2010;5(12):294. KARDIO LIST

Stručni rad Professional article

Rezidualni rizik — danas, sutra ...; još jedan pogled na rezultate ACCORD studije i podstudija

Residual risk — today, tomorrow ...; Another look at the results of the ACCORD study and sub-studies

*Goran Krstačić**

Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Zagreb, Hrvatska

Institute for Cardiovascular Diseases Prevention and Rehabilitation, Zagreb, Croatia

SAŽETAK: *Postoje nedvojbeni dokazi da unatoč učinkovitom sniženju LDL, arterijskog tlaka (AT) i glukoze u krvi (GUK), učinci sniženja vaskularnog rizika nisu dostatni, poglavito zbog aterogene dislipidemije u bolesnika s dijabetesom i metaboličkim sindromom. ACCORD (Action to Control Cardiovasular Risk in Diabetes) predstavlja globalnu kliničku studiju koja je imala za cilj utvrditi mogućnost smanjenja kardiovaskularnih događaja i mikrovaskularnih komplikacija intenzivnom regulacijom GUK (HbA1c <6.0% naspram 7.0-7.9%), dislipidemije (simvastatin i fenofibrat naspram simvastatina) i povišenog AT (vrijednosti sistoličkog AT <120 naspram <140 mmHg). Prva studija "intezivne glukoregulacije" prekinuta je nakon 3,5 godine praćenja (18 mjeseci prije planiranog kraja), poradi 54 smrtna ishoda više u grupi intenzivno liječenih ispitanika sa zaključkom da inzistiranje na normalizaciji glikemije i HbA1c <6% može biti kontraproduktivno te treba zauzeti individualan pristup liječenja kod dijabetičara. Rezultati druge studije nakon pet godina pokazali su da "intenzivna regulacija" AT nije smanjila primarne ishode (nefatalni infarkt miokarda, ukupnu smrtnost ili smrt od kardiovaskularnog uzroka). Treća studija "intenzivnog liječenja" dislipidemije pokazala je da primjena kombinacije fenofibrata i simvastatina ne smanjuje pojavnost smrtonosnog kardiovaskularnog događaja, ne-smrtonosnog infarkta miokarda ili ne-smrtonosnog moždanog udara u usporedbi s monoterapijom simvastatinom. Poslije završetka ACCORD studije razvidno je da u osoba s dijabetesom tipa 2 i povišenim kardiovaskularnim rizikom treba prilagoditi terapijske ciljeve uz obveznu individualizaciju pristupa bolesniku.*

KLJUČNE RIJEČI: *dijabetes tipa 2, arterijski tlak, intenzivne ciljne vrijednosti, kardiovaskularni rizik.*

SUMMARY: *There is undoubted evidence that despite a strong reduction of LDL, blood pressure (BP) and blood glucose, the effects of reducing the vascular risk are not sufficient, especially due to aterogenous dyslipidemia in patients with diabetes and metabolic syndrome. ACCORD (Action to Control Cardiovasular Risk in Diabetes) represents a global clinical study that was aimed at determination of a possibility of reducing cardiovascular events and microvascular complications by intensive regulation of glucose (HbA1c <6.0% vs. 7.0-7.9%), dyslipidemia (simvastatin and fenofibrate vs. simvastatin) and higher BP (the values of systolic BP <120 vs. <140 mmHg). The first study of "intensive glucoregulation" was interrupted after 3.5 years of follow-up (18 months prior to the forecasted end), as a result of 54 fatal outcomes more in the group of intensively treated patients thereby reaching a conclusion that insisting on normalization of glycemia and HbA1c <6% may be counterproductive and an individual approach to treatment in case of diabetics should be taken. The results of the other study after five years showed that "intensive regulation" of BP resulted in no reduction of primary outcomes (non-fatal myocardial infarction, total mortality or death from cardiovascular cause). The third study of "intensive treatment" of dyslipidemia showed that the combination of fenofibirate and simvastatin does not reduce the occurrence of fatal cardiovascular event, non-fatal myocardial infarction or non-fatal stroke compared with monotherapy by using simvastatin. After the end of the ACCORD study, it is obvious that the therapy targets should be adapted to the persons having diabetes type 2 and higher cardiovascular risk thereby taking an individual approach to a patient.*

KEYWORDS: *diabetes type 2, blood pressure, intensive target values, cardiovascular risk.*

CITATION: *Kardio list. 2010;5(12):294-298.*

Inicijativa za smanjenje ostatnog rizika (R3i) je akademska, multidisciplinarna, neprofitna edukacijska fundacija posvećena nastojanjima da se smanji značajan preostali rizik u razvitku makrovaskularnih događaja i mikrovaskularnih komplikacija koje perzistiraju u većine bolesnika unatoč optimalnoj standardnoj terapiji i postizanju ciljnih vrijednosti sukladno smjernicama. Unatoč dokazanoj djelotvornosti postojeće standardne terapije, bolesnici, a navlastito dijabetičari i dalje su izloženi znakovitom ostatnom riziku koji vodi u razvitak makrovaskularnih događaja (infarkta miokarda i cerebrovaskularnog inzulta), odnosno mikrovaskularnih komplikacija (retinopatije, nefropatije i neuropatije)[1]. Značenje rezidualnog ili ostatnog krvožilnog rizika nedvojbeno je, barem dijelom, vezano uz postojanje aterogene dislipidemije (povećani trigliceridi i/ili preniski HDL), kod koje terapija statinima ne postiže

The initiative for reduction of residual risk (R3i) is the academic, multidisciplinary, non-profit educational foundation committed to endeavors to reduce a significant residual risk in development of macrovascular events and microvascular complications that persist in the most of the patients despite the optimum standard therapy and accomplishment of target values according to the guidelines. Besides the proven efficiency of the existing standard therapy, the patients, especially the diabetics are still exposed to significant residual risk that leads to the development of macrovascular events (myocardial infarction and stroke), that is, microvascular complications (retinopathy, nephropathy and neuropathy)[1]. The meaning of the residual cardiovascular risk is undoubtedly at least partly linked to the existence of aterogenous dyslipidemia (increased triglycerides and/or decreased HDL), in case of therapy with statins, no significant results are achieved. For example,

značajnije rezultate. Primjerice, dok je u proteklih tridesetak godina u SAD prevalencija povišenih vrijednosti LDL-a snižena za 7,2%, prevalencija kombinacije povišenih triglicerida i niskog HDL-a je udvostručena, a prevalencija samo povišenih triglicerida je čak upeterostručena![2] To je poglavito u svezi uz sve veći broj pretilih osoba s metaboličkim sindromom i sve veću učestalost dijabetesa tipa 2. Stoga je potrebito razviti novu strategiju koja bi mogla bolje djelovati na rizične čimbenike, poglavito aterogenu dislipidemiju navlastito u cilju snižavanja ostatnog rizika u bolesnika s dijabetesom i krvožilnim bolestima.[3]

ACCORD (*Action to Control Cardiovasular Risk in Diabetes*) je velika i važna globalna klinička studija koju je financirao *National Institute of Health* iz SAD. Ona je obuhvatila tri studije u jednom programu istraživanja i imala je za cilj utvrditi mogućnost smanjenja kardiovaskularnih događaja i mikrovaskularnih komplikacija kod bolesnika s dijabetesom tipa 2 postizanjem intenzivnih ciljnih vrijednosti tri značajna čimbenika rizika u usporedbi sa standardnim pristupom u učinkovitoj prevenciji kardiovaskularnih bolesti:

• intenzivna glukoregulacija (vrijednost HbA1c <6,0% naspram vrijednosti 7-7,9%);

• intenzivno liječenje dislipidemije (simvastatin + fenofibrat naspram simvastatin);

• intezivno liječenje povišenog arterijskog tlaka (AT) (vrijednosti sistoličkog AT <120 mmHg naspram <140 mmHg).

Studija je započela 2001. god. s uključenih 10.251 ispitanika u 73 centra u SAD i Kanadi. Ispitanici su bili dijabetičari tipa 2, prosječne dobi od 62,2 god. U vrijeme uključenja u studiju ispitanici su već liječili dijabetes prosječno deset godina i imali prosječnu vrijednost HbA1c od 8,1% te su imali krvožilnu bolest ili najmanje 2 čimbenika rizika za kardiovaskularni pobol (arterijska hipertenzija, hiperkolesterolemija, pretilost ili pušenje). U ovoj skupini bolesnika stopa smrtnosti inače iznosi 50/1.000 osoba (5% godišnje)[4].

U prvoj studiji, studiji "intenzivne glukoregulacije", ispitanici su podijeljeni u skupinu intenzivnog pristupa u učinkovitoj prevenciji kardiovaskularnih bolesti (HbA1c <6%) koja je analizirana u odnosu na standardni pristup (HbA1c 7-7,9%). Za postizanje terapijskih ciljeva korišteni su metformin, preparati sulfonilureje, tijazolidindioni, inzulin i akarboza. Prosječno je oko 9 mjeseci bilo potrebno da se dostigne terapijski cilj. Ispitanici skupine intenzivnog liječenja kontrolirani su svakih 2 mjeseca, a oni standardno liječeni svaka 4 mjeseca. Primarni cilj je bila pojava prvog ne-fatalnog infarkta miokarda ili ne-fatalnog možданog udara ili smrti kardiovaskularnog uzroka. U trenutku prekidanja studije nakon 3,5 godine praćenja, 18 mjeseci prije planiranog kraja, u skupini intenzivno liječenih ispitanika prosječni HbA1c iznosio je 6,4%, a u grupi standardno liječenih 7,5%. U standardno liječenoj skupini ispitanika zabilježeno je 11 smrtnih ishoda na 1.000 ispitanika tijekom 4 godine praćenja, a u skupini intenzivno liječenih ispitanika 14. U obje skupine ovaj neželjeni ishod bio je znakovito niži od očekivanog, no razlika od 54 smrtna ishoda više u skupini intenzivno liječenih ispitanika (257 prema 203) značio je razliku od 3 osobe na 1.000 osoba u prosjeku tijekom četverogodišnjeg razdoblja praćenja i desetočlani Odbor za praćenje *The National Heart,*

while during the last thirty years, the prevalence of increased values of LDL has been reduced by 7.2% in the USA, the prevalence of the combination of increased triglycerides and low HDL has been doubled, while the prevalence of only increased triglycerides has been increased even five times![2] This is especially connected with ever greater number of obese persons with metabolic syndrome and more frequent diabetes type 2. Therefore, it is necessary to develop a new strategy that may better impact the risk factors, especially aterogenous dyslipidemia mainly for the purpose of lowering the residual risk in patients with diabetes and cardiovascular diseases[3].

ACCORD (Action to Control Cardiovasular Risk in Diabetes) is a large and important global clinical study financed by the National Institute of Health, USA. It included the three studies in one research program with an aim to determine the possibility of reducing the cardiovascular events and microvascular complications in patients with diabetes type 2 by achieving intensive target values of three risk factors in comparison with standard approach in efficient prevention of cardiovascular disease:

• Intensive glucoregulation (value HbA1c <6.0% vs. the value 7-7.9%);

• Intensive treatment of dyslipidemia (simvastatin + fenobrate vs. simvastatin);

• Intensive treatment of higher blood pressure (BP) (value of systolic BP <120 mmHg vs. <140 mmHg).

The study started in 2001 which included 10.251 patients in 73 centers in the USA and Canada. The patients were the diabetics type 2 with average age of 62.2. At the time of involvement in the study, the patients had already been treated from diabetes for ten years on average and had an average value of HbA1c of 8,1% and had a cardiovascular disease or at least 2 risk factors for cardiovascular disease (hypertension, hypercholesterolemia, obesity or smoking). In this group of patients, the mortality rate is generally 50/1000 persons (5% per annum)[4].

In the first study, the study of "intensive glucoregulation", the patients were divided in the group of intensive approach in efficient prevention of cardiovascular diseases (HbA1c <6%) that was analyzed compared to the standard approach (HbA1c 7-7.9%). Metformin, the sulphonilurea, thiazolidinedione drugs, insulin and acarbose were used for the achievement of therapeutic targets. On average, it takes some 9 months to achieve a therapeutic target. The patients included in the group for intensive treatment were controlled every two months, while those who underwent standard treatment were controlled every four months. The primary goal was the occurrence of non-fatal myocardial infarction or non-fatal stroke or death of cardiovascular cause. At the time of interruption of the study, after 3.5 years of follow-up, 18 months prior to the forecasted end, the average HbA1c was 6.4% in the group of intensively treated patients, while there were 7.5% of them in the group undergoing standard treatment. The group of patients undergoing standard treatment recorded 11 fatal outcomes per 1000 during 4 years of follow-up, while the group of patients undergoing intensive treatment recorded 14 fatal outcomes. In the both groups, this adverse outcome was much lower than the expected one, but the difference of 54 fatal outcomes more in the group of patients undergoing intensive treatment (257 vs. 203) meant a difference of 3 persons per 1000 patients on average during the four-year period of follow-up and ten-member follow-up Board The National Heart, Lung, and Blood Institute suggested the interruption of this branch of the study. The patients continued the treatment till the forecasted end of the study by using the standard therapy. The researchers

Lung, and Blood Institute predložio je prekid ove grane studije. Ispitanici su nastavili liječenje do planiranog kraja studije standardnom terapijom. Istraživači su potom analizirali dostupne podatke, ali nisu mogli izdvojiti uzrok veće smrtnosti u intenzivno liječenoj skupini. Razvidno je da hipoglikemija niti neki lijek (uključujući i rosiglitazon koji je zbog upozorenja početkom 2007. godine posebito analiziran kod ispitanika koji su ga koristili) nije bio uzrok registriranoj razlici u preživljavanju. Nije zanemariva niti činjenica da su primarni ishodi, bilježeni zbrojem infarkta miokarda (IM), cerebrovaskularnog inzulta (CVI) i kardiovaskularnih smrtnih ishoda, bili 10% niži u intenzivno liječenih ispitanika[5]. Zaključeno je da u dijabetičara tipa 2 s posebno visokim rizikom za kardiovaskularni pobol inzistiranje na normalizaciji glikemije i HbA1c nižem od 6% može biti kontraproduktivno i da stoga ne bi trebalo zauzeti isti pristup liječenja kod svih dijabetičara. Ovo je u skladu sa preporukama *American Diabetes Association* koja preporuča glukoregulaciju po kojoj HbA1c treba biti niži od 7% ali uz individualnu prilagodbu terapijskih ciljeva. Kod osoba koje su sklone teškim i čestim hipoglikemijama ili osoba s ograničenim očekivanim preživljavanjem treba imati manje ambiciozne ciljeve glukoregulacije. Istraživači su također pokazali da intenzivna glikemijska terapija nije imala značajan učinak na razvijenim mikrovaskularnim komplikacijama na kraju studije nakon 5 godina, ali su registrirali usporenje progresije mikrovaskularnih komplikacija. Zabilježeno je smanjenje albuminurije s primjenom intenzivne glikemijske kontrole (1,44 mmol/L naspram 1,63 mmol/L u standardnoj skupini), jednako kao i usporenje progresije retinopatije i neuropatije usporedivo sa standardnim liječenjem. Ova korist se treba usporediti s potencijalnim negativnim posljedicama povezanim s intenzivnom glikemijskom terapijom o kojoj je ranije ACCORD izvijestio, uključujući tu veću ukupnu smrtnost i smrtnost uslijed kardiovaskularnih posljedica, povećanje tjelesne težine, kao i teške hipoglikemije u bolesnika s visokim rizikom od kardiovaskularnih bolesti[5]. Kontrola glukoze je vjerojatno učinkovitija u prevenciji nego kada već postoje komplikacije dijabetesa. Rezultati ACCORD studije ne mogu se primijeniti na bolesnike s tipom 1 dijabetesa.

U drugoj studiji, studiji "intenzivnog liječenja arterijskog tlaka" 4.733 ispitanika s dijabetesom tip 2 je bilo randomizirano na skupinu intenzivnog liječenja s ciljem sniženja vrijednosti AT <120 mmHg, dok je u drugoj skupini liječenja ciljna vrijednost sistoličkog AT bila <140 mmHg. Prosječno praćenje iznosilo je 4,7 god., a primarni cilj je bio isti kao i u ostale dvije grane ACCORD studija. Rezultati su pokazali da intenzivna regulacija AT nije smanjila primarne ishode (nefatalni IM, ukupnu smrtnost ili smrt od kardiovaskularnog uzroka). Ozbiljni neželjeni učinci (hipotenzija, sinkopa, bradikardija ili aritmije, hiperkalijemija, zatajenje bubrega, smanjenje glomerularne filtracije <30 mL/min/1,73m^2) zabilježeni su u skupini intenzivnog liječenja kod 3,3%, za razliku od standardnog liječenja 1,3% ispitanika. Vrijedi napomenuti da je intenzivno liječenje AT ipak dovelo i do nekih pozitivnih rezultata što se očitovalo kroz smanjenje sekundarnih ciljeva, tj. ukupno smanjenje CVI i nefatalnog CVI [6].

Treća studija, studija intenzivnog liječenja dislipidemije (ACCORD Lipid Trial) trebala je dati odgovor da li bi kombinirano liječenje statinom (simvastatin 20 ili 40 mg) i fenofibratom u dozi 160 mg u odnosu na monoterapiju sta-

analyzed the accessible data afterwards, but they could not determine the cause of increased mortality in the group of patients undergoing intensive treatment. It is obvious that hypoglycemia is not some medicine (including rosiglitazone that was at the beginning of 2007 because of this warning specifically analyzed in examinees that used it) and it was not some cause of registered difference in survival. We should not ignore the fact that the primary outcomes, followed by the sum of myocardial infarction (MI), stroke and cardiovascular fatal outcomes were lower by 10% in intensely treated patients[5]. It was concluded that in diabetics type 2 with especially high risk for cardiovascular disease, insisting on normalization of glycemia and HbA1c lower than 6% may be counter-productive and therefore we should not take the same approach to all diabetics. This is in compliance with the recommendations of American Diabetes Association that recommends the glucoregulation according to which HbA1c should be lower than 7%, but with individual adaptation of therapeutic targets. In patients who tend to suffer from serious and frequent hypoglycemia or persons with limited expected survival, we should have less ambitious glucoregulation targets. The researchers also showed that intensive glycemic therapy did not have a significant effect on developed microvascular complications at the end of the study after five years, recording a slowdown in progression of microvascular complications. The reduction of albuminuria was recorded thereby applying the intensive glycemic control (1.44 mmol/L vs 1.63 mmol/L in the group undergoing standard treatment), and the slowdown of progression of retinopathy and neuropathy applying standard treatment was recorded. This benefit should be compared to potential negative consequences linked to the intensive glycemic therapy as previously reported by ACCORD, including this larger total mortality and mortality as a consequence of cardiovascular diseases, increased body weight and serious hypoglycemia in patients with a high risk of cardiovascular disease[5]. The control of glucose is probably more efficient in prevention than when the diabetes complications already exist. The results of the ACCORD study may not be applied to patients with type 1 diabetes.

In the second study, the study of "intensive treatment of BP" some 4,733 patients with type 2 was randomized to the group undergoing intensive treatment aimed at reducing the value of BP <120 mmHg, while in the second group of persons undergoing the treatment the target value of systolic BP was <140 mmHg. The average follow-up was 4.7 years, while the primary target was the same as in the remaining two branches of the ACCORD studies. The results showed that the intensive regulation of BP did not reduce the primary outcomes (non-fatal MI, total mortality or death from cardiovascular cause). The serious undesired effects (hypotension, syncope, bradycardia or arrhythmia, hypercaliemia, renal failure, reduction of glomerular filtration <30 mL/min/1,73m^2) were recorded in the group of examinees undergoing intensive treatment in 3.3% of them, unlike the group undergoing standard treatment where they were recorded in 1.3% of examinees. It is worth mentioning that the intensive treatment of BP anyway caused some positive results reflected through the reduction of secondary targets, that is, total reduction of stroke and non-fatal stroke[6].

The third study, the study of intensive treatment of dyslipidemia (ACCORD LIPID Trial) should provide an answer whether the combined treatment by using statin (simvastatin 20 or 40 mg) and fenofibrate of 160 mg should re-

tinom smanjilo velike kardiovaskularne događaje. Cilj dodavanja fenofibrata je bio smanjenje razine triglicerida i povišenje HDL kod bolesnika koji već uzimaju statin glede sniženja LDL. U studiji je sudjelovalo 5.518 bolesnika, a prosječno praćenje iznosilo je 4,7 god. Rezultati su pokazali da kombinacija fenofibrata i simvastatina ne smanjuje pojavnost smrtonosnog KV događaja, ne-smrtonosnog IM ili ne-smrtonosnog CVI u usporedbi sa simvastatinom u monoterapiji. Ovi rezultati ne podržavaju rutinsku upotrebu kombinirane terapije u snižavanju rizika kod većine bolesnika s dijabetesom tipa 2. No, u lipidnom kraku ACCORD studije bolesnici s dislipidemijom su imali za 70% veći relativni rizik za razvoj velikog KV događaja u usporedbi sa onima koji su imali trigliceride <2,3 mmol/L i HDL >0,88 mmol/L, unatoč postizanju ciljnih vrijednosti LDL od 2,0 mol/L. Dvadeset ovakvih bolesnika je potrebno liječiti kroz pet godina da bi se spriječio jedan KV događaj (NNT=20). Fibrati su pak, bili posebito učinkoviti u smanjenju kardiovaskularnog relativnog rizika kod bolesnika na terapiji statinom s niskim HDL i povišenim triglyceridima, smanjujući velike kardiovaskularne događaje za 31%. Kombinacija fenofibrata i statina je bila dobro podnošljiva i može se kazati da su rezultati lipidnog kraka ACCORD studije dodatno podržali aktualne smjernice liječenja dislipidemije koje podržavaju važnost sveobuhvatnog pristupa liječenju lipidnih poremećaja[7,8].

Ranije studije su pokazale da dobra regulacija dijabetesa, dislipidemije i AT može biti važna u usporenju mikrovaskularnih komplikacija, poglavito progresije dijabetičke retinopatije. Recentno, ispitivači su objavili rezultate prespecificiranih podstudija učinka terapije na progresiju retinopatije i druge mikrovaskularne komplikacije. Ispitivači "ACCORD Eye Study" prikazali su rezultate prespecificirane podstudije praćenja progresije retinopatije kod 2.856 bolesnika dijabetičara tip 2[9]. Primarni cilj je bio zabilježba promjena na tzv. ljestvici retinopatije objektivizirano serijom fotografija retine koja ukupno sadrži 17 nivoa ili stupnjeva glede smanjenja najmanje tri nivoa (stupnja), ili pak praćenje razvoja retinopatije koja zahtijeva fotokoagulaciju ili vitrektomiju. Sekundarni cilj je bio praćenje smanjenja (gubitka) vida. Četverogodišnje praćenje je pokazalo da u odnosu na standardnu terapiju:

• intenzivna glikemijska terapija signifikantno snižava učestalost progresivne retinopatije (7,3% vs. 10,4%), ali ne i gubitak vida (16,3% vs. 16,7%);

• intenzivno liječenje dislipidemije signifikantno smanjuje učestalost progresivne retinopatije (6,5% vs. 10,2%), ali također ne i gubitak vida (16,0% vs. 15,2%);

• intenzivna antihipertenzivna terapija ne smanjuje progresiju dijabetičke retinopatije ili gubitak vida (10,4% vs. 8,8%; odnosno 19,4% vs. 15,8%).

U ostalim podstudijama praćenja drugih mikrovaskularnih komplikacija bolesnika koji su 3,5 godine bili na intezivnoj glukoregulaciji da bi potom 1,5 godinu bili na standardnom liječenju u usporedbi s ispitanicima koji su svih pet godina bili na standardnom liječenju glukoregulacije zabilježeni su i drugi zanimljivi rezultati. Nakon pet godina zajednički primarni ishod (terminalna faza bubrežne insuficijencije, potreba za dijalizom ili transplantacijom bubrega, porast serumskog kreatinina >3,3mg/dL ili potreba za fotokoagulacijom retine ili vitrektomija) zabilježeno je kod 556 bolesnika u intezivnoj naspram 586 u standard-

duce large cardiovascular events compared to the monotherapy with statin. The goal of adding fenofibrates was the reduction of the level of triglycerides and raising HDL in patients who already take statin for lowering LDL. Some 5,518 of patients participated in the study, and the average follow-up lasted for 4.7 years. The results showed that that the combination of fenofibrates and simvastatin do not reduce the occurrence of fatal cardiovascular event, non-fatal MI and non-fatal stroke in comparison to simvastatin monotherapy. These results do not support the routine use of combined therapy in lowering the risk in most of the patients with diabetes type 2. However, in the lipid branch of the ACCORD study, the patients with dyslipidemia had 70% larger relative risk for development of the large CV event compared to those that had triglycerides <2.3 mmol/L i HDL >0.88 mmol/L, despite the achievement of target values LDL of 2.0 mol/L. Twenty such patients need to be treated throughout a period of 5 years to prevent one CV event (NNT=20). Fibrates were especially efficient in lowering cardiovascular relative risk in patients on statin therapy with lower HDL and raised triglycerides, thereby reducing large cardiovascular events by 31%. The combination of fenofibrates and statin was well tolerable and we may say that the results of the lipid branch of the ACCORD study additionally supported the actual guidelines of treatment of dyslipidemia that support the importance of comprehensive approach to treatment of lipid disorders[7,8].

The previous studies showed that a good regulation of diabetes, dyslipidemia and BP may be important in slowing down microvascular complications, especially the progression of diabetic retinopathy. The investigators have recently published the results of prespecified sub-studies of effect of the therapy on the progression of retinopathy and other microvascular complications. The authors of "ACCORD Eye Study" showed the results of prespecified sub-study of monitoring the progression of retinopathy in 2,856 patients who have diabetes type 2[9]. The primary goal was to record the changes to the so called scale of retinopathy objectivized by applying a series of photos of retina which totally contain 17 levels and degrees with regard to reduction of at least three levels (degrees), or monitoring the development of retinopathy that requires photocoagulation or vitrectomy. The secondary goal was monitoring of the reduction (loss) of eyesight. The four-year follow-up showed the below indicated compared to the standard therapy:

• Intensive glycemic therapy significantly reduces the frequency of progressive retinopathy (7.3% vs. 10.4%), but not the loss of sight (16.3% vs. 16.7%);

• The intensive treatment of dyslipidemia significantly reduces the frequency of progressive retinopathy (6.5% vs. 10.2%), but not the loss of sight (16.0% vs. 15.2%);

• The intensive antihypertensive therapy does not reduce the progression of diabetic retinopathy or loss of eyesight (10.4% vs. 8.8%; that is, 19.4% vs. 15.8%).

The other sub-studies of monitoring some other microvascular complications of patients undergoing intensive glucoregulation for 3.5 years, followed by undergoing standard treatment for 1.5 years compared to the examinees who underwent standard treatment of glucoregulation for all 5 years recorded some different and interesting results. After five years, the common primary outcome (terminal stage of renal insufficiency, the need for dialysis or

noj skupini liječenja od ukupno 5.119 ispitanika[10]. Mikrovaskularne bubrežne komplikacije temeljene na analizi urina ukazale su na signifikantno smanjenje mikroalbuminurije u skupini intezivnog liječenja glukoregulacije. Zabilježeno je smanjenje albuminurije od 21% u fazi tranzicije studije (nakon 3,5 godina praćenja), dok je na kraju studije (pet godina) smanjenje mikroalbuminurije iznosilo 15%, što je međutim i dalje bilo statistički značajno. Ovi rezultati su konzistentni i vrlo slični rezultatima u DAIS i FIELD studijama[11,12]. Sekundarni ciljni ishod (periferna neuropatija zajedno s nefropatijom i retinopatijom) registriran je kod 38,2% ispitanika u skupini intezivnog liječenja i 40% ispitanika standardne skupine. Ako se promatra samo rezultat praćenja periferne neuropatije i to po standardnoj "Michigen neuropathy screening score (MNSI)" ljestvici >2,0, onda je ona bila manje zabilježena u skupini intenzivne glukoregulacije nego standardnoj skupini (55,6% naspram 58,6%). Gubitak tetivno-mišićnih refleksa i osjeta finog dodira su bili rjeđi u skupini intenzivne glokoregulacije na kraju studije, ali gubitak osjeta vibracije se nije razlikovao među skupinama.

Zaključimo osvrt na rezultate ACCORD studije i analize podstudija riječima dr Barbare EK Klein s University of Wisconsin: "Ne vjerujem da će iskustva proizišla iz ACCORD studije dovesti kliničare u dvojbu o važnosti kontrole glikemije u prevenciji mikrovaskularnih komplikacija kod dijabetičara. Moguće je ipak, da je režim liječenja primijenjen u ACCORD studiji bio preagresivan, za razliku od razboritog pristupa kojim uobičajeno pristupamo dijabetičarima tip 2 s povišenim rizikom za krvožilne pobole. No, vrlo je važno da rezultati ACCORD studije ne budu tendenciozno interpretirani, kako se ne bi vratili u lošu kontrolu glikemije. kao što je primjerice bilo prije objave rezultata studije UKPDS".[13-15]

Received: 25th Nov 2010

*Address for correspondence: Poliklinika za prevenciju kardiovaskularnih bolesti i rehabilitaciju, Draškovićeva 13, HR-10000 Zagreb, Croatia; Phone: +385-1-4612-290;

E-mail: goran.krstacic@zg.t-com.hr

transplantation of kidneys, the rise in serum creatinine >3.3mg/dL or a need for photocoagulation of retina or vitrectomy) was recorded in 556 patients in the intensive versus 586 in the standard group of treatment of totally 5.119 examinees[10]. Microvascular renal complications based on the analysis of urine indicated significant reduction of microalbuminuria in the group undergoing intensive treatment of glucoregulation. The reduction of albuminuria of 21% in the stage of transition of the study (after 3.5 years of follow-up) was recorded, while at the end of the study (5 years) the reduction of microalbuminuria was 15%, which was still statistically significant. These results are consistent and very similar to results in DAIS and FIELD studies[11,12]. The secondary target outcome (peripheral neuropathy together with nephropathy and retinopathy) was recorded in 38.2% examinees in the group undergoing intensive treatment and 40% of examinees undergoing standard treatment. If we only consider the screening score of peripheral neuropathy according to the standard "Michigen neuropathy screening score (MNSI)" scale >2.0, then it was less recorded in the group undergoing intensive glucoregulation than in the group undergoing standard glucoregulation (55.6% vs. 58.6%). The loss of tendon and muscular reflexes and fine touch sense were rarer in the group undergoing intensive glucoregulation at the end of the study, but the loss of vibration sense did not differ among the groups.

Let us make a review of the results of the ACCORD study and analysis of sub-studies using the words of Dr Barbara EK Klein from the University of Wisconsin: "I do not think that the experiences gained in the ACCORD study make the clinicians question the importance of controlling glycemia in prevention of microvascular complications in diabetics. Nevertheless, it is possible that the treatment regime applied in the ACCORD study was too aggressive, unlike the rational approach that we usually apply for approaching diabetics type 2 with increased risk of cardiovascular diseases. However, it is very important that the results of the ACCORD study should not be tendentiously interpreted as to prevent bad control of glycemia which occurred prior to the publication of results of the study UKPDS".[13-15]

Literature

1. Krstačić G, Reiner Ž. Inicijativa za smanjenje ostatnog rizika (R3i): Prvi sastanak nacionalnih predavača. Kardio list. 2009:4(8-9):67-9.
2. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol. 2008;102(10 Suppl):1K-34K.
3. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, et al for the Residual Risk Reduction Initiative (R3I). The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patient. Diab Vasc Dis Res. 2008;5:319-35.
4. The ACCORD Study Group. N Engl J Med. 2010;doi:10.1056/NEJMoa1001288.
5. The ACCORD Study Group. Effects of intensive glucose lowering therapy in type 2 diabetes mellitus. N Engl J Med. 2008;358:2545-59.
6. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85.
7. The ACCORD investigators. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563-74.
8. Nilsson PM. ACCORD and risk-factor control in type 2 diabetes. N Engl J Med. 2010;362:1628-30.
9. The ACCORD Study Group and ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010; 363:233-244.
10. Nichols GA. Closer Look at ACCORD's Microvascular Outcomes. http://www.medscape.com/viewarticle/729745 (25.11.2010)
11. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TME, Moffitt MS, et al for the FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. 2007;370:1687-97.
12. Steiner G. The Diabetes Atherosclerosis Intervention Study (DAIS): a study conducted in cooperation with the World Health Organization. Diabetologia. 1996;39:1655-61.
13. UK Prospective Diabetes Study 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;352:837-53.
14. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
15. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ. 1998;317:703-13.