Pregledni rad / Review article

Kardiovaskularni učinci oralnih lijekova za liječenje šećerne bolesti tipa 2

Cardiovascular effects of oral medications in the treatment of type 2 diabetes

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SAŽETAK: Šećerna bolest (DM) je u porastu u cijelom svijetu. Više od 90% pacijenata boluje od DM tipa 2. Najeći dio oboljelih od DM tipa 2 liječi se peroralnim lijekovima. Osim snižavanja glikemije lijekovi za liječenje DM mogu imati ili izravne učinke na srčanožilni sustav ili djelovanje na kardiovaskularne čimbenike rizika. Primjena sulfonil urea i tiazolindindiona pobuđuje najviše pozornosti radi potencijalnog negativnog učinka na povećani rizik smrti, odnosno popuštanja srca. S druge strane, navode se povoljni plejotropni i metabolički učinci pioglitazona i metformina. Repaglinid primijenjen s metforminom može povećati kardiovaskularni rizik, iako ima i pozitivno djelovanje na sniženje upalnih citokina. Inhibitori dipeptidil peptidaze 4 ne povećavaju kardiovaskularne rizike i poboljšavaju metaboličke varijable.

KLJUČNE RIJEČI: peroralni hipoglikemici, kardiovaskularni rizici, sulfonil urea, metformin, tiazolidindioni.

SUMMARY: Diabetes mellitus (DM) is in rise worldwide. More than 90% of patients suffer from type 2 DM. The majority of patients suffering from type 2 DM are treated with oral medications. In addition to lowering glycemia, the medications for treatment of DM may either have direct effects on the cardiovascular system or the effects on cardiovascular risk factors. The administration of sulfonylurea and thiazolidinedione attracts the most attention because of the potential negative impact on the increased risk of death or heart failure. On the other hand, better pleiotropic and metabolic effects of pioglitazone and metformin are known. Repaglinide administered with metformin may increase the cardiovascular risk, although it has a positive effect on lowering inflammatory cytokines. Dipeptidyl peptidase-4 inhibitors do not increase cardiovascular risks, and they improve metabolic variables.

KEYWORDS: oral hypoglycemics, cardiovascular risks, sulfonylurea, metformin, thiazolidinediones.

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Uvod

Šećerna bolest (DM) i njezine kronične komplikacije su veliki svjetski zdravstveni problem i u cijelom svijetu su u velikom porastu. Smatra se da trenutno u svijetu 366 milijuna ljudi boluje od DM, a do 2030. godine broj dijabetičara će se povećati na 552 milijuna. Broj oboljelih od DM povećava se u svim državama, a 80% posto svjetske populacije dijabetičara živi u zemljama u razvoju ili novoindustrijaliziranim zemljama[1].

Prevalencija DM u Hrvatskoj u dobnoj skupini između 18-65 godina iznosi 6,1%. Ukupan broj osoba s DM u 2010. godini iznosio je približno 316.000 od čega nešto preko 190.000 bolesnika ima otkrivenu bolest, dok ih je gotovo 123.000 neotkriveno.[2]

U nedavno objavljenom radu[3] vidljivo je da preko 90% pacijenata s DM koji se liječe u Centru za dijabetes Bjelovarsko-bilogorske županije boluje od tipa 2. Daleko najviše pacijenata liječeno je oralnim lijekovima (43%). Oralna sredstva s inzulinom uzima 38% pacijenata, a samo inzulinom bilo je liječeno 15% bolesnika. Prema smjernicama Hrvatskog dija-

Introduction

Diabetes mellitus (DM) and its chronic complications are the major world health problem having a rising trend in the whole world. It is believed that currently 366 millions of people suffer from DM worldwide, and by the year 2030 the number of diabetics will increase to 552 million. The number of patients with DM rises in all countries and 80% percent of the world's population suffering from diabetes live in developing countries or newly industrialized countries.[1]

The prevalence of DM in Croatia in the age group between 18-65 years is 6.1%. The total number of persons suffering from DM in 2010 was approximately 316,000, of whom over 190,000 patients have the disease discovered, while nearly 123,000 have the disease undiscovered.[2]

The recently published paper shows[3] that over 90% of patients with DM treated at the Center for Diabetes in the Bjelovar-Bilogora County suffer from type 2 of DM. The greatest number of patients was treated with oral medications (43%). 38% of patients take oral agents and insulin and 15% of patients were treated only by insulin. According to the guide-

betološkog društva metformin (Glucophage®, Aglurab®, Siofor®, Belformin®, Gluformin®) je odmah uključen, uz promjene životnog stila, u liječenje DM tipa 2[4,5]. Smjernice također navode da se u slučaju nepostizanja ciljeva liječenja nakon 3 do 6 mjeseci (a "dohvatljivost" opće proklamiranih ciljeva liječenja treba individualizirati za svakog pacijenta ponaosob) kao druga linija terapije mogu propisati i sulfonil urea (Diaprel MR®, Gliclada®, Glica®, Amaryl®, Dibiglim®, Diapirid®, Glimepirid PharmaS®, Glibenclamid Genericon®, Glurenorm®), repaglinid (Novonorm®, Reglinid®, Repaglinid PharmaS®), pioglitazon (Pioglitazon Pliva®), inhibitori dipeptidilpeptidase 4 (Januvia®, Galvus®, Trajenta®), blokatori alfa glukoidaze-akarboza (Glucobay®) ili čak GLP-1 analozi (eng. glucagone like peptide 1; Byetta®, Victosa®) koji više ne pripadaju u jeftinu terapiju[5]. Jednako tako u smjernicama se navode kontroverze o kardiovaskularnim rizicima pri primjeni peroralnih lijekova za liječenje šećerne bolesti.[5] To pobuđuje potrebu za racionalnom primjenom tih medikamenata u kardiovaskularnih bolesnika.

Kardiovaskularni događaji pri primjeni sulfonil urea

Kombinacija metformina i sulfonil uree je relativno česta kombinacija u liječenju DM tipa 2. Ovom kombinacijom postiže se sniženje vrijednosti Hba1c za 1,3%.[5] Podaci o povećanoj smrtnosti radi kardiovaskularnih događaja pri primjeni ove kombinacije lijekova su kontroverzni.[5] U talijanskoj opservacijskoj studiji u ispitanika liječenih metforminom i glibenklamidom registrirana je znatno viša stopa smrtnosti (8,7%) u odnosu na skupinu u kojoj je metformin kombiniran s repaglinidom (3,1%), gliklazidom (2,1%) i glimepiridom (0,4%).[6]

S druge strane u kanadskoj studiji *Juurlink i sur* uspoređivani su kardiovaskularni događaji u starijih pacijenata liječenih ili glibenklamidom (starija generacija sulfonil uree, 1.690 pacijenata) odnosno gliklazidom (novija generacija sulfonil uree, 984 pacijenta) tijekom 2 godine. Među starijim pacijentima hospitaliziranima radi akutnog infarkta miokarda ili perkutane koronarne intervencije uporaba glibenklamida u usporedbi s gliklazidom nije bila povezana s povećanim kardiovaskularnim rizicima.[7]

U literaturi se navodi podatak da sulfonil uree inhibirajući kalijeve ATP kanale povećavaju rizik smrti i popuštanja srca u pacijenata s akutnim koronarnim sindromom. Studija *Nagendran i sur* proučavajući baze podataka pacijenata s koronarnim sindromom, nije pronašla povećani rizik od smrti ili zatajivanja srca.[8] Metaanaliza talijanskih autora koja je proučavala velike kardiovaskularne događaje u dijabetičara liječenih sulfonil ureama u 115 studija pronašla je veću incidenciju moždanih udara u pacijenata s DM liječenih sulfonil ureama, no istodobno nije bila registrirana povećana opća incidencija velikih kardiovaskularnih događaja.[9]

Intenzivna kontrola glikemije upotrebom gliklazida u studiji ADVANCE10 uz redukciju Hba1c za 6,5% polučila je 10% smanjenje makro- i mikrovaskularnih događaja i 21% smanjenje broja dijabetičkih nefropatija. Ovaj efekt gliklazida dijelom se pripisuje i njegovim antioksidativnim svojstvima.[10]

Izvješće o 15 studija koje je analiziralo utjecaj sulfonil urea na kardiovaskularne događaje nije registriralo povećanje incidencije kardiovaskularnih događaja.[11]

lines of the Croatian Diabetes Association, metformin (Glucophage®, Aglurab®, Siofor®, Belformin®, Gluformin®) was immediately included in the treatment of type 2 DM, accompanied by changes in a life style.[4,5] The guidelines also suggest that in the case of failure to meet the objectives of treatment after 3-6 months ("reachability" of generally stated goals of treatment should be individualized for each patient), sulfonylurea (Diaprel MR®, Gliclada®, Glica®, Amaryl®, Dibiglim®, Diapirid®, Glimepirid PharmaS®, Glibenclamid Genericon®, Glurenorm®), repaglinid, (Novonorm®, Reglinid®, Repaglinid PharmaS®), pioglitazone (Pioglitazone Pliva®), dipeptidyl peptidase-4 inhibitors (Januvia®, Galvus®, Trajenta®), alpha-glucosidase-inhibitors acarbose (Glucobay®) or even glucagone like peptide-1 analogue (Byetta®, Victosa®) could be prescribed as the second line therapy, drugs that can no longer be inexpensive therapy[5]. Also, the guidelines suggest controversies about the cardiovascular risks in using oral medications for the treatment of diabetes.[5] This urges us to be rational in prescribing these medications to cardiovascular patients.

Cardiovascular events when using sulfonyl urea

The combination of metformin and the sulfonylurea is a relatively common combination in the treatment of type 2 DM. This combination lowers the value of Hba1c by 1.3%.[5] Data on increased mortality for cardiovascular events while administering this combination of drugs is controversial.[5] The Italian observational study in subjects treated with metformin and glibencamide showed a significantly higher mortality rate (8.7%) compared to the group receiving metformin combined with repaglinide (3.1%), gliclazide (2.1%) and glimepiride (0.4%).[6]

The Canadian study by *Juurlink et al.* compared the cardiovascular events in elderly patients treated with either glibencamide (older generation with sulfonylurea, 1,690 patients) or gliclazide (the more recent generation of sulfonylurea, 984 patients) for 2 years' period. Among elderly patients hospitalized for acute myocardial infarction or percutaneous coronary intervention, the administration of glibenclamide compared with gliclazide was not associated with an increased cardiovascular risk.[7]

The literature notes that inhibiting ATP-sensitive potassium channels, sulfonylureas increase the risk of death and heart failure in patients with acute coronary syndrome. The Study Nagendran et al studying a database of patients with coronary syndrome, found no increased risk of death or heart failure.[8] Meta-analysis of the Italian authors that studied major cardiovascular events in diabetic patients treated with sulfonylurea in 115 studies found a higher incidence of strokes in patients with DM treated with sulfonylurea, thereby not recording an increased overall incidence of major cardiovascular events at the same time.[9]

Intensive glycemic control using gliclazide in the study ADVANCE10 with reduction of HbA1c by 6.5% yielded a 10% reduction in macro- and microvascular events and 21% reduction in the number of diabetic nephropathies. This effect of gliclazide is partly attributed to its antioxidant properties.[10]

The report on 15 studies that analyzed the impact of sulfonylurea in cardiovascular events did not record an increase in the incidence of cardiovascular events.[11]

Učinci metformina na miokard u ishemiji

Metformin, lijek iz dugo poznate skupine bigvanida, danas se smatra temeljem medikamentoznog liječenja DM tipa 2. Stoga je u hrvatskim, kao i svim međunarodnim smjernicama za liječenje DM tipa 2 preporučena njegova uporaba odmah nakon otkrivanja bolesti, ravnopravno s promjenama životnog stila i prehrane.[5]

U bolesnika liječenih metforminom, već nakon šest mjeseci liječenja, uočeno je znatno manje makrovaskularnih komplikacija DM kao što su koronarni incidenti, moždani udari ili smrti povezanih s DM.[12] Kao i svaki lijek, metformin ima kontraindikacije. Ne smije se primijeniti u bolesnika s klirensom kreatinina manjim od 60 ml/min, teškim zatajenjem jetre, u alkoholičara, bolesnika s upalom gušterače te svim hipoksičnim stanjima koja uključuju zatajivanje srčane funkcije, zatajenje respiratorne funkcije te teške smetnje periferne cirkulacije (gangrena).[5]

Potencijalni negativni učinak metformina na preraštavanje endotelom stentova koji otpuštaju lijekove nakon koronarne intervencije opisan je u radu *Habib i sur*. Uočeno je da metformin i mTOR (eng. mammalian target of rapamycin) inhibitori (sirolimus) koji se koriste u stentovima koji otpuštaju lijekove imaju suprotne molekularne učinke. To utječe na oporavak endotela nakon koronarne intervencije S6K (eng. ribosomal S6 kinase) ovisnim mehanizmom. Bolesnici koji koriste metformin i dobili su stent s mTOR inhibitorom, potencijalno su u većem riziku od odgođene endotelizacije krvne žile i imaju veći rizik tromboze stenta.[13]

Pretkliničke studije pokazale su da metformin ograničava ishemiju miokarda i djeluje na reperfuziju, neovisno o svom utjecaju na razinu glukoze. Ovaj kardioprotektivni učinak je posredovan aktivacijom RISK (eng. Reperfusion Injury Salvage Kinase) metaboličkog puta i povećanim stvaranjem adenozina.14 Primjena metformina potencijalno može poboljšati ishod kardiovaskularnog događaja čak i u pacijenata koji nemaju DM.[14] Studija na animalnom modelu (štakorima) koji su kronično dobivali 300 mg metformina dnevno pokazala je da primjena metformina pojačava otpornost miokarda na ishemijsku ozljedu, mehanizmom neovisnim o smanjenju glukoze. To pokazuje pozitivan efekt metformina na strukturu mitohondrija koji je posredovan aktivacijom AMPK (eng. AdenosinMonoPhosphate-activated protein kinase) metaboličkog puta.[15] Nalazi studija koji upućuju da metformin ograničava veličinu infarkta miokarda, sugeriraju da pacijenti koji pate od ishemije miokarda mogu imati koristi od primjene metformina, čak iako nemaju DM.[16]

Pioglitazonska kontroverza

Inzulinska rezistencija je temeljni patogenetski poremećaj u DM tipa 2. Poboljšanje inzulinske osjetljivosti može se postići primjenom lijekova koji imaju utjecaj na genetske mehanizme. To su tiazolidindioni (glitazoni)-PPAR-gamma ligandi, na našem tržištu pioglitazon. Glitazoni su aktivatori nuklearnoga transkripcijskog čimbenika (eng. peroxysome proliferator-activated receptor gamma, PPAR-gamma) koji reguliraju transkripciju inzulin odgovornih gena uključenih u kontrolu stvaranja nosača utilizacije glukoze te metabolizma masti. Radi svog mehanizma djelovanja, jedna od najznačajnijih nuspojava pri primjeni glitazona je porast tjelesne težine. Dijelom je to posljedica zadržavanja tekućine, što može imati utjecaja na eventualno zatajivanje srčane funkcije.[5] Kontraindikacije za primjenu pioglitazona su kongestivno zatajivanje srčane funkcije bilo kojeg stupnja (NYHA I-IV),

Effects of metformin on myocardial ischemia

Metformin, a drug from the group of biguanides is today considered to be the basis of pharmacological treatment of type 2 DM. Therefore, it is to be administered immediately after the discovery of the disease accompanied by the changes in the life style and diet as recommended by the Croatian and all international guidelines for the treatment of type 2 DM.[5]

In patients treated with metformin, already after six months' treatment, it was observed a significantly reduced number of DM macrovascular complications, such as coronary incidents, strokes or deaths associated with DM.[12] Like any medicine, metformin has contraindications. It should not be administered to patients with creatinine clearance less than 60 ml/min, with severe liver failure, in alcoholics, patients with pancreatitis and all hypoxic conditions involving heart failure, respiratory failure and severe peripheral vascular disease (gangrene).[5]

Potential adverse effect of metformin on endothelial recovery after placement of drug eluting stents after the coronary intervention is described in the article by *Habib et al.* It was observed that metformin and mTOR (mammalian target of rapamycin) inhibitors (sirolimus) used in drug eluting stents have adverse molecular effects. It affects the endothelial recovery after coronary intervention S6K (ribosomal S6 kinase) dependent mechanism. Patients who take metformin and have the mTOR inhibitor drug-eluting stent are potentially at a higher risk of delayed endothelialization of the blood vessel and are at a higher risk for stent thrombosis.[13]

Preclinical studies have shown that metformin inhibits myocardial ischemia and has effects on reperfusion, regardless of its effect on the blood glucose level. This cardioprotective effect is mediated by activation of RISK (Reperfusion Injury Salvage Kinase) metabolic pathway and increased formation of adenosine.[14] The administration of metformin can potentially improve the outcome of cardiovascular events, even in patients without DM.[14] The study on the animal model (rats) who were chronically receiving 300mg of metformin a day showed that the administration of metformin enhanced the resistance to myocardial ischemic injury by a mechanism independent of the glucose reduction. This shows the positive effect of metformin on the structure of the mitochondria, which is mediated by the activation of AMPK (AdenosinMonoPhosphate-activated protein kinase) of metabolic pathway.[15] The study results indicating that metformin limits the size of myocardial infarction, suggest that the patients suffering from myocardial ischemia can benefit from the administration of metformin, even if they have no DM.[16]

Pioglitazone controversy

Insulin resistance is the underlying pathogenetic disorder in DM type 2. The improvement of insulin sensitivity can be achieved by using drugs that have an impact on the genetic mechanisms. These are the thiazolidinediones (glitazones)-PPAR-gamma ligands, known as pioglitazone on our market. Glitazones are activators of nuclear transcription factor (peroxysome proliferator-activated receptor gamma, PPAR-gamma) that regulate the transcription of genes responsible for insulin involved in the control of formation of glucose utilization carrier and fat metabolism. Due to its mechanism of action, one of the most significant side effects in the use of glitazones is the weight gain. This is partly a consequence of fluid retention, which can have an impact on a potential heart failure.[5] The contraindications to the use of pioglitazone are congestive heart failure of any degree (NYHA class I-IV), liver disease, creatinine clearance <4ml/min, pregnant

bolest jetre, klirens kreatinina <4 ml/min, trudnice i dojilje, dijabetička ketoacidoza, karcinom mokraćnog mjehura aktivan ili u anamnezi, hematurija.[5]

U literaturi se navode i mnogobrojni povoljni plejotropni učinci primjene pioglitazona, poput povoljanog utjecaja na disfunkciju epitela, sniženje arterijskog tlaka, korekcija metabolizma lipida, sniženje razine inflamatornih citokina i protrombotskih čimbenika.[17] I u usporedbi sa metforminom pioglitazon već nakon 16 tjedana primjene pokazuje veće sniženje razine CRP-a, kao i ostalih markera upale, čimbenika trombogeneze i oksidativnog stresa.[18]

Posljedično ovim antiaterogenim učincima pioglitazon reducira stope smrtnosti, infarkt miokarda, moždanog udara.[18] Ovo je naročito važno istaknuti radi usporedbe s rosiglitazonom, lijekom iz iste skupine koji je radi povećanog rizika od zatajivanja srca, infarkta miokarda i ukupne smrtnosti prije nekoliko godina povučen iz uporabe.[19] Metaanaliza kardiovaskularnih učinka jasno razdvaja negativan učinak rosiglitazona na kardiovaskularne događaje u odnosu na pioglitazon koji ne pokazuje takav učinak.[19]

Repaglinid

Repaglinid je trenutno jedini preparat iz skupine analoga sulfonil uree dostupan na hrvatskom tržištu. Može se primijenjivati uz obrok kao monoterapija ili u dvojnoj terapiji uz inhibitore alfa glukozidaze, DPP 4 inhibitore, tiazolidindione i GLP 1 analoge.[5] Međutim, pri istodobnoj primjeni metformina, nije moguće jamčiti da liječenje neće uzrokovati povećanje kardiovaskularnog rizika, naročito u pacijenata oboljelih od koronarne bolesti srca.[5]

Studija *Schramm I sur* objavljena je prije 2 godine i pratila je više od 107.000 oboljelih od DM tipa 2 kroz 9 godina. Prethodni infarkt miokarda imalo je 9.607 pacijenata uključenih u tu studiju. U usporedbi s metforminom primjena starijih sulfonil urea (glibenklamida, glipizida i tolbutamida) bila je povezana s povećanom smrtnošću u pacijenata s i bez prethodnog infarkta miokarda. Uporaba repaglinida i gliklazida u odnosu na metformin nije bila povezana sa većom smrtnošću.[20]

Također, studija provedena u Danskoj na 96 mršavih pacijenata s DM tipa 2 koja je proučavala razinu biljega upale (čimbenik nekroze tumora alfa, plazminogen activator inhibitor 1 antigen, tkivni plazminogen activator antigen, čimbenik von Willebrand, topiva unutarstanična adhezijska molekula, topivi E-selektin) u pacijenata na metforminu, odnosno repaglinidu pronašla je veći pad upalnih parametara odgovornih za disfunkciju endotela u pacijenata liječenih metforminom, u odnosu na pacijente liječene repaglinidom.[21]

Radi ovakvih dvojbenih mišljenja o kardiovaskularnim učincima repaglinida, indikacije za primjenu ovih lijekova moraju biti postavljene prema strožim kriterijima, posebno kod novootkrivenih bolesnika s DM tipa 2 te bolesnika s poznatom koronarnom bolesti srca.[5]

Blokatori dipeptidil peptidaze 4 (DPP 4 inhibitori)

Mogućnošću povećanja razine inkretinskih hormona u cirkulaciji s ciljem smanjenja glukoze u krvi otvara se novo poglavlje u liječenju DM tipa 2. U tu svrhu koriste se GLP 1 analozi i DPP 4 inhibitori. Inhibitori DPP 4 registrirani u Hrvatskoj su sitagliptin, vildagliptin i linagliptin.

and breasting women, diabetic ketoacidosis, bladder cancer being active or a history of bladder cancer, hematuria.[5]

The literature suggests many favorable pleiotropic effects of administration of pioglitazone such as a favorable effect on epithelial dysfunction, lowering of blood pressure, correction of lipid metabolism, lowering of the level of inflammatory cytokines and protrombotic factors.[17] Compared with metformin, already after 16 weeks of administration, pioglitazone showed a greater reduction in the level of CRP, and other inflammation markers, thrombogenecity factors and oxidative stress.[18]

Consequently, due to these antiatherogenic effects, pioglitazone reduces mortality, myocardial infarction and stroke.[18] This is particularly worth noting for the comparison with rosiglitazone, the drug from the same group that was withdrawn from the market a few years ago due to an increased risk of heart failure, myocardial infarction and total mortality.[19] Meta-analysis of cardiovascular effects clearly indicates the negative effect of rosiglitazone on cardiovascular events compared to pioglitazone, which does not have such an effect.[19]

Repaglinide

Repaglinide is currently the only agent from the group of analogs of sulfonylurea available in the Croatian market. It can be administered with a meal as a monotherapy or as a dual therapy with alpha-glucosidase inhibitors, DPP 4 inhibitors, thiazolidinediones and GLP 1 analogs.[5] However, in concomitant administration of metformin, there is no guarantee that the treatment will not cause an increased cardiovascular risk, especially in patients with coronary heart disease.[5]

The study by *Schramm et al* was published 2 years ago and it followed up more than 107,000 patients with DM type 2 throughout a period of 9 years. 9,607 of patients involved in this study had a history of myocardial infarction. Compared to metformin, the administration of some older sulfonylureas (glibenclamide, glipizide and tolbutamide) was associated with increased mortality in patients with and without history of myocardial infarction. The administration of repaglinide and gliclazide compared to metformin was not associated with higher mortality rate.[20]

Also, a study conducted in Denmark on 96 lean patients with type 2 DM, which studied the level of inflammation markers (tumor necrosis factor alpha, plasminogen activator inhibitor 1 antigen, tissue plasminogen activator antigen, von Willebrand factor, soluble intracellular adhesion molecule, soluble E- selectin) in patients taking metformin or repaglinide found a higher decline in inflammatory parameters responsible for endothelial dysfunction in patients treated with metformin compared to patients treated with repaglinide.[21]

As a result of such controversial opinions on cardiovascular effects of repaglinide, the indications for the administration of these drugs must be set according to strict criteria, particularly in newly diagnosed patients with type 2 DM and patients with known coronary heart disease.[5]

Dipeptidyl peptidase 4 inhibitors (DPP 4 inhibitors)

The possibility to increase the level of incretin hormones in the circulation in order to reduce blood glucose opens up a new chapter in the treatment of type 2 DM. For this purpose, we use the GLP 1 analogs and DPP 4 inhibitors. DPP 4

***Table 1**. Doses, contraindications and possible cardiovascular effects of the oral drugs for the treatment of type 2 diabetes mellitus. Beside above listed contraindications, all of the mentioned drugs should not be used in the treatment of diabetic ketoacidosis and during pregnancy and breast-feeding.*

	Doses	Contraindications	Possible cardiovascular effects
Metformin	0,5-3g/daily	Severe renal, cardiac, respiratory failure and liver disfunction, alcoholism, pancreatitis, gangrene	Enhances resistance to myocardial ischemic injury. Concomitant use with mTOR inhibitors probably slows recovery of endothelium after coronary intervention
Pioglitazone	15-30mg/daily	Heart failure of any grade, kidney and liver disfunction, bladder cancer, hematuria	Favorable effect on epithelial dysfunction, decreases blood pressure, decreases markers of inflammation and oxidative stress.
Repaglinide	1,5-16 mg/daily	End stage renal disease, concomitant use of gemfibrozil	Concomitant use of metformin probably increases cardiovascular risk in patients with coronary artery disease. Smaller decrease of inflammatory parameters responsible for the dysfunction of the epithelium compared with metformin.
Sulfonyl ureas: **• gliclazide** **• glimepiride** **• gliquvidone** **• glibenclamide**	Gliclazide 30-120 mg/daily Glimepiride 1-6mg/daily Gliquvidone 15-120 mg/daily Glibenclamide 1,25-14 mg/daily	Gliclazide: severe liver and kidneys disfunction, concomitant use of miconazole Glimepiride: severe renal and liver disfunction Gliquvidone: pancreatic surgery, severe infections, severe liver failure, acute intemittent hepatic porphyria Glibenclamide: pancreatic surgery, severe renal, hepatic, adrenocortical, thyroid and pituitary disfunction	The combination of metformin and glibenclamide increases the risk of cardiovascular events more than metformin in combination with other sulphonylureas. The ambiguous effect on the risk of death and heart failure is mediated by blocking potassium ATP channels. Gliclazide has antioxidant effect.
DPP 4 inhibitors: **• sitagliptin** **• vildagliptin** **• linagliptin**	Sitagliptin 100 mg/daily Vildagliptin 100 mg/daily Linagliptin 5mg/daily	Sitagliptin: pancreatitis, dose adjustment in the case of liver or kidney damage Vildagliptin: heart failure NYHA III-IV, liver disfunction, careful use in the case of severe renal failure Linagliptin: pancreatitis	Reducing the risk of cardiovascular events-class effect.Vildagliptin and sitagliptin enhances cardiac function by preventing cardial mitochondrial disfunction. Stabilization of variability of heart frequency.

Pored svoje uloge u snižavanju glukoze, linagliptin je u životinjskim modelima pokazao sposobnost smanjenja područja miokarda zahvaćenog infarktom.[22] Također, u usporedbi s glimepiridom (sulfonilureom) u pacijenata liječenih linagliptinom zabilježen je značajno manji relativni rizik od kardiovaskularnih događaja, posebno moždanog udara, neovisno o činjenici da linagliptin uzrokuje manje hipoglikemija od sulfoniluree.[23] Meta analiza koja je uključivala 8 studija u trajanju više od 12 tjedana analizirala je kardiovaskularnu smrtnost (fatalni infarkt miokarda, fatalni moždani udar), nefatalni moždani udar, nefatalni infarkt miokarda, nestabilnu anginu pektoris. Stupanj rizika za ove primarne događaje bio je značajno niži uz primjenu linagliptina u usporedbi s placebom i glimepiridom.[23] Ove analize pokazuju da primjena linagliptina ne povećava kardiovaskularne rizike, već vjerojatno polučuje kardiovaskularne dobrobiti u pacijenata s DM tipa 2.[23]

inhibitors registered in Croatia are sitagliptin, vildagliptin and linagliptin.

In addition to its role in lowering glucose, linagliptin tested on animal models proved to be able to reduce the areas of the affected myocardial infarction.[22] Also, compared to glimepiride (sulphonylurea), the patients treated with linagliptin had a significantly lower relative risk of cardiovascular events, particularly stroke, regardless of the fact that linagliptin causes hypoglycemia less than sulfonylureas.[23] A meta-analysis that involved 8 studies lasting more than 12 weeks analyzed cardiovascular mortality (fatal myocardial infarction, fatal stroke), nonfatal stroke, nonfatal myocardial infarction, unstable angina pectoris. The degree of risk of these primary events was significantly lower with the use of linagliptin compared with placebo and glimepiride.[23] These analyses show that the administration of linagliptin does not increase cardiovas-

Sličan kardioprotektivan učinak sitagliptina pokazan je i u izraelskoj studiji iz 2013. godine. Pacijenti sa tipom 2 DM koji su prije velikog kardiovaskularnog događaja dobivali sitagliptin imali su značajno manje hospitalnih komplikacija (postinfarktna angina, ponovni infarkt miokarda, edem pluća, infekcije, zatajenje bubrega) u usporedbi s pacijentima liječenima samo metforminom ili drugim oralnim hipoglikemizantnim sredstvima.[24] Zaključak da primjena sitagliptina ne povećava kardiovaskularne rizike donosi i analiza 25 randomiziranih kliničkih istraživanja.[25] Štoviše u životinjskim modelima je pokazano da i vildagliptin, kao i sitagliptin, imaju podjednaki kardiovaskularni zaštitni učinak.[26] Štakori hranjeni prehranom s visokim udjelom masti, s visokim indeksom tjelesne mase, razinom inzulina u plazmi, povišenim parametrima oksidativnog stresa i dislipidemijom dobivali su vildagliptin i sitagliptin. Osim poboljšanja navedenih metaboličkih parametara zabilježeno je i poboljšanje srčane funkcije, prevenirana je kardijalna mitohondrijalna disfunkcija te stabilizirana varijabilnost srčane frekvencije.[26]

Zaključak

Mnoštvo oralnih lijekova za liječenje DM tipa 2 pokazuje da se u liječenju ove bolesti iskorištava svaki novi, dostupni i prepoznati patofiziološki mehanizam. Ovo mnoštvo molekula svakako osim na razinu glikemije, može imati izravni učinak na srčanožilni sustav ili učinak na čimbenike rizika. Općenito, kontroverze i dvojbe o srčanožilnoj sigurnosti su veće za starije lijekove za oralno liječenje DM tipa 2, posebno iz skupine sulfonil uree. Sulfonil uree iz starije skupine (glibenklamid) bi trebalo izbjegavati, naročito u kombinciji s metforminom, jer se čini da su njihovom uporabom kardiovaskularni rizici u porastu. Dosadašnja istraživanja pokazuju da je pioglitazon siguran lijek, ali kliničkim pregledom treba detektirati pacijente na koja bi se mogla odnositi gore navedena ograničenja upotrebe. Repaglinid je također siguran lijek, iako u pacijenata sa koronarnom bolesti srca ostaju dvojbe o sigurnosti koje bi trebalo razjasniti daljnjim istraživanjima. Studije koje ukazuju na povoljne učinke na metaboličke parametre i endotelnu funkciju čine novije lijekove iz skupine DPP 4 inhibitora atraktivnijim za propisivanje pacijentima s istodobnom kardiovaskularnom problematikom.

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cular risks, but probably confers cardiovascular benefits in patients with DM type 2.[23]

A similar cardioprotective effect of sitagliptin was shown in the 2013 Israeli study. Patients with type 2 DM who received sitagliptin before the major cardiovascular event had significantly fewer hospital complications (postinfarction angina, myocardial reinfarction, pulmonary edema, infections, renal failure) compared to the patients treated only with metformin or other oral hypoglycemic agents.[24] The conclusion that the administration of sitagliptin does not increase cardiovascular risks is reached by the analysis of 25 randomized clinical trials.[25] Moreover, in animal models vildagliptin and sitagliptin also proved to have equal cardiovascular protective effect.[26] Rats on high fat diet, with high body mass index, high insulin levels in plasma, increased parameters of oxidative stress and dyslipidemia received vildagliptin and sitagliptin. In addition to improving these metabolic parameters, the improvement of cardiac function was also recorded. The mitochondrial dysfunction in cardiac disease was prevented and the heart rate variability was stabilized.[26]

Conclusion

A variety of oral medications for the treatment of type 2 DM shows that every new, available and recognizable pathophysiological mechanism is exploited in the treatment of this disease. Such a great number of molecules can certainly have a direct effect on the cardiovascular system or the effect of the risk factors in addition to blood glucose level. Generally, controversies and doubts regarding cardiovascular safety are greater for older medicines for oral treatment of type 2 DM, especially from the group of sulfonylureas. Sulfonylurea from the older group (glibenclamide) should be avoided, particularly in the combination with metformin, because cardiovascular risks seem to be rising as a result of their administration. Previous studies show that pioglitazone is a safe medicine, but clinical examination should detect patients to whom the above limitation of use might relate. Repaglinide is also a safe medicine, although there are still doubts about the safety of this medicine in patients with coronary heart disease which should be clarified by the research to follow. Studies that suggest beneficial effects on metabolic parameters and endothelial function make the more recent medicines from the group of DPP 4 inhibitors more attractive for prescribing to patients with concomitant cardiovascular disorders.

Literature

1. IDF Diabetes atlas. Fifth edition. http://www.idf.org/diabetesatlas (8.5.2013).

2. Poljičanin T, Šekerija M, Metelko Ž. Šećerna bolest - epidemiološko stanje i javno zdravstvene aktivnosti u Hrvatskoj. http://www.hcjz.hr/old/clanak.php?id=14501 (8.5.2013)

3. Magaš S. Incidence of modifiable cardiovascular risk factors and treatment of persons suffering from diabetes in the Bjelovar-Bilogora County during the period from 2001 to 2012. Cardiol Croat. 2013;8(7-8):246-53.

4. German Diabetes Association, Matthaei S, Bierwirth R, Fritsche A, et al. Medical antihyperglycaemic treatment of type 2 diabetes mellitus: update of the evidence-based guideline of the German Diabetes Association. Exp Clin Endocrinol Diabetes. 2009;117(9):522-57.

5. Kokić S, Prašek M, Renar-Pavlić I i sur. Hrvatske smjernice za liječenje šećerne bolesti tipa 2. Medix. 2011;17 Suppl 2:8-34.

6. Monami M, Luzzi C, Lamanna C, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev. 2006;22(6):477-82.

7. Juurlink DN, Gomes T, Shah BR, Mamdani MM. Adverse cardiovascular events during treatment with glyburide (glibenclamide) or gliclazide in a high-risk population. Diabet Med. 2012;29(12):1524-8.

8. Nagendran J, Oudit GY, Bakal JA, Light PE, Dyck JR, McAlister FA. Are users of sulfonylureas at the time of an acute coronary syndrome at risk of poorer outcomes? Diabetes Obes Metab. 2013 May 13. [Epub ahead of print].

9. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013 Apr 17. [Epub ahead of print].

10. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;12;358(24):2560-72.

11. Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res. 2013;10(4):289-301.

12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. (UKPDS 33). Lancet. 1998;352(9131):837-53.

13. Habib A, Karmali V, Polavarapu R, et al. Metformin impairs vascular endothelial recovery after stent placement in the setting of locally eluted mammalian target of rapamycin inhibitors via S6 kinase-dependent inhibition of cell proliferation. J Am Coll Cardiol. 2013;5;61(9):971-80.

14. El Messaoudi S, Rongen GA, Riksen NP. Metformin therapy in diabetes: the role of cardioprotection. Curr Atheroscler Rep. 2013;15(4):314.

15. Whittington HJ, Hall AR, McLaughlin CP, Hausenloy DJ, Yellon DM, Mocanu MM. Chronic metformin associated cardioprotection against infarction: not just a glucose lowering phenomenon. Cardiovasc Drugs Ther. 2013;27(1):5-16.

16. El Messaoudi S, Rongen GA, de Boer RA, Riksen NP. The cardioprotective effects of metformin. Curr Opin Lipidol. 2011;22(6):445-53.

17. Defronzo RA, Mehta RJ, Schnure JJ. Pleiotropic effects of thiazolidinediones: implications for the treatment of patients with type 2 diabetes mellitus. Hosp Pract (1995). 2013;41(2):132-47.

18. Genovese S, De Berardis G, Nicolucci A, et al. Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Adv Ther. 2013;30(2):190-202.

19. Chen X, Yang L, Zhai SD. Risk of cardiovascular disease and all-cause mortality among diabetic patients prescribed rosiglitazone or pioglitazone: a meta-analysis of retrospective cohort studies. Chin Med J (Engl). 2012;125(23):4301-6.

20. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011;32(15):1900-8.

21. Lund SS, Tarnow L, Stehouwer CD, et el. Impact of metformin versus repaglinide on non-glycaemic cardiovascular risk markers related to inflammation and endothelial dysfunction in non-obese patients with type 2 diabetes. Eur J Endocrinol. 2008;158(5):631-41.

22. Hocher B, Sharkovska Y, Mark M, Klein T, Pfab T. The novel DPP-4 inhibitors linagliptin and BI 14361 reduce infarct size after myocardial ischemia/reperfusion in rats. Int J Cardiol. 2013;15:167(1):87-93.

23. Gallwitz B. Safety and efficacy of linagliptin in type 2 diabetes patients with common renal and cardiovascular risk factors. Ther Adv Endocrinol Metab. 2013;4(3):95-105.

24. Leibovitz E, Gottlieb S, Goldenberg I, Gevrielov-Yusim N, Matetzky S, Gavish D. Sitagliptin pretreatment in diabetes patients presenting with acute coronary syndrome: results from the Acute Coronary Syndrome Israeli Survey (ACSIS). Cardiovasc Diabetol. 2013;12:53.

25. Engel SS, Golm GT, Shapiro D, Davies MJ, Kaufman KD, Goldstein BJ. Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis. Cardiovasc Diabetol. 2013;12:3.

26. Apaijai N, Pintana H, Chattipakorn SC, Chattipakorn N. Effects of vildagliptin versus sitagliptin, on cardiac function, heart rate variability and mitochondrial function in obese insulin-resistant rats. Br J Pharmacol. 2013;169(5):1048-57.