinarne infekcije. Zabilježeno je i nekoliko slučajeve urosepse i euglikemijske ketoacidoze. Zbog toga su FDA u svibnju 2015. i EMA u srpnju 2015. godine izdale posebno upozorenje. Naime, SGLT2 je eksprimiran na α-stanicama Langerhansovih otoka te njegova inhibicija potiče sekreciju glukagona, a moguća je i inhibicija transportera za ketone u bubregu, što može povećati ketonska tijela u krvi[65]. Rizik od ketoacidoze veći je u bolesnika liječenih kombinacijom gliflozina i metformina. SGLT2 inhibitori se ne preporučuju kod eGFR-a < 60 mL/min/1,73 m^2. Ako vrijednost eGFR-a nakon uvođenja lijeka padne na manje od 60, dozu treba smanjiti, a kod eGFR-a < 45 lijek treba ukinuti. Upotrebu gliflozina u bolesnika sa ZS-om ograničava upotreba diuretika i antagonista mineralokortikoidnih receptora zbog povećanog rizika od ortostatske hipotenzije, pogoršanja bubrežne funkcije i hiperkalijemije[65].

0.99; p=0.0382]. Analysis of particular outcomes revealed empagliflozin to have significantly decreased cardiovascular mortality by 38% (p<0.0001), rate of hospitalization for heart failure by 35% (p=0.0017) and total mortality by 32% (p<0.0001)[59].

A meta-analysis of 21 phase 2b and 3 studies investigated the effect of dapagliflozin on MACE. Upon patient stratification for additional risk factors for MACE, it was concluded that dapagliflozin did not increase the risk of MACE either in diabetic patients without [hazard ratio (HR) 0.77; 95% confidence interval (CI) 0.54-1.10] or with additionally increased cardiovascular risk [hazard ratio (HR) 0.80; 95% confidence interval (CI) 0.52-1.22][60].

A number of studies on cardiovascular safety and efficacy of SGLT2 inhibitors are just being under way (REFORM, CANVAS, CREDENCE, and DECLARE-TIMI 58) (**Figure 2**)[61-64].

The possible side effects of gliflozin include hypoglycemia (more frequently in the population of diabetic patients treated with a combination of gliflozin and sulfonylureas or insulin), renal function worsening, orthostatic hypotension and urogenital infections. Several cases of urosepsis and euglycemic ketoacidosis have also been described. Therefore, a specific warning was issued by FDA in May 2015 and by EMA in July 2015. Namely, SGLT2 was expressed on α cells of the islands of Langerhans and its inhibition stimulates glucagon secretion; the more so, ketone transporters in the kidney may also be inhibited, which would increase the level of ketone bodies in the blood[65]. The risk of ketoacidosis is greater in patients treated with a combination of gliflozin and metformin. SGLT2 inhibitors are not recommended at eGFR <60 mL/min/1.73 m^2. If eGFR falls below 60 upon drug introduction, the dose should be decreased and at eGFR <45 the drug should be discontinued. In patients with heart failure, the use of gliflozin is limited by the use of diuretics and mineralocorticoid receptor antagonists due to the higher risk of orthostatic hypotension, renal function impairment and hyperkalemia[65].

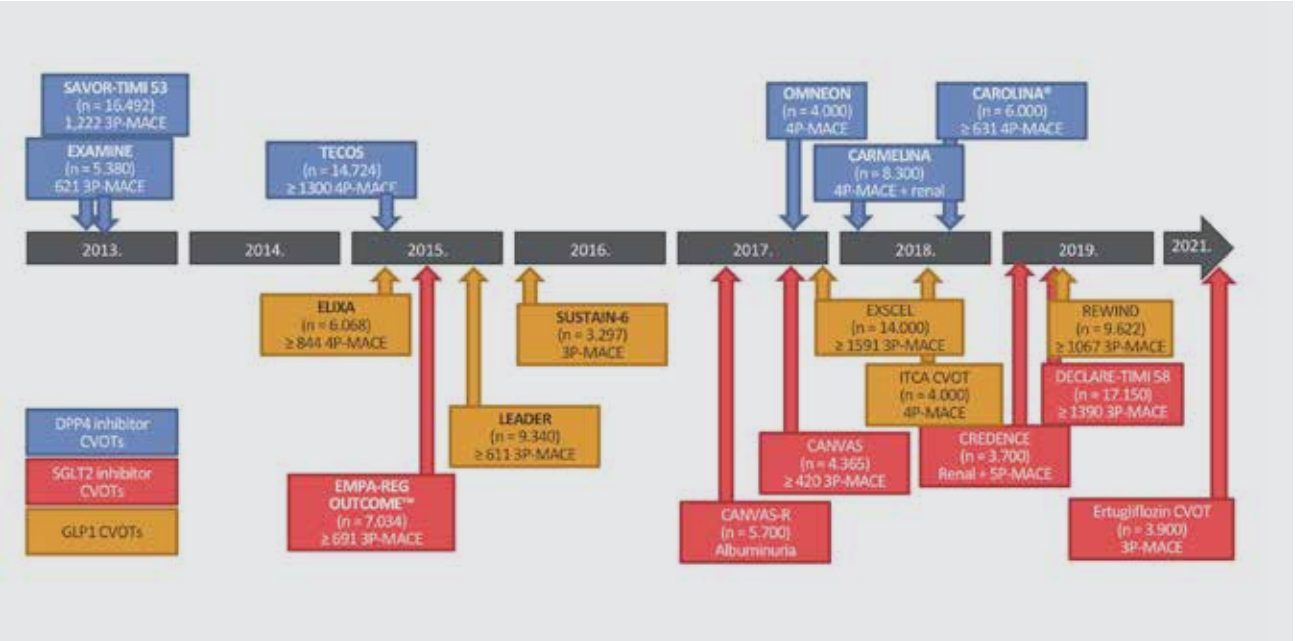

FIGURE 2. Overview of cardiovascular outcome trials (CVOTs) of glucose-lowering drugs.

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