

# Godina 2019. u kardiologiji: slikovne metode

## The year in cardiology: imaging The year in cardiology 2019

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### Uvod

Multimodalno oslikavanje i umjetna inteligencija primijenjeni u slikovnim metodama 2019. godine su godine bili od velikog interesa. Patohistološki uvidi koje su razni modaliteti oslikavanja omogućili u različitim kliničkim scenarijima (zatajivanje srca, koronarna bolest srca te bolesti srčanih zalistaka) utječu na način na koji procjenjujemo i zbrinjavamo ovakve bolesnike. Konvencionalna metoda oslikavanja srčanih struktura i funkcije još uvijek je metoda prvog izbora u procjeni bolesnika i u donošenju odluke o liječenju. Ipak, napredne metode ehokardiografije sa *strainom*, tkivna karakterizacija kardiovaskularnom magnetnom rezonancijom (CMR) te procjena bioloških procesa nuklearnim slikovnim metodama, pomogle su u procjeni korisnosti od ranih intervencija u svrhu preveniranja ili usporavanja progresije bolesti. Primjenom metoda strojnog učenja na sve ove metode oslikavanja u mogućnosti smo stvoriti protokole koji mogu identificirati određena obilježja bolesti ili rizike

### Introduction

Multimodality imaging and artificial intelligence applied to imaging techniques have been a major interest in this year. The pathophysiological insights that various imaging modalities have provided in numerous clinical scenarios (heart failure, coronary artery disease, and valvular heart disease) influence the way we evaluate and manage patients. Conventional imaging to assess cardiac structure and function is still the first approach to evaluate patients and decide the management. However, advanced echocardiography with strain imaging techniques, tissue characterization with cardiovascular magnetic resonance (CMR), and assessment of biological processes with nuclear imaging techniques have helped to understand that early intervention may be needed in order to prevent or halt the progression of the disease. By applying machine learning techniques to all these imaging modalities, we are able to generate algorithms that can identify certain patterns of disease or risk

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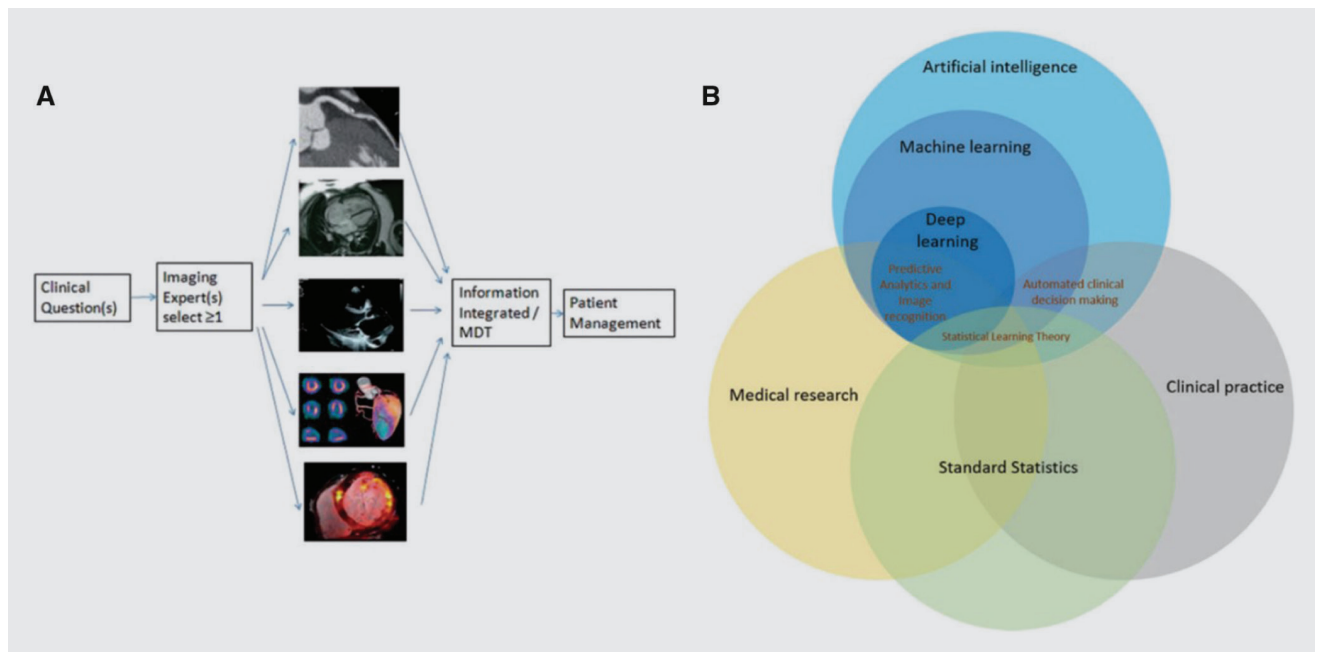


od razvoja bolesti, te razviti donošenje odluka na individualiziranoj razini. Ovaj pregledni članak sažima najrelevantnija istraživanja na polju slikovnih metoda, objavljena protekle godine.

Godine 2019. je primjena umjetne inteligencije i strojnog učenja na slikovne metode u kardiologiji jedna od glavnih novosti. Druge novosti u slikovnim metodama u neinvazivnoj kardiologiji objavljene tijekom 2019. sažete su u ovome preglednom članku (**Slika A – Take home figure**<sup>1,2</sup>).

and develop decisions in a more personalized way. This Year in Cardiology review articles summarize the most relevant studies in the field of imaging published in the last year.

This year, artificial intelligence and machine learning applied to cardiac imaging has been one of the main novelties. Other advances in non-invasive cardiac imaging published in 2019 are summarized in this Year in Cardiology review article (**Figure A – Take home figure**<sup>1,2</sup>).



**FIGURE A. Take home figure: Multimodality imaging and artificial intelligence in cardiac imaging.** The use of the different imaging modalities should be based on a clinical question. Selecting the most appropriate imaging techniques and integrate them to answer that specific question will be key to improve the outcomes of patients (A). In the future, many of the process the clinicians are used to do to integrate all the information gathered from the imaging modalities may be automated by using artificial intelligence techniques. How artificial intelligence interacts with medical research, clinical practice and statistics will be the focus of ongoing research (B). Reproduced with permission from Fox et al.<sup>1</sup> and Krittanawong et al.<sup>2</sup>

## Ehokardiografija

Rano otkrivanje disfunkcije lijeve klijetke (LK) u različitim skupinama bolesnika bila je tema velikoga broja publikacija tijekom 2019. godine. Dijastolička disfunkcija lijeve klijetke uobičajeno prethodi njezinoj sistoličkoj disfunkciji te je povezana s kardiovaskularnim morbiditetom i mortalitetom. U populacijskoj studiji, *Copenhagen City Heart Study*, koja je uključila 6238 ispitanika, Lassen *i sur.*<sup>3</sup> procjenjivali su povezanost između tlakova punjenja LK mjerenih tkivnim doplerom (E/E') i ehokardiografije primjenom metode *speckle tracking* (E/E' sr) s pojavnošću kardiovaskularne smrti i prijma zbog zatajivanja srca (ZS) ili infarkta miokarda. Od 1238 ispitanika, 140 njih (11,3 %) postiglo je primarni ishod za vrijeme srednjega vremena praćenja od 11 godina. Nakon prilagodbe različitih kliničkih i ehokardiografskih parametara, E/E' sr bio je neovisno povezan s ishodom (omjer rizika (HR) 1,08, 95 % interval pouzdanosti (CI) 1,02 – 1,13 povećanje za svakih 10 cm; P = 0,003), dok E/E' nije bio povezan s ishodom. Dodatno

## Echocardiography

Early detection of left ventricular (LV) dysfunction in various populations has been the focus of numerous publications in 2019. Left ventricular diastolic function usually precedes LV systolic dysfunction and is associated with cardiovascular morbidity and mortality. From the Copenhagen City Heart Study, a population-based study including 6238 individuals, Lassen *et al.*<sup>3</sup> evaluated the association between LV filling pressures measured on tissue Doppler imaging (E/E') and speckle tracking echocardiography (E/E' sr) with the occurrence of cardiovascular death, admission for incident heart failure or myocardial infarction (MI). Of 1238 participants, 140 (11.3%) reached the primary endpoint during a median follow-up of 11 years. After adjusting for various clinical and echocardiographic parameters, E/E' sr was independently associated with the endpoint [hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.02–1.13 per each 10 cm increase; P = 0.003] whereas E/E' was not. In addition, E/E' sr provided incremen-

je E/E' sr pružio inkrementalnu prognostičku vrijednost veću od primjene bodovnog sustava za procjenu kardiovaskularnog rizika SCORE koje se trenutno upotrebljuje za procjenu rizika od kardiovaskularnog morbiditeta i mortaliteta u općoj populaciji. Povećanje tlakova punjenja LK mogu reflektirati i procesi starenja srca karakterizirani povećanjem fibroze. Fibroza može voditi poremećajima provođenja koji pogađaju kontraktilnu funkciju LK. Modin *et al.*<sup>4</sup> procijenili su na 1138 ispitanika uključenih u *Copenhagen City Heart Study* prognostičku vrijednost mehaničke disperzije LK koja je mjerena kao standardna devijacija vremena do vršnoga longitudinalnog *strain*a u apikalnom prikazu triju šupljina. Srednja vrijednost mehaničke disperzije u općoj populaciji jest  $45 \pm 38$  ms i povećava se s dobi, arterijskom hipertenzijom, povećanjem indeksa tjelesne mase te prisutnošću infarkta miokarda (IM). Velika mehanička disperzija LK bila je povezana s lošijom sistoličkom i dijastoličkom funkcijom LK. Svaki 10 ms povećanja mehaničke disperzije LK bilo je neovisno povezano s povećanim rizikom od kardiovaskularne smrti (HR 1,04, 95% CI 1,01 – 1,06; P = 0,004).

Unatoč rastućem broju dokaza dijagnostičke i prognostičke vrijednosti mjerenja sistoličke i dijastoličke funkcije dobivenih metodom *strain*a, istisna frakcija LK ostaje glavni parametar stratifikacije rizika u kliničkoj praksi. Povezanost između istisne frakcije LK koju je procjenjivao liječnik i preživljenja analizirana je u 403 977 ehokardiograma učinjenih u 203 135 bolesnika iz SAD-a<sup>5</sup>. Pedeset posto populacije imalo je istisnu frakciju LK između 55 i 65 %. Tijekom srednjeg vremena praćenja od 4 godine 23 % bolesnika je umrlo. U obliku povezanosti između istisne frakcije LK i sveukupne smrtnosti opažen je u kategoriji bolesnika s istisnom frakcijom 60 – 65 %. Ovi su rezultati reproducirani u neovisnoj bazi podataka s Novog Zelanda koji su uključili 45 531 ehokardiogram obavljen u 35 976 bolesnika. U obliku odnosa također je uočen u muškaraca i žena, bolničkih i vanjskih bolesnika sa ZS-om, a devijacija od istisne frakcije od 60 do 65 % bila je povezana s većim multiplicitirajućim povećanjem rizika u mlađih bolesnika u usporedbi sa starijim bolesnicima.

Istisna frakcija LK također je parametar u klasifikaciji ZS-a. Od 10 do 20 % bolesnika sa ZS s reduciranom istisnom frakcijom (LVEF <40 %) može imati poboljšanje istisne frakcije LK. Ipak, dokazi učestalosti i ishoda bolesnika sa ZS i oporavljenom istisnom frakcijom LK temeljeni su na odabranoj kohorti bolesnika randomiziranih kliničkih istraživanja. Od ukupno 3124 bolesnika sa ZS s početno reduciranom istisnom frakcijom, liječena suvremenom terapijom, u njih 37,6 % registrirano je poboljšanje istisne frakcije LK s 26 na 46 %, kroz medijan praćenja od 17 mjeseci<sup>6</sup>.

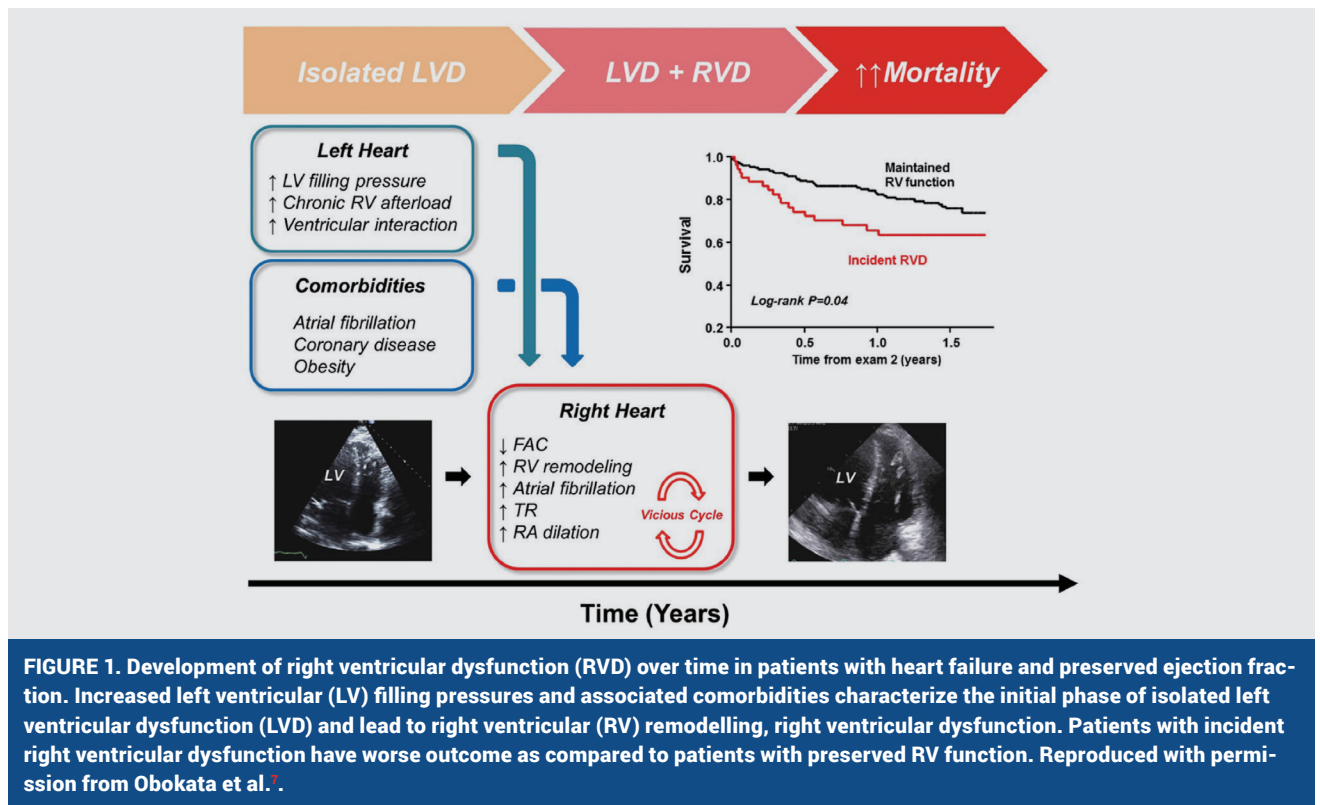
Bolesnici sa ZS i oporavljenom istisnom frakcijom LK imali su nižu stopu sveukupne smrtnosti, sveukupne hospitalizacije, srčane transplantacije te implantacije uređaja za potporu funkcije LK nego bolesnici u kojih je istisna frakcija LK ostala niska. Ne manje bitna jest karakterizacija remodeliranja desne klijetke (DK) u bolesnika sa ZS-om. U 271 bolesnika sa ZS-om i očuvanom istisnom frakcijom LK (HFpEF) *RV fractional area change* smanjena je za 10 %, a dijastolička areja DK povećana je za 21 % kroz medijan praćenja od 4 godine<sup>7</sup>. Ove su promjene premašile odgovarajuće promjene LK. Dodatno, prevalencija trikuspidalne insuficijencije povećana je za 45 %. Fibrilacija atrijska, povećana tjelesna težina, koronarna bolest srca, povećani plućni i tlakovi punjenja LK, kao i dilatacija

tal prognostic value over the SCORE risk chart, currently used to evaluate the risk of cardiovascular morbidity and mortality in the general population. Increased LV filling pressures may reflect the ageing process of the heart characterized by increased fibrosis. This fibrosis may lead to conduction abnormalities that influence the contractile function of the LV. Modin *et al.*<sup>4</sup> evaluated in 1138 participants of the Copenhagen City Heart Study the prognostic value of LV mechanical dispersion which is measured as the standard deviation from time to peak longitudinal strain of the three LV apical views. The mean value of LV mechanical dispersion in the general population was  $45 \pm 38$  ms and increased with age, hypertension, body mass index, and presence of MI. Large LV mechanical dispersion was associated with worse LV systolic and diastolic function. Each 10 ms increase in LV mechanical dispersion was independently associated with increased risk of cardiovascular death (HR 1.04, 95% CI 1.01–1.06; P = 0.004).

Despite the growing evidence on the diagnostic and prognostic value of strain derived measures of LV systolic and diastolic function, LV ejection fraction (EF) remains the mainstay parameter for risk stratification in clinical practice. The association between physician-reported LVEF and survival was assessed in 403 977 echocardiograms performed in 203 135 patients from USA.<sup>5</sup> Fifty percent of the population had an LVEF between 55% and 65%. Over a median follow-up of 4 years, 23% of patients died. A U-shaped relationship between LVEF and all-cause mortality was observed with the nadir at the 60–65% LVEF category. These results were reproduced in an independent dataset from New Zealand including 45 531 echocardiograms from 35 976 patients. The U-shaped relationship was also observed in men and women, inpatients and outpatients with heart failure, and deviations from LVEF of 60–65% were associated with greater multiplicative increase in risk for younger patients as compared to old patients.

Left ventricular ejection fraction is also the parameter to classify heart failure patients. Ten to 20% of patients with heart failure with reduced LVEF ( $\leq 40\%$ ) may improve in LVEF. However, the evidence on the frequency and outcomes of patients with heart failure and recovered LVEF is based on selected cohort of patients or randomized clinical trials. Of 3124 heart failure patients with reduced LVEF at baseline treated with contemporary heart failure medications, 37.6% presented improvement in LVEF from 26% to 46% over a median follow-up of 17 months.<sup>6</sup>

Patients with heart failure and recovered LVEF had lower rates for all-cause mortality, all-cause hospitalizations, cardiac transplantation, or LV assist device implantation than the patients who remained with reduced LVEF. Not less important is the characterization of the right ventricular (RV) remodelling in heart failure patients. In 271 patients with heart failure and preserved LVEF (HFpEF), RV fractional area change reduced by 10% and RV diastolic area increased by 21% over a median follow-up of 4 years.<sup>7</sup> These changes exceeded the corresponding changes in the LV. In addition, the prevalence of tricuspid regurgitation increased by 45%. Atrial fibrillation, higher body weight, coronary artery disease, higher pulmonary pressures and LV filling pressures and RV dilation were associated with development of RV dysfunction (**Figure 1**).<sup>7</sup> Patients with HFpEF developing RV dysfunction had two-fold increased risk of death. In this group of heart fail-



DK povezani su s razvojem disfunkcije DK (slika 1).<sup>7</sup> Bolesnici s HFpEF-om u kojih se razvije disfunkcija DK imaju dvaput veći rizik od smrtnog ishoda. U ovoj grupi bolesnika sa ZS-om procjena funkcije lijeve pretkljetke pokazuje vrijedna nova saznanja. U 308 bolesnika s HFpEF-om Feed *i sur.*<sup>8</sup> pokazali su da je kruta lijeva pretkljetka (oštećena funkcija rezervoara lijeve pretkljetke) povezana s povećanom plućnom vaskularnom rezistencijom i sniženom vršnom potrošnjom kisika, te je, neovisno, povezan s ukupnim ishodima kardiovaskularne hospitalizacije ili smrti. Treba istaknuti da istraživanja nisu definirala povezanost između funkcije lijeve pretkljetke kao rezervoara i ukupnih ishoda za neurohormonalne markere te, kao što su naglasili autori, da su malobrojna istraživanja koja etabliraju referentne vrijednosti *straina* lijeve pretkljetke kroz ehokardiografske sustave i analize.

U bolesnika s asimptomatskom teškom aortnom stenozom i očuvanom istisnom frakcijom globalni longitudinalni *strain* LK (GLS) na ehokardiografiji *speckle trackingom* osjetljivija je metoda od procjene istisne frakcije LK u identifikaciji ranih promjena sistoličke funkcije LK u vrijeme praćenja. Vrijednost GLS-a >-18,2 % (teže oštećen) povezan je s većim rizikom od razvoja simptoma i potrebom za intervencijama na aortnom zalistku u usporedbi s očuvanim vrijednostima GLS-a LK (<-18,2 %).<sup>9</sup> Ehokardiografija je metoda prvog izbora u procjeni bolesti srčanih zalistaka. Kvantifikacija sekundarne mitralne insuficijencije ostaje izazov. U 423 bolesnika sa zatajivanjem srca Bartko *i sur.*<sup>10</sup> razvili su jedinstven algoritam koji kombinira efektivnu regurgitirajuću areju ušća (EROA), regurgitirajući volumen te regurgitirajuću frakciju, koji imaju bolju snagu identifikacije bolesnika s povećanim smrtnim rizikom od trenutnih definicija temeljenih na smjernicama. Bolesnike s ni-

ure patients, assessment of left atrial function has provided important new insights. In 308 patients with HFpEF, Freed *et al.*<sup>8</sup> showed that impaired left atrial reservoir strain (stiff left atrium) was associated with increased pulmonary vascular resistance and decreased peak oxygen consumption and was independently associated with the composite outcome of cardiovascular hospitalization or death. It should be noted that the study did not correct the association between left atrial reservoir strain and the composite outcome for neurohormonal markers and as acknowledged by the authors, the studies establishing the reference values of normal left atrial strain values across the echocardiographic systems and analysis platforms are scarce.

In patients with asymptomatic severe aortic stenosis and preserved LVEF, LV global longitudinal strain (GLS) on speckle tracking echocardiography is more sensitive than LVEF to identify early changes in LV systolic function during the follow-up. An LV GLS of >-18.2% (more impaired) is associated with higher risk of developing symptoms and needing aortic valve intervention as compared to more preserved values of LV GLS (≤-18.2%).<sup>9</sup> Echocardiography is the imaging technique of first choice to assess valvular heart disease. Secondary mitral regurgitation quantification remains challenging. In 423 heart failure patients, Bartko *et al.*<sup>10</sup> developed a unifying algorithm combining effective regurgitant orifice area (EROA), regurgitant volume, and regurgitant fraction that had better discrimination power to identify patients with increased mortality risk than current guideline-based definitions. Low-risk patients were characterized by an EROA of <20 mm<sup>2</sup> and a regurgitant volume of <30 mL whereas high-risk patients were defined by an EROA of ≥30 mm<sup>2</sup> and a regurgitant volume



skim rizikom karakteriziraju EROA <20 mm<sup>2</sup> te regurgitirajući volumen <30 mL, dok bolesnike visokog rizika definiraju EROA >30 mm<sup>2</sup> te regurgitirajući volumen >45 mL. Bolesnici s umjerenim rizikom (s EROA između 20 i 29 mm<sup>2</sup> i regurgitirajućim volumenom 30 – 44 mL) reklasificirani su kao visoko rizični ako je regurgitirajuća frakcija ≥50 %. Ipak, ovakav postupnik ima umjerenu diskriminacijsku moć (areja ispod krivulje 0,63).

Primjena orijentacijskog pregleda srca ultrazvukom (FoCUS) ima sve veću popularnost u jedinicama hitne službe te u intenzivnim jedinicama. Među 839 bolesnika sa sumnjom na akutni aortni sindrom izračunan rizik detekcije aortalne disekcije na ≤1 i negativna FoCUS ehokardiografija mogu isključiti akutni aortalni sindrom sa senzitivnošću od 94 % i stopom promašaja od 1,9 %.<sup>11</sup>

Konačno, povećan karotidni arterijski val izmjeren duplex doplerom neovisno je povezan s bržom kognitivnom deterioracijom među 3191 ispitanika uključenih u *Whitehall II* istraživanje<sup>12</sup> naglašavajući važnost primjene ultrazvuka izvan područja srca.

## Magnetna rezonancija srca

Studija *ICELAND-MI* donosi značajne novosti za razumijevanje IM-a i fibroze u osoba starije životne dobi. U prvom izvješću Shanbhaga i sur.<sup>13</sup> o istraživanju provedenom u 397 bolesnika u dobi od 72 do 81 godine ispitivani su učinci kasnog bojenja gadolinijem (LGE) na MR srca s obzirom na posljedice kao što su infarkt miokarda (subendokardijalni) i drugi poremećaji (druge morfologije LGE-a). U tijeku praćenja od 5,8 godina dogodila su se 192 neželjena događaja. Autori su zaključili da je veliki neishemijski obrazac fibroze bio jedini neovisni čimbenik predikcije ishoda (slika 2).<sup>13</sup>

U drugom izvješću iz studije *ICELAND-MI* Acharya i sur.<sup>14</sup> ispitivali su prediktivnu vrijednost neprepoznatog IM-a na dugoročnu prognozu bolesnika u kohorti od 935 starijih bole-

of ≥45 mL. Intermediate-risk patients (with an EROA between 20 and 29 mm<sup>2</sup> and a regurgitant volume of 30–44 mL) were reclassified as high risk if the regurgitant fraction was ≥50%. However, this algorithm had a rather modest discrimination power (area under the curve 0.63).

The use of transthoracic focused cardiac ultrasound (FoCUS) is gaining popularity at the emergency department and intensive care units. Among 839 patients with suspected acute aortic syndrome, an aortic dissection detection risk score of ≤1 and a negative FoCUS could rule out an acute aortic syndrome with a sensitivity of 94% and a failure rate of 1.9%.<sup>11</sup>

Finally, elevated carotid artery wave intensity measured on Duplex Doppler ultrasound was independently associated with faster cognitive decline among 3191 individuals enrolled in the Whitehall II study,<sup>12</sup> highlighting the relevance of ultrasound imaging outside the heart.

## Cardiovascular magnetic resonance

The ICELAND-MI study is providing significant new data in the understanding of MI and fibrosis in elderly adults. In the first report by Shanbhag *et al.*,<sup>13</sup> 397 patients aged 72–81 years were studied using CMR incorporating late gadolinium enhancement (LGE) imaging which identifies myocardial fibrosis due to MI (subendocardial) and other causes (other patterns). During the follow-up of 5.8 years, 192 events were recorded. The authors found that major non-ischaemic fibrosis was the only independent predictor of outcome (Figure 2).<sup>13</sup>

In the second report from the ICELAND-MI trial, Acharya *et al.*<sup>14</sup> report on the long-term predictive value of unrecognized MI (UMI) in an elderly cohort of 935 subjects aged 67–93 years. Previous reports have suggested a poor short-term prognosis but this study extends follow-up to 13.3 years. The authors

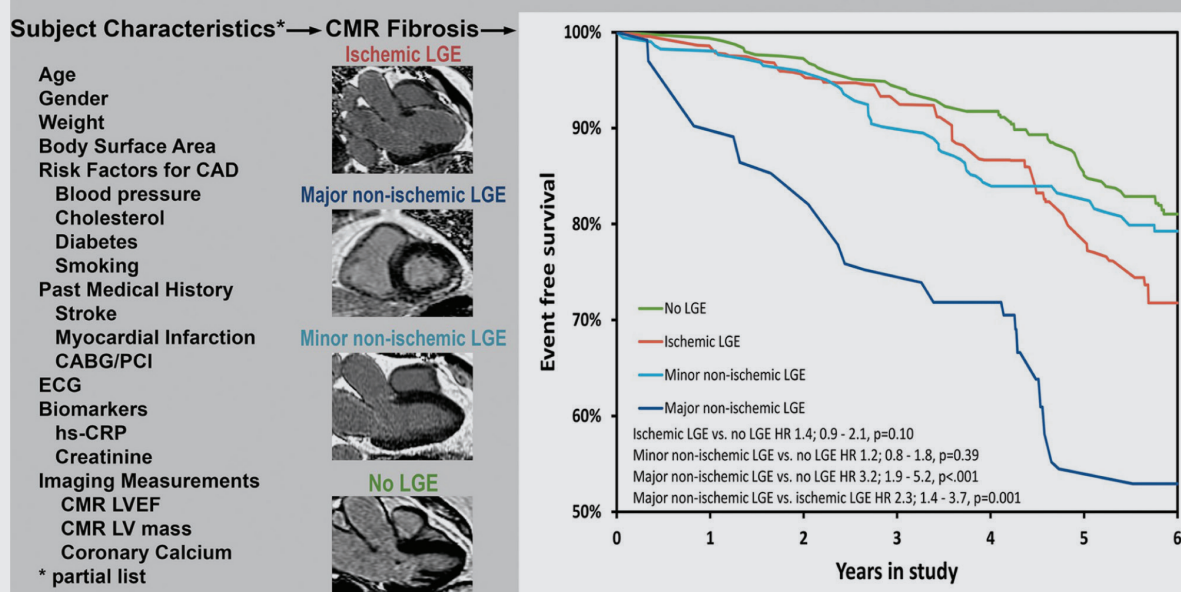


FIGURE 2. Inverse propensity adjusted prognosis of ischaemic and non-ischaemic myocardial fibrosis. Reproduced with permission from Shanbhag *et al.*<sup>13</sup>.

snika u dobi od 67 do 93 godine. Prethodne su studije upućivale na lošiju dugoročnu prognozu, a spomenuta studija imala je produljeno razdoblje praćenja od 13,3 godine. Autori su prikazali da je ukupna smrtnost zbog neprepoznatih IM-a manja nego zbog prepoznatih, barem u 5 godina praćenja, a podjednaka tijekom 10 godina. U svim točkama praćenja neprepoznati IM imao je veću stopu mortaliteta nego u bolesnika bez IM-a. Nije poznato bi li sekundarna prevencija bila korisna u bolesnika s neprepoznatim IM.

MR srca dao je velik doprinos dijagnostici i zbrinjavanju bolesnika s kardiomiopatijama otkrivanjem i karakterizacijom uzoraka miokardijalne fibroze u kasnom bojenju gadolinijem, tkivnoj karakterizaciji preko T1, T2 i T2\* mapiranja, te pouzdano procjenom funkcije klijetki i procjenom mase. Gutman *et al.*<sup>15</sup> ispitivali su značajnost prisutnosti miokardijalne fibroze s pomoću LGE-a kod 452 bolesnika s neishemijskom dilatacijskom kardiomiopatijom (DCM). U bolesnika s fibrozom učestalost mortaliteta smanjila se ugradnjom implantabilnog kardioverterskog defibrilatora (ICD) sa stopom rizika HR 0,45 ( $P = 0,003$ ), a u bolesnika bez prisutnosti fibroze nije opaženo poboljšanje preživljenja nakon ugradnje ICD-a (HR 1,22,  $P = 0,64$ ). Autori zaključuju da u neishemijskoj DCM prisutnost fibroze može unaprijediti izbor sekcije bolesnika koji bi imali indikaciju za ugradnju ICD-a. Galan-Arriola *et al.*<sup>16</sup> koristili su se serijskim MR-om srca za utvrđivanje ranih stadija antraci-klinke kardiotoksičnosti pri istraživanju na svinjama. Najranija detektibilna abnormalnost bila je povišena T2 relaksacija, koja je bila povezana s histologijom intramiocitnog edema, bez promjene u ekstracelularnom prostoru. Promjene u T1 i ekstracelularnom volumenu u T1 mapiranju dogodile su se mnogo ranije i koincidirale su s poremećajima kontraktilnosti. Zaustavljanje doxorubicina nakon otkrivanja T2 abnormalnosti dovelo je do oporavka intramiocitne vakuolizacije, upućujući na to da su rane T2 promjene izražene u stadiju u kojemu je reverzibilnost još uvijek moguća. Pronalazak navedenih obilježja ima veliku kliničku važnost za primjenu onkološke terapije. Scally *et al.*<sup>17</sup> ispitivali su 55 bolesnika s *takotsubo* kardiomiopatijom MR-om srca, primjenom ultramalih paramagnetičkih čestica željezova oksida (USPIO), koji su locirani u upalnim makrofagima. U akutnoj prezentaciji signal USPIO bio je smanjen u zoni baloniranja za 27 % ( $p < 0,001$ ) u usporedbi s normalnim miokardom bez baloniranja (19 %,  $p = 0,02$ ). Nisu pronađene nikakve razlike vizualnih pojačanja ni u jednoj zoni na 5 mjeseci. Autori zaključuju da *Takotsubo* kardiomiopatiju karakterizira faza akutne infiltracije upalnim makrofagima, koja je najizraženija u zoni baloniranja. Aung *et al.*<sup>18</sup> izvještavaju o 3920 osoba iz *UK Biobank* studije koje su bile bez poznate kardiovaskularne bolesti, ali su bile kronično izložene ambijentalnim zračnim polutantima, uključujući i čestice nitratnog dioksida. Pronađen je porast volumena u terminalnoj dijastoli za LV i RV, te volumena LV-a u terminalnoj sistoli u odnosu prema porastu izloženosti čestica dijametra  $< 2,5 \mu\text{m}$ . Podjednako tomu, biventrikularni volumeni bili su veći pri većoj izloženosti nitratnom dioksidu. Autori zaključuju da je onečišćenost zraka neprepoznati kardiovaskularni čimbenik rizika, koji dovodi do pojave zatajivanja srca.

Tenzor difuzna (DT) MR srca nova je tehnika koja prikazuje asimetrije difuzije molekula vode kako bi definirala citoarhitekturu tkiva. Tkiva poput neurona i miokarda mogu se ispitivati zbog njihove longitudinalne zrnatosti. Tehnika je tek nedavno postala dostupna i validirana za *in vivo* snimanje na ljudima. Trodimenzionalni (3D) odnosi arhitekture slojeva srca već su dobro poznati i prezervirani u sojevima sisavaca implicirajući da navedena strukturna organizacija

showed that all-cause mortality in UMI patents was lower than recognized MI for at least 5 years, but similar at 10 years. At all time-points UMI had a higher mortality than patients with no MI. It is not known whether secondary prevention would be useful in UMI patients.

Cardiovascular magnetic resonance has made an enormous contribution to the diagnosis and management of the cardiomyopathies through the presence and patterns of myocardial fibrosis from LGE imaging, tissue characterization through T1, T2, and T2\* mapping, and accurate measures of ventricular function and mass. Gutman *et al.*<sup>15</sup> studied 452 patients with non-ischaemic dilated cardiomyopathy (DCM) stratified by the presence or absence of non-ischaemic myocardial fibrosis by LGE. In patients with fibrosis, the mortality was reduced by an implantable cardioverter-defibrillator (ICD) with HR 0.45 ( $P = 0.003$ ), but in patients without fibrosis there was no improvement in mortality with ICD (HR 1.22,  $P = 0.64$ ). The authors conclude that in non-ischaemic DCM, the presence of fibrosis may allow for improved selection of patients requiring ICD. Galan-Arriola *et al.*<sup>16</sup> used serial CMR to identify the early stages of anthracycline-induced cardiotoxicity in a pig study. The earliest detectable abnormality was increased T2 relaxation which was correlated on histology with intramyocyte oedema, without change in the extracellular space. Changes in T1 and the extracellular volume on T1 mapping occurred much later and coincided with wall motion abnormalities. Stopping doxorubicin upon detection of T2 abnormality resolved intramyocyte vacuolization, indicating that the early T2 findings are at a stage when reversibility is still possible. These findings have important clinical implications for cancer therapy. Scally *et al.*<sup>17</sup> studied 55 patients with takotsubo cardiomyopathy using CMR including ultrasmall paramagnetic particles of iron oxide (USPIO) which localize in inflammatory macrophages. During the acute presentation, USPIO signal was reduced in the ballooning zone by 27% ( $P < 0.001$ ) as compared to non-ballooning zone (19%  $P = 0.02$ ). No enhancement was visible in either zone at 5 months. The authors conclude that takotsubo cardiomyopathy is characterized by an acute myocardial macrophage inflammatory infiltrate, most marked in the ballooning zone. Aung *et al.*<sup>18</sup> report on 3920 subjects from the UK Biobank study who were free of overt cardiovascular disease but had chronic exposure to ambient air pollutants including particulates and nitrogen dioxide. There was an incremental increase in LV and RV end-diastolic and LV end-systolic volumes with increasing exposure to particulates with a diameter of  $< 2.5 \mu\text{m}$ . Likewise, biventricular volumes were increased with higher nitrogen dioxide exposure. The authors conclude that air pollution is an under-recognized cardiac risk factor that may contribute to heart failure.

Diffusion tensor (DT) CMR is a new technique that images the asymmetry of water diffusion to define tissue architecture. Tissues such as neurons and the myocardium can be interrogated because of their longitudinal grain. The technique has recently become possible *in vivo* in humans and has been well validated. The three-dimensional (3D) architecture of the layers of the heart is now well described and is preserved across mammalian species suggesting that the observed structure has functional importance. Khalique *et al.*<sup>19</sup> report the first series of patients in whom the 3D architecture is deranged, these being those with situs inversus totalis (SIT, dextrocardia). The normal epicardial

ima funkcionalnu važnost. Khalique *i sur.*<sup>19</sup> prvi opisuju seriju bolesnika s poremećenom 3D arhitekturom srca, s kompletnom inverzijom unutarnjih organa (situs inversus totalis, dekstrokardija). Normalni je ljevostrani epikardijalni heliks miocita promijenjen u desnostrani na bazi, s povratkom u ljevostrani na apeksu. Endokard je slično tomu bio invertiran na bazi, s varijabilnim stupnjem raspada organizacije više prema apikalno. Pronađen je reducirani *strain* u bolesnika sa situs inversus totalis dekstrokardijom. Dugoročne posljedice spomenutih nalaza nisu još poznate, no mogu govoriti u prilog hipotezi da su bolesnici sa SIT dekstrokardijom skloniji nastanku ZS-a uz prisutnost drugog čimbenika rizika poput arterijske hipertenzije ili infarkta. Ariga *i sur.*<sup>20</sup> s pomoću DT-MR-a srca prikazali su redukciju difuzijskih parametara, nazvanoj frakcionalna anizotropija (FA), u bolesnika s pojavom ventrikularnih aritmija [odds ratio (OR) 2,5, P = 0,015] u seriji 50 bolesnika s hipertrofičnom kardiomiopatijom. Frakcionalna anizotropija karakterizira pakiranje miocita i stoga može biti reducirana pri gubitku organizacije kardiomiocita. Iako trenutačno nema patohistološke potvrde hipoteze, autori zaključuju da povezanost FA i pojave aritmija može govoriti u prilog gubitka organizacije kardiomiocita. Potrebna su dodatna istraživanja za validaciju ovih intrigantnih nalaza.

MR srca primjenjuje se desetljećima za oslikavanje aorte i aortnog zalistka. Musa *i sur.*<sup>21</sup> izvijestili su o seriji od 674 bolesnika s teškom aortnom stenozom u kojih je obavljen MR srca s LGE u 6 centara iz Velike Britanije. Prisutnost i opseg fibroze miokarda neovisni su pretkazatelji mortaliteta, s dvostruko povećanom stopom kasnog mortaliteta. Guala *i sur.*<sup>22</sup> prikazali su 117 bolesnika u multicentričnoj studiji ishoda. Tijekom 86 mjeseci praćenja stopa porasta promjera aorte bila je 0,62 mm/godina, a učestalost neželjenih događaja neovisno je predviđana longitudinalnim *strainom* proksimalne aorte. Autori zaključuju da bi ova jednostavna mjera mogla biti uključena u procjenu rizika u bolesnika s Marfanovim sindromom.

## Nuklearna slikovna obrada

Trenutačno ograničenje koronarne angiografije kompjutoriziranom tomografijom (CCTA) jest u njezinoj suboptimalnoj prediktivnoj vrijednosti za identifikaciju ishemije miokarda. Perfuzijsko snimanje miokarda (MPI) primjenom CT-a može nadomjestiti navedenu limitaciju. Alessio *i sur.*<sup>23</sup> proveli su dinamički kontrastni CT srca i rubidijsku pozitronsku emisijsku tomografiju (PET) u 34 visokorizična bolesnika. Globalni miokardijalni protok krvi procijenjen CT-om značajno je korelirao s mjerenjima na PET-u ( $r = 0,92$ ;  $P < 0,001$ ). Nadalje, prosječni globalni protoci krvi procijenjeni CT-om, odnosno s pomoću PET-a bili su slični ( $0,9 \pm 0,3$  prema  $1,0 \pm 0,2$  mL/min/g u mirovanju i  $2,1 \pm 0,7$  prema  $2,0 \pm 0,8$  mL/min/g u stresu). No procjena miokardijalnog protoka krvi na CT-u imala je značajne interindividualne varijacije, sa standardnom greškom procjenjivanja od 0,44 mL/min/g. Rezultati su obećavajući, ali je potreban dodatni razvoj kako bi se poboljšala pouzdanost metodologije na individualnoj razini. Dodatno tomu, studija je mjerila samo globalnu perfuziju, dok su regionalne razlike možda i veće vrijednosti za kliničku primjenu. Druga nova metoda za procjenu funkcionalnosti koronarne lezije jest transluminalni atenuacijski gradijent (TAG), koji se može mjeriti iz standardnih podataka koji se dobiju s pomoću CCTA-a. U prisutnosti značajnih koronarnih stenoza luminalna se atenuacija smanjuje i na CCTA se može mjeriti s pomoću TAG-a. U studiji Bom *i sur.*<sup>24</sup> transluminalni gradijent atenuacije uspoređivan je prema kvantitativnoj PET perfuziji i invazivnoj frakcijskoj rezervi protoka (FFR), gdje je pokazano da TAG nije

left-handed myocyte helix was switched to right handed at the base with a return to left handed at the apex. The endocardium was likewise inverted at the base, with variable derangement more apically. There was reduced strain in the SIT hearts. The long-term consequences of these findings are not yet known, but it could be hypothesized that SIT patients may be more susceptible to heart failure from a second insult such as hypertension or infarction. Ariga *et al.*<sup>20</sup> used DT-CMR to examine 50 patients with hypertrophic cardiomyopathy and report a reduction in the diffusion parameter called fractional anisotropy (FA) in patients with ventricular arrhythmias [odds ratio (OR) 2.5, P = 0.015]. Fractional anisotropy reflects packing of the myocytes and could therefore be reduced in myocardial disarray. Whilst there is no direct evidence of this from histology, the authors conclude that connection of reduced FA with arrhythmias might reflect disarray. Further work is needed to validate this intriguing study.

Cardiovascular magnetic resonance has been used for decades to image the aorta and the aortic valve. Musa *et al.*<sup>21</sup> report on 674 patients with severe aortic stenosis who also underwent LGE CMR at six UK centres. The presence and extent of myocardial fibrosis independently predicted mortality with a two-fold increase in late mortality. Guala *et al.*<sup>22</sup> report on 117 Marfan patients in a multicentre study of outcome. During 86 months of follow-up, the growth rate of the aortic diameter was 0.62 mm/year, and events were independently predicted by the proximal aorta longitudinal strain. The authors suggest that this simple measure could be included in risk assessment of Marfan patients.

## Nuclear imaging

The current limitation of coronary computed tomography angiography (CCTA) is its suboptimal positive predictive value for the identification of myocardial ischaemia. Myocardial perfusion imaging (MPI) using CT could solve that limitation. Alessio *et al.*<sup>23</sup> performed a dynamic contrast-enhanced cardiac CT and <sup>82</sup>rubidium positron emission tomography (PET) imaging in 34 high-risk patients. The CT-derived global myocardial blood flow values correlated highly with those measured on PET ( $r = 0,92$ ;  $P < 0,001$ ). In addition, the mean global myocardial blood flow values estimated on CT vs. PET were comparable ( $0,9 \pm 0,3$  vs.  $1,0 \pm 0,2$  mL/min/g at rest and  $2,1 \pm 0,7$  vs.  $2,0 \pm 0,8$  mL/min/g during stress, respectively). However, myocardial blood flow estimates on CT contained substantial individual variance with a standard error of the estimate of 0.44 mL/min/g. The results are promising but further development is needed to improve reliability of the methodology at individual level as well. Furthermore, the study measured only global perfusion, while regional values would be more clinically meaningful. Another novel method to determine whether a coronary lesion is functionally significant is transluminal attenuation gradient (TAG) that can be measured using standard CCTA data. In the presence of significant coronary stenosis, luminal attenuation will decrease rapidly on CCTA and can be measured with TAG. In the study by Bom *et al.*<sup>24</sup> Transluminal attenuation gradient was compared against quantitative PET perfusion imaging and invasive fractional flow reserve (FFR) and demonstrated that TAG did not discriminate between vessels with or without ischaemia as defined by either PET or FFR. The lack of diag-



dobro razlikovao žile s ishemijom ili bez ishemije u usporedbi s PET-om ili FFR-om. Nedostatak dijagnostičke vrijednosti TAG-a bio je povezan s velikom varijabilnosti koronarnih luminalnih dimenzija.

Umjetna je inteligencija trenutačno vruća tema u slikovnoj analizi. Strojno učenje, osobito duboko učenje, pokazalo se kao obećavajuće za detekciju i klasifikaciju primjenom slikovnih podataka. Betancur *et al.*<sup>25</sup> ispitivali su duboko učenje za automatsku predikciju opstruktivne koronarne bolesti srca iz polarnih mapa jednofotonske emisijske CT MPI (SPECT-MPI) u 1638 bolesnika sa sumnjom na koronarnu bolest srca. Površina ispod ROC krivulje za predikciju bolesti s pomoću dubokog učenja bila je veća od standardne analize (po bolesniku: 0,80 prema 0,78; po žili: 0,76 prema 0,73;  $P < 0,01$ ). Rezultati pokazuju da metode dubokog učenja imaju potencijal za automatsku interpretaciju MPI snimanja, uz pouzdanost barem podjednaku standardnoj analizi.

Dok dijagnostička i prognostička snaga MRI-ja ima dobro poznata obilježja, postoji malo dokaza da ove informacije mogu voditi zbrinjavanju bolesnika. Patel *et al.*<sup>26</sup> ispitivali su kohortu PET MPI od 12 594 bolesnika sa sumnjom ili s već poznatom koronarnom bolesti srca. Bolesnici su praćeni 3,2 godine. Kako je očekivano, niža globalna pričuva perfuzije bila je povezana s većom učestalosti ukupne smrtnosti. Ono što je zanimljivije, bolesnici s globalnom pričuvom perfuzije  $< 1,8$  imali su prednost u preživljenju nakon rane revaskularizacije, bez obzira na stupanj regionalne ishemije. No u bolesnika s očuvanom perfuzijskom pričuvom nije bilo koristi od revaskularizacije u usporedbi s optimiziranom terapijom lijekovima (slika 3)<sup>26</sup>. Rezultati su podudarni s ranijim nalazima da velika zona ishemije opravdava revaskularizaciju<sup>27,28</sup> i ekstrapolatu ovog nalaza na globalnu pričuvu perfuzije.

Snimanje s pomoću 18-F-fluorid-PET-a prihvatljivo je u različitim stanjima kao indikator tkivnih mikrokalcifikacija, koje se događaju uz aterosklerozu. Creager *et al.*<sup>29</sup> ispitivali su u *ex vivo* studiji ima li akumulacija 18F-fluorida u aterosklerotskim plakovima veze s razvojem mikrokalcifikata koji nisu vidljivi na CT-u. U toj kompleksnoj studiji signal 18F-fluorida u

nostic value of TAG was related to the large variability of coronary luminal dimensions.

Artificial intelligence is currently a hot topic in medical image analysis. Machine learning, especially deep learning has been shown to be promising in disease detection and classification using image data. Betancur *et al.*<sup>25</sup> explored deep learning for automatic prediction of obstructive CAD from the polar plots of single photon emission CT (SPECT) MPI in 1638 patients with suspected CAD. The area under the receiver operating characteristic curve for disease prediction by deep learning was higher than that of the standard analysis (per patient: 0.80 vs. 0.78; per vessel: 0.76 vs. 0.73;  $P < 0.01$ ). The results demonstrate that deep learning has the potential to perform automatic interpretation of MPI images with at least the same accuracy than the standard analysis.

While the diagnostic and prognostic power of MPI has been well characterized, there is little evidence on how this information should guide patient management. Patel *et al.*<sup>26</sup> examined a cohort of 12 594 patients with suspected or known CAD undergoing PET MPI. The patients were followed-up for 3.2 years. As expected, the low global perfusion reserve was associated with greater hazard of all-cause death. More interestingly, the patients with global perfusion reserve  $\leq 1.8$  had a survival benefit with early revascularization, regardless of the level of regional ischaemia. However, the patients with preserved perfusion reserve had no benefit of revascularization over medical therapy (Figure 3).<sup>26</sup> The results are concordant with earlier findings showing that large ischaemia justifies revascularization<sup>27,28</sup> and extend this notion also to global myocardial perfusion reserve.

<sup>18</sup>F-fluoride PET imaging is gaining increasing interest in various conditions as an indicator of tissue microcalcification, which is occurring in atherosclerosis. Creager *et al.*<sup>29</sup> investigated in an *ex vivo* study if <sup>18</sup>F-fluoride accumulation on atherosclerotic plaques are related to the development of microcalcifications that are not visible on CT. In this complex study, <sup>18</sup>F-fluoride signal in tissue analysis of human and mouse specimens was found to be clearly linked with small

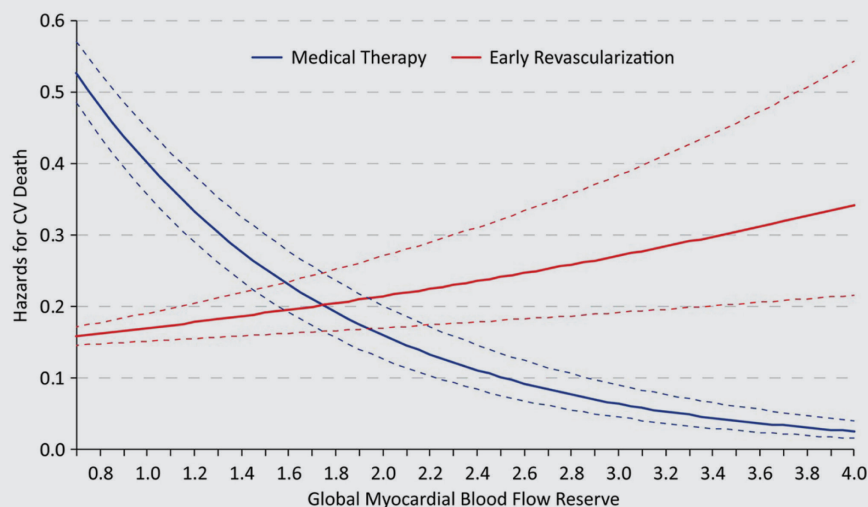


FIGURE 3. Hazards for cardiac death with early revascularization compared to medical therapy based on global myocardial blood flow reserve by positron emission tomography myocardial perfusion imaging. Reproduced with permission from Patel *et al.*<sup>26</sup>.



tkivnoj analizi humanih i mišjih uzoraka bio je vrlo jasno povezan s mikrokalifikacijama koje nisu vidljive na CT-u. Ovi rezultati potvrđuju da je mineralizacija plaka aktivan proces i da 18F-fluorid-PET može otkriti visokorizične koronarne i karotidne plakove.

U studiji Cardilege *i sur.*<sup>30</sup> degeneracija bioprostetskog aortnog zalistka ispitala se primjenom 18F-fluorid-PET-a. U *ex vivo* analizi unos 18F-fluorida bio je kolokaliziran s regijama tkivne degeneracije na histološkim preparatima. U bolesnika s bioprotezom aorte porast unosa 18F-fluorid na PET snimanju bio je povezan s bržim propadanjem funkcije zalistka tijekom dvogodišnjeg razdoblja praćenja. Disfunkcija aortne bioproteze otkrivena je u 10 bolesnika i u svih njih bio je prikazan unos 18F-fluorida na početku dok je još hemodinamika bila uredna. U multivarijantnoj analizi unos 18F-fluorida bio je jedini neovisni čimbenik prognoze disfunkcije bioproteze. Iako je potrebna veća kohorta bolesnika, snimanje PET-om s pomoću 18F-fluorida izgleda kao obećavajuća metoda za procjenu disfunkcije bioproteza zalistaka.

Snimanje infekcije i upale primjenom molekularnih slikovnih metoda etablirana je tehnika za endokarditis i upale prostetskih zalistaka. Swart *i sur.*<sup>31</sup> ispitali su čimbenike koji bi ometali dijagnostičku točnost 18F-fluoro-dezoksiglukoze (FDG) PET/CT-a. U multicentričnu studiju uključeno je 160 bolesnika sa sumnjom na endokarditis prostetskih zalistaka i 77 kontrolnih. Autori su pronašli da je niska upalna aktivnost (CRP <40 mg/L) vjerojatno povezana s produljenom antibiotskom terapijom u trenutku izvođenja snimanja te da je primjena kirurških adheziva tijekom implantacije zalistaka čimbenik koji znatno ometa dijagnostičku točnost, dok nedavno ugrađivanje zalistka nije bilo problematično za procjenu.

Drugi je izazov u populacije bolesnika sa sumnjom na infekciju implantabilnih kardioloških uređaja. U studiji Calais *i sur.*<sup>32</sup> dijagnostički pozitivna i negativna prediktivna vrijednost bile su 80 % i 91 % za FDG-PET i 100 % i 85 % za leukocitni SPECT, redosljedom kako je navedeno. Prolongirana antibiotska terapija prije dijagnostike uzrokovala je smanjenje senzitivnosti obiju tehnika. Kako FDG nije specifičan za upalu, već za unos glukoze, razvijeni su specifičniji dijagnostički modaliteti za potvrđivanje infekcije.

## Kompjutorizirana tomografija

Kompjutorizirana tomografija srca evoluirala je kao alat dijagnostike jedne obrade koji donosi vrijedne dijagnostičke i prognostičke informacije u bolesnika sa sumnjom na bolest ili s poznatom koronarnom bolesti srca. Procjena sadržaja kalcija na CT-u može se iskoristiti za procjenu rizika i uvođenje statinske terapije. Mitchel *i sur.*<sup>33</sup> procjenjivali su relativni učinak statina na neželjene kardiovaskularne događaje, stratificiran prema kalcijском zbroju (CAC) u 13 644 bolesnika (prosjeck dobi 50 godina; 71 % muškarci), koji su praćeni tijekom medijana razdoblja od 9,4 godine. Bolesnici bez CAC-a imali su izvrsnu prognozu neovisno o primjeni statinske terapije, dok je primjena statina u bolesnika s CAC-om >0 imala učinak na smanjenje neželjenih događaja (adjusted sub HR 0,76; 95 % CI 0,60 – 0,95; P = 0,015). Učinak uvođenja statina na velike neželjene kardiovaskularne događaje bio je značajno povezan s težinom CAC-a (p <0,001 za interakciju), s brojem potrebnih za liječenje za prevenciju 1 velikog neželjenog događaja u razdo-

microcalcifications, which were not detected on CT. These results confirm that plaque mineralization is an active process and that 18F-fluoride PET imaging detects coronary and carotid plaques with high-risk features.

In the study by Cartlidge *et al.*,<sup>30</sup> the degeneration of bioprosthetic aortic valve was investigated using <sup>18</sup>F-fluoride PET. In *ex vivo* analyses, the <sup>18</sup>F-fluoride uptake colocalized with tissue degeneration on histology. In patients with aortic bioprostheses, increased valve <sup>18</sup>F-fluoride uptake in PET imaging was associated with more rapid deterioration in valve function at 2-year follow-up. Aortic bioprosthesis dysfunction was detected in 10 patients and all of them showed <sup>18</sup>F-fluoride uptake at baseline when still the valve haemodynamics were normal. On multivariable analysis, <sup>18</sup>F-fluoride uptake was the only independent predictor of future bioprosthetic dysfunction. Although a larger patient cohort is needed, <sup>18</sup>F-fluoride PET imaging appears promising method in predicting dysfunction of bioprosthetic valves.

Infection and inflammation imaging using molecular imaging methods is an established technique in prosthetic valve endocarditis and device infections. Swart *et al.*<sup>31</sup> investigated the possible confounders that may impact on the accuracy of <sup>18</sup>F-fluoro-deoxyglucose (FDG) PET/CT. In a multicentre study, 160 patients with suspected prosthetic valve endocarditis and 77 control patients were scanned. The authors found that low inflammatory activity (C-reactive protein <40 mg/L)—possibly linked with prolonged antibiotic therapy at the time of imaging—and use of surgical adhesives during prosthetic heart valve implantation were significant confounders, whereas recent valve implantation was not.

Another challenging population is patients with suspected infection of cardiac implantable electronic devices. In a study by Calais *et al.*,<sup>32</sup> the diagnostic positive and negative predictive values were 80% and 91% for FDG PET and 100% and 85% for white blood cell SPECT, respectively. A prolonged antibiotic therapy before imaging tended to decrease the sensitivity for both techniques. As FDG is not specific for inflammation but for glucose uptake, more specific imaging agents for infection are being developed.

## Computed tomography

Cardiac computed tomography has evolved into a one-stop-shop imaging tool that can provide valuable diagnostic and prognostic information in patients with suspected or known CAD. Assessment of coronary artery calcium (CAC) score on CT can be used as a risk modifier and may guide statin therapy. Mitchel *et al.*<sup>33</sup> assessed the relative impact of statins on adverse cardiovascular events stratified by CAC scores in 13 644 patients (mean age 50 years; 71% men) who were followed-up for a median of 9.4 years. Patients without CAC had an excellent prognosis irrespective of statin therapy whereas in patients with CAC >0 statin therapy was associated with reduced risk of major adverse cardiovascular events (adjusted sub-HR 0.76; 95% CI 0.60–0.95; P = 0.015). The effect of statin use on major adverse cardiovascular events was significantly related to the severity of CAC (P < 0.0001 for interaction), with a number needed to treat to prevent 1 initial major adverse cardiovascular events over 10 years ranging from 100 (when CAC was 1–100) to 12 (if CAC >100). A recent *post hoc* analysis of the SCOT-HEART trial demonstrated that coronary heart disease death or non-fatal MI was three times more frequent

blju od 10 godina od 100 (kada je vrijednost CAC-a bila 1 – 100) do 12 (ako je CAC iznosio >100). Nedavnom *post hoc* analizom studije *SCOT-HEART* pokazano je da su smrt od koronarne bolesti srca ili nefatalni IM-a triput češći u bolesnika s plakovima visokog rizika (pozitivni remodeling ili niska atenuacija plaka) i dvaput učestaliji u bolesnika s opstruktivnim oblikom koronarne bolesti.<sup>34</sup> No ove povezanosti nisu bile neovisne o iznosu CAC-a, surrogatne mjere opterećenja aterosklerozom.

Grupa istraživača iz studije *PROMISE* ispitala je prevalenciju i kliničke prediktore visokorizične koronarne bolesti srca (definirane kao stenoza debla lijeve glavne koronarne arterije ili  $\geq 50\%$  ili  $\geq 70\%$  stenoza trožilna ili dvožilna bolest koja zahvaća proksimalni dio LAD-a).<sup>35</sup> Visokorizična koronarna bolest pronađena je kod 6,6 % ( $\geq 50\%$  stenoza) i 2,4 % ( $\geq 70\%$  stenoza). Varijable koje su bile prediktivne za visokorizičnu koronarnu bolest uključivale su obiteljsku anamnezu rane koronarne bolesti, dob, muški spol, nižu stopu glomerularne filtracije, dijabetes, više vrijednosti sistoličkog tlaka i pojava angine pektoris. Visokorizična koronarna bolest povezana je s većom stopom invazivnih intervencija u usporedbi s nevisokorizičnim oblicima bolesti.

Intrigantna studija ispitala je prognostičku vrijednost kombiniranih informacija od lezijom-specifične FFR i neželjenih obilježja plaka procijenjenih CCTA.<sup>36</sup> Autori su evaluirali 772 žile (u 292 bolesnika) s pomoću mjerenja CCTA i invazivne FFR. Zanimljivo, prisutnost  $\geq 3$  obilježja visokorizičnog plaka bio je neovisni čimbenik povezan s pojavom kliničkih događaja u skupini s vrijednosti FFR-a >0,8, no nije u skupini s FFR-om  $\leq 0,8$ . Čini se da dvojna integracija ishemije specifične za leziju i CT obilježje plaka mogu donijeti bolju stratifikaciju rizika od obiju komponenta pojedinačno, osobito u bolesnika s FFR-om >0,80.

Primjenom kompjutorskih simulacija dinamike fluida CT-om u današnje vrijeme omogućena je neinvazivna procjena FFR-a. U studiji Norgaard *i sur.*<sup>37</sup> provedena je procjena kliničkih ishoda u kliničkoj praksi nakon dijagnostičke strategije koja je kao prvi korak uključivala CTA sa selektivnim FFR(CT) testiranjem. Studija je analizirala rezultate 3674 uzastopna bolesnika sa stabilnim bolom u prsima s pomoću CTA i FFR(CT). Prisutnost srednjeg rizika od koronarne bolesti srca i FFR(CT) >0,80 bilo je povezano s povoljnim kliničkim ishodima, podjednako kao i u bolesnika bez dokaza ili uz minimalni dokaz koronarne bolesti. Nakon FFR(CT) simulacije, stresna CT perfuzija pojavila se kao potencijalna mogućnost za analizu anatomskih i funkcionalnih odjeka koronarne bolesti srca. Dostupni su uređaji za snimanje cijelog srca koji imaju robusniji stresni CT MPI (CTP). Dijagnostičku točnost uređaja najnovije generacije testirali su Pontone *i sur.*<sup>38</sup> u 100 simptomatskih bolesnika srednjeg do visokog rizika sa sumnjom na koronarnu bolest. CCTA sam imao je senzitivnost, specifičnost, negativnu prediktivnu vrijednost, pozitivnu prediktivnu vrijednost i točnost od 98 %, 76 %, 99 %, 63 % i 83 %, kako je navedeno. Kombinacija CCTA sa stresnim CTP-om donosi vrijednosti 91%, 94%, 96%, 86% i 93%, kako je navedeno, uz znatno poboljšanje u specifičnosti, pozitivnoj prediktivnoj vrijednosti i točnosti. Prosječna doza radijacije za CCT i stresni CTP bile su  $2,8 \pm 1,4$  mSv i  $2,5 \pm 1,1$  mSv.

Bolesnici sa šećernom bolesti čine kohortu s visokim rizikom od kardiovaskularnih neželjenih događaja. Grupa je istraživača u studiji *PROMISE* ispitala je li dijagnostička strategija osnovana na CCTA-u bolja od funkcionalnih stresnih testova za smanjenje smrtnosti ili pojave IM-a u bolesnika s dijabetesom [n = 1908 (21%)] ili onih bez dijabetesa [n = 7058 (79%)].<sup>39</sup> Bolesnici s dijabetesom koji su bili na CCTA-u

in patients with high-risk plaque features (positive remodeling or low attenuation plaque) and was twice as frequent in those with obstructive CAD.<sup>34</sup> However, these associations were not independent of CAC score, a surrogate measure of atherosclerosis burden.

The investigators of the PROMISE Trial assessed the prevalence and clinical predictors of high-risk CAD (defined as left main stenosis or either  $\geq 50\%$  stenosis or  $\geq 70\%$  stenosis of 3 vessels or 2-vessel CAD involving the proximal left anterior descending artery).<sup>35</sup> High-risk CAD was identified in 6.6% ( $\geq 50\%$  stenosis) and 2.4% ( $\geq 70\%$  stenosis) of patients. Variables predictive of high-risk CAD included family history of premature CAD, age, male sex, lower glomerular filtration rate, diabetes mellitus, elevated systolic blood pressure, and angina. High-risk CAD was associated with more frequent invasive interventions and adverse events as compared to non-high-risk CAD.

An intriguing study has investigated the prognostic value of combined information of lesion-specific ischaemia (FFR) and adverse plaque features by CCTA.<sup>36</sup> The authors evaluated 772 vessels (299 patients) by both CCTA and invasive FFR measurement. Interestingly, the presence of  $\geq 3$  high-risk plaque features was independently associated with clinical events in the FFR > 0.80 group, but not in the FFR  $\leq 0.80$  group. It seems that the integration of both lesion-specific ischaemia and CT plaque features may provide better prognostic stratification than either individual component alone, especially in patients with n FFR >0.80.

Using computational fluid dynamics simulations CT is now capable to provide non-invasive FFR measurements. A study by Norgaard *et al.*<sup>37</sup> assessed real-world clinical outcomes following a diagnostic strategy including first-line coronary CTA with selective FFR<sub>CT</sub> testing. The study reviewed the results of 3674 consecutive patients with stable chest pain evaluated with CTA and FFR<sub>CT</sub> testing. The presence of intermediate-range CAD and FFR<sub>CT</sub> >0.80 was associated with favourable clinical outcomes similar to the prognosis in patients without or with minimal evidence of CAD. Beyond FFR<sub>CT</sub> simulation stress CT perfusion has emerged as a potential strategy to acquire anatomic and functional evaluation of CAD. Whole heart coverage CT scanners have become readily available, which allow a more robust stress CT MPI (CTP). The diagnostic accuracy of latest scanner generation was tested by Pontone *et al.*<sup>38</sup> in 100 intermediate- to high-risk symptomatic patients with suspected CAD. CCTA alone demonstrated a sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83%, respectively. Combining CCTA with stress CTP, these values were 91%, 94%, 96%, 86%, and 93%, respectively, with a significant improvement in specificity, positive predictive value, and accuracy. The mean effective radiation dose for CCTA and stress CTP were  $2.8 \pm 1.4$  mSv and  $2.5 \pm 1.1$  mSv.

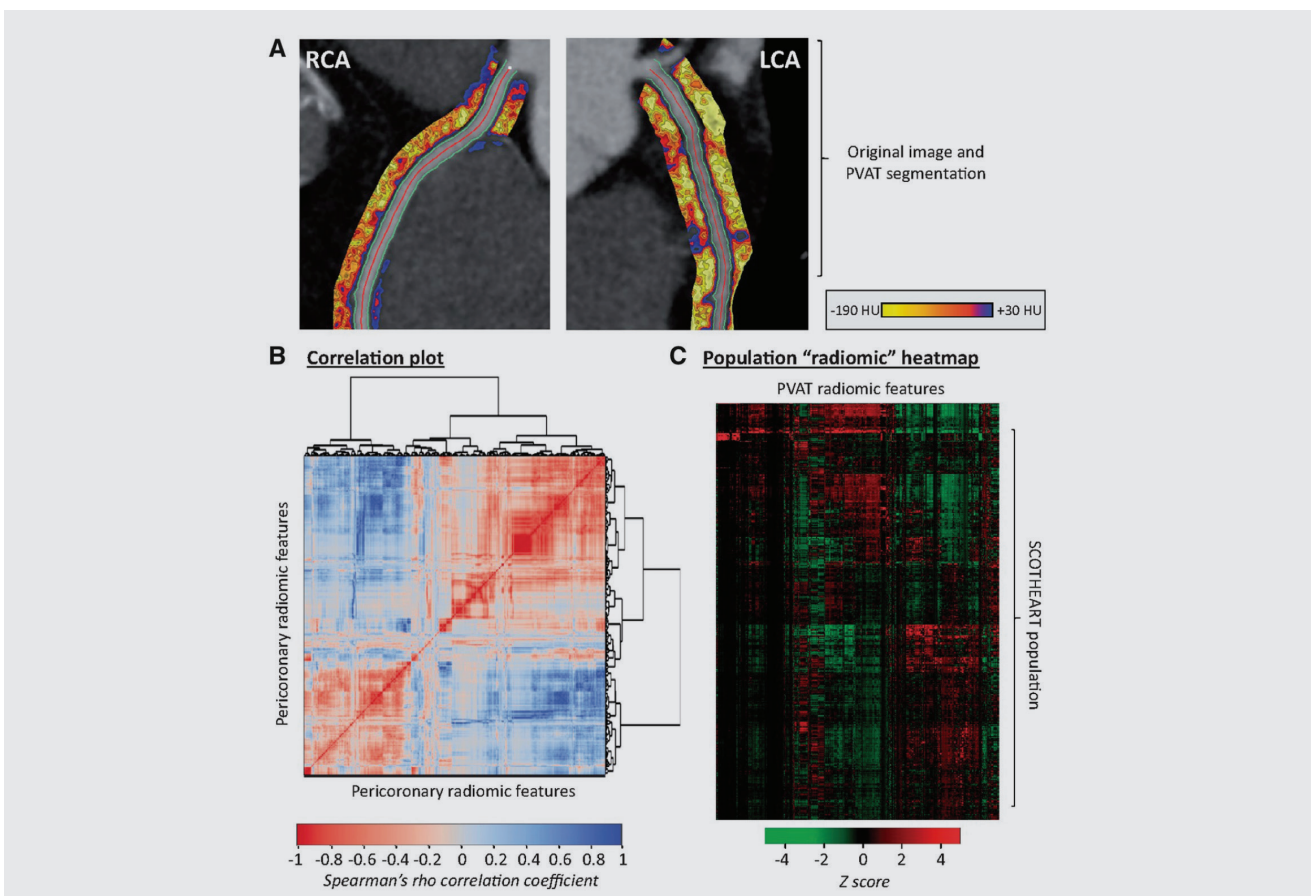
Patients with diabetes are a high-risk patient cohort for adverse cardiovascular outcomes. The PROMISE Trial investigators assessed whether a diagnostic strategy based on CCTA is superior to functional stress testing in reducing cardiovascular death or MI among symptomatic patients with diabetes [n = 1908 (21%)] vs. patients without diabetes [n = 7058 (79%)].<sup>39</sup> Patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI compared with func-

imali su manji rizik od kardiovaskularne smrtnosti ili IM-a, u usporedbi s funkcionalnim stresnim testovima [CCTA: 1,1 % (10 od 936) nasuprot stresni test: 2,6 % (25 od 972); prilagođeni HR 0,38; 95 % CI 0,18 – 0,79; P = 0,01]. U drugoj studiji, koja je također uključivala dijabetičare, ispitivani su učestalost i iznos progresije plaka, promjene u obilježjima plaka i kliničke prediktore progresije plaka.<sup>40</sup> Ukupno 1602 bolesnika koji su prošli serijske CCTA (medijan intervala retesta bio je 3,8 godina) bila su uključena i analizirana u studiji *Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging*.<sup>41</sup> Šećerna je bolest bila nezavisni čimbenik rizika za progresiju plaka (OR 1,526, 95 % CI 1,100 – 2,118; P = 0,011).

Preciznija procjena rizika koja uključuje detekciju koronarne upale ubraja se u grupu personalizirane medicine. Nove analitičke tehnike kao perivaskularna atenuacija masti osnovne ili plak-osnovane radiomike mogu ubrzati detekciju i kvantifikaciju perikoronarne upale i aktivnosti aterosklerotskog plaka.<sup>42,43</sup> Inovativna studija Oikonomou *i sur.*<sup>44</sup> prikazala je da analiza profila perikoronarne masti (FRP) s pomoću umjetne inteligencije znatno poboljšava predikciju velikih neželjenih kliničkih događaja i izvan tradicionalnih čimbenika rizika, CAC, stupnja koronarne stenozе i visokorizičnih obilježja plaka na CCTA u studiji SCOT-HEART (slika 4). Autori zaključuju da FRP donosi znatno poboljšanje procjene kardi-

tional stress testing [CCTA: 1.1% (10 of 936) vs. stress testing: 2.6% (25 of 972); adjusted HR 0.38; 95% CI 0.18–0.79; P = 0.01]. Another study including also individuals with diabetes, investigated the rate and extent of plaque progression, changes in plaque features, and clinical predictors of plaque progression.<sup>40</sup> A total of 1602 patients who underwent serial CCTA (median scan interval 3.8 years) were enrolled and analysed from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) trial.<sup>41</sup> Diabetes was an independent risk factor for plaque progression (OR 1.526, 95% CI 1.100–2.118; P = 0.011).

A more precise risk assessment that incorporates the detection of coronary inflammation would allow personalized medical interventions. Novel analytical techniques such perivascular fat attenuation index or plaque-based radiomics may facilitate the detection and quantification of pericoronary inflammation and atherosclerotic plaque activity.<sup>42,43</sup> An innovative study by Oikonomou *et al.*<sup>44</sup> demonstrated that artificial intelligence powered pericoronary fat radiomic profile (FRP) analysis significantly improved major adverse cardiovascular events prediction beyond traditional risk stratification that included risk factors, CAC, coronary stenosis, and high-risk plaque features on CCTA in the SCOT-HEART trial (Figure 4). The authors conclude that FRP leads to a signifi-



**FIGURE 4.** Radiomic phenotyping of coronary perivascular adipose tissue. (A) The perivascular adipose tissue (PVAT) of the right (RCA) and left (LCA) coronary was segmented and used to calculate a number of shape-, attenuation-, and texture-related statistics. (B) Correlation plot of all 1391 stable radiomic features in the SCOT-HEART population (n= 1575 patients), with hierarchical clustering revealing distinct clusters of radiomic variance. (C) Heatmap of scaled radiomic features in the SCOT-HEART population revealing between-patient variance across the cohort. Reproduced with permission from Oikonomou *et al.*<sup>44</sup>.



ovaskularnog rizika i iznad trenutnog stupnja znanja, koji može pomoći da se identificiraju bolesnici s povećanim rezidualnim rizikom od neželjenih kardiovaskularnih događaja.

## Napredno oslikavanje, fuzijsko snimanje, oslikavanje s pomoć umjetne inteligencije

Kardiovaskularno oslikavanje (invazivno i neinvazivno) razvija se ultrabrzim ritmom i današnji kliničar svakodnevno se suočava s različitim dostupnim modalitetima oslikavanja, uz veliki tehnološki razvoj, ali isto tako i fuzijskog oslikavanja i uvođenja metoda umjetne inteligencije i strojnog učenja. Iz kliničke perspektive, kardiovaskularni liječnik sutrašnjice mora biti upoznat s različitim izborima o tome kada primijeniti koju tehniku i u kojem kliničkom scenariju. Grupa unutar Europskog udruženja za kardiovaskularni imaging (dio ESC-a) izdala je izjavu o organizaciji multimodalitetnih tehnika oslikavanja u radiologiji, primjenom različitih modaliteta, kao i metoda svladavanja metoda i istraživanja u doba multimodaliteta.<sup>1</sup>

Ramos *i sur.*<sup>45</sup> istraživali su cijeljenje miokarda nakon infarkta u miševa primjenom serijskih snimanja (7. i 21. dan nakon infarkta) s pomoću 3T MR i 19F/1H tjelesne zavojnice. Injicirani 19F-perfluorocarbon nanopartikli koristili su se za evaluaciju umnožavanja inflamatornih stanica (makrofaga) i injiciranog gadolinijskog kontrasta koji veže elastin kako bi se procijenio elastinski sadržaj. Kombinacija ovih slikovnih tehnika omogućila je procjenu vremenskog tijeka remodelinga i procesa cijeljenja, kao i razvoja ožiljka.

Engel *i sur.*<sup>46</sup> proveli su istraživanje u 25 bolesnika sa stabilnom koronarnom bolesti ili sumnjom na akutni koronarni sindrom, primjenom neinvazivnog vezanja albumina na sondu gadofosveset-kontrastnog CMR, uz invazivnu koronarnu angiografiju i optičku koherentnu tomografiju (OCT). CMR se izvodio u dvama navratima: prije osnovnog pregleda i 24 sata nakon primjene gadofosveset-trinatrija. Bolesnici sa sumnjom na akutni koronarni sindrom otkrili su mnogo veće pojačanje signala na CMR nakon aplikacije gadofosveset-trinatrija na segmente koji su bili u žili odgovornoj za događaj, u usporedbi s bolesnicima sa stabilnom koronarnom bolesti. Na OCT-u ovi su se bolesnici prezentirali fibroateromima tanke kape. Nove CMR tehnike omogućuju vrlo ranu detekciju bolesnika s potencijalnim akutnim koronarnim sindromom.

Vrijedi istaknuti nekoliko radova u području multimodalitetnog i funkcijskog slikanja. Kalcifikacija mitralnog prstena primijećena je u bolesnika s mitralnom regurgitacijom/stenozom i važna je pri razmatranju za transkatetersku zamjenu zalistka. Da bi bolje razumjeli patofiziologiju, Massera *i sur.*<sup>47</sup> napravili su CT kalcijski zbroj mitralnog prstena, kao i PET s 18F-fluoridom (kalcifikacijska aktivnost) i 18F-FDG (upalna aktivnost) u 104 bolesnika. Kalcifikacija mitralnog prstena pronađena je u 35 bolesnika koji su imali 18F-fluorid unos i FDG unos, implicirajući povećanu lokalnu kalcifikaciju i upalu.

Fernandez-Friera *i sur.*<sup>48</sup> primjenjivali su hibridni FDG PET / MRI kako bi procijenili aterosklerotske plakove u arterijama osoba srednje životne dobi (n = 755). S pomoću navedenog sofisticiranog slikovnog modaliteta autori su procjenjivali multiteritorialnost ateroskleroze (karotidna, aortna, iliofemorale arterije): plakovi su bili prisutni na MR-u u 90,1 % (73,9 % femoralnih, 55,8 % ilijaki i 53,1 % karotida), dok je PET-om upa-

cant improvement of cardiac risk prediction over and above the current state-of-the-art, which might help to identify patients with elevated residual risk for cardiovascular events.

## Advanced imaging, fusion imaging, and applied artificial intelligence in imaging

Cardiovascular (invasive and non-invasive) imaging is developing at ultrafast pace and the clinician of today gets daily confronted with different imaging modalities, with major technological developments, but also fusion imaging and introduction of artificial intelligence and machine learning. From a clinical perspective, the cardiovascular imager of tomorrow needs to be familiar with the different modalities, when to apply which technique in which clinical scenario. A dedicated task force of The European Association of Cardiovascular Imaging (part of the ESC) has published a statement on the organization of multimodality imaging services in cardiology, the use of the different modalities as well as training and research in the multimodality era.<sup>1</sup>

Ramos *et al.*<sup>45</sup> used an animal (mice) model to study myocardial healing after infarction using serial imaging (7 days and 21 days post-infarction) with 3 T magnetic resonance imaging (MRI) and a 19F/1H surface coil. Injected 19F-perfluorocarbon nanoparticles were used to evaluate recruitment of inflammatory cells (e.g. macrophages), and an injected gadolinium-based elastin-binding contrast agent was used to assess elastin content. The combination of these imaging techniques enabled assessing the time course of the remodelling and healing process, as well as scar development.

Engel *et al.*<sup>46</sup> evaluated 25 patients with either stable CAD or presenting with suspected ACS using a non-invasive albumin-binding probe gadofosveset-enhanced CMR, as well as invasive coronary angiography and optical coherence tomography (OCT). CMR was performed twice: prior to baseline examination and 24 h after gadofosveset-trisodium administration. The patients with suspected ACS revealed significantly higher signal enhancement on CMR following gadofosveset-trisodium application on the segments containing a culprit lesion as compared to patients with stable CAD. On OCT, these patients presented with thin-cap fibroatheroma. The novel CMR approach may enable early detection of patients with potential ACS.

Several articles in the field of multimodality and fusion imaging are worth to highlight. Mitral annular calcification is observed in patients with mitral regurgitation/stenosis and is important when transcatheter valve replacement is considered. To better understand pathophysiology, Massera *et al.*<sup>47</sup> performed CT calcium score of the mitral annulus, as well as PET with <sup>18</sup>F-fluoride (calcification activity) and <sup>18</sup>F-FDG (inflammation activity) in 104 patients. Mitral annular calcification was noted in 35 patients who exhibited increased <sup>18</sup>F-fluoride uptake and FDG uptake, suggesting increased local calcification and inflammation.

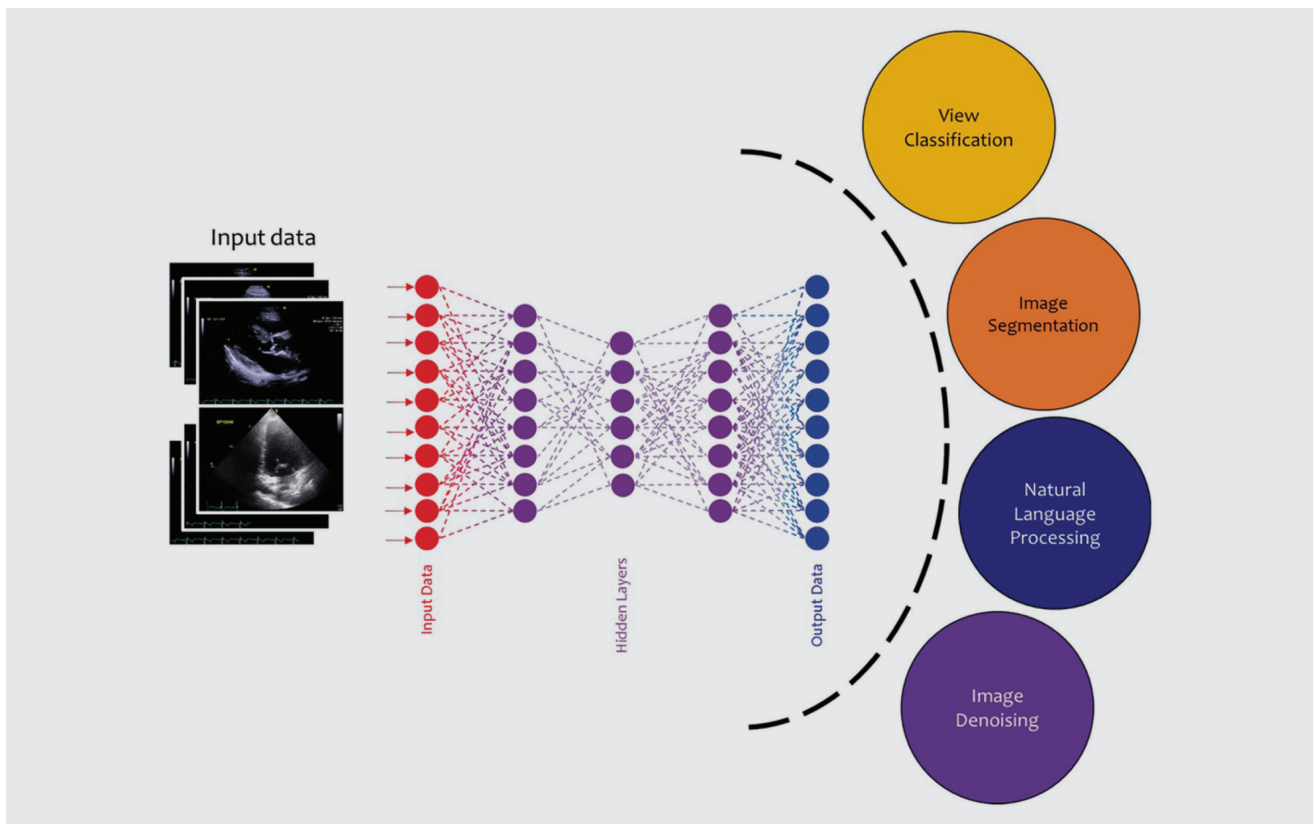
Fernandez-Friera *et al.*<sup>48</sup> used hybrid FDG PET/MRI to assess arterial vascular plaques in middle-aged individuals (n = 755). With this sophisticated imaging technology, the authors evaluated multi-territorial atherosclerosis (carotid, aortic, and ilio-femoral arteries); plaques were present on MRI in 90.1% (73.9% femorals, 55.8% iliacs, and 53.1% carotids), where-

la pronađena u 48,2 % (24,4 % femoralnih, 19,3 % aorta, 15,8 % karotida i 9,3 % ilijaki). Autori zaključuju da je arterijska upala pronađena kod 50 % arterijskih plakova u osoba srednje dobi.

Trenutačno stanje umjetne inteligencije i metoda strojnog učenja pregledno su prikazali Al'Aref *i sur.*<sup>49</sup> Porastom digitalizacije podataka u velike setove dostupne i lake za procesiranje, strojno je učenje omogućilo da autonomno stječe znanja ekstrakcijom uzoraka iz velikih setova podataka. Osobito u kardiologiji, metode strojnog učenja vrlo su se brzo počele primjenjivati u različitim segmentima kako bi se omogućila automatizirana analiza elektrokardiograma i slikanja (ultrazvuk, nuklearno perfuzijsko oslikavanje i CCTA) (slika 5).

as inflammation was observed on PET in 48.2% of individuals (24.4% femorals, 19.3% aorta, 15.8% carotids, and 9.3% iliacs). The authors concluded that arterial inflammation is noted in 50% of arterial plaques in middle-aged individuals.

The current status of artificial intelligence and machine learning was elegantly reviewed by Al'Aref *et al.*<sup>49</sup> With the increasing digitization of data making big datasets available and easier to process, machine learning has enabled to autonomously acquire knowledge by the extraction of patterns from these large datasets. Particularly in cardiology machine learning has been rapidly adopted in various fields, to permit automated analysis of electrocardiograms and imaging (echocardiography, nuclear perfusion imaging, and CCTA) (Figure 5).



**FIGURE 5. Machine learning algorithms applied to echocardiography. Echocardiographic data are post-processed to automate many processes performed in clinical practice by cardiologists and sonographers such as view classification and image segmentation that will lead to the interpretation of the data and the diagnosis. Reproduced with permission from Al'Aref *et al.*<sup>49</sup>.**

Drugi pregledni članak objavila je grupa Krittanawong *i sur.*<sup>2</sup> dajući spoznaje o dubokom učenju. To je grana umjetne inteligencije koja uključuje kompjutorsku znanost, statistiku i teoriju odluka kako bi se otkrili uzorci u kompleksnim i velikim setovima podataka. Casaclang-Verzosa *i sur.*<sup>50</sup> primjenjivali su strojno učenje za naprednu analizu mreža kako bi prikazali procjenu hipertrofije LV-a kao odgovora na stenozu aortnog zalistka iz ultrazvučnih snimaka. Naposljetku, Zhank *i sur.*<sup>51</sup> objavili su izvorno istraživanje o primjeni metoda dubokog učenja za analizu ultrazvučnih podataka (n = 14 035 ehokardiograma), potpuno automatizirano, uključujući (i) identifikaciju projekcije, (ii) segmentaciju slike, (iii) kvantifi-

Another excellent review was published by Krittanawong *et al.*<sup>2</sup> providing further insight in deep learning. This is a branch of artificial intelligence, which combines computer science, statistics and decision theory to discover patterns in complex and big data. Casaclang-Verzosa *et al.*<sup>50</sup> applied machine learning to advanced network analysis to demonstrate automated assessment of LV (hypertrophy) in response to aortic valve stenosis from echocardiographic images. Finally, Zhang *et al.*<sup>51</sup> published original research on the use of deep learning to analyse echocardiographic data (n = 14 035 echocardiograms), in a fully automated fashion, including (i) view identification, (ii) image segmentation, (iii) quantification of structure and func-

kaciju strukture i funkcije i (iv) otkrivanje bolesti. Specifično, konvolucijske neuralne mreže utrenirane su da otkriju hipertrofičnu kardiomiopatiju, amiloidozu srca i plućnu hipertenziju sa značajnom C statistikom od 0,92, 0,87 i 0,85.

tion, and (iv) disease detection. Specifically, convolutional neural networks were trained to detect hypertrophic cardiomyopathy, cardiac amyloidosis, and pulmonary arterial hypertension with respective C statistics of 0.93, 0.87, and 0.85.

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