Godina 2017. u kardiologiji: prevencija

The year in cardiology 2017: prevention

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Uvod

Tijekom 2017. objavljeni su rezultati nekoliko studija koje imaju praktične implikacije za prevenciju i kontrolu čimbenika rizika od aterosklerotske kardiovaskularne bolesti (ATSKVB), poput lipida, lipoproteina, upale, šećerne bolesti, arterijske hipertenzije i zdravog stila života. Izabrali smo izraz ATSKVB kako bismo pojednostavnili čitanje članka za nespecijaliste, iako moramo napomenuti da se točna dijagnoza ATSKVB-a ponešto razlikuje od studije do studije. Napominjemo da u dijelu gdje se ATSKVB ne može smatrati relevantnim čimbenikom ishoda (npr. istraživanja u arterijskoj hipertenziji), ne koristimo se izrazom ATSKVB, nego rabimo izraze za čimbenike ishoda specifične pojedinom području. Sve relevantne studije provedene su uz optimalnu farmakološku terapiju, prema postojećim Smjernicama Europskog kardiološkog društva (ESC) i Europskog društva za aterosklerozu (EAS) za prevenciju ATSKVB i liječenje dislipidemija.[1,2] Primjerice, u okrilju novih znanstvenih dokaza o dodatnom

Preamble

During 2017 several landmark studies have been published that have practical implications for atherosclerotic cardiovascular disease (ASCVD) prevention and risk factor control, such as lipids and lipoproteins, inflammation, diabetes, hypertension, and healthy lifestyle. We use the term 'ASCVD' where relevant to simplify the reading of this article for the non-specialist, although the exact definition as ASCVD differ slightly from study to study. However, in sections where ASCVD clearly is not the relevant endpoint (e.g. in hypertension research) we do not use 'ASCVD', but instead of use other words to describe endpoints. All relevant trials have been performed on a background of optimal medical therapy, such as described in the European Society of Cardiology(ESC)/European Atherosclerosis Society (EAS) guidelines on ASCVD prevention and management of dyslipidaemia for lipid-lowering.[1,2] For example, important new evidence for

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smanjenju rizika, primjenjuju se nove generacije hipolipemika [inhibitori PCSK9 (engl. *proprotein convertase subtilisin-kexin type 9 inhibitors*)[3] te inhibitori djelovanja kolesterol ester transfer proteina[4]], kontrolom sistemskoga upalnog procesa (inhibicija interleukina-1b[5]) i antitrombotskom terapijom (niskodozni antagonisti faktora Xa[6]). Budući da ovdje spomenuti novi oblici liječenja do ovoga trenutka još nisu ispitani u kombinacijama te zbog praktičnih i ekonomskih ograničenja, vrlo veliki izazov postaje izbor bolesnika za buduće studije. Također pritom valja imati na umu rizike koji se mogu povezati s primjenom novih oblika liječenja te njihovih kombinacija. Ovaj pregledni članak namijenjen je liječniku praktičaru kako bi mogao uspješno identificirati potencijalne kandidate za optimizaciju sekundarne prevencije, koji bi imali najviše koristi od primjene novih oblika liječenja (**slika 1**), a u isto vrijeme donosi sveobuhvatan prikaz noviteta u primarnoj i sekundarnoj prevenciji ATSKVB-a. Primjena i šira dostupnost novih oblika liječenja ovisit će primarno o tome živi li bolesnik u državi s visokim, srednjim ili nižim primanjima, broju čimbenika rizika, učestalosti kardiovaskularnog mortaliteta te različitosti potencijala za prevenciju, specifičnog u pojedinim zemljama.[7]

Životni stil

Opservacijskim epidemiološkim istraživanjima iz sfere životnoga stila teško se može u potpunosti vjerovati, dijelom zbog visokog rizika od isprepletenosti (trećina čimbenika rizika djeluje istodobno i na bolest i stil života) te obrnute uzročnosti (bolest mijenja životni stil bolesnika). Stoga moramo imati na umu da su mnogo vrednije randomizirane intervencijske studije te studije s genetskom Mendelovom randomizacijom. No nijedan oblik dizajna studije nije savršen.[8-10] Važno je napomenuti da je pokatkad vrlo teško primijeniti randomizirano intervencijsko istraživanje za čimbenike iz sfere životnoga stila te smo prisiljeni koristiti se opservacijskim ili genetskim studijama. U daljnjem su tekstu navedene studije iz 2017. godine koje bismo željeli posebno istaknuti.

additional risk reduction relates to lipid-lowering [proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition,[3] cholesteryl ester transfer protein (CETP) inhibition[4]] to the reduction of systemic inflammation (interleukin-1β inhibition[5]) and to anti-thrombotic therapy (low-dose factor Xa antagonism[6]). Since these novel treatments have not yet been tested in combination and because of the practical and economic limitations, an important challenge for the years to come is patient selection. Also, the benefit to risk dimension of any new therapeutic agent needs to be considered. This review article is intended to provide the practicing physician with the information needed to identify patients in secondary prevention that may benefit the most from additional novel treatments (**Figure 1**), and at the same time give a comprehensive update of novel insights relevant both to primary and secondary prevention of ASCVD. Use and accessibility of novel treatments will depend critically on whether patients live in high income, upper middle-income or lower middle-income countries, as levels of cardiovascular risk factors, cardiovascular mortality rates, and thus the prevention potential differ between such countries.[7]

Lifestyle

Observational epidemiology in the field of lifestyle is difficult to trust due to the high-risk of confounding (a third factor influences both disease risk and lifestyle) and reverse causation (diseases will change a person's lifestyle), and therefore only randomized intervention trials and genetic Mendelian randomizations studies can be trusted. However, each of these study designs have limitations.[8-10] Importantly, as randomized intervention trials are very difficult to conduct for lifestyle factors, we often are left with observational and genetic studies in this field. Below is what we choose to highlight for 2017.

The concept of 'metabolically healthy obesity', namely that in the absence of metabolic dysfunction, individuals with ex-

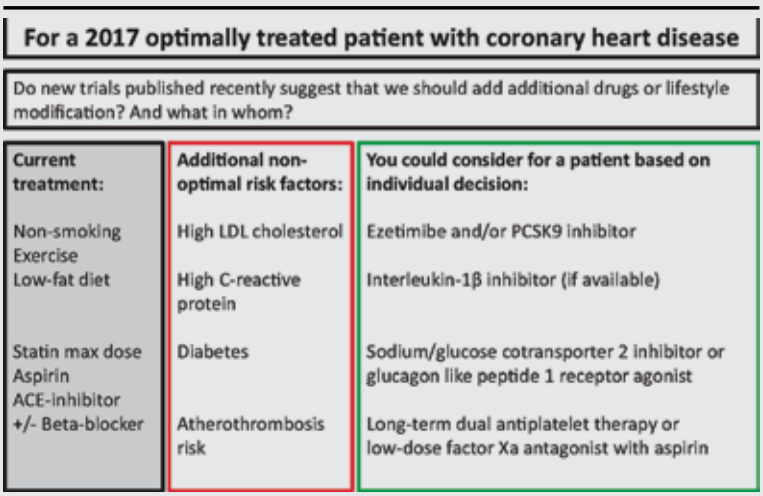

FIGURE 1. A 2017 optimally treated patient with coronary heart disease on statin, aspirin, angiotensin-converting enzyme inhibitor, and beta-blocker. Do new trials suggest that we should add additional drugs or lifestyle modification, and what in whom?

PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low-density lipoprotein cholesterol; ACE, angiotensin converting enzyme.

This Figure has been reprinted with permission of Oxford University Press on behalf of European Society of Cardiology.

Koncept „metabolički zdrave pretilosti", poglavito u smislu odsutnosti metaboličkog disbalansa, kao i smatranja da osobe s prevelikom tjelesnom težinom nemaju povećan kardiovaskularni rizik ostaje kontraverzan. Nedavno objavljena paneuropska studija o raku i prehrani (*European Prospective Investigation into Cancer and Nutrition study,* EPICCVD) utvrdila je povećan kardiovaskularni rizik, povezan s općom i centralnom adipoznošću.[11] Druge kohortne studije dovele su u pitanje ovaj koncept objavljujući podatke o povišenome kardiovaskularnom riziku u metabolički zdravih pretilih osoba, u usporedbi s pojedincima normalne tjelesne težine.[12-15] Spomenute studije ističu važnost sustavnoga pristupa prevenciji pretilosti na populacijskoj razini, ciljajući na prehrambene navike i primjenu tjelesne aktivnosti. Važno je naglasiti da se u bolesnika s koronarnom bolesti srca preporučuje postupan i kontinuirani gubitak tjelesne težine jer je usporedba najviših i najnižih varijacija u tjelesnoj težini povezana sa 64 %-tnim i 124 %-tnim povećanjem broja neželjenih smrti.[16]

Konzumacija kave u opservacijskim se studijama povezivala sa smanjenom učestalosti ukupne, kardiovaskularne i drugih specifičnih oblika smrtnosti.[17-19] No valja istaknuti da obrnuta uzročnost i isprepletenost s drugim čimbenicima životnoga stila mogu utjecati na rezultate. Zanimljivo je stoga da studije s Mendelovom randomizacijom, neopterećene isprepletenošću i s drugim čimbenicima, nisu našle uzročno-posljedične veze između konzumacije kave i ukupne ili kardiovaskularne smrtnosti ili učinka na kardiovaskularnu bolest.[19] U slično dizajniranim studijama pronađeno je da unos mlijeka nije uzročno povezan s rizikom od razvoja arterijske hipertenzije ili kardiovaskularne bolesti.[20,21]

Novije studije upućuju na to da postoji veza između konzumacije piva u vrijeme Oktoberfesta u Münchenu i veće učestalosti aritmija srca i sinusnih tahikardija.[22] Veće britanske i američke kohortne studije utvrdile su da je umjerena konzumacija alkohola povezana s redukcijom većeg dijela neželjenih kardiovaskularnih događaja, dok su pretjerana konzumacija alkohola i teža opijanja bila povezana s povišenim učestalosti kardiovaskularnih bolesti i smrtnih ishoda.[23-25]

Studije s Mendelovom randomizacijom ispitivale su genotipove povezane sa stupnjem edukacije te utvrdile su da osobe s nižim obrazovnim stupnjem imaju više s ATSKVB-om povezanih neželjenih događaja.[26] Analizom podataka iz britanske Biobanke opažena je povezanost između tjelesne aktivnosti i smrtnosti tako da su najviše stope smrtnosti bile povezane s najnižim stupnjem tjelesne snage i kondicije[27]. Čini se da prevencija ili odgađanje kardiovaskularne ili šećerne bolesti odgađa razvoj kognitivnog propadanja i vjerojatno demencije.[28]

Održavanje navika zdravog života, prestanak pušenja, blaga do umjerena konzumacija alkohola, viši stupanj tjelesne aktivnosti, unos voća i povrća, te održavanje normalne tjelesne težine bili su povezano sa znatno manjom učestalošću ATSKVB-a u kineskoj populaciji,[29] u skladu s rezultatima u ranijim europskim istraživanjima. Zanimljivo španjolsko istraživanje utvrdilo je povezanost nekoronarne i generalizirane ateroskleroze s preskakanjem doručka, neovisno o drugim čimbenika kardiovaskularnog rizika.[30] Važno je istaknuti da promjene životnih navika mogu donijeti koristi osobama s akutnim koronarnim sindromom ili već prije revaskulariziranih bolesnika.[31]

Nadalje, u studiji PURE, koja je diljem svijeta uključila 135 355 osoba u razdoblju od 2003. do 2013., uz praćenje do 2017. godine, pronađeno je da je viši unos voća, povrća i grahorica povezan s nižom učestalošću nekardiovaskularne i ukupne smrtnosti te s neznačajnim trendom smanjenja kardiovaskularnog rizika.

cess adiposity are not at greater cardiovascular risk, has been controversial. A recent pan-European case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition study (EPIC-CVD), observed higher cardiovascular risk with increasing general and central adiposity.[11] Other cohort studies have challenged this concept reporting an excess of cardiovascular risk in metabolically healthy obese as compared to normal weight individuals.[12–15] These results highlight the importance of population-wide prevention of obesity with lifestyle intervention targeting eating behaviour and physical activity. Importantly however, steady and sustained weight loss is preferable as in patients with coronary heart disease the highest vs. lowest variation in body weight was associated with 64% more coronary and 124% more mortality events.[16]

Coffee consumption is observationally associated with reduced all-cause, cardiovascular and other cause-specific mortality.[17–19] However, both reverse causation and confounding by other lifestyle factors may bias such results. Interestingly therefore, Mendelian randomization studies free of confounding found no causal effect of coffee intake on all-cause or cardiovascular mortality, or on cardiovascular disease.[19] Likewise, in Mendelian randomization studies milk intake appears not to influence risk of hypertension or cardiovascular disease.[20,21]

Alcohol intake: novel findings include that acute beer alcohol consumption during the Munich Octoberfest was associated with cardiac arrhythmias and sinus tachycardia.[22] Large UK and USA cohorts found moderate alcohol intake associated with less of most cardiovascular disease endpoints while heavy and binge drinking or alcohol abuse were associated with more cardiovascular disease or deaths.[23–25]

A Mendelian randomization study of genotypes associated with higher education suggested that low education is causally associated with ASCVD events.[26] Using UK-Biobank participants, it was observed that the association between physical activity and mortality was strongest in those with lowest strength and lowest cardiorespiratory fitness, suggesting that these subgroups would benefit the most from more physical activity[27]; preventing or delaying cardiovascular disease or diabetes seemed to delay cognitive decline and possibly dementia.[28]

Adherence to a healthy lifestyle consisting of non-smoking, light to moderate alcohol intake, high physical activity, fruit and vegetables intake, and normal body weight was associated with a substantially lower burden of ASCVD in Chinese,[29] like previously observed in Europeans. Interestingly, in Spain skipping breakfast was associated with more non-coronary and generalized atherosclerosis, independent of other cardiovascular risk factors.[30] Importantly however, lifestyle can be difficult to change, even for patients with acute coronary syndrome and/or revascularization.[31]

Further, in the PURE study covering all major parts of the World and recruiting 135 335 individuals between 2003 and 2013 with follow-up until 2017, higher intake of fruit, vegetables, and legumes was associated with lower non-cardiovascular and total mortality, with a non-significant trend for cardiovascular mortality.[32] The findings also included that as little as three servings per day consisting of only 375 g per day were associated with similar benefit. This indicate that optimal health benefits may be achieved with a more modest

skularne smrtnosti.[32] Studija također nalazi da čak i tri takva obroka, s ukupno 375 g na dan mogu biti povezani s podjednakom koristi. Ovi podatci upućuju na to da se optimalna razina zdravstvene dobrobiti može bolje postići umjerenom konzumacijom voća, povrća i grahorica, nego onakvom kakva je preporučena u razvijenim zemljama Europe i SAD-a s visokim primanjima, u smislu da se može bez većih problema primijeniti u zemljama s nižim i srednjim primanjima. Suprotno popularnom vjerovanju, visok unos masnoća nije bio povezan s ATSKVB-om ili smrtnim ishodima.

Naposljetku, onečišćenost zraka, buka i drugi okolišni stresori, ovisno o tome gdje osoba živi, mogu utjecati na kardiovaskularno zdravlje i smrtnost.[33,34] Primjerice, dugotrajna izloženost prometnoj buci i zagađenjima okoliša bili su povezani s negativnim kardiovaskularnim biokemijskim čimbenicima rizika[35] i samostalno prijavljenom učestalošću arterijske hipertenzije.[36] Onečišćenost zraka aerodinamičnim polutantima promjera <2,5 mm bila je peti po redu čimbenik smrtnosti diljem svijeta, s osobitim porastom u posljednjih 25 godina.[37]

LDL kolesterol

Uzročno-posljedična veza između visokog LDL kolesterola s ATSKVB-om jednoznačno je dokumentirana u velikim metaanalizama koje su uključivale više od 200 prospektivnih kohorti, u studijama mendelovske randomizacije te u randomiziranim

consumption of fruit, vegetables, and legumes than that recommended in high-income Europe and the USA, an approach that is more likely to be affordable in low-income and middle-income countries. In contrast to popular opinion, higher fat intake was not associated with ASCVD or death.

Finally, air pollution, noise, and other environmental stressors, depending on where a person choose to live, may influence cardiovascular health and mortality.[33,34] For example, long-term exposure to road traffic noise and ambient air pollution were associated adversely with cardiovascular biochemical risk factors[35] and self-reported hypertension.[36] Worldwide ambient air pollution with aerodynamic diameter <2.5 µm was the fifth-ranked mortality factor in 2015, and has increased in importance over 25 years.[37]

Low-density lipoprotein cholesterol

The causal role of high LDL cholesterol for ASCVD was clearly documented using large meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized trials including more than 2 million individuals with over 20 million person-years and over 150 000 ASCVD events.[38] Notably, this effect increased with duration of exposure to high LDL cholesterol, suggesting that the exposure in genetic Mendelian randomization studies determines the life-time ASCVD risk (**Figure 2**). Interestingly, as judged by

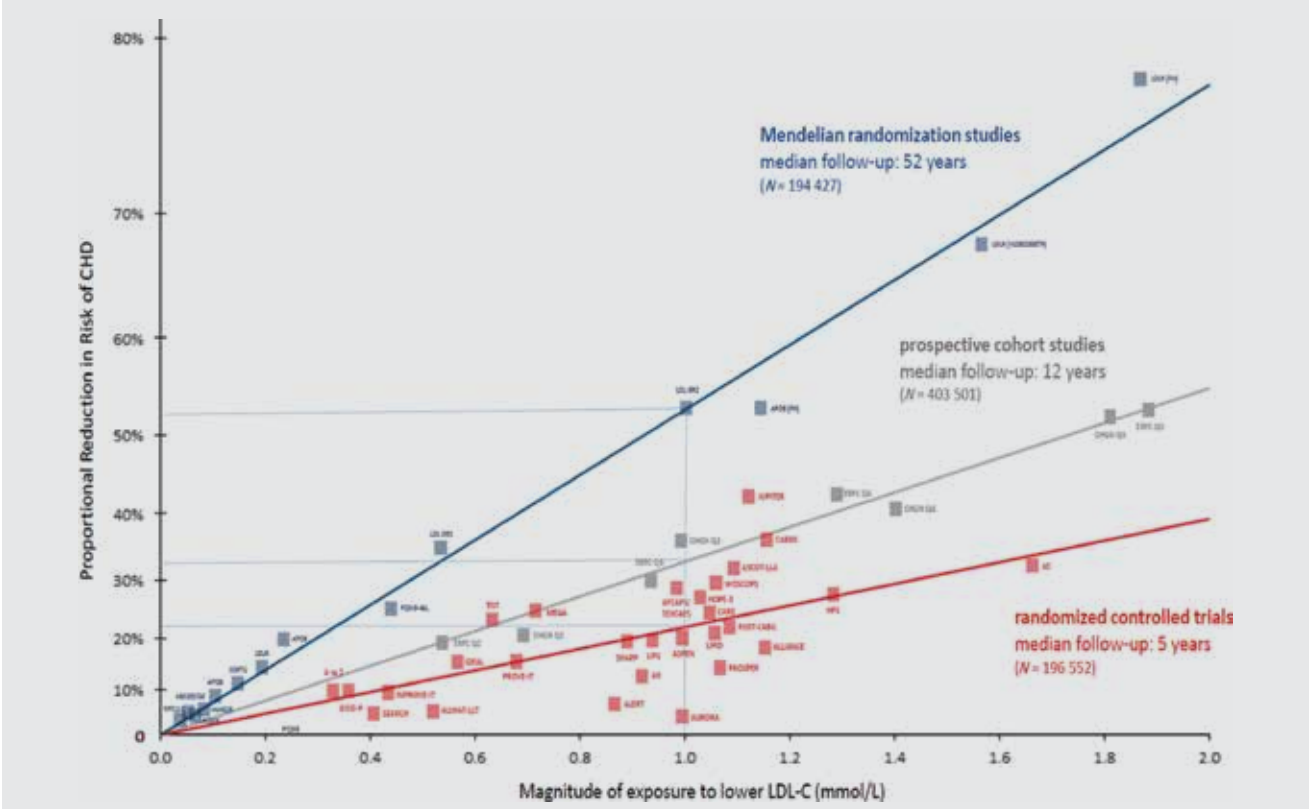

FIGURE 2. Association of change in LDL-C with risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies with lifelong 52 years exposure (=follow-up), prospective epidemiologic cohort studies with 12 years exposure, and randomized trials with 5 years exposure. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL cholesterol has both a causal and a cumulative effect on the risk of cardiovascular disease.

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol. Reproduced with permission from Ference *et al.*[38]

studijama koje su uključivale više od 2 milijuna pojedinaca, s 20 milijuna osoba na godinu te s više od 150 000 događaja u vezi s ATSKVB-om.[38] Nadalje, ovakav je učinak bio veći u odnosu prema dužini trajanja izloženosti visokim vrijednostima LDL kolesterola, implicirajući da je izloženost tom čimbeniku u genetskim mendelovski randomiziranim studijama povezana s učestalosti pojave ATSKVB-a (**slika 2**). Zanimljivo, procjenom kalcifikata koronarnih arterija u populaciji stočara i ratara bolivijske Amazone s LDL kolesterolom od samo 2,4 mmol/L te unatoč visokom infektivnom opterećenju registrirane su pet puta nižu učestalost koronarne ateroskleroze u usporedbi s populacijama iz industrijaliziranih zemalja.[39]

Najšire propisivani lijekovi koji smanjuju koncentraciju LDL kolesterola trenutačno su statini, koji ostvaruju svoj učinak smanjenjem endogene sinteze kolesterola. Primjenom maksimalnih doza statini mogu smanjiti vrijednost LDL kolesterola do 50 %, uz posljedično smanjenje učestalosti s ATSKVB-om povezanih neželjenih događaja također od 50 %. No, tako veliki učinci često se ne uspiju postići zbog nepridržavanja plana uzimanja lijekova, kao i interindividualnih razlika u djelovanju tih lijekova. Inhibitori PCSK9 ostvaruju djelovanje u sinergiji sa statinima, uz doprinos očuvanju LDL receptora te povećanju njihove gustoće na membranama jetrenih stanica, dodatno smanjujući koncentracije LDL kolesterola.

Važne studije uključuju i one s inhibitorima PCSK9, skupinom koja trenutačno ima najpotentniji učinak na redukciju LDL kolesterola. U studiji FURIER ukupno je 27 564 bolesnika s ATSKVB-om i LDL kolesterolom ≥1,8 mmol/L (ili ne-HDL kolesterol >2,6 mmol/L) liječeno intenziviranom statinskom terapijom i bilo randomizirano na evolokumab ili placebo[3]; LDL kolesterol je snižen za 59 %, na 0,8 mmol/L, s ATSKVB-om povezani neželjeni događaji za 15 % (apsolutno smanjenje rizika od 1,5 %), a učestalost infarkta miokarda smanjena je za 27 % (apsolutno smanjenje rizika 1,2 %). Nadalje, u dodatnoj analizi podataka iz studije FOURIER dokazana je smanjena učestalost ATSKVB-a pri koncentraciji LDL-a <0,2 mmol/L.[40] Iznenađujuće, nije bilo sigurnosnih problema s vrlo niskim vrijednostima LDL kolesterola tijekom 2,2 godine praćenja, uključujući nepromijenjenu učestalost šećerne bolesti, no ukupno je pronađeno da je genetski smanjen PCSK9 bio povezan s povećanim rizikom od razvoja šećerne bolesti.[41]

Nadalje, podstudija EBBINGHAUS iz studije FURIER nije pronašla razlika glede procjene kognitivnih funkcija između ispitivanih skupina u razdoblju praćenja od 19 mjeseci.[42] Podjednako, u studiji mendelovske randomizacije, koja je uključivala 111 194 ispitanika, niska vrijednost LDL kolesterola zbog genetskih varijanti PCSK9 i HMGCR nije imala uzročno-posljedičnih učinaka na rizik od razvoja Alzheimerove bolesti, vaskularne demencije, bilo koje vrste demencije ili Parkinsonove bolesti.[43] Također, u grupiranju 14 studija faze 2. i 3. s alirokumabom ili placebom, vrijednosti LDL kolesterola niže od 0,4 mmol/L nisu bile povezane s porastom neurokognitivnih događaja.[44] Slični su zaključci doneseni i grupiranjem podataka iz 12 studija faze 2. i 3. s evolukumabom ili placebom.[45] Naposljetku, u studiji IMPROVE-IT pacijenti na ezetimibu s vrijednostima LDL kolesterola <0,8 mmol/L imali su podjednak sigurnosni profil tijekom 6-godišnjeg razdoblja u usporedbi s bolesnicima koje su imali više koncentracije LDL kolesterola.[46]

Dvije randomizirane placebo kontrolirane studije koje su ispitivale PCSK9 inhibitor bokocizumab prekinute su u ranoj fazi zbog razvoja humaniziranih monoklonskih protutijela na bokocizumab[47,48]: ovaj PCSK9 inhibitor gubio je učinak kroz vrijeme, usporedo s razvojem protutijela na lijek. Bokocizu-

coronary artery calcification a forager-horticulturalist population of the Bolivian Amazon with LDL cholesterol of only 2.4 mmol/L (91 mg/dL) and despite high infectious inflammatory burden, had five-fold lower coronary atherosclerosis as compared to industrialized populations.[39]

The most prescribed drugs for LDL cholesterol lowering at present are statins that reduce endogenous cholesterol synthesis. Using maximal doses, statins can reduce LDL cholesterol levels by up to 50% and in consequence ASCVD events by up to 50%; however, such large effect sizes are not always obtained likely due to poor compliance and inter-individual variability in drug effects. Working synergistically with statins, PCSK9 inhibitors contribute to preservation of LDL receptors and increase their density at the membrane of liver cells, thus enhancing the reduction of LDL cholesterol.

Landmark trials include those with PCSK9 inhibition, currently the most effective approach to lower LDL cholesterol. In the FOURIER trial, 27 564 patients with ASCVD and LDL cholesterol ≥1.8 mmol/L (70 mg/dL) [or non-HDL cholesterol >2.6 mmol/L (100 mg/dL)] treated with intense statin therapy, were randomized to evolocumab or placebo[3]: LDL cholesterol was reduced 59% to 0.8 mmol/L (30 mg/dL), ASCVD events 15% (absolute risk reduction 1.5%), and myocardial infarction was reduced 27% (absolute risk reduction 1.2%). Moreover, a prespecified secondary analysis of FOURIER suggested reduced ASCVD at achieved LDL cholesterol <0.2 mmol/L (8 mg/dL).[40] Conversely, there were no safety concerns with very low LDL cholesterol over 2.2 years including no change in risk of diabetes; however, lifelong genetically reduced PCSK9 did appear to cause a small increase in risk of diabetes.[41]

Further, the EBBINGHAUS substudy of FOURIER examining cognitive function did not detect between-group differences over 19 months.[42] Similarly, in a Mendelian randomization study involving 111 194 individuals, low LDL cholesterol caused by *PCSK9*, and *HMGCR* genetic variants had no causal effect on the risk of Alzheimer's disease, vascular dementia, any dementia, or Parkinson's disease.[43] Also, pooling data from 14 phase 2 and 3 studies of alirocumab vs. placebo, LDL cholesterol levels <0.4 mmol/L (15 mg/dL) was not associated with increases in neurocognitive events.[44] A similar conclusion came from pooling data from 12 phase 2 and 3 studies of evolocumab vs. placebo.[45] Finally, in the IMPROVE-IT trial using ezetimibe patients achieving LDL cholesterol <0.8 mmol/L (30 mg/dL) had a similar safety profile over a 6-year period compared with patients achieving higher LDL cholesterol concentrations.[46]

Two randomized trials comparing the PCSK9 inhibitor bococizumab with placebo were stopped prematurely due to immunogenic effects of the humanized monoclonal antibody bococizumab[47,48]: this PCSK-9 inhibitor lost efficacy with time due to developments of anti-drug autoantibodies. Bococizumab had no benefit with respect to ASCVD events in the trial involving lower-risk patients with a very short follow-up, but did have a significant benefit in the trial involving higher-risk patients with a longer follow-up. The ODYSSEY clinical outcomes study using PCSK9 inhibition with alirocumab in patients after an acute coronary syndrome is still ongoing. Based on the new PCSK9 endpoint trials, an updated ESC/EAS consensus document reported recommendations on the use of PCSK9 inhibition in clinical practice in patients with ASCVD or familial hypercholesterolaemia (FH).[49]

mab nije imao učinak na pojavu događaja ATSKVB u uvjetima koji su uključivali bolesnike niskog rizika s kratkim razdobljem praćenja, ali je pokazao dobrobit u studiji koja je uključivala bolesnike s visokim rizikom uz dulje praćenje. Studija ODYSSEY, koja prati kliničke ishode PCSK9 inhibitora alirokumaba u bolesnika s akutnim koronarnim sindromom, još je uvijek u tijeku. Na temelju studija ishoda novih inhibitora PCSK9 objavljena je dopuna ESC/EAS smjernica za primjenu inhibitora PCSK9 u kliničkoj praksi u bolesnika s ATSKVB-om ili porodičnom hiperkolesterolemijom (FH).[49]

Nadalje, pronađeno je da mala interferencija PCSK9 terapije s RNA terapijom incliseranom dovodi do pada PCSK9 i LDL kolesterola u istraživanju faze 1. na zdravim dobrovoljcima[50] te u bolesnika s povišenim kardiovaskularnim rizikom u studiji faze 2.[51] Nakon 180 dana vrijednosti su kolesterola bile snižene za 28 – 42 % primjenom jedne doze incliserana, a za 36 – 53 % nakon primjene dviju doza.[51] Ovaj se lijek trenutačno testira u fazi 3. kliničkog istraživanja. Terapije koje interferiraju s RNA izazivaju pad PCSK9 proteina i njihova je prednost u tome da dugo djeluju pa se mogu primjenjivati jednom u tri do šest mjeseci.

U studijama koje su ispitivale APOE3*Leiden.CETP miševe, pokazano je da PCSK9 imunizacija, primjenom AT04A i anti-PCSK9 cjepiva, dovodi do znatnog pada u plazmatskim koncentracijama lipida, sistemske i vaskularne upale te aterosklerotskih lezija u aorti.[52] Trenutačno je u tijeku istraživanje faze 1., koja ispituje primjenu cjepiva.

U studiji HIJ-PROPER ispitivan je dodatak ezetimiba uz pitavastatin u bolesnika s akutnim koronarnim sindromom, ali to nije rezultiralo smanjenjem učestalosti neželjenih događaja povezanih s ATSKVB-om. Studija je bila limitirana brojem ispitanika <2000 te se u onih u kojih je apsorpcija kolesterola bila visoka za 29 % smanjila učestalost neželjenih događaja u vezi s ATSKVB-om (apsolutno smanjenje rizika od 9,7 %).[53]

Porodična hiperkolesterolemija

Jedan od najvećih potencijala za prevenciju ATSKVB-a širom svijeta jest u ranom pronalasku i liječenju osoba s FHom. Zbog činjenica da se FH može pronaći u 1/250 (prije nego 1/500)[54-56], zbog nedovoljnog dijagnosticiranja i liječenja[57-59] te zbog toga što inhibitori PCSK9 u kombinaciji sa statinima dovode do učinkovitog pada LDL kolesterola u FH, povećava se interes za istraživanja FH. Nakon optimirane statinske terapije, primjena inhibitora PCSK9 dodatno snizuje vrijednosti LDL kolesterola do 65 % u heterozigota za FH te podjednako toliko u homozigota za FH, što znatno ovisi o vrste prisutnih mutacija te o posljedičnoj mogućnosti da djeluje na LDL receptore.

Studija iz Japana pronašla je da su klinički znakovi FH i mutacije FH kumulativno dodavali rizik od ATSKVB, povrh samo vrijednosti LDL kolesterola.[60] Od toga treba izuzeti Nizozemsku, Norvešku i brojne druge europske zemlje, kao i Kanadu, te većinu zemalja svijeta u kojima se FH slabo dijagnosticira te se ne primjenjuju metode genskog testiranja (**grafikon 1 - poruka članka**).[61] Premda Japan ima relativno visoku učestalost probira na FH, u isto vrijeme genetski se testovi zapravo malokad primjenjuju. Prednosti genskog testiranja leže u kaskadnom otkrivanju inicijalnih slučajeva FH te članova njihovih obitelji[62], a takvo testiranje u Velikoj Britaniji uključuje uvođenje terapije antilipemikom, uz procjenu troškova za dodatnoga člana obitelji od samo 1.212 eura (1.092 funti), ako se 3,2 rođaka inicijalno pozitivnog bolesnika testiraju.[63] Stoga možemo li si dopustiti da ne provodimo probir na FH?[64]

Notably, PCSK9 small interfering RNA therapy with inclisiran was found to lower PCSK9 and LDL cholesterol levels in a phase 1 study of healthy volunteers[50] and among patients at high cardiovascular risk in a phase 2 study.[51] At day 180, the mean reductions in LDL cholesterol levels were 28–42% after only one single dose of inclisiran and 36–53% after two doses.[51] This compound is currently entering a phase 3 clinical study program. RNA interfering therapies lower the PCSK9 protein and their advantage lies to the long dosing possibility, once every 3 or 6 months.

Moreover, in experimental studies in APOE*3Leiden.CETP mice it was shown that PCSK9 immunisation using the AT04A anti-PCSK9 vaccine resulted in a significant reduction of plasma lipids, systemic and vascular inflammation, and atherosclerotic lesions in the aorta.[52] A phase 1 study using the vaccine is currently ongoing.

Finally, in the HIJ-PROPER study of acute coronary syndrome patients ezetimibe added to pitavastatin did not significantly lower ASCVD events overall; however, the study size was limited with <2000 patients and in those with higher cholesterol absorption a 29% reduced ASCVD event rate was observed (absolute risk reduction 9.7%).[53]

Familial hypercholesterolaemia

One of the biggest potential for preventing ASCVD worldwide is to find and treat individuals with FH early in life. Because of the recognition that FH is found in roughly 1/250 (rather than 1/500),[54–56] because FH is underdiagnosed and undertreated,[57–59] and because PCSK9 inhibitors together with statins now offer efficient LDL cholesterol reduction in FH, interest in FH research is increasing. After optimal statin therapy, PCSK9 inhibitors can reduce LDL cholesterol by an additional up to 65% in individuals with heterozygous FH, and up to the same absolute extent in the very rare individuals with homozygous FH but depending critically on the types of mutations involved and thus the ability to up-regulate LDL receptors.

A Japanese study documented that clinical signs of FH and FH mutations additively added to ASCVD risk above high LDL cholesterol alone[60]; importantly however, except for the Netherlands, Norway, a number of other European countries, and Canada, in most countries in the World FH is underdiagnosed and genetic testing is not used (**Chart 1 - Take home figure**)[61]; although Japan has a relatively high rate of FH screening, genetic testing is still only used rarely in Japan. The advantage of genetic testing is the use in cascade screening of FH index cases and their family members,[62] and such testing in the UK including consequent cholesterol-lowering treatment has an estimated lifetime cost per relative tested of only 1212 Euro (£1092) if 3.2 relatives are tested per mutation-positive index case.[63] Thus, can we afford not to screen for FH?[64]

To better select individuals for genetic testing for FH, based on Dutch data with validation in Canada, an online calculator to estimate the probability of an FH mutation in individual patients has been developed.[65] Further, among Spanish patients with acute coronary syndrome and LDL cholesterol ≥4.1 mmol/L (160 mg/dL), 9% had an FH mutation.[66] Also, using the Dutch Lipid Clinic Network Criteria or simply a high LDL cholesterol alone also improved finding those with FH mutations[55]; the most optimal threshold for LDL cholesterol concentration to discriminate between Danish mutation carriers and non-carriers was 4.4 mmol/L (170 mg/dL).

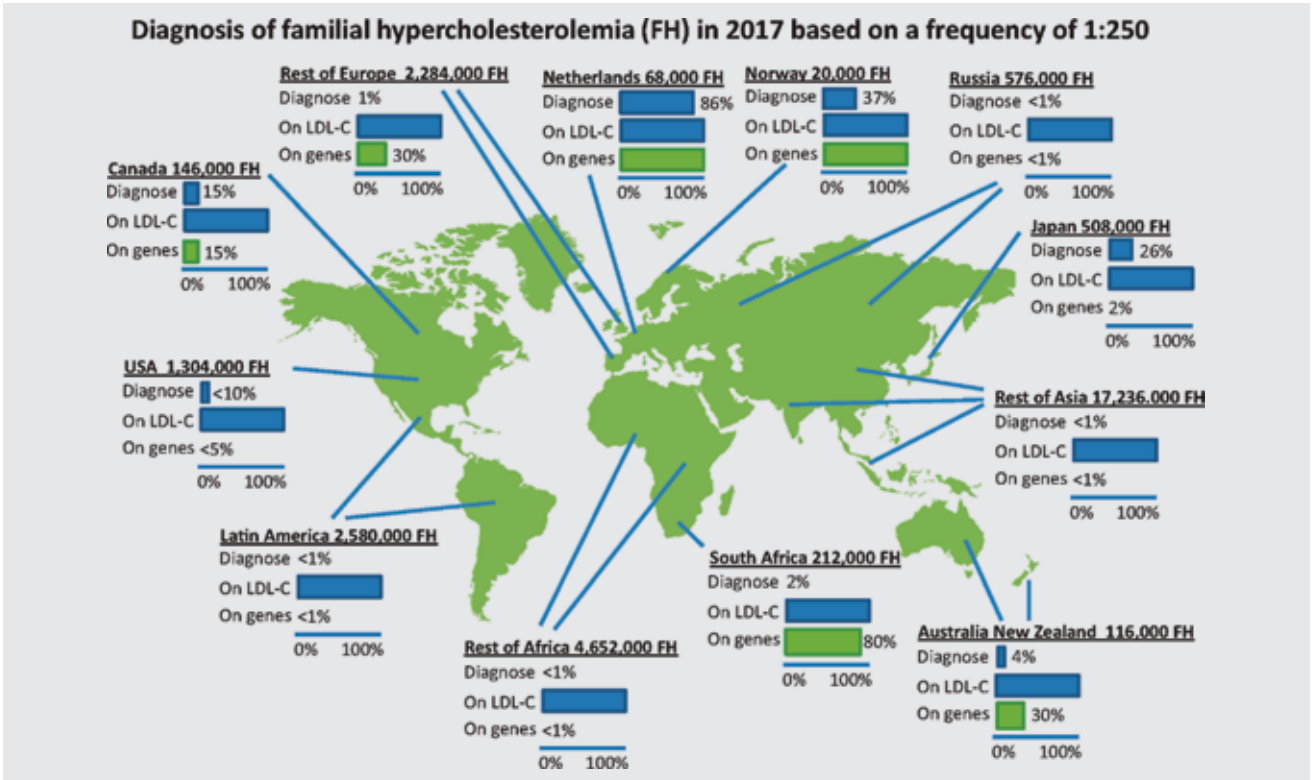

CHART 1 - *Take home figure*. Number of individuals with familial hypercholesterolaemia based on an estimated frequency of 1:250 in the general population. *Diagnose*, estimate of individuals diagnosed with familial hypercholesterolaemia in 2017, as the fraction of all individuals with familial hypercholesterolaemia. *On LDL-C*, estimate of the fraction of all individuals diagnosed with familial hypercholesterolaemia who have the familial hypercholesterolaemia diagnosis based solely on LDL cholesterol (possibly together with clinical signs of familial hypercholesterolaemia). *On genes*, estimate of the fraction of all individuals diagnosed with familial hypercholesterolaemia who have the familial hypercholesterolaemia diagnosis based on a combination of genetic screening for mutations in the low-density lipoprotein receptor, apolopoprotein B, or proprotein convertase subtilisin/kexin type 9 genes together with LDL cholesterol and possibly clinical signs.

FH: familial hypercholesterolaemia. Reproduced with permission from Nordestgaard and Benn.[61]

Kako bi se bolje identificirali pojedinci za gensko testiranje FH, a temeljem Nizozemskih smjernica validiranih u Kanadi, stvoren je *on-line* kalkulator za procjenu vjerojatnosti FH mutacija u pojedinaca.[65] Nadalje, kada su u Španjolskoj testirani bolesnici s akutnim koronarnim sindromom i vrijednostima LDL kolesterola ≥4,1 mmol/L, njih 9 % imalo je mutaciju FH.[66] Također, primjena nizozemskih kliničkih kriterija za lipide ili, jednostavno, samo visoke vrijednosti LDL kolesterola pomogle su pri identifikaciji slučajeva s mutacijom FH[55]; optimalna granica vrijednosti LDL kolesterola koja je razdvajala nositelje danskih mutacija i nenositelje bila je 4,4 mmol/L.

U djece homozigota za FH rosuvastatin je dovodio do pada vrijednosti LDL kolesterola od 22 %[67], a u djece heterozigota za FH rosuvastatin je usporavao progresiju zadebljanja intime-medije karotide[68], podržavajući rano uvođenje statinske terapije u djece s FH. Zanimljivo, proinflamatorni fenotip monocita bolesnika s FH premošten je terapijskom redukcijom vrijednosti LDL kolesterola.[69] Nadalje, na temelju rezultata iz registra SAFEHEART iz Španjolske, procjena rizika od ATSKVB-a ovisila je o dobi, spolu, prethodnim ATSKVB-ima, vrijednostima arterijskoga tlaka, indeksu tjelesne mase,

In children with homozygous FH rosuvastatin reduced LDL cholesterol by 22%[67] and in children with heterozygous FH rosuvastain slowed the progression of carotid intima-media thickness,[68] supporting early statin therapy in children with FH. Interestingly, the pro-inflammatory phenotype of monocytes in FH patients was dampened by LDL cholesterol lowering.[69] Further, based on the Spanish SAFEHEART registry, ASCVD risk prediction depended on age, sex, previous ASCVD, blood pressure, body mass index, smoking, LDL cholesterol, and lipoprotein(a)[70]; an independent predictive value of lipoprotein(a) in FH for ASCVD agrees with previous findings.[71] Finally, based on WOSCOPS trial 20-years follow-up data we can now say definitively that statin treatments of primary prevention patients with LDL-C ≥4.9 mmol/L (190 mg/dL) is safe and leads to significant reductions in ASCVD events and total mortality.[72]

Lipoprotein(a)

Genetic evidence documents that lipoprotein(a) is causally related to myocardial infarction, atherosclerotic stenosis, and

pušenju, LDL kolesterolu i vrijednostima lipoproteina(a)[70]; identificirajući nezavisno djelujuću prediktivnu vrijednost lipoproteina(a) u FH za razvoj ATSKVB-a, koja je u skladu s ranijim istraživanjima.[71] Naposljetku, na osnovi studije WOSCOPS s 20-godišnjim praćenjem danas možemo definitivno reći da je statinsko liječenje u primarnoj prevenciji osoba s LDL-C ≥4,9 mmol/L sigurno te da dovodi do smanjenje razvoja događaja u vezi s ATSKVB-om i ukupne smrtnosti.[72]

Lipoprotein(a)

Genska istraživanja potvrđuju da je lipoprotein(a) uzročno-posljedično povezan s razvojem infarkta miokarda, aterosklerotskim stenozama i stenozom aortnog zalistka, no ne nužno povezan s razvojem rane ateroskleroze.[73,74] Do sada je fokus istraživanja bio na genskim varijacijama koje dovode do porasta lipoproteina(a) te porasta rizika od obolijevanja, no u 2017. identificirane su male izoforme lipoproteina(a) kao nove genske varijante koje dovode do smanjivanja lipoproteina(a) i sniženja ukupnog rizika od kardiovaskularnih bolesti.[75] Novim pristupom u genetskim istraživanjima, koji analizira genske varijante koje su povezane s koncentracijom lipoproteina(a), a ne s brojem kringle IV-2, ili obrnuto, pokazujući da je povećan rizik od razvoja šećerne bolesti uz niže vrijednosti lipoproteina(a) objašnjen preko visokih vrijednosti kringle IV-2, a ne samo preko niskih vrijednosti lipoproteina(a) *per se*.[76] Za buduće pak agresivnije terapijsko snizivanje vrijednosti lipoproteina(a)[74,77] to je ohrabrujuća činjenica.

Vrijednosti lipoproteina(a) variraju širom Europe, no visoke su vrijednosti povezane s visokim rizikom od ATSKVB-a u svim regijama[78], uz napomenu da su vrijednosti koncentracija lipoproteina(a) bile niže u navedenoj studiji od onih u drugim studijama, te posljedičnim stvaranjem potrebe da se mjerenja lipoproteina(a) standardiziraju.

U ovom je trenutku statinska terapija indicirana u osoba s visokim vrijednostima lipoproteina(a) kako bi se smanjio rizik ATSKVB. Druga terapijska istraživanja uključivala su aferezu, inhibitore PCSK9 i antisense-oligonukleotide kojima je svrha bila proizvodnja lipoproteina(a).[74,77] Zanimljivo i iznenađujuće, u studiji na samo 20 bolesnika s refraktornom anginom afereza je dovodila do poboljšanja perfuzije miokarda, smanjenja aterosklerotskih plakova, boljeg podnošenja tjelesnih opterećenja i poboljšanja simptoma[79], što implicira vrijednost za pokretanje dodatnih istraživanja u sličnom okruženju primjenom PCSK9 inhibitora ili antisense-oligonukleotida.[80]

Trigliceridi i ostatne čestice

U tijeku su tri velike randomizirane dvostuko slijepe studije učinka lijekova koji snizuju trigliceride omega-3 masnim kiselinama ili pemafibratima [studije REDUCE-IT (NCT01492361), STRENGTH (NCT02104817) i PROMINENT (NCT03071692)] na ishode ATSKVB-a kod osoba koje su već na terapiji statinima. U međuvremenu jačaju genski dokazi da su, uz LDL kolesterol i trigliceridima bogati lipoproteni te ostatni kolesterol neovisni čimbenik rizika za ATSKVB[9]. Ostatni kolesterol sadržava sve trigliceridima bogate lipoproteine i može se izračunati (razlika LDL i HDL kolesterola) ili se sada može izravno mjeriti u standardnim bolničkim laboratorijskim analizatorima.[81]

Osobe s mutacijom gubitka funkcije angiopoetin-nalik proteina 3 (ANGPTL3), poznatog inhibitora lipoproteinske lipaze, koja razgrađuje trigliceridne lipoproteine, imale su 27 % niže

aortic valve stenosis, but not necessarily with development of early atherosclerosis.[73,74] Until now focus has been on genetic variants that increases lipoprotein(a) and increases disease risk, but in 2017 in individuals with small apolipoprotein(a) isoforms a novel genetic variant that reduces lipoprotein(a) and cardiovascular disease risk was documented.[75] Another novel genetic approach include the use of genetic variants solely associated with lipoprotein(a) concentrations and not with number of kringle IV-2, or *vice versa*, to show that the higher diabetes risk observed at low lipoprotein(a) is explained by high kringle IV-2 and not by low lipoprotein(a) *per se*[76]; for future aggressive lipoprotein(a) lowering,[74,77] this is a reassuring finding.

Across Europe lipoprotein(a) levels vary; however, high lipoprotein(a) was associated with high ASCVD risk in all regions[78]; absolute lipoprotein(a) concentrations were lower in this study than in many others, pointing towards the need for further standardization of lipoprotein(a) measurements.

At present, statins are applied to individuals with high lipoprotein(a) to reduce ASCVD risk. Other investigational therapies include apheresis, PCSK9 inhibitors, and most importantly antisense oligonucleotides targeting apolipoprotein(a) production.[74,77] Interestingly and surprisingly, in a study of only 20 patients with refractory angina lipoprotein apheresis improved myocardial perfusion, atheroma burden, exercise capacity, and symptoms[79]; these findings may initiate studies in similar patients using PCSK9 inhibitors or antisense oligonucleotides.[80]

Triglycerides and remnants

Three large randomized double-blind ASCVD endpoint trials of triglyceride-lowering with omega-3 fatty acids or pemafibrate in individuals already on a statin, the REDUCE-IT (NCT01492361), STRENGTH (NCT02104817), and PROMINENT (NCT03071692) trials, are now ongoing. In the meantime, the genetic evidence that triglyceride-rich lipoproteins and remnant cholesterol represent an independent cause of ASCVD beyond LDL cholesterol is increasing in strength[9]; remnant cholesterol is the cholesterol content of all triglyceride-rich lipoproteins and can either be calculated (total minus LDL minus HDL cholesterol) or now also measured directly on standard hospital autoanalysers.[81]

Individuals with loss-of-function mutations in angiopoietin-like protein 3 (ANGPTL3), a known inhibitor of triglyceride-degrading lipoprotein lipase, had 27% lower triglycerides, 9% lower LDL cholesterol, and 41% lower ASCVD risk[82]; similar findings were observed in an independent study.[83] Pharmacologically, antibodies against ANGPTL3 reduced triglycerides by up to 76% and LDL cholesterol up to 23%,[82] while antisense oligonucleotides against ANGPTL3 messenger RNA reduced triglycerides by up to 63% and LDL cholesterol up to 33%.[84]

Conversely, loss-of-function mutations in lipoprotein lipase lead to increased triglycerides and increased ASCVD risk,[85] supporting earlier findings.[86] Another novel observation include that autoantibodies against glycosylphosphatidylinositol-anchored HDL binding protein 1 (GPI-HBP1), a facilitator of lipoprotein lipase, lead to severely elevated triglycerides.[87] Together with previous evidence,[9] the above mentioned findings from 2017 suggest that pharmacological improved lipoprotein lipase activity, directly or through blocking inhibitors of the enzyme, will lead to lower triglycerides and lower ASCVD risk.

trigliceride, 9 % niži LDL kolesterol te 41 % niži rizik od ATSKVB-ak[82]; slični su rezultati utvrđeni i u jednoj neovisnoj studiji.[83] Farmakološki, protutijela protiv ANGPTL3 snizila su vrijednost triglicerida i do 76 %, a LDL kolesterol do 23 %,[82] dok su antisense-oligonukleotidi protiv ANGPTL3 glasničke RNA smanjili vrijednost trigicerida do 63 % i LDL kolesterol do 33 %.[84]

Suprotno tomu, mutacija gubitka funkcije lipoproteinske lipaze dovodi do povećanja triglicerida i povećanja rizika od ATSKVB-a[85] podupirući prijašnja zapažanja.[86] Druga, novija spoznaja uključuje da autoantitijela protiv glycosylphosphatidylinositol-sidreni HDL vezujućeg proteina 1 (GPI-HBP1), facilitatora lipoproteinske lipaze, uzrokuju visoki porast triglicerida.[87] Zajedno sa starijim dokazima[9] gore navedni podatci iz 2017. godine upućuju na to da će farmakološkim pojačanjem aktivnosti lipoproteinske lipaze, izravno ili blokirajući inhibitore enzima, nastupiti snizivanje vrijednosti triglicerida i smanjivanje rizika od ATSKVB-a.

Još jedna novija spoznaja jest da su genske varijante triglicerida povezane s kalcifikatima mitralnog anulusa[88]; buduće bi studije trebale ispitati hoće li smanjivanje razine triglicerida smanjiti bolest mitralnog zalistka. Konačno, kako sada mnoge smjernice diljem svijeta preporučuju analizu lipidnoga profila bez prethodnog gladovanja radije nego natašte, prosječne vrijednosti triglicerida tijekom ciklusa od 24 sata bit će ubuduće vidljive mnogim bolesnicima i kliničarima.[89]

HDL kolesterol

Niska vrijednost HDL kolesterola smatra se markerom rizika (ne uzročnim čimbenikom) za ATSKVB. Prije se mislilo da će visoka vrijednost HDL kolesterola prevenirati ili pomoći u

Another novel observation is that triglyceride-related genetic variant were associated with mitral annular calcification[88]; future studies should examine if lowering of triglycerides will reduce mitral valve disease. Finally, as many guidelines worldwide now recommend non-fasting rather than fasting lipid profiles the average triglyceride levels during most of a 24 h cycle will be obvious for many patients and clinicians in the future.[89]

High-density lipoprotein cholesterol

Low HDL cholesterol is considered a risk marker (not a causal factor) for ASCVD. Previously, it was thought that high HDL cholesterol would prevent or help reverse atherosclerosis by mediating transfer of cholesterol from the arterial wall to the liver for excretion. Cholesteryl ester transfer protein inhibitors increase the concentration of HDL cholesterol by blocking cholesterol transfer between HDL and other lipoprotein particles, and not necessarily through cholesterol uptake from the arterial wall.

Results of recent trials showed that treatment with CETP inhibitors increased HDL cholesterol in the ACCELERATE trial[90] and in the dal-OUTCOMES study,[91] without profound reductions of apolipoprotein B, and had no effect on ASCVD (**Figure 3**); the Dal-GenE randomized trial is ongoing to examine cardiovascular effects of dalcetrapib in a genetically defined population.[92] In the ILLUMINATE trial with 72% higher HDL cholesterol increases in ASCVD and all-cause mortality was observed[93]; the negative outcome in ILLUMINATE have been associated with off-target effects. Although the recent REVEAL HPS-3/TIMI-55 study observed 9% less ASCVD (ab-

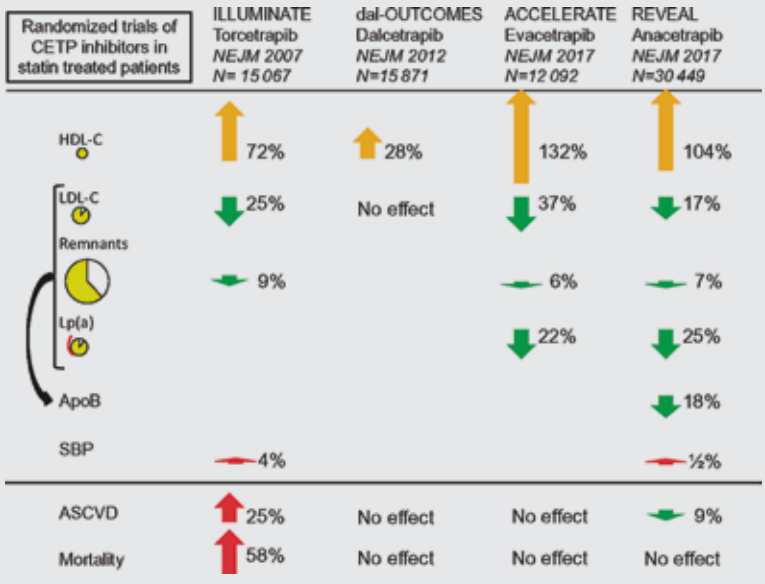

FIGURE 3. Summary of main results from randomized, double-bind, placebo-controlled trials of cholesterol ester transfer protein inhibition in statin treated patients. This figure does not illustrate in detail the contrasting safety profiles of these four cholesterol ester transfer protein inhibitors.

ASCVD, atherosclerotic cardiovascular disease; ApoB, apolopoprotein B; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); CETP, cholesterol ester transfer protein.

This Figure has been reprinted with permission of Oxford University Press on behalf of European Society of Cardiology.

obrnutom tijeku ateroskleroze sudjelovanjem u preuzimanju i prijenosu kolesterola iz arterijske stijenke do jetre i njegove ekskrecije. Inhibitori kolesteril ester transfer proteina povećavaju vrijednost HDL kolesterola blokirajući transfer kolesterola između HDL-a i ostalih lipoproteina, a ne nužno preuzimanjem kolesterola iz arterijske stijenke.

Rezultati novijih istraživanja pokazali su da je liječenje inhibitorima CETP povećalo HDL kolesterol u studijama ACCELERATE[90] i dal-OUTCOMES[91], bez znatnog smanjenja apolipoproteina B i bez učinka na ATSKVB (**slika 3**). Radomizirana studija Dal-GenE je u tijeku i ispituje kardiovaskularne učinke dalcetrapiba u genetski definirane populacije.[92] U studiji ILLUMINATE uz 72 % povišenja HDL kolesterola registriran je porast učestalosti ATSKVB-a i ukupne smrtnosti[93]; negativni ishod u ILLUMINATE studiji bio je povezan s neželjenim učincima. Premda se u novijoj studiji REVEAL HPS-3/TIMI-55 prikazano smanjenje ATSKVB-a za 9 % (apsolutno smanjenje rizika 1,0 %) podudara sa 104 %-tnim porastom HDL kolesterola, smanjenje lipoproteina koji sadržavaju apolipoprotein B vjerojatno je objašnjenje pozitivnog učinka[4], a to je podržano i studijom s genetskom Mendelovom randomizacijom.[94] Nijedan od inhibitora CETP neće biti dostupan u kliničkoj praksi. Važno je istaknuti da aktualne ESC/EAS smjernice za dislipidemiju ne preporučuju vrijednost HDL kolesterola kao ciljno liječenja u prevenciji ATSKVB-a.[2]

Osim toga, bitno je da se povoljni kardiovaskularni učinci anacetrapiba ne bi smjeli izravno uspoređivati s učincima statina, ezetimiba, ili inhibitora PCSK9, koji svi djeluju tako da pojačavaju učinak LDL receptora na uklanjanje LDL kolesterola. Suprotno tomu, CETP inhibicija utječe na količinu kolesterola u LDL-u, drugim apolipoproteinima B i HDL-u učinkom na izmjenu kolesterola i triglicerida između lipoproteinskih čestica.

solute risk reduction 1.0%) coinciding with 104% higher HDL cholesterol, a reduction in apolipoprotein B containing lipoproteins more likely explains the beneficial effects,[4] as also supported by a genetic Mendelian randomization study.[94] None of the CETP inhibitors will be available for clinical practice. Importantly, current ESC/EAS dyslipidaemia guidelines do not recommend HDL cholesterol as a treatment target in ASCVD prevention.[2]

Importantly, the cardiovascular benefit of anacetrapib should not be compared directly to that of statins, ezetimibe, or PCSK9 inhibitors, all working mainly through up-regulation of LDL receptors to reduce LDL cholesterol. In contrast, CETP inhibition influence levels of cholesterol in LDL, other apolipoprotein B containing lipoproteins and HDL through exchange of cholesterol and triglycerides between lipoprotein particles.

Notably, it has previously been suggested that vascular effects of HDL are altered in patients with ASCVD and chronic kidney disease, in part due to alterations of the protein cargo and small molecules such as symetric dimethylarginine.[95] These findings are now further supported by recent data, indicating that in patients with high symetric dimethylarginine levels increased HDL cholesterol is associated with adverse cardiovascular outcomes.[96]

Moreover, in a large-scale analysis from two Copenhagen prospective population-based studies, it was observed that men and women in the general population with extreme high HDL cholesterol paradoxically have high all-cause mortality[97] (**Figure 4**); this further indicates that high HDL cholesterol levels have to be interpreted with caution and are not necessarily beneficial. Certainly, at high HDL cholesterol concentrations the HDL particle may not be functioning properly.

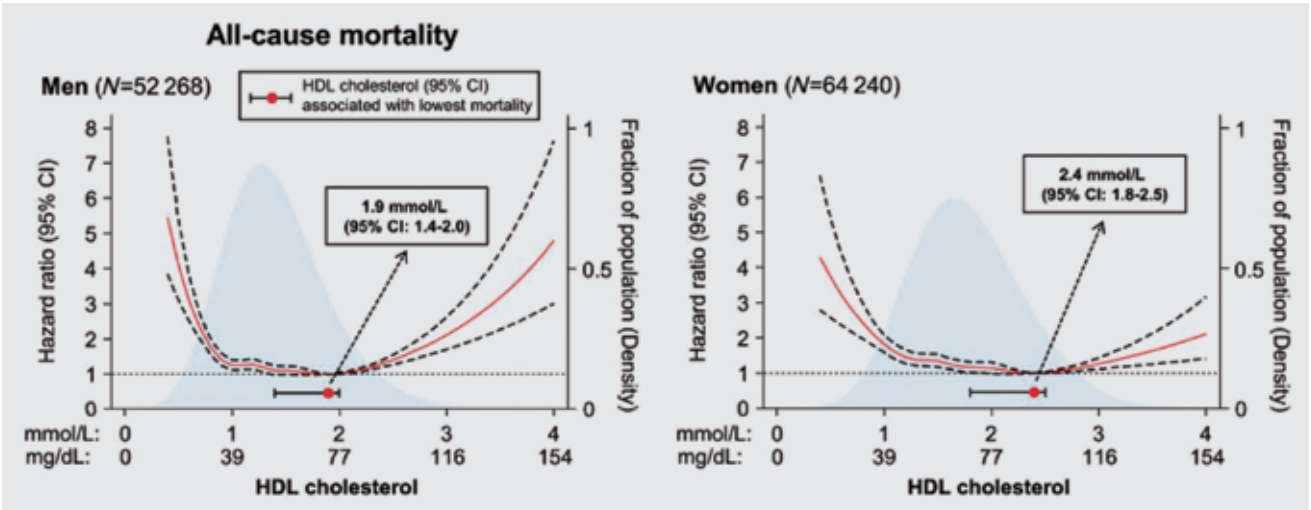

FIGURE 4. HDL cholesterol and risk of all-cause mortality in the general population. This data illustrate that in contrast to previous belief, extremely high HDL cholesterol is not always associated with beneficial outcomes. The mechanism behind this finding is presently unclear. This data also illustrate that patients with extremely high HDL cholesterol may be candidates for preventive effort to reduce the risk of early death. Based on 52 268 men and 64 240 women from the Copenhagen General Population Study and the Copenhagen City Heart Study combined. Hazard ratio (solid line) and 95% confidence interval (dashed lines) from age and study adjusted Cox regression using restricted cubic splines. The concentration of HDL cholesterol associated with lowest mortality was used as reference. The light blue area indicates the distribution of HDL cholesterol concentrations in men and women.

CI, confidence interval; HDL, high-density lipoprotein. Reproduced with permission from Madsen *et al.*[97]

Posebice je upozoreno da su vaskularni učinci HDL-a promijenjeni kod ATSKVB-a i u kroničnih bubrežih bolesnika, dijelom zbog promijenjenih proteina nosača i malih molekula kao što je simetrični dimetylarginin.[95] Ta su saznanja poduprta modernijim istraživanjima, koja pokazuju da je u bolesnika s visokom razinom simetričnog dimethylarginina povišena vrijednost HDL-a povezana s nepovoljnim kardiovaskularnim ishodima.[96]

Opsežnom analizom iz dviju Kopenhaških prospektivnih populacijskih studija utvrđeno je da muškarci i žene u općoj populaciji s ekstremno visokim vrijednostima HDL kolesterola imaju paradoksalno visoku ukupnu smrtnost[97] (**slika 4**), što navodi na zaključak da se visoka razina HDL kolesterola treba interpretirati s oprezom i nema nužno povoljni učinak. Sigurno je da pri visokoj koncentraciji HDL kolesterola čestice HDL-a ne funkcioniraju ispravno.

Upala

Upala ima ključnu ulogu kod ateroskleroze i ATSKVB-a[98], kao i kod tumora.[99] Lipoproteini akumulirani unutar arterija započinju i moduliraju upalu niskoga stupnja i proizvodnju citokina i CRP-a. Međutim, usprkos agresivnom liječenju statinima i kontroli vrijednosti LDL kolesterola, preostaje rezidualni rizik. Takva, rezidualna upala i rezidualni rizik bili su ispitivani u novijoj velikoj studiji CANTOS.

Studija CANTOS uključila je 10 061 bolesnika s preboljenim infarktom miokarda koji su usprkos primjeni strategija agresivne sekundarne prevencije imali vrijednosti CRP ≥2 mg/L. Rezultati spomenute studije pokazali su da je protuupalno liječenje canakinumabom koji djeluje na interleukin–1 beta, u najvećoj dozi, smanjuje ATSKVB za 14 % (apsolutno smanjenje rizika oko 2 %), ukupnu smrtnost od karcinoma za 51 % (apsolutno smanjenje rizika oko 2,5 %) i incidenciju karcinoma pluća za 67 % (apsolutno smanjenje rizika za oko 1,6 %).[5,100] Nepovoljni su učinci bili mali apsolutni porast fatalnih infekcija ili sepsi, ali isto tako povoljan učinak na osteoartritis i uloge (giht). Povoljan kardiovaskularni učinak postignut sa 150 mg canakinumaba prati povećanje smrtnosti od infekcije, što upućuje na usku terapijsku širinu takvoga protuupalnog pristupa.

U daljnjem je praćenju utvrđeno da veličina redukcije CRP-a nakon jedne doze canakinumaba omogućuje jednostavnu kliničku metodu probira osoba koje će vjerojatno postići najveću dobrobit od nastavka terapije.[101] Ti podatci, dalje, upućuju na to da su niže vrijednosti bolje za smanjenje upale canakinumabom.

Još nije poznato hoće li i kada canakinumab biti dostupan za preveciju ASTKVB-a. Kako god, važno je prepoznati vrijednost rezultata kliničke studije kao što je CANTOS za mehanistički pristup pogledu na razvoj infarkta miokarda.[102] Primjerice, bi li takvi podatci utjecaja na upalu vaskulature mogli pomoći boljem razumijevanju povezane uloge rupture plaka ili erozije plaka u infarktu mokarda?

Važno je da značajan rezidualan rizik od ATSKVB-a ostaje i uz primjenu optimalnoga životnog stila i medicinsku terapiju sukladnu Smjernicama ESC/EAS[1,2], a isto tako i nakon dodatne terapije canakinumabom[5] snizivanjem vrijednosti lipida inhibitorom apsorpcije kolesterola ezetimibom[103], inhibitorom PCSK9 evolokumabom[3] i bokocizumabom[48], bezafibratom[104] ili s inhibitorom CETP anacetrapibom.[4] Stoga i dalje ostaje neostvarena potreba za prevencijom ASTKVB-a.

Inflammation

Inflammation plays a critical role in atherosclerosis and ASCVD,[98] as well as in cancer.[99] Intra-arterial accumulated lipoproteins initiate and modulate low grade inflammation and the production of cytokines and C-reactive protein. However, even after aggressive treatment and control of LDL cholesterol with statins, there remains residual risk. This residual inflammation and residual risk was addressed by the recent landmark CANTOS trial.

The CANTOS trial enrolled 10 061 patients with previous myocardial infarction and C-reactive protein ≥2 mg/L despite the use of aggressive secondary prevention strategies. Findings of this study include that anti-inflammatory therapy targeting interleukin-1β with canakinumab in the highest dose reduced ASCVD by 14% (absolute risk reduction ≈2%), total cancer mortality by 51% (absolute risk reduction ≈2.5%), and lung cancer incidence by 67% (absolute risk reduction ≈1.6%).[5,100] Adverse events included a small absolute increase in fatal infection or sepsis, but also a beneficial effect on osteoarthritis and gout. The cardiovascular benefit obtained at the 150 mg dose of canakinumab came at the expense of an excess of mortality from infection, implying a narrow therapeutic window for such an anti-inflammatory approach.

In a follow-up study, it was suggested that the magnitude of reduction in C-reactive protein following a single dose of canakinumab might provide a simple clinical method to identify individuals most likely to accrue the largest benefit from continued treatment.[101] These data further suggested that lower is better for inflammation reduction with canakinumab.

It is yet unclear if and when canakinumab will be available for ASCVD prevention. However, it is also important to recognize the value of clinical trial results like those from CANTOS for mechanistic insight in development of myocardial infarction.[102] For example could such data of the vascular impact of targeting inflammation help us better understand the relative role of plaque rupture and plaque erosion in myocardial infarction?

Importantly, substantial residual ASCVD risk remains even after optimal lifestyle and medical therapy according to ESC/EAS Guidelines,[1,2] as well as after additional canakinumab therapy,[5] lipid-lowering therapy with the cholesterol absorption inhibitors ezetimibe,[103] the PCSK9 inhibitors evolocumab[3] and bococizumab,[48] bezafibrate,[104] or with the CETP inhibitor anacetrapib.[4] Therefore, there remain large unmet medical needs for ASCVD prevention.

Diabetes

A paradigm shift in the management of type 2 diabetes (T2D) has been observed with sodium/glucose cotransporter 2 inhibitors (SGLT-2i). This class of agents prevent re-absorption of glucose from the urine, thus resulting in glycosuria and lower blood glucose levels. It seems however that they possess additional, yet not fully identified effects that enhance their protective effect on the cardiovascular system. These drugs reduce the risk of cardiovascular complications, kidney disease, and death beyond glycaemic control,[105–107] benefits that recently were confirmed in 10 142 patients with T2D and high cardiovascular risk from CANVAS and CANVAS-Renal trials designed to assess effects on albuminuria[108]; canagliflo-

Šećerna bolest

Pomak paradigme u liječenju šećerne bolesti tipa 2 (T2D) uočen je primjenom inhibitora natrij/glukoza kotransportera 2 (SGLT-2i). Ova skupina lijekova sprječava reapsorpciju glukoze iz urina, što dovodi do glukozurije i snizivanja glikemije. Osim toga, registrirano je da ti lijekovi imaju dodatne, zasad još sasvim nedefinirane učinke koji pospješuju njihov zaštitni učinak na kardiovaskularni sustav. Oni smanjuju rizik od kardiovaskularnih komplikacija, bolesti bubrega i smrtnog ishoda uz učinak na kontrolu glikemije[105-107], a povoljni su im učinci nedavno potvrđeni u 10 142 bolesnika sa T2D i visokim kardiovaskularnim rizikom u studijama CANVAS i CAVAS-Renal dizajniranima za praćenje učinka na albuminuriju[108]. Kanagliflozin je također smanjio progresiju albuminurije i gubitak funkcije bubrega. Razmatrajući uočeni povećani rizik od amputacija, oprez je obvezan kod primjene kanagliflozina u bolesnika koji su pod tim rizikom[108]. Slično tomu, liraglutid, agonist receptora glukagonu sličnog peptida 1 (GLP1), snizuje ne samo ATSKVB[109] već i razvoj i progresiju dijabetičke bolesti bubrega.[110]

Nadalje, velika opservacijska studija CVD-REAL koja je uključila bolesnike sa T2D, od kojih 15 % s utvrđenim ATSKVB-om i 85 % bez utvrđene bolesti, dokazala je da su lijekovi iz SGLT-2i skupine povezani s nižim rizikom od srčanog zatajivanja i ukupne smrtnosti.[111] Studija CVD-REAL Nordic zahvaljujući cjelovitim populacijskim registrima u Danskoj, Norveškoj i Švedskoj pokazala je da su SGLT-2i bili povezani sa smanjenjem kardiovaskularne smrtnosti i pobola.[112] Ovakve retrospektivne kohortne studije nastavile su se na rezultate studije EMPA-REG OUTCOME[106] i studije CANVAS[108] koje su ispitivale neselektirane populacije sa T2D. Potvrdu ovih rezultata očekujemo u studijama koje su u tijeku, primjerice tijekom 2019. studija DECLARE-TIMI 58 (dapagliflozin; NCT01730534), koja će zasigurno utjecati na kliničku praksu u primarnoj prevenciji.

U bolesnika s inzulinskom rezistencijom (ali ne šećernom bolesti) i anamnestičkim podatkom o moždanom udaru, pioglitazon – lijek iz skupine tiazolidinediona – u studiji IRS pokazao je smanjenje ASTKVB-a od 24 % (apsolutno smanjenje rizika 2,8 %) i smanjenje progresije dijabetesa[113] osnažujući potrebu pristupa ciljanim liječenjem vaskularne bolesti i time bi pioglitazon mogao biti opcija za sekundarnu prevenciju u odabranih bolesnika s cerebrovaskularnom bolesti. Nadalje, studija TOSCA IT pokazala je kardiovaskularnu sigurnost druge linije lijekova za liječenje šećerne bolesti[114]; studija je pratila učinak dodanog pioglitazona u usporedbi sa sulfonilurejom na incidenciju događaja povezanih s ATSKVB-om u bolesnika s neadekvatno reguliranom glikemije uz metformin i zaustavljena je ranije zbog procjene da nije efikasna. Potvrđen sigurnosni profil u kombinaciji sa širokom dostupnošću pioglitazona i sulfonilureje mogli bi pospješiti studije koje bi uspoređivale ishode sa „novijim" hipoglikemicima.

Studija EXCEL do sada je uključila najveću populaciju bolesnika iz studija s kardiovaskularnim ishodima na lijekovima iz skupine agonista GLP1 receptora s više od 14 500 bolesnik a iz 35 zemalja.[115] U bolesnika sa T2D i širokim rasponom kardiovaskularnog rizika, eksenatid s produženim djelovanjem primjenjivan je jednom tjedno. U usporedbi s placebom lijek je pokazao kardiovaskularnu sigurnost. Primarni ciljni ishod nije postigao statističku značajnost za ATSKVB, bilo je 11,4 % događaja u vezi s ATSKVB-om u skupini na eksenatidu prema 12,2 % u onoj na placebu. Očekuju se dodatne informacije iz studija koje su u tijeku o učincima specifičnih lijekova, što će omogućiti iscrpniji uvid u mehanizme kardiovaskularnih

zin also lowered progression of albuminuria and loss of kidney function. In consideration of the increased risk of amputations seen, care is warranted in the use of canagliflozin in patients at such risk.[108] Similarly, liraglutide, a glucagon like peptide 1 (GLP1) receptor agonist, reduced not only ASCVD[109] but also development and progression of diabetic kidney disease.[110]

Further, CVD-REAL, a large observational study of T2D patients of 15% with and 85% without established ASCVD, found that the SGLT-2i drug class was associated with a lower risk of heart failure and all-cause mortality.[111] The CVD-REAL Nordic—thanks to a complete population-level registries in Denmark, Norway, and Sweden—demonstrated that SGLT-2i also were associated with reduced cardiovascular mortality and morbidity.[112] These retrospective cohort studies extend the results of EMPA-REG OUTCOME[106] and CANVAS[108] to the unselected T2D population. A putative confirmation of these results by the ongoing trials such as DECLARE-TIMI 58 (dapagliflozin; NCT01730534), due in 2019, would certainly impact clinical practice in primary prevention.

In patients with insulin resistance (but not diabetes) and a history of cerebrovascular accidents, the thiazolidinedione drug pioglitazone in the IRIS trial showed a 24% reduction of ASCVD (absolute risk reduction 2.8%) and lower progression to diabetes,[113] reinforcing the emerging precision-medicine approaches to vascular disease and that pioglitazone may represent an option for secondary prevention in selected patients with cerebrovascular disease. Furthermore, the TOSCA IT trial showed cardiovascular safety of second-line glucose lowering drugs[114]; the study examined effects of add-on pioglitazone vs. sulfonylureas on the incidence of ASCVD events in patients inadequately glucose-controlled with metformin and was stopped early because of futility. The confirmed safety profile in combination with the wide affordability of pioglitazone and sulfonylureas might promote trials comparing outcomes with 'newer' glucose-lowering drugs.

The EXSCEL trial recruited the hitherto largest patient population of any cardiovascular outcomes trial of the GLP1 receptor agonist class with more than 14 500 patients across 35 countries.[115] In patients with T2D at a wide range of cardiovascular risk, exenatide extended-release once weekly compared with placebo showed cardiovascular safety. Although the primary efficacy objective of ASCVD events missed statistical significance, nominally 11.4% ASCVD events were observed in the exenatide vs. 12.2% in the placebo arm. Additional information from ongoing studies are awaited to define the effects of specific drugs, provide further insights into the mechanisms of cardiovascular benefit and put these results in the perspective of current treatment algorithms and healthcare economy.

In patients with T2D and high ASCVD risk, the long-acting insulin degludec compared with basal insulin glargine caused 40% fewer severe hypoglycaemic events and was non-inferior with respect to ASCVD.[116] Further, intensive lifestyle intervention in patients with T2D lead to reduced use of glucose-lowering medication, but not to better glycaemic control.[117]

Interestingly, although diabetes risk was not increased during short-term therapy with PCSK9 inhibitors[3,48] lifelong genetically reduced PCSK9 and corresponding lower LDL cholesterol did appear to cause a small increase in risk of

povoljnih učinaka i pozicionirati dobivene rezultate u suvremene algoritme liječenja i ekonomiju zdravstvenog sustava.

U bolesnika sa T2D i visokim rizikom od ATSKVB-a, dugodjelujući inzulin degludek u usporedbi s bazalnim inzulinom glarginom uzrokovao je 40 % manje epizoda teških hipoglikemija i bio je neinferioran u odnosu prema ATSKVB-u.[116] Nadalje, intenzivna promjena životnog stila u bolesnika sa T2D dovodi do redukcije uporabe hipoglikemika, ali ne do bolje kontrole glikemije.[117]

Zanimljivo, iako rizik od šećerne bolesti nije bio povećan tijekom kratkotrajne primjene inibitora PCSK9 [3,48], doživotno genetski reduciran PCSK9 i sukladno tome niži LDL kolesterol čini se da uzrokuju mali porast rizika od šećerne bolesti, ali samo u onih s oštećenom glikemijom natašte.[41] Isto tako genetski je dokazano da prekomjerna tjelesna težina i pretilost, bilo povećanim indeksom tjelesne mase ili indeksom omjera struk – bokovi, uzročno su povezani s povećanim rizikom za šećernu bolest i ASTKVB.[118-121] Konačno, u zdrave azijske populacije bez komorbiditeta oštećena glikemija natašte i prehipertenzija bile su važan čimbenik rizika za fibrilaciju atrija.[122]

Arterijska hipertenzija

Slabo pridržavanje uzimanja lijekova i kasno započinjanje snizivanja vrijednosti arterijskoga tlaka (AT) važna su, ali propuštena prilika za kardiovaskularnu prevenciju. Ranije su studije izvještavale o sniženju AT-a nakon kateterske renalne denervacije.[123] Međutim, velika studija SIMPLICITY HTN-3 nije potvrdila te rezultate[124], moguće zbog nedostatne ablacije, pridržavanja uzimanja antihipertenzivne terapije i/ili izbora bolesnika.[125] Zbog toga je studija SPYRAL HTN-OFF MED randomizirala hipertenzivne bolesnike bez ukinute terapije ili s ukinutom terapijom u opsežnijoj i distalnijoj denervaciji renalnih arterija, a slijepi je dizajn uključivao lažnu proceduru u kontrolnoj skupini i testiranje lijekova za procjenu bolesnikove suradljivosti.[125] Sistolički tlak mjeren u ordinaciji snizio se za 10 mmHg, a prosječni 24-satni za 6 mmHg i pritom nisu bili registrirani značajni neželjeni događaji. Iako su ovi, noviji podatci o renalnoj denervaciji zanimljivi, trebaju se interpretirati s oprezom u svjetlu prethodnog neuspjeha u toj kategoriji. Osim toga, ovi rezultati sa strogim dizajnom lažne procedure postavili su novi standard za buduća intervencijske i kirurške kliničke studije.

Znatno sniženje AT-a može potencijalno uzrokovati teške nuspojave, poput rezultata u studiji SPRINT u osoba koje su bile podvrgnute intenzivnom snizivanju AT-a od 15 mmHg i posljedično su profitirale snizivanjem učestalosti kardiovaskularnih događaja i smrtnih ishoda[126], međutim, takve su bolesnici imali slične tjelesne i mentalne ishode i razinu depresivnosti u usporedbi s onima liječenima standardnim liječenjem.[127] Metaanaliza u hipertenzivnih bolesnika starijih od 65 godina na intenzivnom snizivanju AT-a dokazala je smanjenu učestalost kardiovaskularne bolesti, kardiovaskularne smrtnosti i zatajivanja srca, ali i veću učestalost bubrežnog zatajenja.[128] Naposljetku, nedavna populacijska studija dokazala je transgeneracijski rizik od arterijske hipertenzije s djedova i baka preko roditelja na unuke.[129]

Arterijska i venska tromboza

Arterijska tromboza, posebice u koronarnim arterijama, najčešći je precipitirajući čimbenik akutnih vaskularnih sindroma, kao što su infarkt miokarda i ishemija udova. U studiji COMPA-

diabetes, but only in those with impaired fasting glucose.[41] Also, genetic evidence document that overweight and obesity, either through increased body mass index or wait-to-hip ratio, is causally related to increased risk of both diabetes and ASCVD.[118–121] Finally, in a healthy Asian population without comorbidities impaired fasting glucose and prehypertension were important risk factors for atrial fibrillation.[122]

Hypertension

Poor medication adherence and late initiation of blood pressure (BP)-lowering represent important but missed opportunities for cardiovascular prevention. Previous studies had reported BP-lowering following catheter ablation for renal denervation.[123] However, the large SYMPLICITY HTN-3 trial did not confirm these findings,[124] possibly due to insufficient ablation, adherence to antihypertensive therapy and/or patient selection.[125] Therefore, SPYRAL HTN-OFF MED randomized drug-naive or drug-discontinued hypertensive patients to more extensive and more distal denervation of renal arteries, in a blinded design including a sham procedure in controls and drug testing for patient compliance.[125] Office systolic BP decreased by 10 mmHg and 24 h ambulatory BP by 6 mmHg, without major adverse events. Although these new data on renal denervation are interesting, they should be interpreted cautiously in light of the prior failures in this field. Nevertheless, these results with rigorous sham-design set a new standard for future interventional and surgical clinical studies.

Substantial BP-lowering could potentially cause severe side effects, like in the SPRINT trial of individuals who received intensive BP-lowering of 15 mmHg and consequently, benefitted from reduced cardiovascular events and mortality;[126] however, these individuals reported similar physical, mental, and depressive outcomes compared with those receiving standard treatment.[127] Also, in meta-analyses of hypertensive patients ≥65 years intensive BP-lowering reduced cardiovascular disease, cardiovascular mortality, and heart failure, but increased renal failure.[128] Finally, a recent population-based study documented transgenerational risk of hypertension from grandparents through parents to grandchildren.[129]

Arterial and venous thrombosis

Arterial thrombosis, especially in the coronary arteries, represents the most common precipitant of acute vascular syndromes, such as myocardial infarction and limb ischaemia. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial assigned 27 395 patients with stable atherosclerotic vascular disease to receive rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone.[6] The study was prematurely stopped due to 24% fewer ASCVD events (absolute risk reduction 1.3%) and 18% fewer deaths (absolute risk reduction 0.7%) in the rivaroxaban-plus-aspirin group compared with the aspirin-alone group; however, this was at the cost of 70% increased major bleeds (absolute risk increase 1.2%). Younger individuals compared with the elderly showed relatively larger reduction of ASCVD and lower bleeding risk. The effects of proton pump inhibitors on bleeds that are tested in a partial factorial design are pending. It is unclear how very low dose rivaroxaban + aspirin would compare with dual antiplatelet therapy or to the combination of rivar-

SS ukupno je 27 395 bolesnika sa stabilnom aterosklerotskom vaskularnom bolesti randomizirano na one koje dobivaju rivaroksaban i acetilsalicilatnu kiselinu (ASK), samo rivaroksaban i samo ASK.[6] Studija je zaustavljena ranije zbog 24 % manje događaja povezanih s ATSKVB-om (apsolutno smanjenje rizika 1,3 %) i 18 % manje smrtnih ishoda (apsolutno smanjenje rizika 0,7 %) u skupini liječenoj rivaroksabanom zajedno s ASK-om u usporedbi sa skupinom koja je uzimala samo ASK; međutim, to je postignuto uz cijenu od 70 %-tnog povećanja učestalosti značajnih krvarenja (apsolutno povećanje rizika 1,2 %). Mlađe osobe u usporedbi sa starijim osobama imale su relativno veću redukciju ATSKVB-a i niži rizik od krvarenja. Učinci inhibitora protonske crpke na krvarenja testirani su parcijalnim faktorijalnim dizajnom i nisu jasni. Nije jasno kako bi se niskodozna primjena kombinacije rivaroksaban + ASK mogla uspoređivati s dvojnom antitrombocitnom terapijom ili s kombinacijom rivaroksaban + P2Y12 inhibitor. U podgrupi studije COMPASS, koju je činilo 27 % bolesnika s kroničnom perifernom arterijskom bolesti, uz rivaroksaban i ASK u usporebi sa samim ASK-om dodatno je smanjen broj amputacija.[130] Budući da su dokazima potkrijepljena liječenja za bolesnike s perifernom vaskularnom bolesti oskudna, niskodozni rivaroksaban otvara važnu novu strategiju za takve rizične bolesnike.

U bolesnika s akutnim koronarnim sindromom dvojna antitrombocitna terapija niskodoznim rivaroksabanom ili ASK-om, u kombinaciji s klopidogrelom ili tikagrelorom, uzrokuje sličan rizik od krvarenja kod 5 % bolesnika.[131] Važno je napomenuti da će prestanak uzimanja bilo koje direktne oralne antikoagulancije 3 dana prije elektivne invazivne procedure osigurati minimalne koncentracije periproceduralno u gotovo svih bolesnika.[132]

Danska je studija randomizirala >50 000 muškaraca u dobi od 65 do 74 godina za uvrštenje ili neuvrštenje u probir aneurizme abdominalne aorte, periferne arterijske bolesti i arterijske hipertenzije. Onima koji su dijagnosticirani u probirnoj grupi ponuđeno je daljnje praćenje ili liječenje, uključujući kirurški zahvat ili antihipertenzive, što je bilo povezano sa 7 %-tnim smanjenjem ukupne smrtnosti (apsolutno smanjenje rizika 0,6 %) primarno u vezi sa vezano započinjanjem farmakološke terapije.[133] Važno je napomenuti da se smrtnost vezana za aneurizmu abdominalne aorte može razlikovati između različitih zemalja i može biti određena stopom kirurških zahvata i promjera aneurizme pri zahvatu.[134] Nizak pedobrahijalni indeks pomaže identificirati bolesnike s aneurizmom abdominalne aorte i perifernom arterijskom bolesti i predviđa ATSKVB događaje, iako u manjoj mjeri od povećane kalcifikacije koronarnih arterija.[135]

Arterijska tromboza ovisi o vulnerabilnosti arterijskoga plaka, koja se vjerojatno razlikuje kod osoba koje uzimaju i koje ne uzimaju statine zbog smanjene lipidima potaknute upale u osoba na statinima.[136] Zanimljivo je da novi podatci potvrđuju da kronično podražen hematopoetski sustav potencijalno proizvodi upalu niskoga stupnja kod bolesnika s ateroklerozom.[137]

Kod venskog tromboembolizma metanalize opservacijskih studija dokazale su 27 % niži rizik od ponavljanja venske tromboembolije povezan s uzimanjem statina[138], što je u skladu s rezultatima studije JUPITER.[139] Konačno, u bolesnika s venskim tromboembolizmom kojima je predviđeno kontinuirano antikoagulantno liječenje, rizik od ponavljanog događaja bio je otprilike 70 % niži uz rivaroksaban u usporedbi s ASK-om, bez znatnog povećanja učestalosti krvarenja[140], što potvrđuje rezultate prethodnih studija s drugim, novim oralnim antikoagulansima.

oxaban + P2Y12 inhibitor. In the COMPASS subgroup of 27% with chronic peripheral arterial disease, rivaroxaban plus aspirin vs. aspirin alone in addition reduced amputations.[130] Since evidence-based treatments for patients with peripheral arterial disease are scarce, low-dose rivaroxaban provides an important novel strategy for this high-risk population.

In patients with acute coronary syndrome dual antiplatelet therapy of low-dose rivaroxaban or aspirin, in combination with clopidogrel or ticagrelor, lead to similar risk of bleeding in 5% of patients.[131] Importantly, discontinuation of any direct oral anticoagulant 3 days prior to elective invasive procedures will secure minimal concentrations pre-procedure in almost all patients.[132]

A Danish study randomized >50 000 men aged 65–74 to screening or not for abdominal aortic aneurism, peripheral arterial disease, and hypertension; those diagnosed in the screening group were offered relevant follow-up and treatment including surgery and antihypertensive medication, which was associated with a 7% reduced all-cause mortality (absolute risk reduction 0.6%) primarily linked to initiation of pharmacological therapy.[133] Importantly, mortality related to abdominal aortic aneurism may differ from country to country, and can be influenced by rate of surgical repair and aneurysm diameter at repair.[134] A low ankle-brachial index help identify patients with abdominal aortic aneurism and peripheral arterial disease and predict ASCVD events, although to a lesser extent than increased coronary artery calcification.[135]

Arterial thrombosis depends on atherosclerotic plaque vulnerability, which likely differs in individuals taking statins or not due to reduced lipid-driven plaque inflammation in those on statins.[136] Interestingly, new data support that a chronically affected haematopoietic system potentially drive low-grade inflammation in patients with atherosclerosis.[137]

For venous thromboembolism, meta-analyses of observational studies found a 27% reduced risk of recurrent venous thromboembolism associated with statin use,[138] in accordance with findings in the randomized JUPITER trial.[139] Finally, in patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was reduced approximately 70% by rivaroxaban compared with aspirin, without a significant increase in bleeding rates;[140] this confirms previous studies with other novel oral anticoagulants.

Guidelines and consensus statements

Despite evidence-based recommendation for widespread use of statins in both primary and secondary prevention of ASCVD,[1,2] statin compliance is a major problem worldwide,[141,142] partly due to negative press[143,144] and in consequence discontinuation of statin use and increased risk of myocardial infarction and cardiovascular mortality.[143–146] In support, in the ASCOT-LLA trial muscle-related adverse events were similar in those receiving atorvastatin and placebo during blinding, however, after un-blinding and follow-up for an additional 2.3 years muscle-related adverse events were now 41% higher in those who knew they were receiving atorvastatin.[147] Therefore, any patient claiming statin intolerance including muscle symptoms needs careful counselling with his or her physician, including better diagnostics of statin intolerance and

Smjernice i konsenzusna priopćenja

Usprkos na dokazima utemeljenoj preporuci za široku primjenu statina u primarnoj i sekundarnoj prevenciji ATSKVB-a[1,2] suradljivost pri uzimanju statina velik je problem diljem svijeta[141,142], dijelom i zbog negativnog publiciteta[143,144]. Prekid uporabe statina rezultira povećanim rizikom od infarkta miokarda i kardiovaskularnom smrtnošću.[143-146] Kao podrška, u studiji ASCOT-LLA tijekom slijepog pokusa mišićne nuspojave bile su slične učestalosti u onih koji su primali atorvastatin i u onih na placebu, no nakon otkrivanja terapijskog režima i praćenja daljnje 2 do 3 godine mišićne su nuspojave bile za 41 % više u bolesnika koji su znali da primaju atorvastatin.[147] Stoga svaki bolesnik koji ne podnosi statin, uključujući i mijalgije treba pažljivo savjetovanje s liječnikom, uključujući bolju dijagnostičku obradu nepodnošenja lijeka i savjet kako nastaviti terapiju statinima usprkos uočenim nuspojavama.[141,142,148]

U posljednje je vrijeme objavljeno više obnovljenih izdanja vodećih smjernica za prevenciju kardiovaskularnih bolesti[1,149-154] i usprkos uporabi istih znanstvenih dokaza upute za promjenu životnih navika i predložene medicinske intervencije razlikuju se između smjernica. Na primjer, Smjernice ACC/AHA u usporedbi sa Smjernicama ESC/EAS pozicionirale su veći prioritet propisivanja statina u primarnoj prevenciji u usporedbi s onima u kojih se poslije razvije ATSKVB[155]; ova je razlika uglavnom objašnjena činjenicom da američke smjernice propisuju terapiju statinima većem broju osoba od europskih smjernica. To znači da su europske smjernice ograničene primjenom bodovnog sustava SCORE za procjenu rizika baziranog samo na smrtnosti od ASTKVB-a u kohortama regrutiranima prije mnogo godina i ograničenima na dob od 40 do 65 godina.[156,157] Iako rizik od ATSKVB-a raste povećanjem dobi na više od 65 godina[156], i životna je dob najvažniji prediktor rizika za ATSKVB, argumenti se razlikuju glede toga koliko bi ona trebala biti važna pri odlučivanju o propisivanju terapije statinima.[158,159]

Iako ACC/AHA bodovni sustav procjene rizika precjenjuje rizik od ATSKVB-a, posebice u Kineza[160], europski bodovni sustav SCORE mogao bi precijeniti rizik kod nekih populacija još i više.[155] Stoga idealna procjena rizika od ATSKVB-a treba biti kalibrirana za svaku zemlju i za svaku etničku skupinu prije nego što se iskoristi za propisivanje terapije statinima. U 2017. godini upravo se to dogodilo za UK QRISK3 algoritam za predikciju rizika u Smjernicama NICE[149] koristeći se aktualnim podatcima iz 981 ambulante opće medicine i 7,9 milijuna pacijenata u životnoj dobi od 25 do 84 godine iz Engleske kako bi se razvili novi pokazatelji, dok se drugih 328 ambulanti i 2,7 milijuna pacijenata koristilo za provjeru novih algoritama.

Od 2017. godine preporučeno je vađenje lipidograma bez prethodnog gladovanja u usporedbi s prethodnom preporukom za pretragu natašte što je sada sadržano u mnogim smjernicama i konsezusnim priopćenjima širom svijeta[89], uključujući UK[149], Europu[1,2,162], Kanadu[150,151], Brazil[163] i SAD.[153,164,165] Konačno, nove američke smjernice snizile su prag za definiciju hipertenzije na ≥130/80 mmHg sistolički/dijastolički arterijski tlak (prije 140/90 mmHg),[166] stavljajući velik dio odraslih osoba SAD-u u poziciju potencijalnih korisnika antihipertenziva ili primjenjujući intenzivirano snizivanje vrijednosti AT-a.

Zaključak

Godina 2017. bila je vrlo uzbudljiva godina za studije u prevenciji ATSKVB-a, uključujući velike kliničke studije, genetske Mendelove randomizirane studije i opservacijske prospektivne kohortne studije. **Slika 1** prikazuje neke od novih koncepata za dodatne preventivne mjere u sekundarnoj prevenciji u bolesnika s koronarnom bolešću koji već uzimaju statin, aspirin, ACE inhibitor i beta-blokator. Naravno, mnogi novi koncepti čekaju potvrdu dodatnim studijama i njihovu provjeru u kliničkoj praksi.

Važno je napomenuti da je primijećena znatna međuindividualna varijabilnost u odgovoru na brojne spomenute lijekove u ovom pregledu. Stoga je za sve nove (i stare) lijekove važno pratiti odgovor, posebice u vrijeme kada ekonomski pritisci obvezuju liječnike da koriste terapijske lijekove optimalno i na personaliziranoj osnovi.

Sukob interesa: nije deklariran

Conclusion

2017 has been a very exciting year for studies in ASCVD prevention, including landmark clinical trials, genetic Mendelian randomization studies, and observational prospective cohort studies. **Figure 1** illustrates some of the new concepts for additional preventive measures in secondary prevention in a patient with coronary heart disease already on statin, aspirin, ACE inhibitor, and beta-blocker. Naturally, many new concepts await confirmation by additional studies and their test in clinical practice.

Importantly, considerable inter-individual variability has been noted in the response to a number of the agents discussed in this review. Therefore, for all new (and old) drugs, it is important to monitor response, particularly at a time when economic pressures oblige clinicians to use therapeutic agents in an optimal manner on a personalised basis.

Conflict of interest: none declared

pektivne kohortne studije. **Slika 1** prikazuje neke od novih ideja za dodatne preventivne mjere u sekundarnoj prevenciji u bolesnika s koronarnom bolesti srca koji su već na terapiji statinima, ASK-om, ACE inhibitorom i beta-blokatorom. Naravno, većina nove ideja čeka potvrdu dodatnim studijama i njihovom provjerom u kliničkoj praksi.

Važno je da su znatne interindividualne razlike registrirane u odgovoru na brojne lijekove o kojima se raspravljalo u ovom pregledu. Stoga je za sve nove (i stare) lijekove važno pratiti odgovor, posebice u vremenu kada ekonomski pritisak obvezuje kliničare na uporabu optimalne terapije na personaliziranoj osnovi.

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