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Almanah 2012.: kardiovaskularni izračuni rizika. Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja donose napredak u kliničkoj kardiologiji

Almanac 2012: cardiovascular risk scores. The national society journals present selected research that has driven recent advances in clinical cardiology

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Opći izračuni rizika koriste podatke na razini pojedinca o nepromjenjivim čimbenicima rizika (npr. dob, spol, etnička pripadnost i obiteljska anamneza) i promjenjivim čimbenicima rizika (npr. pušenje i arterijski tlak) kako bi se za pojedinca predvidio apsolutni rizik od nepovoljnog događaja tijekom određenog vremenskog razdoblja u budućnosti. Izračuni kardiovaskularnog rizika imaju dvije glavne primjene u praksi. Prvo, mogu se koristiti kako bi se ljudi podijelili u dvije grupe, od kojih je u jednoj grupi osnovni rizik, a time i potencijalna apsolutna korist, dovoljno visok da opravda troškove i rizike povezane s intervencijom (bilo da se radi o liječenju ili prevenciji), dok su u drugoj grupi osobe s niskim apsolutnim rizikom, kojima je intervencija obično uskraćena. Drugo, mogu se koristiti za ocjenjivanje učinkovitosti intervencije (npr. prestanak pušenja ili liječenje arterijske hipertenzije) u smanjenju rizika od budućih nepovoljnih događaja kod pojedinca. U tom kontekstu oni mogu pomoći kod informiranja bolesnika, motiviranja bolesnika da promijene svoj stil života i naglašavanja važnosti daljnje suradljivosti (pridržavanja naputaka).

Kako su se razvili izračuni rizika?

Naše razumijevanje o tome kako najbolje izmjeriti rizik i suočiti se s njime razvijalo se tijekom niza godina. U prošlosti individualne čimbenike rizika mjerilo se i njima se upravljalo odvojeno, a zatim su usvojeni globalni izračuni rizika koji izračunavaju ukupni rizik na temelju niza čimbenika rizika. Nadalje, oportunističko korištenje izračuna rizika kod ljudi koji dolaze na liječenje kod zdravstvenih radnika zamijenjeno je češćim korištenjem masovnih pregleda ili ciljanih pregleda rizičnih skupina stanovništva u nastojanju da se utvrde nezadovoljene potrebe i smanje zdravstvene nejednakosti. Zahvaljujući ugradnji kalkulatora za izračun rizika u

Global risk scores use individual level information on non-modifiable risk factors (such as age, sex, ethnicity and family history) and modifiable risk factors (such as smoking status and blood pressure) to predict an individual's absolute risk of an adverse event over a specified period of time in the future. Cardiovascular risk scores have two major uses in practice. First, they can be used to dichotomise people into a group whose baseline risk, and therefore potential absolute benefit, is sufficiently high to justify the costs and risks associated with an intervention (whether treatment or prevention) and a group with a lower absolute risk to whom the intervention is usually denied. Second, they can be used to assess the effectiveness of an intervention (such as smoking cessation or antihypertensive treatment) at reducing an individual's risk of future adverse events. In this context, they can be helpful in informing patients, motivating them to change their lifestyle, and reinforcing the importance of continued compliance.

How have risk scores evolved?

Our understanding of how best to measure and respond to risk has evolved over a number of years. Historically, individual risk factors were measured and managed in isolation, but this has been replaced by the adoption of global risk scores that calculate overall risk based on a range of risk factors. Also, the opportunistic use of risk scores among people who present to healthcare workers has been replaced by increased use of either mass screening or targeted screening of at-risk populations in an effort to identify unmet need and reduce health inequalities. The integration of risk calculators into administrative software packages and

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administrativne softverske pakete i dostupnosti na internetu, izračuni rizika su dostupni svim liječnicima opće prakse u Ujedinjenom Kraljevstvu.[1] Područje primjene izračuna rizika proširilo se u zadnje vrijeme s koronarne bolesti srca na druge bolesti, kao na primjer zatajivanje srca ili dijabetes. Nadalje, s obzirom da su otkriveni novi biomarkeri kardiovaskularnih bolesti, sve je veći broj istraživanja koja ispituju imaju li oni dodatnu vrijednost za postojeće izračune rizika. Na kraju, s obzirom da su istraživači utvrdili genske lokuse povezane s kardiovaskularnim bolestima, istraživanja su počela ispitivati mogu li oni igrati neku ulogu u predviđanju rizika, bilo odvojeno ili u kombinaciji s tradicionalnim čimbenicima rizika.

I naš pristup ocjenjivanju uspješnosti izračuna rizika se također mijenjao tijekom vremena. U početku su usvajane metode ocjenjivanja putem testova probira u kojima su se koristile mjere razlikovanja poput osjetljivosti i specifičnosti. S obzirom da su se mnogi prediktivni modeli mogli izraziti kao kontinuirane varijable, rastao je interes za ocjenjivanjem uspješnosti prediktivnih modela kroz cijeli niz vrijednosti. To je postignuto usporedbom osjetljivosti i 1-specifičnosti za sve vrijednosti, kako bi se dobila krivulja karakteristika kojima upravlja primatelj (ROC krivulja). Područje ispod ROC krivulje, koje se naziva i statistikom slaganja, kreće se od 0,5 (nema mogućnosti predikcije) do 1,0 (savršeno razlikovanje). U svrhu primjene u kliničkoj ili javnoj zdravstvenoj praksi, kontinuirano mjerenje rizika mora se svesti na dvije ili više kategorija, no ROC graf može biti koristan za utvrđivanje najboljih graničnih vrijednosti koje treba primijeniti. Istraživači su u novije vrijeme ponovno klasificirali različite rizične skupine kako bi usporedili uspješnost razlikovanja različitih izračuna rizika. Rezultati mogu biti jednostavno predstavljeni kao ukupni postotak bolesnika koji su ponovno klasificirani u različite rizične skupine, a daje se prednost indeksu konačne ponovne klasifikacije koji se računa iz formule: (udio slučajeva koji idu prema gore — udio slučajeva koji idu prema dolje) — (udio kontrola koje idu prema gore — udio kontrola koje idu prema dolje).

Stodeset načina mjerenja rizika!

U prošlosti se izračun kardiovaskularnog rizika fokusirao na koronarnu bolest srca; bilo da se radilo o predikciji rizika od nepovoljnih događaja kod opće populacije ili kod bolesnika s dijagnozom, kao na primjer onih s akutnim koronarnim sindromom. Danas postoji 110 različitih izračuna kardiovaskularnog rizika razvijenih za primjenu kod opće populacije.[2] Noviji izračuni rizika, kao na primjer ASSIGN (procjena kardiovaskularnog rizika uz primjenu SIGN-a, prema eng. *ASsessing cardiovascular risk using SIGN*) i QRISK (algoritam kardiovaskularnog rizika QRESEARCH, prema eng. *QRESEARCH cardiovascular risk algorithm*), razlikuju se od ranijih izračuna jer u mjerenje općeg rizika uključuju društveno-ekonomsku neimaštinu i obiteljsku anamnezu.[3-5] Kao rezultat toga, mogu izbjeći neka ograničenja ranijih izračuna rizika, koji su znali uključiti društveno-ekonomski bias u otkrivanje i liječenje kardiovaskularnih rizika.[4] Međutim, uspješnost svih izračuna rizika ovisi o trenutnoj dostupnosti potpunih i točnih podataka. U nedavnom istraživanju, u kojem je šest izračuna rizika primijenjeno na podatke iz rutinske primarne liječničke prakse, de la Iglesia i *sur.*[4] naglasili su zabrinutost zbog podataka koji nedostaju, osobito onih vezanih za obiteljsku anamnezu.

Poznavanje izračuna rizika može značiti bolje dijagnosticiranje i manji rizik.[6] Međutim, u nedavnom preglednom članku Liew *i sur.*[7] naglasili su niz problema u razvoju izračuna rizika, uključujući nedostatak standarda u mjerenju prediktora i ishoda rizika te neuspjeh većine istraživanja koja stvaraju nove izračune rizika da uzmu u obzir osobe koje već uzima-

online access have made risk scores readily accessible to all general practitioners in the UK.[1] The scope of risk scores has recently widened beyond coronary heart disease to other conditions, such as heart failure and diabetes mellitus. Also, as new biomarkers for cardiovascular disease have been identified, there has been an increasing number of studies examining whether they can add value to existing risk scores. Finally, as investigators have identified genetic loci associated with cardiovascular conditions, studies have started to address whether they could play a role in risk prediction, either in isolation or combined with traditional risk factors.

Our approach to evaluating the performance of risk scores has also evolved over time. Initially, methods were adopted from the assessment of screening tests, using measures of discrimination such as sensitivity and specificity. As many predictive models could be expressed as continuous variables, interest grew in assessing the performance of predictive models across the whole range of values. This was achieved by plotting sensitivity versus 1-specificity for all values to produce a receiver operating characteristic (ROC) curve. The area under the ROC curve, also referred to as the c statistic, ranges from 0.5 (no predictive ability) to 1.0 (perfect discrimination). For use in clinical or public health practice, a continuous measure of risk needs to be reduced to two or more categories, but the ROC plot can be useful in determining the best cut-off values to apply More recently, investigators have used reclassification between different risk groups to compare the discriminatory performance of different risk scores. Results can be presented simply as the total percentage of patients reclassified into a different risk group, but the preferred measure is the net reclassification index, which is calculated from: (proportion of cases moving up — proportion of cases moving down) — (proportion of controls moving up — proportion of controls moving down).

One hundred and ten ways to measure risk!

Historically, cardiovascular risk scores have focused on coronary heart disease; either predicting the risk of adverse events in the general population or among patients with established disease such as those presenting with acute coronary syndromes. There are now 110 different cardiovascular risk scores that have been developed for use in the general population.[2] More recent risk scores, such as ASSIGN (*ASsessing cardiovascular risk using SIGN*) and QRISK (*QRESEARCH cardiovascular risk algorithm*), have differed from earlier scores by incorporating socioeconomic deprivation and family history into the measurement of global risk.[3-5] As a result, they have been able to overcome some of the limitations of earlier risk scores, which tended to introduce socioeconomic bias into the detection and treatment of cardiovascular risk.[4] However, the performance of all risk scores is dependent on ready access to complete and accurate data. In a recent study, in which they applied six risk scores to routine general practice data, de la Iglesia and colleagues[4] highlighted missing data as a concern, especially in relation to family history.

Knowledge of risk scores can translate into improved prescribing and reduced risk.[6] However, in a recent systematic review, Liew and colleagues[7] highlighted a number of problems in the development of risk scores including a lack of standardisation in the measurement of risk predictors and outcomes, and failure of most studies constructing new risk

ju lijekove koji utječu na mjerenje rizika, kao na primjer antihipertenzive ili hipolipemike. Ovo potonje može navoditi na krivi zaključak jer bi primarna prevencija u idealnim uvjetima trebala biti usmjerena na pojedinca prije nego što se razviju čimbenici rizika i prije prijevremenepojave bolesti. Jedno od ograničenja postojećih izračuna rizika koji se temelje na epizodama tijekom točno određenog vremenskog razdoblja od obično 10 godina je da na izračun jako utječe dob. Stoga nije vjerojatno da će mlade osobe doseći prag za intervenciju bez obzira na njihove sadašnje i buduće čimbenike rizika. Jedan od pristupa izdvajanju podskupine mladih osoba s većih rizikom je koristiti životni rizik umjesto rizik tijekom točno određenog vremenskog perioda. Hippisley-Cox i sur.[8] nedavno su usporedili korištenje QRisk2 kao životnog rizika od kardiovaskularne bolesti (u obliku određenih centila za dob i spol) i kao rizika tijekom desetogodišnjeg razdoblja. Prva metoda izdvojila je veliki udio mladih osoba s rizikom od budućih bolesti. Također je izdvojila i veliki udio osoba koje su pripadale etničkim manjinama i s pozitivnom obiteljskom anamnezom, kod kojih je postojao rizik od budućih kardiovaskularnih događaja. Oba čimbenika su povezana s visokim rizikom od prijevremene pojave kardiovaskularnih događaja. Dok su rano otkrivanje i sprječavanje idealni, neselektivan probir mlađeg stanovništva može ipak imati manju troškovnu učinkovitost.

Primjena izračuna rizika kod bolesnika s akutnim koronarnim sindromom je danas ustaljena i u istraživanjima i u kliničkoj praksi. U nedavnom radu objavljenom u časopisu Heart Bueno i Fernandez-Aviles[9] pregledali su 11 izračuna rizika razvijenih za predviđanje nepovoljnih epizoda nakon akutnog koronarnog sindroma. Izračuni rizika GRACE (globalni registar akutnih koronarnih epizoda, prema eng. *Global Registry of Acute Coronary Event*s) i TIMI (tromboliza kod infarkta miokarda, prema eng. *Thrombolysis in Myocardial Infarction*) su bili najčešće primjenjivani. Fox i sur.[10] su nedavno ispitivali do koje mjere je izračun rizika GRACE verificiran i primjenjivan od njegovog prvog nastanka 2003. Izračun rizika GRACE je do danas eksterno potvrđen u 67 zasebnih istraživanja koja su obuhvatila najmanje 500 bolesnika s akutnim koronarnim sindromom, infarktom miokarda s elevacijom ST segmenta ili infarktom miokarda bez elevacije ST segmenta. Izračun rizika se lako koristi u kliničkom okruženju, a njegova uspješnost je dobra u usporedbi s drugim izračunima rizika. Stoga je uključen u mnoge smjernice, uključujući one Europskoga kardiološkog društva (*European Society of Cardiology* — ESC), Američkog koledža za kardiologiju (*American College of Cardiologists* — ACC), Američke udruge za srce (*American Heart Association* — AHA), Škotske mreže međuakademskih smjernica (*Scottish Intercollegiate Guidelines Network* — SIGN) i Nacionalnog instituta za zdravstvo i kliničku izvrsnost (*National Institute for Health and Clinical Excellence* — NICE).

Sljedeća faza izračuna rizika?

Pažnja je sada usmjerena na proširivanje korištenja izračuna rizika kod drugih bolesti osim koronarne bolesti srca. Dva nedavna istraživanja razvila su izračune rizika za primjenu kod bolesnika sa zatajivanjem srca. Izračun rizika HF-Action (Zatajivanje srca: kontrolirani pokus koji ispituje ishode vježbanja, prema eng. Heart Failure: *A Controlled Trial Investigating Outcomes of Exercise TraiNing*) razvijen je na temelju skupine bolesnika s kroničnim zatajivanjem srca i sistoličkom disfunkcijom.[11] Izračun rizika je dobiven iz podataka o trajanju vježbe, dušiku iz ureje u serumu, indeksu tjelesne mase i spolu, a pokazao se uspješnim u predikciji smrti koja je nastupila iz raznih uzroka tijekom prve godine praćenja. Devetnaest posto bolesnika u najvišem decilnom razredu izračuna rizika je umrlo, u usporedbi s 2% u najnižem decilnom razredu. Statistika slaganja izračuna bila je 0,73.

scores to take account of individuals who are already taking medications that modify risk measurement, such as antihypertensive and lipid-lowering agents. The latter may be misleading because primary prevention should, ideally, be directed at individuals before the development of risk factors and the occurrence of premature disease. One of the limitations of existing risk scores based on events over a fixed period of time, commonly 10 years, is that the score is heavily influenced by age. Therefore, young individuals are unlikely to reach the threshold for intervention irrespective of their current and future risk factors. One approach to identifying the subgroup of young people at increased risk is to use lifetime risk rather than risk over a fixed period. Hippisley-Cox and colleagues[8] recently compared the use of QRisk2 reported as the lifetime risk of cardiovascular disease (in terms of age-sex specific centiles) with it reported as risk over a 10-year period. The former identified a greater a proportion of younger individuals as being at risk of future events. It also classified a greater proportion of individuals from ethnic minority groups and with a positive family history as being at risk of future cardiovascular events. Both factors are associated with an increased risk of premature cardiovascular events. While early identification and prevention are the ideal, the unselected screening of a younger population may, nonetheless, be less cost-effective.

The application of risk scores to patients presenting with acute coronary syndrome is now well established in both research and clinical practice. In a recent Education in Heart paper, Bueno and Fernandez-Aviles[9] reviewed 11 risk scores developed for the prediction of adverse events following acute coronary syndrome. Of these, the GRACE (*Global Registry of Acute Coronary Events*) and TIMI (*Thrombolysis in Myocardial Infarction*) risk scores have been most widely adopted. Fox and colleagues10 recently reviewed the extent to which the GRACE risk score has been validated and adopted since first developed in 2003. To date, the GRACE risk score has been externally validated in 67 individual studies comprising at least 500 patients with acute coronary syndrome, ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction. The risk score is easy to use in a clinical setting and performs well when compared with other risk scores. Therefore, it has been incorporated into many guidelines including those produced by the European Society of Cardiology (ESC), American College of Cardiologists (ACC), American Heart Association (AHA), Scottish Intercollegiate Guidelines Network (SIGN) and National Institute for Health and Clinical Excellence (NICE).

Where next for risk scores?

Attention is now focusing on expanding the use of risk scores beyond coronary heart disease. Two recent studies have developed risk scores for use in patients with heart failure. The HF-Action (Heart Failure: *A Controlled Trial Investigating Outcomes of Exercise TraiNing*) risk score was developed using a cohort of patients with chronic heart failure and systolic dysfunction[11]. The risk score was derived from information on exercise duration, serum urea nitrogen, body mass index and sex, and performed well at predicting all-cause death within 1-year of follow-up. Nineteen per cent of patients in the top decile for risk score died, compared with 2% in the bottom decile. The score had a c statistic of 0.73. The GWTG-HR (Get With The Guidelines-Heart Failure) risk score was developed using a cohort of patients

Izračun rizika GWTG-HR (u skladu sa smjernicama — zatajivanje srca, prema eng. *Get With The Guidelines — Heart Failure*) razvijen je na temelju skupine hospitaliziranih bolesnika sa zatajivanjem srca.[12] Sastavni čimbenici uključivali su dob, sistolički arterijski tlak, dušik iz ureje u krvi, frekvenciju srca, natrij, popratnu kroničnu opstruktivnu plućnu bolest i rasu. Rizik od smrti u bolnici bio je između 0,4% i 9,7% u svim decilnim razredima izračuna rizika, a izračun je bio uspješan kod bolesnika i s očuvanom i sa smanjenom sistoličkom funkcijom lijeve klijetke, dok je statistika slaganja u obje grupe bila 0,75.

Zbog sve veće raširenosti dijabetesa tipa 2 raste svijest o potrebi za ciljanim probirom osoba koje pate od te bolesti i nastojanjima da se ona spriječi. Van Dieren *i sur.*[13] izradili su pregledno istraživanje istraživanja objavljenih između 1966. i 2011., koja su razvila izračune kardiovaskularnih rizika prikladne za primjenu kod bolesnika s dijabetesom tipa 2. Od 45 izdvojenih izračuna, samo ih je 12 prvobitno dobiveno na temelju skupine osoba s dijabetesom, od kojih su samo dva bila ograničena na bolesnike kod kojih je dijabetes dijagnosticiran nedavno. Samo devet istraživanja navelo je statistiku slaganja. Šest izračuna je prošlo internu validaciju kroz samopodržavanje (eng. *bootstrapping*) ili dijeljenje uzorka (prema eng. *split sample*), dok ih je šest prošlo eksternu validaciju. Dva istraživanja nisu prošla niti internu niti eksternu validaciju. Autori su izdvojili dodatna 33 izračuna koja su se temeljila na općoj populaciji, ali su imala dijabetes kao predvidiv čimbenik. Samo 12 izračuna rizika je interno validirano kroz dijeljenje uzorka, unakrsnu validaciju ili samopodržavanje, a samo osam ih je prošlo eksternu validaciju na osobama s dijabetesom. S obzirom na sve veću raširenost dijabetesa tipa 2 i njegov sve veći utjecaj na kardiovaskularne bolesti, potrebno je provesti daljnja istraživanja na tom području.

Imaju li biomarkeri dodatnu vrijednost?

Nekoliko novije objavljenih istraživanja proučavalo je poboljšava li se uspješnost izračuna rizika kod opće populacije dodavanjem biomarkera. Sva ta istraživanja fokusirala su se na postizanje boljeg razlikovanja unutar podskupina pojedinaca koji su trenutno svrstani u srednje rizičnu grupu (10-20% rizika od nepovoljnog događaja tijekom 10 godina). Melander i sur.[14] procijenili su dodatnu vrijednost niza biomarkera, C reaktivnog proteina (CRP), cistatina C, fosfolipaze A2 vezane za lipoprotein (Lp-PLA2), srednje regionalnog proadrenomedulina (MR-proADM), srednje regionalnog proatrijskog natriuretskog peptida i N terminalnog pro-B tipa (NT-proBNP) u predviđanju slučajnih kardiovaskularnih događaja u kohorti švedskog stanovništva. U statistici slaganja zabilježen je neznačajan porast. Vezano za predviđanje kardiovaskularnih događaja, 8% ih je u potpunosti ponovno klasificirano, a samo 1% ih je uvršteno u visoko rizičnu kategoriju. Nije bilo konačne ponovne klasifikacije. U srednje rizičnoj skupini, nakon dodavanja biomarkera ponovno je klasificirano 16% slučajeva vezano za rizik od kardiovaskularnih epizoda, a samo 3% slučajeva je uvršteno u visoko rizičnu skupinu. Konačna ponovna klasifikacija poboljšana je za 7,4%. Dakle, poboljšanja u klasifikaciji su uglavnom postignuta uvrštavanjem u skupine nižeg rizika, a ne utvrđivanjem većeg udjela visoko rizičnih osoba.

Rana i sur.[15] proučavali su dodatnu vrijednost niza pojedinačnih biomarkera u predviđanju koronarnih događaja kod stanovništva Ujedinjenog Kraljevstva: CRP, mijeloperoksidaza, paraoksonaza, aktivna fosfolipaza A2 grupe IIA, Lp-PLA2, fibrinogen, makrofagni kemoatraktantni protein 1 i adiponektin. Najviše ponovne klasifikacije bilo je s CRP-om, čije dodavanje je dovelo do 12% ukupne konačne ponovne klasifikacije, a 28% u srednje rizičnoj skupini. Zathelius i

hospitalised with heart failure.[12] The component factors included age, systolic blood pressure, blood urea nitrogen, heart rate, sodium, concomitant chronic obstructive pulmonary disease and race. The risk of in-hospital death ranged from 0.4% to 9.7% across the risk score deciles and performed well among both patients with preserved and impaired left ventricular systolic function with a c statistic of 0.75 in both groups.

Due to the rising prevalence of type II diabetes, there has been increased awareness of the need to target screening and prevention efforts at people with this condition. Van Dieren et al[13] undertook a systematic review of studies published between 1966 and 2011 that had developed cardiovascular risk scores suitable for use in patients with type II diabetes mellitus. Of the 45 scores identified, only 12 were originally constructed from a cohort of individuals with diabetes and only two of these were restricted to patients in whom diabetes had been recently diagnosed. Only nine studies reported the c statistic. Six scores had undergone internal validation, using bootstrapping or a split sample, and six had been subject to external validation. Two studies had neither internal nor external validation. The authors identified an additional 33 scores that were constructed from the general population but included diabetes as a predictive factor. Only 12 had internally validated their risk score using a split sample, cross-validation or bootstrapping, and only eight had been externally validated in a population with diabetes. Given the increasing prevalence of type II diabetes and its increasing contribution to cardiovascular disease, further research is required in this area.

Do biomarkers add value?

Several recently published studies have examined whether the addition of biomarkers improved the performance of risk scores in the general population. A common focus of these studies has been trying to achieve better discrimination within the subgroup of individuals currently classified as having intermediate risk (10-20% risk of an adverse event over 10 years). Melander and colleagues[14] evaluated the added value of a panel of biomarkers, C-reactive protein (CRP), cystatin C, lipoprotein-associated phospholipase A2 (Lp-PLA2), mid-regional pro-adre-nomedullin (MR-proADM), mid-regional pro-atrial natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-proBNP), in predicting incident cardiovascular events in a Swedish population cohort. There was a non-significant increase in the c statistic. In relation to predicting cardiovascular events, 8% were reclassified overall but only 1% were moved into the high-risk category. There was no net reclassification. Among the intermediate risk group, the addition of biomarkers resulted in reclassification of 16% in terms of their risk of cardiovascular events, but only 3% were moved into the high-risk group. The net reclassification improvement was 7.4%. Therefore, the improvements in classification were largely achieved by down-grading, rather than dentifying a greater proportion of high-risk individuals.

Rana and colleagues[15] examined the added value of a series of individual biomarkers in the UK population in predicting coronary events: CRP, myeloperoxidase, paraoxonase, group IIA secretory phospholipase A2, Lp-PLA2, fibrinogen, macrophage chemoattractant protein 1 and adiponectin. Reclassification was greatest for CRP, the addition of which resulted in 12% net reclassification improvement overall and 28% in the intermediate group. Zethelius and colleagues[16]

sur.[16] proučili su dodatnu vrijednost četiriju biomarkera (troponin I, NT-proBNP, cistatin C i CRP) kod primjene na kohortu starijih muškaraca u Švedskoj. Dodavanje svih četiriju biomarkera znatno je povećalo statistiku slaganja, i to s 0,66 na 0,77. Prema njihovim rezultatima ukupna konačna ponovna klasifikacija iznosila je 26%. Istraživanja provedena do danas navode na zaključak da testiranja s biomarkerima mogu poboljšati razlikovanje kad se dodaju postojećim izračunima rizika. Međutim, njihova primjena košta i traži logistiku, osobito kad se izračuni rizika primjenjuju na velike skupine. Potrebna su daljnja istraživanja troškovne učinkovitosti dodavanja biomarkera postojećim izračunima rizika, osobito vezano za probir opće populacije.

Lorgis i sur.[17] pokazali su da dodavanje NT-proBNP-a izračunu rizika GRACE može poboljšati mogućnost prognoziranja kod bolesnika s akutnim koronarnim sindromom. Bolesnici s visokim vrijednostima prema izračunu rizika GRACE i s visokom razinom NT-proBNP-a imali su 50% izgleda za smrt tijekom jednogodišnjeg praćenja. To je bilo šest puta više od referentne skupine. Pokazalo se da je dodavanje NT-proBNP-a bilo korisno u svim dobnim skupinama, ali ne kod pretilih bolesnika, kod kojih je razina NT-proBNP-a bila puno niža.[18] Slični rezultati dobiveni su kad su osim izračuna rizika TIMI korišteni i troponin i moždani natriuretski peptid.[19] Njihovim dodavanjem statistika slaganja se samo malo povećala, no, kao što je bio i slučaj s NT-proBNT-om, mogla se izdvojiti podskupina unutar visoko rizične skupine po TIMI-ju u kojoj je postojao visoki rizik od nepovoljnih događaja i za koju se može odobriti agresivan pristup terapiji lijekovima i intervencije.[18] Damman *i sur.*[20] proučavali su skupinu bolesnika kod kojih je učinjena primarna perkutana koronarna intervenca kod infarkta miokarda s elevacijom ST segmenta. Pokazali su da je dodavanje biomarkera (glukoza, NT-proBNP i procijenjena stopa glomerularne filtracije) poboljšalo predviđanje smrtnosti, što je pak znatno poboljšalo konačnu ponovnu klasifikaciju (49%, p<0,001) i integrirano razlikovanje (3%, p<0,01).

Izračuni rizika, kao npr. CHADS2-VASC2, mogu predvidjeti rizik od cerebrovaskularnih događaja kod bolesnika s atrijskom fibrilacijom te se koriste kod donošenja kliničkih odluka o primjeni antikoagulacijske terapije. Danas su poznati brojni biomarkeri koji su povezani s učestalošću atrijske fibrilacije i njezinom prognozom. U nedavnom preglednom radu Brugts i sur.[21] naglasili su da je potrebno provesti daljnja istraživanja kako bi se utvrdilo može li korištenje tih biomarkera poboljšati postojeće rezultate istraživanja rizika i mogu li oni poslužiti za predviđanje rizika u ranoj fazi izdvajanjem bolesnika kod kojih postoji rizik od atrijske fibrilacije ili rizik od napredovanja od stanja bez kliničkih znakova do trajnog stanja bolesti.

Postoje mnogi patofiziološki mehanizmi koji dovode do zatajivanja srca. Avellino i sur.[22] proučili su nedavno biomarkere povezane s relevantnim putovima. Zaključili su da su biomarkeri koji su trenutno najviše obećavaju u smislu raslojavanja rizika: Lp-PLA2 (upala), neutrofilni lipokalin povezan s gelatinazom i cistatin C (oba biljega za bubrežno oštećenje), prokolagen-1-polipeptid (remodeliranje ekstracelularnog matriksa), moždani natriuretski peptid, NT-proBNP, MR-proADM, topivi receptor ST2 i kopeptin (sve biljezi oštećenja srčanih miocita) i endotelin 1 (neurohormonalna regulacija). Gustav Smith sa suradnicima[23] pokazao je, vezano za predviđanje epizode zatajivanja srca i atrijske fibrilacije kod opće populacije, da je dodavanje niza biomarkera (srednje regionalni proatrijalni natriuretski peptid, NT-proBNP, MR-proADM, cistatin C, CRP i kopeptin) konvencionalnim čimbenicima rizika poboljšalo razlikovanje. Konačna ponovna

examined the added value of four biomarkers (troponin I, NT-proBNP, cystatin C and CRP) when applied to a population cohort of elderly Swedish men. The addition of all four biomarkers significantly increased the c statistic from 0.66 to 0.77. They reported a 26% net improvement in reclassification overall. The studies to date suggest that biomarker assays may improve discrimination when added to existing risk scores. However, their use has cost and logistical implications, particularly if risk scores are applied on a wide scale. Further research is needed on the cost-effectiveness of adding biomarkers to existing risk scores, particularly in relation to general population screening.

Lorgis and colleagues[17] demonstrated that adding NT-proBNP to the GRACE risk score can improve its prognostic value among patients presenting with acute coronary syndrome. Patients with both a high GRACE risk score and high NT-proBNP level had a 50% risk of dying within 1 year of follow-up. This was sixfold higher than the referent group. NT-proBNP was found to be a useful addition across all age groups but not in obese patients, in whom NT-proBNP levels were much lower.[18] Similar findings were reported when troponin and brain natriuretic peptide were used in addition to the TIMI risk score.[19] Their addition produced only a slight increase in the c statistic but, as with NT-proBNP, they were able to identify a subgroup of the TIMI high-risk group who were at very high risk of adverse events, and in whom an aggressive approach to drug therapy and interventions might be warranted.[18] Damman and colleagues[20] examined a cohort of patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction. They demonstrated that the addition of biomarkers (glucose, NT-proBNP and estimated glomerular filtration rate) improved the prediction of mortality, resulting in significant improvements in net reclassification (49%, p<0.001) and integrated discrimination (3%, p<0.01).

Risk scores, such as CHADS2-VASC2, can predict the risk of cerebrovascular events among patients with atrial fibrillation, and are used to inform clinical decisions on the use of antico-agulant therapy. A number of biomarkers has now been identified that are associated with the incidence and prognosis of atrial fibrillation. In a recent review paper, Brugts and colleagues[21] highlighted the need for further research to determine whether the use of these biomarkers may improve the existing risk scores and whether they offer the potential for risk prediction at an earlier stage by identifying patients at risk of developing atrial fibrillation or at risk of progressing from the subclinical to permanent stage of the condition.

Many pathophysiological mechanisms contribute to the development of heart failure. Avellino and colleagues[22] reviewed recently identified biomarkers associated with the relevant pathways. They concluded that the biomarkers currently showing most promise, in terms of risk stratification, were Lp-PLA2 (inflammation), neutrophil gelatinase-associated lipocalin and cystatin C (both renal stress), procollagen-1-polypeptide (extracellular matrix remodelling), brain natriuretic peptide, NT-proBNP, MR-proADM, soluble ST2 receptor and copeptin (all cardiac myocyte stress), and endothelin 1 (neurohormone regulation). Gustav Smith and colleagues23 demonstrated that, in terms of predicting incident heart failure and atrial fibrillation in a general population cohort, the addition of a panel of biomarkers (mid-regional pro-atrial natriuretic peptide, NT-proBNP, MR-proADM, cystatin C, CRP and copeptin) to conventional risk factors improved discrimation. The net reclassification

klasifikacija poboljšala se za 22% kod zatajivanja srca i za 7% kod atrijske fibrilacije. Ponovna klasifikacija uglavnom je postignuta utvrđivanjem dodatnih visoko rizičnih osoba. U nedavnom istraživanju Ketchum i Levy[24] naveli su da izračuni rizika igraju sve važniju ulogu kod bolesnika s težim oblikom zatajivanja srca, čiji izgledi za preživljavanje su se poboljšali zahvaljujući terapijskom i tehnološkom napretku. Naveli su da se izračuni rizika mogu pomoći u izboru bolesnika za transplantaciju, za uređaje za potporu funkcije lijeve klijetke i za impantabilni kardioverter defibrilator. Haines i sur.[25] razvili su nedavno izračun rizika za predviđanje postoperacijskih komplikacija vezanih za ugradnju kardioverter defibrilatora. Izračun rizika se temeljio na 10 trenutno dostupnih varijabli: dob, spol, NYHA klasu, prisutnost atrijske fibrilacije, prethodna operacija zaliska, kronična plućna bolest, dušik iz ureje u krvi, ponovna ugradnja iz razloga nevezanih za zamjenu generatora, uporaba dvokomornih ili biventrikulskih uređaja i ne-elektivne operacije. Kod 4% stanovništva koje se ubraja u visoko rizičnu kategoriju bilo je 8% rizika od komplikacija, u usporedbi s manje od 1% u nisko rizičnoj skupini.[25]

Istraživanja su nedavno počela promatrati može li neinvazivno snimanje krvnih žila dodati vrijednost postojećim izračunima rizika.[26] Količina kalcija u krvnim žilama je marker oštećenja žila i u uzajamnom je odnosu s općim problemom ateroskleroze.[23] Koronarna CT angiografija može otkriti nekalcificirani plak i ukazati na ozbiljnost koronarne arterijske stenoze.[26] Pokazalo se da oboje imaju dodatnu vrijednost u predviđanju rizika kod bolesnika koji imaju simptome, no istraživanja općenito ne daju dovoljno informacija o korisnosti njihovog uključivanja u izračune rizika kod osoba bez simptoma. Debljina intime i medije karotida je značajni prediktor rizika od kardiovaskularnih događaja kod osoba koje nemaju karotidni plak.[27] U kombinaciji s podacima o broju segmenata s plakom na temelju kojih se računa ukupni teret karotidne ateroskleroze, statistika slaganja i indeks konačne ponovne klasifikacije su se poboljšali za 6,0%, odnosno za 17,1%. Trošak snimanja je obično veći od troška krvnih biomarkera. Stoga će dodatni trošak vjerojatno onemogućiti rutinsko uključivanje u izračune rizika za opću populaciju. Istraživanja o troškovnoj učinkovitosti moraju ispitati jesu li dodatni troškovi opravdani za podskupinu osoba koje nemaju simptome, ali koji su izdvojeni u postojećim izračunima rizika.

Jedno od malobrojnih istraživanja koja su procijenila troškovnu učinkovitost dodavanja biomarkera kliničkim izračunima rizika proučavalo je bolesnike sa stabilnom anginom pektoris koji u bili na listi čekanja za premoštenje koronarne arterije pomoću presatka.[28] Uspoređena je status quo strategija neformalnog određivanja prioriteta s određivanjem prioriteta samo temeljem kliničkog izračuna rizika i s određivanjem prioriteta nakon dopunjavanja kliničkih izračuna rizika dodatnim podacima biomarkera koristeći rutinski ocijenjene biomarkere (procijenjena stopa glomerularne filtracije), nove biomarkere (CRP) ili oboje. Pokazalo se da je dodavanje rutinski ocijenjenih biomarkera poboljšalo troškovnu učinkovitost što se tiče konačnog učinka na dugoročne troškove i godine života poboljšane kvalitete. Za razliku od toga, dodavanje novih biomarkera nije bilo troškovno učinkovito.

Imaju li genetski markeri dodatnu vrijednost?

Kardiovaskularna bolest je složeno stanje s nekoliko prijelaznih fenotipa, kojemu pridonose i čimbenici okoline i čimbenici genetskog rizika. Kako se utvrđuje sve veći broj genetskih markera, postaje sve jasnije da je i genetska sastav-

improvement was 22% for heart failure and 7% for atrial fibrillation. Reclassification was mainly achieved by the identification of additional high-risk individuals. In a recent review, Ketchum and Levy[24] suggested that risk scores had an increasing role to play among patients with advanced heart failure whose survival has improved due to therapeutic and technological advances. They suggested that risk scores could be used to assist the selection of patients for transplantation, left ventricle assist devices and implantable cardioverter defibrillators. Haines and colleagues[25] recently developed a risk score to predict post-procedural complications associated with the implantation of cardioverter defibrillators. The risk score was based on 10 readily available variables: age, sex, New York Heart Association class, presence of atrial fibrillation, previous valve surgery, chronic lung disease, blood urea nitrogen, re-implantation for reasons other than battery change, use of a dual chamber or biventricular device and a non-elective procedure. The 4% of the population in the highest risk category possessed a 8% risk of complications, compared with less than 1% in the lowest risk group.[25]

Studies have recently started to address whether non-invasive imaging of the coronary vessels could add value to existing risk scores.[26] The coronary artery calcium score is a marker of vascular injury and correlates well with the overall atherosclerotic burden.[23] Coronary CT angiography can detect non-calcified plaque and indicates the severity of coronary artery stenoses.[26] Both have been shown to be of incremental value in risk prediction among symptomatic patients, but studies are generally lacking on the utility of incorporating them into risk scores for use among asymptomatic people. Carotid intimamedia thickness is a significant predictor of the risk of cardiovascular events in individuals without carotid plaques.[27] When combined with information on the number of segments with plaque, to produce a total burden of carotid atherosclerosis score, the c statistic and net reclassification index are improved by 6.0% and 17.1%, respectively. The cost of imaging is generally greater than for blood biomarkers. Therefore, the incremental cost is likely to be prohibitive in terms of the routine addition to general population risk scores. Cost-effectiveness studies are required to explore whether the additional costs can be justified in a subgroup of asymptomatic individuals identified by existing risk scores.

One of the few studies to assess the cost-effectiveness of adding biomarkers to clinical risk scores examined patients with stable angina who were on the waiting list for coronary artery bypass grafting.[28] They compared the status quo strategy of no formalised prioritisation with prioritisation using a clinical risk score in isolation and prioritisation after supplementing the clinical risk scores with additional biomarker information using a routinely assessed biomarker (estimated glomerular filtration rate), a novel biomarker (CRP), or both. They demonstrated that the addition of the routinely assessed biomarker improved cost- effectiveness in terms of the net effect on lifetime costs and quality-adjusted life-years. In contrast, addition of the novel biomarker was not cost-effective.

Do genetic markers add value?

Cardiovascular disease is a complex condition, with several intermediate phenotypes, to which both environmental and genetic risk factors predispose. As increasing numbers of genetic markers has been identified, it has become increas-

nica također složena, a njezin doprinos iz velikog broja gena je dosta malen. Stoga se pažnja posvećuje razvoju izračuna genetskih rizika u više lokusa, gdje se zbraja ukupni rizik iz poznatih genetskih markera. U posljednjih nekoliko godina, nekoliko istraživanja je ispitivalo može li izračun genetskih rizika imati dodatnu vrijednost u utvrđenim izračunima rizika, od kojih neki već sadrže podatke o obiteljskoj anamnezi. Istraživanja su provedena na različitim populacijama, ali su doneseni zaključci dosljedni.

Ripatti *i sur.*[29] proučavali su sedam skupina srednjovječnih muškaraca i žena opće populacije u Finskoj i Švedskoj. Koristili su objavljena istraživanja kako bi izdvojili 13 nedavno otkrivenih slučajeva polimorfizma pojedinačnih nukleotida povezanih ili s infarktom miokarda ili s koronarnom bolesti srca. Za svaku osobu osmislili su izračun genetskog rizika u više lokusa, a izračun se temeljio na zbroju rizičnih alela za svaki od 13 polimorfizama pojedinačnih nukleotida pomnoženim veličinom učinka. Izračun genetskih rizika bio je neovisni prediktor izgledne koronarne bolesti srca, kardiovaskularne bolesti i infarkta miokarda nakon prilagodbe za dob, spol i tradicionalne čimbenike rizika. U usporedbi s najnižom kvintilom izračuna genetskih rizika, prilagođeni omjer rizika od koronarne bolesti srca kod osoba u najvišoj kvintili iznosio je 1,66 (95% CI 1,35 do 2,04). Međutim, dodavanje izračuna genetskih rizika tradicionalnim čimbenicima rizika nije znatno poboljšalo statistiku slaganja. Znatno poboljšanje zabilježeno je kod konačne ponovne klasifikacije srednje rizičnih osoba (predviđen rizik za 10 godina od 10 do 20%), no nije bilo značajnog poboljšanja u ukupnoj konačnoj ponovnoj klasifikaciji.

Paynter *i sur.*[30] su proveli slično istraživanje na skupini poslovnih žena bjelkinja u SAD-u. Oni su koristili internetske kataloge istraživanja povezanosti na cijelom genomu kako bi izdvojili 101 polimorfizam pojedinačnih nukleotida za koje se pokazalo da su povezani s bilo kojim oblikom kardiovaskularne bolesti (uključujući moždani udar) ili bilo kojim prijelaznim fenotipom (npr. dijabetes i arterijska hipertenzija) te su dobili rezultat izračuna genetskih rizika zbrajajući sve rizične alele bez množenja. Također su ponovno izradili analize samo 12 polimorfizama pojedinačnih nukleotida za koje se pokazalo da su povezani s kardiovaskularnim bolestima. U usporedbi s najnižom tercilom izračuna genetskih rizika, kod osoba u najvišoj terciliomjer rizika od kardiovaskularnih događaja je bio viši (omjer rizika 1,22, 95% CI 1,02 do 1,45), ali razlika u apsolutnom desetogodišnjem riziku od kardiovaskularne bolesti u najvišoj i najnižoj tercili bila je mala (3,7% prema 3,0%). Za razliku od obiteljske anamneze (koja obuhvaća ukupni naslijeđeni rizik), izračun genetskih rizika nije bio značajno povezan s kardiovaskularnim događajima nakon prilagođavanja za tradicionalne čimbenike rizika. Dodavanje izračuna genetskih rizika nije polučilo nikakva značajna poboljšanja niti u statistici slaganja niti u konačnoj ponovnoj klasifikaciji.

Qi *i sur.*[31] proveli su istraživanje parova kod osoba koje su preživjele infarkt miokarda u Kostarici. Ispitali su polimorfizam pojedinačnih nukleotida povezan s infarktom miokarda i koronarnom arterijskom bolesti u najmanje dva prethodna istraživanja povezanosti na cijelom genomu. Od 14 polimorfizama pojedinačnih nukleotida koji su izdvojeni iz literature, sedam ih je bilo značajno povezano s rizikom od infarkta miokarda u španjolskoj skupini. Oni su korišteni za izračunavanje genetskog rizika na temelju zbroja rizičnih alela. Oni su pokazali odnos doza, gdje je rizik od infarkta miokarda rastao s povećanjem rezultata izračuna genetskih rizika, koje se nastavilo nakon prilagođavanja za tradicionalne čimbenike rizika, uključujući obiteljsku anamnezu. Međutim, dodavanje izračuna genetskih rizika samo je povećalo statistiku slaganja s 0,67 na 0,68.

ingly clear that the genetic component is also complex, with relatively small contributions from a large number of genes. Therefore, attention has focused on the development of a multilocus genetic risk score that summates the overall risk from known genetic markers. In the past couple of years, several studies have investigated whether a genetic risk score can add value to established risk scores, some of which already include information on family history. The studies have been undertaken in a variety of populations but have reached consistent conclusions.

Ripatti and colleagues[29] studied seven cohorts of middle-aged men and women recruited from the general populations in Finland and Sweden. They used published studies to identify 13 recently discovered single nucleotide polymorphisms (SNP) associated with either myocardial infarction or coronary heart disease. They constructed a mulilocus genetic risk score for each individual by summing the number of risk alleles for each of the 13 SNP weighted by effect size. The genetic risk score was an independent predictor of incident coronary heart disease, cardiovascular disease and myocardial infarction when adjusted for age, sex and traditional risk factors. In comparison with the lowest quintile of genetic risk score, individuals in the top quintile had an adjusted RR of coronary heart disease of 1.66 (95% CI 1.35 to 2.04). However, addition of the genetic risk score to traditional risk factors did not significantly improve the c statistic. There was a significant improvement in net reclassification of people at intermediate risk (10-year predicted risk of 10-20%) but there was no significant improvement in net reclassification overall.

Paynter and colleagues[30] undertook a similar study using a cohort of white professional women in the USA. They used an online catalogue of genome-wide association studies to identify 101 SNP shown to be associated with any form of cardiovascular disease (including stroke) or any intermediate phenotype (such as diabetes and hypertension), and derived a genetic risk score from the sum of all risk alleles without weighting. They also reran the analyses including only the 12 SNP shown to be associated with cardiovascular disease. In comparison with the lowest tertile of genetic risk score, individuals in the highest tertile had a higher RR of cardiovascular events (RR 1.22, 95% CI 1.02 to 1.45) but the difference in the absolute 10-year risk of cardiovascular disease in the top and bottom tertiles was small (3.7% vs 3.0%). Unlike family history (which encompasses overall inherited risk), the genetic risk score was not significantly associated with cardiovascular events after adjustment for traditional risk factors. Addition of the genetic risk score produced no significant improvement in either the c statistic or net reclassification.

Qi and colleagues[31] undertook a case-control study of myocardial infarction survivors in Costa Rica. They examined SNP associated with myocardial infarction and coronary artery disease in at least two previous genome-wide association studies. Of the 14 SNP identified from the literature, seven had significant associations with the risk of myocardial infarction in their Hispanic cohort. These were used to calculate a genetic risk score based on the sum of the risk alleles. They demonstrated a dose relationship, whereby the risk of myocardial infarction increased with increasing genetic risk score and persisted after adjustment for traditional risk factors, including family history. However, addition of the genetic risk score only increased the c statistic from 0.67 to 0.68.

Isto kao u prethodnom istraživanju Paynter *i sur.*[30] i Thanassoulis *i sur.*[32] radili su dva različita izračuna genetskih rizika: ograničeni izračun koji se temelji na 13 polimorfizama pojedinačnih nukleotida koji su bili prethodno povezani s koronarnom bolesti srca ili infarktom miokarda i manje ograničen izračun koji je uključivao dodatnih 89 polimorfizama pojedinačnih nukleotida povezanih s prijelaznim fenotipom. U oba pristupa korišten je i jednostavni izračun rizičnih alela i umnožak. Na kraju su ponovno napravili ograničene izračune, dodavši dodatnih 16 nedavno izdvojenih polimorfizama pojedinačnih nukleotida. Izračuni genetskih rizika primijenjeni su kod skupine potomaka u Framinghamu. Ograničeni izračun genetskih rizika bio je uspješniji od manje ograničenog izračuna te je bio neovisni prediktor i koronarne bolesti srca i kardiovaskularnih događaja. Ipak, nije poboljšao razlikovanje niti klasifikaciju, čak ni nakon dodavanja dodatnih polimorfizama pojedinačnih nukleotida.

Ta istraživanja dosljedno pokazuju da čak i u slučaju ubrajanja genotipskih podataka u ukupni izračun rizika, oni ne poboljšavaju uspješnost postojećih izračuna rizika, pa stoga trenutno nemaju jasnu kliničku primjenu u odabiru srednjovječnih osoba za intervencije. Potrebno je dalje istražiti igra li izračun genetskih rizik ikakvu ulogu u izdvajanju podskupine mladih ljudi kod kojih ima najviše izgleda za dobivanje visokorizičnih rezultata u budućnosti, te ako igra, potrebno je istražiti troškove, rizike i koristi od pružanja preventivnih mjera, kao npr. edukacije ove podskupine u ranoj fazi.

Proceduralni izračun rizika

Faroq i sur.[33,34] nedavno su preispitali primjenu izračuna rizika kod bolesnika podvrgnutih koronarnoj revaskularizaciji. Izračuni kliničkih rizika, kao na primjer PARSONNET (predvidiv izračun za operacije kod stečenih bolesti srca u odraslih: dodatni i logistički regresijski modeli, prema eng. *Predictive score for acquired adult heart surgery: Additive and Logistic Regression models*) i EuroSCORE (europski sustav za procjenu rizika operacija srca, prema eng. *European System for Cardiac Operative Risk Evaluation*), su u širokoj primjeni u kliničkoj praksi kod bolesnika podvrgnutih koronarnoj revaskularizaciji. Izračuni rizika koji se temelje na anatomiji, a koji ne sadrže kliničke podatke, razvijeni su koristeći podatke dobivene dijagnostičkom angiografijom. S obzirom da se koronarni arterijski presatci koji se koriste u premošćivanju stenoze i anastomoze postavljaju distalno u odnosu na dio zahvaćen bolesti, dodatni anatomski podaci ne poboljšavaju znatno uspješnost izračuna kliničkih rizika kod bolesnika podvrgnutih operaciji. Suprotno tome, ozbiljnost, dužina i distribucija stenoze su kritični pri izboru bolesnika podvrgnutih perkutanoj koronarnoj intervenciji i za ishod intervencije. Izračuni koji se temelje na anatomiji, kao na primjer SYNTAX (sinergija perkutana koronarne intervencije, TAXusa i operacije, prema eng. *SYNergy between PCI with TAXus and surgery*), pokazali su da mogu predvidjeti kliničke ishode perkutane koronarne intervencije,[35] no vizualno tumačenje angiograma krvnih žila može biti različito, ovisno o promatraču. Stoga funkcionalni izračuni koji se temelje na anatomiji i koji obuhvaćaju objektivne podatke iz frakcijske rezerve protoka ili kvantitativne angiografije krvnih žila imaju bolju sposobnost predikcije.

U posljednje vrijeme razvijeni su brojni izračuni rizika koji kombiniraju kliničke i anatomske podatke.[36-42] Ljestvica Euro-Heart proizlazi iz 12 kliničkih karakteristika i četiri karakteristike lezija. Razvijen je i validiran na 46.064 bolesnika koji su sudjelovali u anketi Euro-Heart o perkutanoj koronarnoj intervenciji, a uspješnost u izdvajanju bolesnika kod kojih postoji rizik od smrti u bolnici je bila dobra, sa statistikom slaganja od 0,90.[36] Klinički izračun SYNTAX kombinira izračun

In common with the previous study by Paynter and colleagues,[30] Thanassoulis and colleagues[32] calculated two different genetic risk scores: a more restrictive score derived from 13 SNP previously associated with coronary heart disease or myocardial infarction, and a less restrictive score that included an additional 89 SNP associated with intermediate phenotypes. In both approaches, they also used both a simple and weighted count of risk alleles. Finally, they reran the restrictive score adding an additional 16 recently identified SNP. The genetic risk scores were applied to the Framingham Offspring Cohort. The restrictive genetic risk score performed better than the less restrictive score and was an independent predictor of both coronary heart disease and cardiovascular events. Nonetheless, it did not improve discrimination or classification even after addition of the additional SNP.

These studies consistently demonstrate that, even if genotypic information is summarised into an overall risk score, it does not improve the performance of existing risk scores and therefore has no obvious clinical utility, at present, in selecting middle-aged people for interventions. Further research is required to explore whether genetic risk scores have any role to play in identifying the subgroup of young people who are most likely to acquire a high-risk score in the future and, if so, the costs, risks and benefits of providing preventive interventions, such as education, to this subgroup at an earlier stage.

Procedure risk scores

Faroq and colleagues[33,34] recently reviewed the use of risk scores for patients undergoing coronary revascularisation. Clinical risk scores, such as PARSONNET (*Predictive score for acquired adult heart surgery: Additive and Logistic Regression models*) and EuroSCORE (*European System for Cardiac Operative Risk Evaluation*), have been widely adopted into clinical practice for patients undergoing coronary revascularisation. Anatomy-based risk scores, which contain no clinical information, have been developed using information derived from diagnostic angiography. As coronary artery grafts are used to bypass stenoses and the anastomoses are positioned distal to the diseased segment, additional anatomical information does not significantly improve the performance of clinical risk scores among patients being managed surgically. In contrast, the severity, length and distribution of stenoses are critical to the selection and outcome of patients undergoing PCI. Anatomy-based scores, such as SYNTAX (*SYNergy between PCI with TAXus and surgery*), have been shown to be predictive of clinical outcomes following PCI,[35] but visual interpretation of coronary angiograms is subject to interobserver variation. Therefore, functional anatomy-based scores, which incorporate objective information from fractional flow reserve or quantitative coronary angiography, have better prognostic ability.

More recently, a number of risk scores has been developed that combine clinical and anatomical information.[36-42] The Euro-Heart score is constructed from 12 clinical characteristics and four lesion characteristics. It was developed and validated on the 46,064 patients recruited to the EuroHeart Survey of PCI and performed well at identifying patients at risk of in-hospital death, producing a c statistic of 0.90.[36] The Clinical SYNTAX Score (CSS) combines the anatomically derived SYNTAX score with a modified version of the clinical ACEF (*Age, Creatinine and Ejection Fraction*) score. Patients in the highest tertile of CSS had higher rates of

SYNTAX dobiven na temelju anatomskih podataka s izmijenjenom verzijom kliničkog izračuna ACEF (dob, kreatinin i ejekcijska frakcija). Bolesnici u najvišoj tercili kliničkog izračuna SYNTAX imali su viši postotak ponovljene revaskularizacije (21%) i teške nepovoljne srčane i cerebrovaskularne događaje (32%) tijekom prve godine nakon perkutane koronarne intervencije, s dokazima o odnosu doza u tercilima.[37] U kliničkom izračunu SYNTAX statistika slaganja bila je viša nego samo u izračunu SYNTAX ili u izračunu ACEF kad se radi o predviđanju teških nepovoljnih srčanih i cerebrovaskularnih događaja, kao i smrti koja je nastupila iz raznih uzroka.[37] Capodanno i sur.[38] usporedili su dvije kombinacije izračuna rizika koji se temelje na kliničkim i anatomskim podacima (klasifikacija općeg rizika i izračun kliničkih rizika SYNTAX), dva izračuna kliničkih rizika (ACEF i EuroSCORE) i jedan izračun rizika koji se temelji na anatomiji (SYNTAX) kod bolesnika sa stenozom glavnog stabla lijeve arterije koji su podvrgnuti perkutanoj koronarnoj intervenciji ili premošćivanju koronarne arterije pomoću presatka. Najbolje karakteristike predviđanja dobivene su korištenjem izračuna kliničkog rizika (ACEF) kod bolesnika podvrgnutih operaciji, u usporedbi s kombiniranim izračunom rizika koji se temelji na kliničkim i anatomskim podacima kod perkutane koronarne intervencije. Chen i sur.[39] napravili su sličnu usporedbu između kombiniranog izračuna koji se temelji na kliničkim i anatomskim podacima NERS (novi izračun raspodjele rizika, prema eng. *New Risk Stratification Score*) i kliničkog izračuna SYNTAX za predviđanje rizika od teških nepovoljnih srčanih i cerebrovaskularnih događaja tijekom šestomjesečnog praćenja bolesnika kod kojih je koronarni stent ugrađen zbog stenoze glavnog stabla lijeve arterije. U usporedbi s izračunom kliničkih rizika, kombinirani izračun je imao veću osjetljivosti i veću određenost.[39] Chakravarty i sur.[40] također su pregledali bolesnike koji su bili podvrgnuti operaciji ili perkutanoj koronarnoj intervenciji zbog bolesti glavnog stabla lijeve arterije. Usporedili su uspješnost kombiniranog izračuna rizika, dobivenim kombiniranjem izračuna rizika PARSONNET i SYNTAX, i samo izračuna rizika koji se temelji na anatomskim podacima. Bolesnici su praćeni u prosjeku tri godine. Istraživanje je pokazalo da korištenje samo anatomskih podataka nije predvidjelo ishod nakon operacije. Za razliku od toga, izračun rizika SYNTAX je predviđao ishode kod bolesnika podvrgnutih perkutanoj koronarnoj intervenciji, no mogao se poboljšati dodavanjem kliničkih podataka.

Mnogi izračuni rizika razvijeni za primjenu kod bolesnika podvrgnutih koronarnoj revaskularizaciji postojali su prije široke primjene stentova koji izlučuju lijek, pa je stoga njihova uspješnost kod takvih bolesnika manja nego kod onih podvrgnutih balonskoj angioplastici. Stolker i sur.[43] nedavno su razvili i validirali izračun rizika koji kombinira kliničke, proceduralne i anatomske podatke koristeći registar EVENT (ocjena stentova koji izlučuju lijek i ishemijskih epizoda, prema eng. *Evaluation of Drug Eluting Stents and Ischaemic Events*), a ocijenili su njegovu sposobnost predviđanja revaskularizacije ciljane lezije tijekom jednogodišnjeg praćenja. Relativno jednostavan izračun imao je samo šest varijabli: dob, prethodna perkutana koronarna intervencija, perkutana koronarna intervencija glavnog stabla lijeve arterije, položaj presatka u veni safeni, minimalni promjer stenta i ukupna dužina stenta. Istraživači su pokazali trostruku razliku u revaskularizaciji ciljane lezije između visoko rizičnih i nisko rizičnih kategorija (7,5% naspram 2,2%).

Zaključak

Izračuni kardiovaskularnih rizika postoje već mnogo godina, ali su još uvijek predmet novih i zanimljivih istraživanja. Sve

repeat revascularisation (21%) and major adverse cardiac and cerebrovascular events (MACCE) (32%) over 1-year following PCI, with evidence of a dose relationship across the tertiles.[37] The CSS had a higher c statistic than either the SYNTAX score or ACEF score used in isolation in relation to predicting both MACCE and all-cause death.[37] Capodanno and colleagues[38] compared two combined clinical/anatomical risk scores (*the Global Risk Classification and the Clinical SYNTAX risk score*), two clinical risk scores (ACEF and EuroSCORE) and one anatomy-based risk score (SYNTAX) among patients with left main stem stenosis undergoing either PCI or coronary artery bypass grafting. The best predictive characteristics were obtained using a clinical risk score (ACEF) for surgical patients compared with a combined clinical/anatomical risk score (GRC) for PCI. Similarly, Chen and colleagues[39] compared the combined clinical/anatomical NERS (*New Risk Stratification Score*) with the CSS in terms of predicting the risk of MACCE over 6 months follow-up, among patients in whom coronary stents were implanted for left main stem stenoses. In comparison with the clinical risk score, the combined score had both higher sensitivity and higher specificity.[39] Chakravarty and colleagues[40] also examined patients treated by surgery or PCI for left main stem disease. They compared the performance of a combined risk score, produced by combining the PARSONNET and SYNTAX risk scores, with using the latter, an anatomical risk score, in isolation. Patients were followed up for a median of 3 years. The study suggested that using anatomical information in isolation did not predict outcome following surgery. In contrast, the SYNTAX risk score was predictive among patients undergoing PCI but could be improved by the addition of clinical information.

Many of the risk scores developed for use in patients undergoing coronary revascularisation predated the widespread adoption of drug-eluting stents and, therefore, perform less well in these patients than in those undergoing balloon angioplasty. Stolker and colleagues[43] recently developed and validated a risk score that combined clinical, procedural and anatomical information using the EVENT (*Evaluation of Drug Eluting Stents and Ischaemic Events*) Registry, and evaluated its ability to predict target lesion revascularisation at 1-year followup. The relatively simple score was composed of only six variables: age, previous PCI, left main PCI, saphenous vein graft location, minimum stent diameter and total stent length. The investigators demonstrated a threefold difference in target lesion revascularisation between the highest risk and lowest risk categories (7.5% vs 2.2%).

Conclusion

Cardiovascular risk scores have existed for many years but they are still subject to new and interesting research. They are increasingly being applied to conditions other than coronary heart disease, such as type II diabetes and heart failure, which are of increasing importance for public health. New biomarkers have been identified that improve discrimination but, inevitably, the marginal benefit decreases with each additional predictor. Also, improved discrimination needs to be weighed against increased cost and complexity, especially when risk scores are applied to the general population. As highlighted in a recent Heart editorial, ease of use has a major impact on the implementation of risk scores.[3] Recent research has focused on identifying new biomarkers and evaluating their effectiveness, but there is a paucity of applied research on cost-effectiveness and cove-

više se primjenjuju i na druge bolesti osim koronarne bolesti srca, kao na primjer dijabetes tipa 2 i zatajivanje srca, koje su sve važnije za javno zdravstvo. Utvrđeni su novi biomarkeri koji poboljšavaju razlikovanje, ali sa svakim dodatnim prediktorom marginalna korist je neizbježno manja. Nadalje, bolje razlikovanje treba odvagati u usporedbi s povećanim troškovima i složenošću, osobito kad se izračuni rizika primjenjuju na opću populaciju. Kao što je naglašeno u nedavnom časopisu Heart, jednostavnost korištenja je od velike važnosti za uvođenje izračuna rizika.[3] Novija istraživanja fokusirala su se na utvrđivanje novih biomarkera i na ocjenu njihove učinkovitosti, no premalo je primijenjenih istraživanja o troškovnoj učinkovitosti i primjeni. Time bi se trebalo baviti. Zaključci se mogu razlikovati ovisno o mjestu u kojem se radi izračun rizika ili o podskupini stanovništva na koju se on primjenjuje. Do danas nije bilo dokaza da genetski markeri poboljšavaju predviđanje rizika kod srednjovječnog stanovništva. Ako i igraju neku ulogu, to je možda kod mlađih osoba, kod kojih tradicionalni izračuni rizika nemaju veliku vrijednost. Drugi pristup prepoznavanju rizičnih osoba mlađe dobi je izračun životnog rizika. Bez obzira koji se pristup usvoji, potrebno je dobro procijeniti troškovnu učinkovitost ranih pregleda i intervencija.

rage. This needs to be addressed. The conclusions may differ depending on the location in which risk scores are being measured and the subgroup of the population to which they are applied. To date, there is no evidence that genetic markers improve risk prediction when used in middle-aged populations. If they have a role to play, it may be in younger people in whom traditional risk scores are of little value. Another approach to identifying atrisk individuals at a younger age is lifetime risk. Irrespective of the approach adopted, the cost-effectiveness of earlier screening and intervention needs to be properly evaluated.

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