Godina 2016. u kardiologiji: oslikavanje

The year in cardiology 2016: imaging

Victoria Delgado[1], **Oliver Gaemperli**[2], **Massimo Lombardi**[3], **Philipp A Kaufmann**[4], **Jeroen J Bax**[1]*

[1]Heart Lung Centrum, Leiden University Medical Center, Leiden, The Netherlands

[2]Cardiac Imaging, University Heart Center, Zurich, Switzerland

[3]Multimodality Cardiac Imaging Section, IRCCS Policlinico San Donato, San Donato Milanese Milan, Italy

[4]Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Zürich, Switzerland

RECEIVED:
February 27, 2017

ACCEPTED:
February 28, 2017

CITATION: Cardiol Croat. 2017;12(5-6):175-190. | https://doi.org/10.15836/ccar2017.175

***ADDRESS FOR CORRESPONDENCE:** Jeroen J Bax, Heart Lung Centrum, Leiden University Medical Center, Albinusdreef 2, 2300 RC, Leiden, The Netherlands. / Phone: +31 71 526 2020; Fax: +31 71 526 6809 / E-mail: j.j.bax@lumc.nl

Uvod

Kardiovaskularne bolesti (KVB) i dalje su vodeći uzrok smrti u Europi.[1] Aktualne mortalitetne statistike upućuju na to da više od 4 milijuna osoba umire od KVB-a svake godine. Neinvazivne metode oslikavanja u kardiologiji zauzimaju središnju ulogu u dijagnostici i liječenju kardiovaskularnih bolesnika. Tijekom 2016. godine objavljeni su mnogi članci čija je središnja tema prognostički učinak trenutačno aktualnih metoda oslikavanja i tehnoloških inovacija u kardiologiji. Izabrani članci iz te skupine koji se bave neinvazivnim metodama oslikavanja u kardiologiji, uključujući ehokardiografiju, kompjutoriziranu tomografiju (CT), kardiovaskularnu magnentnu rezonanciju (CMR), nuklearne metode oslikavanja te hibridne metode, prikazani su ovdje.

Ehokardiografija

Ehokardiografija je prvi izbor među metodama oslikavanja pri evaluaciji kardiovaskularnih bo-

Preamble

Cardiovascular diseases remain the main cause of death in Europe.[1] Current mortality statistics show that more than 4 million people die from cardiovascular diseases every year. Non-invasive cardiovascular imaging plays a central role in the diagnosis and management of patients with cardiovascular diseases. In 2016, many articles focused on prognostic impact of current non-invasive imaging techniques and technological innovations were published. A selection of these articles on the use of non-invasive cardiovascular imaging, including echocardiography, computed tomography (CT), cardiovascular magnetic resonance imaging (CMR), nuclear imaging, and fusion imaging is presented here.

Echocardiography

Echocardiography is the imaging technique of first choice to evaluate patients with cardio-

lesnika. Nedavna analiza najveće javno dostupne baze stacionarnih bolesnika u SAD-u pokazala je da je tijekom 2001. i 2011. godine učinjeno otprilike 7 669 000 ehokardiograma te je utvrđen stalni porast njihova broja s prosječnom godišnjom stopom rasta od 3,41 %.[2] Iako bi ovi brojevi mogli upozoriti na prekomjernu primjenu ovoga dijagnostičkog postupka, rezultati nacionalnog uzorka stacionarnih bolesnika iz 2010. godine pokazali su da to nije tako. Pri analizi pet kliničkih stanja koja su bila osnova za 3,7 milijuna hospitalizacija (cerebrovaskularne bolesti, srčane aritmije, kronično zatajivanje srca /KZS/, akutni infarkt miokarda i sepsa), ehokardiografija je bila učinjena u samo 8 % od navedenoga broja hospitalizacija, što upućuje na mnogo nižu uporabu te metode oslikavanja. Još bitnije, primjena ehokardiografije bila je povezana s mnogo nižim izgledima za smrtni ishod hospitaliziranih bolesnika u 5 navedenih kliničkih stanja. Bit će potrebna dodatna istraživanja da bismo dobili više informacija o povezanosti između dostupnosti ehokardiografije i kliničkih ishoda.

Ultrazvuk pluća još je jedan način primjene ehokardiografije te se smatra testom prvog izbora u procjeni plućne kongestije u bolesnika sa suspektnim akutnim zatajivanjem srca (AZS).[3] Detekcija B-linija (refleksija diskretnih artefakata na granici zrak/tekućina između kolabiranih, tekućinom ispunjenih, te normalnih, zrakom ispunjenih, alveola) na anterolateralnom oslikavanju toraksa upućuje na progresivno povećanje količine ekstravaskularne tekućine u plućima. Broj B-linija može se sumirati te tako proizvesti semikvantitativni biljeg količine ekstravaskularne tekućine u plućima.[4] Povećanje dijagnostičke i prognostičke važnosti primjene ultrazvuka pluća istraženo je u 195 ambulantnih bolesnika sa ZS-om i simptomima II. do IV. stupnja prema NYHA (*New York Heart Association*) klasifikaciji.[5] Od 185 bolesnika s adekvatnim snimkama ultrazvuka pluća, 59 (32 %) imalo je ≥ 3 B-linije, dok je samo 17 (9 %) imalo krepitacije pri auskultaciji. Bolesnici s većim brojem B-linija imali su teže simptome ZS-a te višu razinu NT-proBNP-a. Također, bolesnici s ≥ 3 B-linije imali su četiri puta veći rizik od primarnog ishoda (hospitalizaciju zbog pogoršanja ZS-a ili smrtni ishod) tijekom praćenja od 6 mjeseci u usporedbi s bolesnicima bez B-linija (prilagođeni omjer rizika [HR] 4,08; 95 %-tni interval pouzdanosti [CI] 1,95 – 8,54; P < 0,001). Primjena ultrazvuka pluća pružila je povećanu prognostičku vrijednost u usporedbi s auskultacijom, što je dokazano povećanom sposobnošću predviđanja primarnog ishoda od 6,4 %. Ovakvi su rezultati obećavajući te pokazuju da bi ultrazvuk pluća mogao pomoći u stupnjevanju rizika u bolesnika sa ZS-om. Standardizacija tehnike, adekvatni trening za snimanje i interpretaciju snimki te dokazi da terapija vođena ultrazvukom pluća rezultira boljim ishodom pomoći će uvođenju ove tehnike u kliničku praksu.[6]

Iako je ejekcijska frakcija lijeve klijetke (LVEF) važan kriterij pri odlučivanju u kardiovaskularnih bolesnika, globalni longitudinalnu deformaciju lijeve klijetke (LV GLS) mjeren dvodimenzijskom *speckle tracking* ehokardiografijom pokazao je veću osjetljivost u usporedbi s LVEF-om u detekciji supkliničke sistoličke disfunkcije te ima povećanu sposobnost predviđanja ishoda.[7] U populacijskoj kohortnoj studiji u koju je bio uključen 791 bijeli Europljanin (52 % žena, srednje dobi 50,8 ± 15,5 godina), *Kuznetsova i sur.* pokazali su povećanu prognostičku vrijednost LV GLS-a u predviđanju učestalosti kardiovaskularnih događaja (npr. koronarnih zbivanja, moždanog udara, novonastale fibrilacije atrija, ZS-a, životno ugrožavajućih aritmija i aortnih zbivanja).[8] Tijekom medijana praćenja ispitanika od 7,9 godina (5729 osoba – godina praćenja), 96 osoba imalo je bar jednan kardi-

vascular diseases. A recent analysis of the largest, publicly available, all-payer inpatient database of the United States has shown that during 2001 and 2011 approximately 7 669 000 echocardiograms were performed and a steady increase in the volume of echocardiograms was noted with an average annual grew rate of 3.41%.[2] Although these numbers would suggest an overuse of this diagnostic procedure, the results from the 2010 nationwide inpatient sample showed otherwise. When analysing five clinical scenarios accounting for 3.7 million hospital admissions (cerebrovascular disease, cardiac arrhythmia, chronic heart failure, acute myocardial infarction, and sepsis), echocardiography was performed only in 8% of the cases indicating a significant underuse of echocardiography. Importantly, the use of echocardiography was associated with significantly lower odds of all-cause in-hospital mortality in these five clinical scenarios. Additional studies will be warranted to provide more information on the association between access to echocardiography and clinical outcomes.

Lung ultrasound is another application of echocardiography and is considered a first-line test to assess pulmonary congestion in patients with suspected acute heart failure.[3] The detection of B-lines (reflection of discrete air/fluid interfaces between collapsed, fluid-filled, and well-aerated alveoli) on the anterolateral chest scan indicates a progressive increase of extravascular lung water. The number of B-lines can be summed to generate a semiquantitative score of the extravascular lung water content.[4] The incremental diagnostic and prognostic value of the use of lung ultrasound was investigated in 195 heart failure patients with New York Heart Association (NYHA) class II–IV symptoms evaluated at the outpatient clinic.[5] Of the 185 patients with adequate lung ultrasound data, 59 (32%) had ≥3 B-lines while only 17 (9%) had crackles on auscultation. Patients with higher number of B-lines showed more severe heart failure symptoms and higher levels of NT-pro brain natriuretic peptide. In addition, patients with ≥3 B-lines had a four-fold higher risk of the primary endpoint (hospitalization for worsening of heart failure or all-cause mortality) at 6 months follow-up compared with patients without B-lines (adjusted hazard ratio [HR] 4.08; 95% confidence interval [CI] 1.95–8.54; P < 0.001). The use of lung ultrasound provided incremental prognostic value over auscultation as shown by an incremental discrimination improvement of 6.4% for the primary endpoint. These results are promising and indicate that the use of lung ultrasound may help in the risk stratification of heart failure patients. Standardization of the technique, adequate training to obtain and interpret the data and demonstration that lung ultrasound-guided therapy results in better outcome will help to implement this imaging technique in clinical practice.[6]

Although left ventricular (LV) ejection fraction (EF) is an important criterion in the decision making of patients with cardiovascular disease, LV global longitudinal strain (GLS) measured with two-dimensional speckle tracking echocardiography has shown to be more sensitive than LVEF to detect subclinical LV systolic dysfunction and has incremental value to predict outcomes.[7] In a population-based cohort of 791 white Europeans (52% women, 50.8 ± 15.5 years old), Kuznetsova and colleagues demonstrated the incremental prognostic value of LV GLS to predict the occurrence of cardiovascular events (i.e. coronary events, stroke, new-onset atrial fibrillation, heart failure, life-threatening arrhythmias, and aortic events).[8] During a median follow-up of 7.9 years (5729 person-

ovaskularni događaj (16,8 događaja na 1000 osoba – godina). U multivarijatnoj analizi, svako smanjenje u LV GLS-u od 1 SD bilo je povezano sa 75 %-tnim povećanjem rizika od kardiovaskularnih događaja. Osim toga, dodatak LV GLS-a modelu koji sadržava nekoliko demografskih i kliničkih kovarijabli rezultiralo je poboljšanjem diskriminacijske sposobnosti modela između bolesnika s događajem i bez njega (neto poboljšanje reklasifikacije od 0,31; *P* = 0,003). Povećanje prognostičke vrijednosti LV GLS-a u odnosu prema LVEF-u dodatno je pokazano u studiji koja je uključivala 1065 bolesnika sa ZS-om s reduciranim vrijednostima LVEF-a.[9] Primarni ishod (ukupna smrtnost) dostignulo je 177 (16,7 %) bolesnika nakon medijana praćenja od 40 mjeseci. Bolesnici koji su preminuli pokazivali su lošiju vrijednost LVEF-a (23,8 ± 9,9 % nasuprot 28,2 ± 9,1 %; P < 0,001) i GLS-a (-8,1 ± 3,0% nasuprot -9,9 ± 3,2%; P < 0,001) u usporedbi s bolesnicima koji su preživjeli. Kada su bolesnici raspoređeni u tercile prema vrijednostima GLS-a, oni u najvišoj tercili (s najlošijim GLS-om) imali su triput veći rizik od ukupne smrtnosti u usporedbi s bolesnicima najniže tercile (najbolji GLS) (HR 3,38, 95 % CI 2,3 – 5,1; P < 0,001). Nakon prilagodbe za kliničke i ehokardiografske varijable, LV GLS bio je jedini ehokardiografski parametar neovisno povezan s ukupnom smrtnošću (HR 1,15 za svakih 1 % povećanja – manje negativnog – u GLS-u; *P* = 0,008) i njegovo dodavanje u model rezultiralo je povećanjem od 9,27% u neto reklasifikaciji poboljšanja. Ovi nalazi upućuju na to da i u bolesnika s niskim LVEF-om dodatna analiza primjenom LV GLS-a upućuje na još lošiju funkciju lijeve klijetke (LV) i time poboljšava stratifikaciju rizika. Procjena sistoličke funkcije LV-a mogla bi biti kompliciranija u bolesnika s reduciranim LVEF-om i znatnom sekundarnom mitralnom regurgitacijom. Pražnjenjem LV-a u lijevi atrij LVEF bi mogao precijeniti stvarnu sistoličku funkciju LV-a. Hipoteza da bi LV GLS mogao bolje pokazivati stvarnu sistoličku funkciju LV-a u bolesnika sa znatnom mitralnom regurgitacijom testirana je u studiji koja je uključivala 150 bolesnika s ne-

years of follow-up), 96 individuals presented at least with one cardiovascular event (16.8 events per 1000 person-years). On multivariate analysis, each 1 SD decrease in LV GLS was associated with 75% increase in the risk of cardiovascular events.Furthermore, the addition of LV GLS to a model containing several demographic and clinical covariates resulted in a moderate improvement in the ability of the model to discriminate between patients with and without events (net reclassification improvement 0.31; *P* = 0.003). The incremental prognostic value of LV GLS over LVEF was additionally demonstrated in a study including 1065 heart failure patients with reduced LVEF.[9] The primary endpoint (all-cause mortality) was reached by 177 (16.7%) patients after a median follow-up of 40 months. Patients who died showed worse LVEF (23.8 ± 9.9% vs. 28.2 ± 9.1%; P < 0.001) and GLS (-8.1 ± 3.0% vs. -9.9 ± 3.2%, P < 0.001) compared with patients who were alive. When patients were divided according to GLS tertiles, patients within the highest GLS tertile group (most impaired GLS) had three times higher risk of all-cause mortality compared with patients of the lowest tertile (best GLS) (HR 3.38, 95% CI 2.3–5.1; P < 0.001). After adjusting for clinical and echocardiographic variables, LV GLS was the only echocardiographic parameter independently associated with all-cause mortality (HR 1.15 per each 1% increase – less negative – in GLS; *P* = 0.008) and its addition to the model resulted in 9.27% increment in the net reclassification improvement. These findings suggest that, even in patients with poor LVEF, LV GLS shows even more deteriorated LV performance and improves risk stratification. Assessment of LV systolic function may be more complicated in patients with reduced LVEF and significant secondary mitral regurgitation. By unloading the LV into the left atrium, LVEF may overestimate the true LV systolic function. The hypothesis that LV GLS may better reflect the true LV systolic function in patients with significant mitral regurgitation was tested in a

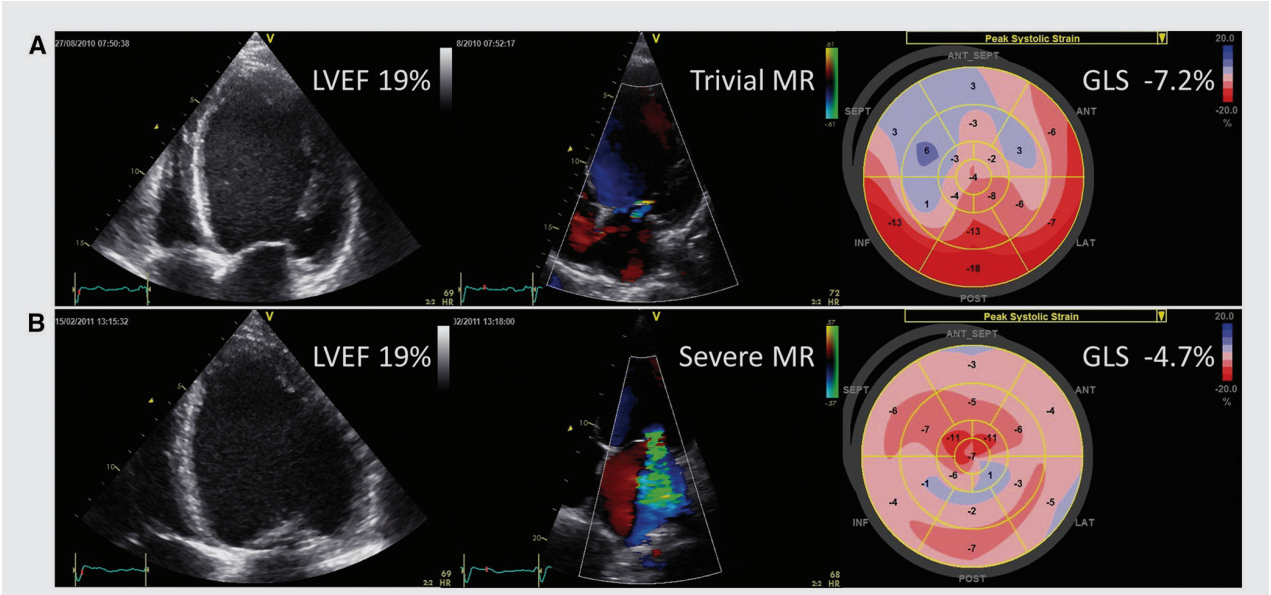

FIGURE 1. Left ventricular global longitudinal strain vs. left ventricular ejection fraction to assess left ventricular systolic function in patients with secondary mitral regurgitation. Example of two patients with non-ischaemic cardiomyopathy. Despite comparable left ventricular ejection fraction (LVEF), the patient with severe mitral regurgitation (MR) has more impaired left ventricular global longitudinal strain (GLS) as compared with the patient without MR.

Reproduced with permission of Oxford University Press from Kamperidis *et al.*[10]
This Figure has been reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

ishemijskom kardiomiopatijom, od kojih je 50 % imalo znatnu sekundarnu mitralnu regurgitaciju.[10] Unatoč podjednakoj vrijednosti LVEF-a, što je bio jedan od uključnih kriterija, bolesnici sa znatnom mitralnom regurgitacijom imali su mnogo lošiji LV GLS u usporedbi s bolesnicima bez mitralne regurgitacije (-8,08 ± 3,33 nasuprot -9,78 ± 3,78%; *P* = 0,004) (**Slika 1**).

Trodimenzijska transezofagusna ehokardiografija (TEE) mitralne valvule pokazala je znatne razlike u deformaciji mitralne valvule u sistoličkoj fazi u bolesnika s organskom mitralnom regurgitacijom i u zdravih kontrolnih ispitanika[11]: stražnji je mitralni listić pokazao veći intenzitet naprezanja nego prednji mitralni listić, a distribucija visokog naprezanja konzistentno je praćena na komisurama, graničnim zonama blizu mitralnoga prstena i u koaptacijskoj liniji, dok je središnja zona listića imala najniže naprezanje. Iako su bolesnici s organskom mitralnom regurgitacijom imali više razine intenziteta naprezanja u prednjim i stražnjim mitralnim listićima u usporedbi s kontrolnim ispitanicima, raspodjela visokog naprezanja bila je slična. Klinička važnost ovakvih nalaza zahtijeva daljnja istraživanja. Napokon, rezultati studija upućuju na to da bi težina kalcifikacije aortne valvule mogla biti povezana sa spolom i hemodinamskim promjenama aortne valvule. U velikoj kohorti od 888 bolesnika s teškom aortnom stenozom koji su podvrgnuti zamijeni aortne valvule, *Thaden i sur.* pokazali su da su muški spol, pušenje, bikuspidna morfologija i veća površina izlaznog dijela lijeve klijetke neovisno povezani s većom masom uklonjene aortne valvule, dok su dijabetes i arterijska hipertenzija povezani s manjom masom uklonjene valvule.[12] Unatoč sličnoj površini aortne valvule, muškarci su imali veću masu aortne valvule i teži stupanj kalcifikacije od žena, što upućuje na to da ozbiljnost težine stenoze aortne valvule ne objašnjava razlike u masi i težini kalcifikacija uklonjenih aortnih valvula.

Kompjutorizirana tomografija

Tijekom 2016. godine objavljeno je više važnih publikacija na polju kardiovaskularne kompjutorizirane tomografije (CT). U 5185 sudionika studije MESA (*Multi-Ethnic Study of Atherosclerosis*), *Yeboah i sur.* istražili su prognostičku važnost netradicionalnih čimbenika rizika (kalcijski *score* koronarnih arterija [CACS], pedobrahijalni indeks, visoko senzitivni C-reaktivni protein i obiteljsku anamnezu aterosklerotskih kardiovaskularnih bolesti [ASCVD] u usporedbi s *pooled cohort equation* (trenutačnim standardom za procjenu rizika preporučena u smjernicama *American College of Cardiology* [ACC]/*American Heart Association* [AHA]).[13] Od svih čimbenika, jedina varijabla koja poboljšava prediktivnu vrijednost *pooled cohort equation* jest CACS, što je izmjereno znatnim, iako skromnim povećanjem u Harrelovoj c-statistici (0,76 nasuprot 0,74, *P* = 0,04) i totalnim neto poboljšanjem reklasifikacija od 0,119 (95 % CI, 0,080 – 0,256). Trenutačne ACC/AHA smjernice o vrijednostima kolesterola proširile su indikacije za uporabu statina u primarnoj prevenciji podižući zabrinutost o pretjeranom liječenju i povećanju troškova.[14] U drugoj publikaciji iz studije MESA-e, *Nasir i sur.* istraživali su vrijednost CACS = 0 u reklasifikaciji bolesnika koji trenutačno ispunjavaju uvjete za statine u kategoriji niskoga rizika, pri čemu terapija statinima možda više nije potrebna.[15] Od 2966 sudionika koji su ispunjavali kriterije za terapiju statinima (statini preporučeni ili razmatrani), 1316 (44 %) imalo je CACS = 0 u vrijeme uključivanja i promatranu 10-godišnju ASCVD stopu događaja 4,2 na 1000 osoba/godina. Stoga bi šira upotreba CACS-a mogla pomoći u snizivanju kategorije rizika znatnoga

study including 150 non-ischaemic cardiomyopathy patients, 50% of them with significant secondary mitral regurgitation.[10] Despite having comparable LVEF as per inclusion criteria, patients with significant mitral regurgitation had significantly more impaired LV GLS compared with patients without (-8.08 ± 3.33 vs. -9.78 ± 3.78%, respectively; *P* = 0.004) (**Figure 1**).

Three-dimensional transoesophageal echocardiography (TEE) data of the mitral valve analysed with proprietary software has shown important differences in mitral valve deformation (strain) along the systolic phase in patients with organic mitral regurgitation and normal controls:[11] the posterior mitral leaflet showed higher strain intensity than the anterior mitral leaflet and the distribution of high strain was consistently observed in the commissures, boundary zones near the mitral annulus and coaptation line while the central leaflet zone had the lowest strain. Although patients with organic mitral regurgitation had higher strain intensities in the anterior and posterior mitral leaflets compared with controls, the distribution of high strain was similar. The clinical implications of these findings need further investigations. Finally, it has been suggested that the aortic valve calcification burden may be associated with sex and aortic valve haemodynamics. In a large cohort of 888 patients with severe aortic stenosis who underwent aortic valve replacement, Thaden *et al.* showed that male sex, current smoking, bicuspid morphology, and larger LV outflow tract area were independently associated with high weight of the excised aortic valve whereas diabetes and hypertension were associated with lower weight of aortic valve.[12] Despite similar aortic valve area, male had higher aortic valve weight and calcification burden than women suggesting that the aortic valve stenosis severity does not explain sex-related differences in excised aortic valve weight and calcification burden.

Computed tomography

The year 2016 has witnessed a number of important publications in the field of cardiovascular CT. In 5185 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), Yeboah *et al.* explored the incremental prognostic value of non-traditional risk markers (coronary artery calcium score [CACS], ankle-brachial index, high-sensitivity C-reactive protein, and family history of atherosclerotic cardiovascular disease [ASCVD] over traditional risk estimation by the pooled cohort equation (the current standard of risk estimation recommended by the American College of Cardiology [ACC]/American Heart Association [AHA] guidelines).[13] Of all risk markers, CACS was the only parameter to improve the predictive accuracy of the pooled cohort equation as measured by a significant albeit modest increase in the Harrel's c-statistic (0.76 vs. 0.74, *P* = 0.04) and a total net reclassification improvement of 0.119 (95% CI, 0.080–0.256). Current ACC/AHA cholesterol management guidelines have broadened indications for statins in primary prevention raising concerns of overtreatment and increased costs.[14] In another MESA publication, Nasir and colleagues explored the value of a zero CACS to reclassify patients currently eligible for statins into a low-risk category where statin therapy may no longer be required.[15] Of 2966 participants eligible for statins (i.e. statin either recommended or considered), 1316 (44%) had a CACS = 0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1000 person-years. Thus, more widespread use of CACS may help to 'de-risk' a sizable

broja bolesnika da bi se izbjegla terapija statinima u primarnoj prevenciji.

U podstudiji studije PROMISE (*Prospective Multicenter Imaging Study for Evaluation of Chest Pain*) ishodi kvalitete života (QoL) uspoređeni su u 5985 bolesnika sa stabilnom koronarnom bolesti srca (KBS) dokazanih anatomskom strategijom (koronarna CT angiografija [CTA]) u usporedbi s funkcionalnim dijagnostičkim strategijama.[16] Nakon 24 mjeseca nije bilo razlike u rezultatima *Duke Activity Status Index niti u Seattle Angina Questionnaire*, a ni u drugim sekundarnim mjerilima QoL. Randomizirana studija CRESCENT (*Computer Tomography* vs. *Exercise Testing in Suspected Coronary Artery Disease*) imala je sličan dizajn kao PROMISE studija, ali s mnogo manjim uzorkom ispitanika (n = 350).[17] Povrh toga, bolesnici u anatomskom ogranku studije slijedili su CT protokol uključujući ulazno CACS skeniranje nakon kojeg je slijedila CTA, i to samo ako su vrijednosti CACS-a bile između 1 i 400. Nakon praćenja od 1,2 godine nisu registrirano novih događaja u 97,2 % ispitanika u skupini randomiziranih na CT testiranje i u 89,8% u skupini randomiziranih za funkcijsko testiranje registrirani novi događaji. Nakon CT-a, konačna je dijagnoza postavljena prije i rjeđe je bilo potrebno dodatno testiranje, što je rezultiralo nižim ukupnim troškovima dijagnostike (369 eura nasuprot 440 eura; P < 0,0001). Ukupno gledajući, studije PROMISE i CRESCENT unaprjeđuju dokumentiranu neinferiornost početne anatomske slikovne strategije bazirane na CT-u u usporedbi s tradicionalnim strategijama funkcijskoga testiranja (npr. ergometrija, stres ehokardiografija i perfuzijska scintigrafija miokarda) u bolesnika sa stabilnim KBSom.

Studija *The Better Evaluation of Acute Chest Pain with Computed Tomography Angiography* (BEACON) randomizirala je 500 bolesnika niskog rizika s akutnim bolovima u prsima koji su se javili u hitnu službu sedam nizozemskih bolnica, na skupinu u kojoj je rađena hitna CTA nasuprot standardnom zbrinjavanju, uključujući serijsko testiranje visoko osjetljivim troponin-testom (hsTrop).[18] Skupina s CTA-om imala je manje izravne troškove liječenja (337 eura nasuprot 511 eura; P < 0,01) i manje ambulantnih pretraga nakon prvog posjeta hitnoj službi (4 % *vs.* 10%, P < 0,01). Suprotno prije objavljenim Američkim studijama sa standardnim troponinskim testovima nije bilo registrirane razlike u broju revaskularizacija, otpustima iz hitne službe ni u dužini boravka u bolnici. Stoga u eri *hsTrop* (koja dopušta točnije i brže isključivanje infarkta miokarda) studija BEACON postavlja pitanje korisnosti ranih koronarnih CTA-a u bolesnika sa sumnjom na akutni koronarni sindrom.

Za CT deriviranu *fractional flow reserve* (FFR_{CT}) nastavlja rasti zanimanje i tijekom 2016.: u podstudiji *studije Analysis of Coronary Blood Flow Using CT Angiography: Next Steps* (NXT), *Gaur i sur.* procjenjivali su povezanost između težine stenoze koronarnih arterija, obilježja plakova i FFR_{CT}-a na 484 žile u 254 bolesnika.[19] Prisutnost nekalcificiranih plakova male gustoće (≥ 30 mm^3) i FFR_{CT} (≤ 0,80) znatno je povećala dijagnostičku preciznost koronarnih stenoza u otkrivanju ishemija specifičnih za leziju (kao što se procjenjuje invazivnim FFR-om), što je dokumentirano povećanjem površine ispod ROC krivulje od 0,71 na 0,90 (P < 0,001). Nerandomizirana studija PLATFORM (*Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource IMpacts*) procjenjivala je utjecaj FFR_{CT}-a na kliničke ishode, daljnju uporabu resursa i troškove u dvama paralelnim opservacijskim ograncima, jednom s namjerom invazivne strategije (n = 380) i drugom s namjerom neinvazivnih testiranja (n = 204).[20] U

number of subjects where statin therapy for primary prevention could be avoided.

In a substudy of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, quality-of-life (QoL) outcomes of an anatomical (coronary CT angiography [CTA]) vs. functional diagnostic testing strategy were assessed in 5985 stable coronary artery disease (CAD) patients.[16] At 24 months, there were no strategy-related differences in the Duke Activity Status Index and the Seattle Angina Questionnaire frequency scale, or any of the secondary QoL measures. The randomized Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) trial had a similar design than PROMISE albeit with a considerably smaller study population (n = 350).[17] Moreover, patients in the anatomical arm followed a tiered CT protocol including a 'gate-keeper' CACS scan followed by coronary CTA only if CACS was between 1 and 400. After 1.2 years, event-free survival was 96.7% for patients randomized to CT and 89.8% for patients randomized to functional testing (*P* = 0.011). After CT, the final diagnosis was established sooner, and additional downstream testing was required less frequently, resulting in lower cumulative diagnostic costs (€369 vs. €440; P < 0.0001). Taken together, PROMISE and CRESCENT further document non-inferiority of an initial CT-based anatomical imaging strategy compared with traditional functional testing strategies (i.e. stress ECG, stress echocardiography, myocardial perfusion scintigraphy) in stable CAD patients.

The Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON) study randomized 500 low-risk patients with acute chest pain presenting to the emergency department of seven Dutch hospitals to immediate coronary CTA vs. standard care including serial testing with high-sensitivity troponin assays (hsTrop).[18] The coronary CTA group had lower direct medical costs (€337 vs. €511, P < 0.01) and less outpatient testing after the index emergency department visit (4% vs. 10%, P < 0.01). However, (in contrast to previously published American trials with standard troponin assays) there were no differences in the number of revascularizations, the emergency department discharge rates, or the length of stay. Hence, in the era of hsTrop (allowing more accurate and faster rule-out of myocardial infarction), the BEACON study questions the utility of early coronary CTA in suspected acute coronary syndrome patients.

CT-derived fractional flow reserve (FFR_{CT}) continues to raise interest in 2016: in a substudy of the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT)-trial, Gaur and colleagues evaluated the association between coronary stenosis severity, plaque characteristics and FFR_{CT} in 484 vessels from 254 patients.[19] The presence of low-density non-calcified plaque (≥30 mm^3) and FFR_{CT} (≤0.80) increased significantly the diagnostic accuracy of coronary stenoses to detect lesion-specific ischemia (as assessed by invasive FFR), documented by an increase in the area under the receiver operating characteristic curve from 0.71 to 0.90 (P < 0.001). The non-randomized Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource IMpacts (PLATFORM) trial assessed the impact of FFR_{CT} on clinical outcomes, downstream resource utilization and costs in two parallel observational arms, one with an intended invasive strategy (n = 380) and one with planned non-invasive testing (n = 204).[20] In the planned invasive stratum, FFR_{CT} lowered mean costs by 33% ($8,127 vs.

skupini s planiranim invazivnim strategijama FFR_{CT} je snizio srednju vrijednost troškova za 33 % (8,127 nasuprot 12,145 USD; P < 0,0001) nakon jedne godine praćenja; međutim, u skupini s planiranim neinvazivnim pretragama srednja vrijednost troškova bila je malo viša kada se primjenjuje cijena FFR_{CT}-a koja je jednaka cijeni koronarne CTA.

Nakon koronarnih arterija, ovogodišnje publikacije iz područja oslikavanja CT-om istaknule su klinički potencijal ove metode u procjenjivanju valvularnih bolesti. Rano hipo-atenuirano zadebljanje listića (HALT) transkateterskih implantata aortne valvule (TAVI) pojavilo se kao novo stanje s nesigurnim prognostičkim i terapijskim implikacijama. *Pache i sur.* pratili su 156 bolesnika s TAVI uz primjenu rane rutinske koronarne CTA (medijan – 5 dana nakon TAVI-ja s balonskom ekspandirajućom protezom) te su pronašli HALT u 16 bolesnika (10,3 %) (**Slika 2**).[21] Pojavnost HALT-a nije povezana s antiagregacijskom terapijom ni s početnim ili proceduralnim obilježjima. Prisutnost HALT-a nije bila povezana sa simptomima, ali je povezana s restriktivnim pomicanjem listića te nešto većim srednjim transaortnim gradijentom tlaka (14,9 ± 5,3 nasuprot 11,6 ± 3,4 mmHg; *P* = 0,026). Puna doza antikoagulantne terapije vratila je normalnu morfologiju listića te njihovu pokretljivost u gotovo svih bolesnika. *Gündüz i sur.* istraživali su korisnost CT-a u razlikovanju panusa od tromba nakon kirurške zamjene aortne valvule.[22] U 37 bolesnika s disfunkcijom mehaničke aortne valvule i dokaza periprotetičke mase, CT je pokazao mnogo nižu atenuaciju trombotskih masa (definiranih kao mase koje su potpuno nestale nakon trombolize ili su kirurški identificirane kao tromb) u usporedbi s panusom (87 ± 59 nasuprot 322 ± 122 Hounsfieldove jedinice [HU]; P < 0,001). Granica na 145 HU dala je visoku osjetljivost (87,5 %) i specifičnost (95,5 %) u razlikovanju panusa od tromba. Konačno, CT je također pokazao kliničku vrijednost u procjeni mitralnoga paravalvularnog curenja nakon kirurške zamjene mitralne valvule. *Suh i sur.* usporedili su dijagnostičku preciznost CT-a, transtorakalne ehokardiografije i TEE-a u 204 bolesnika s ranijom kirurškom zamjenom mitralne valvule, od kojih je 78 podvrgnuto ponovnoj operaciji.[23] CT je imao vrlo sličnu točnost u usporedbi s TEE-om, ali se činilo da ima bolju osjet-

$12,145; P < 0.0001) on 1 year follow-up; however, in the planned non-invasive stratum, mean costs were slightly higher when using an FFR_{CT} cost weight equal to coronary CTA.

Beyond coronary arteries, this year's CT publications have highlighted the clinical potential of the technique to assess valvular disease. Early hypo-attenuated leaflet thickening (HALT) of trans-catheter aortic valve implants (TAVI) has emerged as a new entity with uncertain prognostic and therapeutic implications. Pache and colleagues followed 156 TAVI patients with early routine coronary CTA (a median of 5 days post-TAVI with a balloon-expandable prosthesis) and found HALT in 16 (10.3%) patients (**Figure 2**).[21] The occurrence of HALT was not associated with antiplatelet regimen or any of the baseline or procedural characteristics. HALT did not produce any symptoms but was associated with restrictive cusp motion and slightly higher transaortic mean pressure gradient (14.9 ± 5.3 vs. 11.6 ± 3.4 mmHg, *P* = 0.026). Full anticoagulation restored normal cusp morphology and motion in almost all patients. Gündüz and colleagues investigated the utility of CT to distinguish pannus from thrombus after surgical aortic valve replacement.[22] In 37 patients with mechanical prosthetic aortic valve dysfunction and evidence of periprosthetic mass, CT demonstrated significantly lower attenuation of thrombotic masses (defined as masses which completely resolved upon thrombolysis or were surgically identified as a clot) compared with pannus (87 ± 59 vs. 322 ± 122 Hounsfield units [HU]; P < 0.001). A cut-off at 145 HU provided high sensitivity (87.5%) and specificity (95.5%) in discriminating pannus from thrombus. Finally, CT has also demonstrated clinical value for the assessment of mitral paravalvular leakage after surgical mitral valve replacement. Suh and co-workers compared the diagnostic accuracy of CT, transthoracic echocardiography, and TEE in 204 patients with previous surgical mitral valve replacement, of which 78 underwent redo surgery.[23] CT had very comparable accuracy to TEE, but appeared to have superior sensitivity and negative predictive value than transthoracic echocardiography (although the difference did not reach statistical significance). TEE, however, was better in

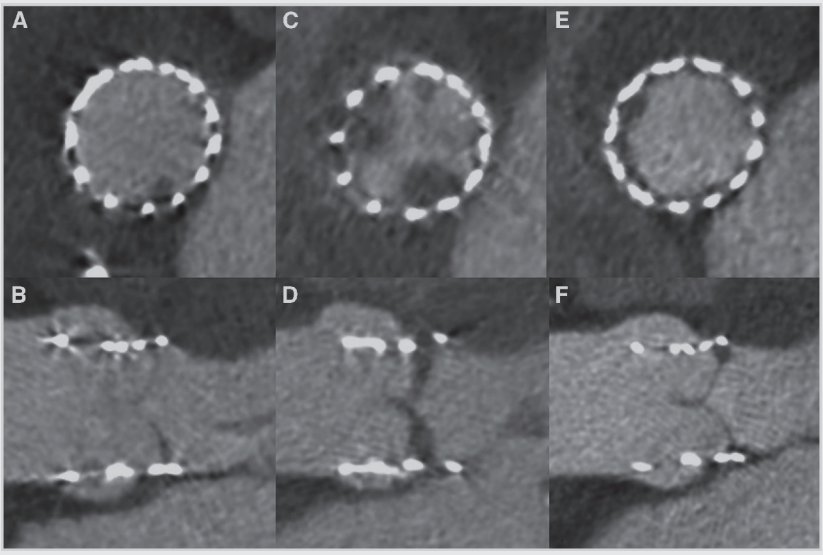

FIGURE 2. Axial and sagittal oblique reconstructions of a CORONARY CTA scan in an 80-year-old female immediately after implantation of a balloon-expandable transcatheter aortic valve prosthesis (*A* and *B*), at 3 months- (*C* and *D*), and at 6 months-follow-up (*E* and *F*). Note subtle early hypo-attenuated thickening (HALT) of the non-coronary cusp (*A* and *B*) which progressed to 5 mm thickening of the non-coronary cusp and included the right coronary cusp (*C* and *D*). After a combination of clopidogrel and phenprocoumon follow-up coronary CTA showed almost complete resolution of HALT. (*E* and *F*).

Reproduced with permission of Oxford University Press from Pache *et al*.[21]
This Figure has been reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

ljivost i negativnu prediktivnu vrijednost nad transtorakalnom ehokardiografijom (iako razlika nije dosegnula statističku značajnost). TEE je, međutim, bio bolji u predviđanju točnoga mjesta paravalvularnog curenja od CT-a (86 prema 76 %).

Kardiovaskularna magnetna rezonancija

Dokazi koji upućuju na dijagnostičku i prognostičku vrijednost oslikavanja tehnikom CMR-a u osoba s povećanim kardiovaskularnim rizikom, u bolesnika s valvularnim bolestima srca ili u bolesnika s kardiomiopatijama, sve su brojniji. Osnovni patofiziološki mehanizmi aortopatija u bolesnika s bikuspidnom aortnom valvulom bili su žarište ekstenzivnih istraživanja magnetnom rezonancijom. Da bi pokazali kako transvalvularni reološki poremećaji utječu na ekspresiju i težinu aortopatije povezane s aortnom stenozom, *Girdauskas i sur.*[24], koristeći se konvencionalnim CMR-om, procijenili su 190 bolesnika s teškom aortnom stenozom koji su bili podvrgnuti kirurškoj zamijeni valvule uz istodobni zahvat na proksimalnoj ascendentoj aorti ili bez njega: 197 bolesnika je imalo bikuspidni zalistak, a preostala 53 imala su trikuspidni zalistak. Aortopatija je definirana endodijastoličkim poprečnim presjekom ≥ 22 mm/m^2 ili ≥ 40 mm na bilo kojoj razini proksimalne aorte. Udio bolesnika s aortopatijom bio je veći među bolesnicima s bikuspidnim aortnim zalistkom nego u bolesnika s trikuspidnim zalistkom (35 prema 11 %, *P* = 0,008). Kada se govori o reološkim parametrima dobivenima CMR-om, bolesnici s bikuspidnom aortnom valvulom imali su veći kut između izlaznog dijela LV-a i aortnog korijena te su češće imali asimetrični otvor aortne valvule u usporedbi s bolesnicima s trikuspidnom valvulom. Nakon provedene logističke regresijske analize, samo su kut između izlaznog dijela LV-a i aortnog korijena te kut između mlaza sistoličkoga protoka i aortne stijenke neovisno povezani aortopatijom, dok morfologija valvule nije bila povezana, što upućuje na to da bi u bolesnika s aortnom stenozom ovi reološki parametri mogli biti važniji za aortopatiju od same morfologije aortne valvule. Četverodimenzijski protočni CMR dao je dodatan uvid u odnos između protoka krvi u ascendentnoj aorti i u morfologiju valvule.[25,26] Koristeći se ovom tehnikom, *Garcia i sur.*[25] u 50 bolesnika s bikuspidnom i u 50 bolesnika s trikuspidnom valvulom i dilatiranom aortom pokazali su da bolesnici s bikuspidnom valvulom imaju višu vršnu vrijednost brzine protoka mlaza između izlaznog dijela LV-a i sinotubularnoga spoja u usporedbi s bolesnicima s trikuspidnom valvulom, unatoč sličnim dimenzijama aorte. Pri multivarijatnoj analizi, dob i vršna vrijednost brzine protoka mlaza jedini su znatno korelali s maksimalnim dimenzijama aorte. Osim toga, u 37 bolesnika s različitim stupnjevima aortne stenoze i u 37 zdravih volontera, spiralne i vertikalne formacije protoka te ekscentričnosti protoka procjenjivani su u ascendentoj aorti primjenom četverodimenzijskoga protočnog CMR-a.[26] U usporedbi s zdravim volonterima, bolesnici s aortnom stenozom češće su pokazivali uočljivu spiralnu i vertikalnu formaciju protoka uz ekscentrični protok s asimetričnom i povišenom distribucijom vršnog naprezanja stijenke u sistoli u ascendentnoj aorti. Manje površine otvora aortne valvule povezivane su s više vertikalnih formacija protoka i ekscentričnoga protoka s asimetričnim protokom, dok je morfologija bikuspidne aortne valvule znatno povezana s intenzivnom spiralnom formacijom protoka i višim pomakom protoka te vršnog naprezanja stijenke u sistoli.

Karakterizacije tkiva s kasnim nakupljanjem gadolinija (LGE) i T1 mapirajućim CMR tehnikama pokazale su se osjetljivije od

predicting the exact location of paravalvular leakage than CT (86% vs. 76%).

Cardiovascular magnetic resonance

The evidence showing the diagnostic and prognostic value of CMR techniques in individuals with increased cardiovascular risk, patients with valvular heart disease or patients with cardiomyopathies is accumulating. The underlying pathophysiological mechanisms of aortopathy in patients with bicuspid aortic valve have been the focus of extensive CMR research. To demonstrate how transvalvular rheological disturbances influence the expression and severity of aortopathy associated with aortic stenosis, Girdauskas *et al.*[24] evaluated with conventional CMR 190 patients with severe aortic stenosis who underwent surgical aortic valve replacement with or without concomitant surgery of the proximal ascending aorta: 137 patients had a bicuspid aortic valve while the remaining 53 had a tricuspid aortic valve. Aortopathy was defined by an end-diastolic cross-sectional diameter ≥22 mm/m2 or ≥40 mm at any level of the proximal aorta. The proportion of patients with aortopathy was higher among patients with bicuspid aortic valve as compared to patients with tricuspid valve (35% vs. 11%, *P* = 0.008). In terms of CMR-derived rheological parameters, patients with bicuspid aortic valve had greater angle between the LV outflow tract and the aortic root and more frequently asymmetric aortic valve orifice compared with their counterparts. On logistic regression analysis, only the angle between the LV outflow tract and the aortic root, and the angle between the systolic flow jet and the aortic wall were independently associated with aortopathy whereas valve morphology was not associated, suggesting that, in patients with aortic stenosis, these rheological variables may be more related to aortopathy than aortic valve morphology per se. Four-dimensional flow CMR has provided further insight into the relation between blood flow patterns in the ascending aorta and valve morphology.[25,26] Using this technique, Garcia *et al.*[25] showed in 50 patients with bicuspid and 50 patients with tricuspid aortic valve and dilated aorta that patients with bicuspid aortic valve have higher peak flow jet velocity between the LV outflow tract and the sinotubular junction compared with patients with tricuspid valve, despite having comparable aortic dimensions. On multivariate analysis, age and peak flow jet velocity were the only significant correlates of maximal aortic dimensions. Furthermore, in 37 patients with various grades of aortic stenosis and 37 healthy volunteers, helical and vertical flow formations and flow eccentricity were assessed in the ascending aorta using four-dimesional flow CMR.[26] Compared with healthy volunteers, patients with aortic stenosis showed more frequently marked helical and vertical flow formation and eccentric flow with asymmetrical and elevated distribution of peak systolic wall stress in the ascending aorta. Smaller aortic orifice areas were associated with more vertical flow formation and eccentric flow and higher flow displacement whereas bicuspid aortic valve morphology was significantly associated with intense helical flow formation and higher flow displacement and peak systolic wall shear stress.

Tissue characterization with late gadolinium enhancement (LGE) and T1 mapping CMR techniques have shown to be more sensitive than electrocardiographic parameters or biomarkers to detect myocardial scar and fibrosis. Of 1840

elektrokardiografskih parametara ili biomarkera u otkrivanju ožiljaka ili fibroze miokarda. Od 1840 sudionika u studiji MESA koji pri prvom pregledu nisu imali kliničkih znakova KVB-a (2000. – 2002.) i učinjen im je LGE CMR prilikom pregleda nakon 10 godina (2010. – 2012.), 146 (7,9 %) osoba imalo je ožiljke miokarda.[27] U 78 % osoba ožiljci miokarda nisu bili prepoznati elektrokardiogramom ni kliničkom evaluacijom. Dob, muški spol, indeks tjelesne mase, arterijska hipertenzija i vrijednost CACS-a (prilagođena spolu, dobi i etničkoj skupini) pri prvom pregledu povezani su s prisutnošću ožiljaka miokarda nakon 10 godina. Omjer šansi za nastajanje ožiljka miokarda pri vrijednosti CACS-a višoj od 400, triput je veći nego pri CACS-u vrijednosti 0, no prognostički potencijal spomenutih vrijednosti do sada nije utvrđen. *Chin i sur.*[28] istraživali su povezanost fibroze miokarda u području srednjeg djela stijenke s neželjenim ishodom u bolesnika s aortnom stenozom. Ukupno 147 ispitanika s aortnom stenozom srednjega do teškoga stupnja, bez prethodnog infarkta miokarda, pristupilo je LGE-CMR-u. Osmišljen je model koji uključuje kliničke, ehokardiografske i elektrokardiografske varijable te biomarkere. Navedene su varijable bile neovisno povezane s prisutnošću ožiljaka miokarda u području srednjeg djela stijenke. Niski rizik od fibroze miokarda određen je rezultatom < 7 %, dok je visoki rizik određen rezultatom > 57 %. Prognostička vrijednost ovog modela validirana je s pomoću dviju kohorti asimptomatskih bolesnika s minimalno srednjim stupnjem aortne stenoze: 127 bolesnika u sklopu unutarnje kohorte te 289 bolesnika vanjske kohorte, ukupno 1560 bolesnik na godinu. U internoj kohorti visok je rezultat bio povezan sa sedmerostrukim povećanjem stope smrtnosti (13 *vs.* 2,1 ukupni mortalitet na 100 pacijenata na godinu; P < 0,001). U skladu s navedenim rezultatima, u vanjskoj kohorti bolesnici visokog rizika imali su 31,6 ishoda povezanih s aortnom stenozom (srčana smrt, ZS te pojava novih simptoma) na 100 bolesnika/godina u usporedbi s 4,6 ishoda na 100 bolesnika/godina u skupni s rezultatom niske razine rizika (p < 0,001).

Utvrđivanje reaktivne difuzne fibroze miokarda s pomoću T1 tehnike mapiranja omogućilo je diferencijaciju između hipertrofijske kardiomiopatije i hipertrofije lijeve klijetke nastale zbog arterijske hipertenzije.[29] Nativna T1 vremena i frakcija izvanstaničnog volumena (ECV) odraz su stupnja intersticijske fibroze miokarda. Studija *International T1 Multicenter CMR* obuhvatila je ukupno 95 ispitanika s hipertrofijskom kardiomiopatijom, 69 ispitanika s esencijalnom arterijskom hipertenzijom, 23 nositelja mutacija gena za sarkomere u kojih se nije razvio fenotip hipertrofije LV te 23 zdrava pojedinca. Ispitanici s hipertrofijskom kardiomiopatijom imali su dulje nativno T1 vrijeme (1169 ± 41 ms *vs.* 1058 ± 29 ms; *P* < 0,001) te viši ECV (0,31 ± 0,06 *vs.* 0,24 ± 0,04; *P* < 0,001), u usporedbi s ispitanicima s esencijalnom arterijskom hipertenzijom. Važno je istaknuti kako su nositelji mutacija gena za sarkomere imali mnogo dulje nativno T1 vrijeme u usporedbi sa zdravim ispitanicima (1105 ± 17 ms vs. 1044 ± 18 ms; *P* < 0,001), no slične vrijednosti ECV-a. Zaključuje se da se u bolesnika s mutiranim genom za sarkomere, posebice u onih bez fenotipskih obilježja, mapiranjem s pomoću T1 CMR tehnologije omogućuje rana detekcija strukturnih promjena. Isto tako, izračunom vremena T1, vrijednosti ECV-a te vremena T2 omogućeno je razlikovanje bolesnika s ranom neishemijskom dilatacijskom kardiomiopatijom od onih s fiziološkom prilagodbom miokarda na vježbanje (ispitanici s tzv. sportskim srcem).[30] Ispitanici s ranom prezentacijom dilatacijske kardiomiopatije, s obzirom na ispitanike koji se bave aerobnim aktivnostima više od 6 sati na dan, pokazali su znatno produženje

participants in the MESA study who were free of clinical cardiovascular disease at baseline (in 2000–2002) and underwent LGE CMR in the 10th year examination (2010–2012), 146 (7.9%) individuals showed myocardial scar.[27] In 78% of them, myocardial scar was unrecognized by electrocardiogram or clinical evaluation. Age, male sex, body mass index, hypertension, and CACS (adjusted for age, sex, and ethnicity) at baseline were associated with presence of myocardial scar at year 10. The odds ratio for myocardial scar of a CACS value ≥400 was three-fold higher compared with CACS of 0. The prognostic implications of these findings were not evaluated. The association between presence of midwall myocardial scar/fibrosis and adverse outcomes in patients with aortic stenosis was investigated by Chin *et al.*[28] From 147 patients with mild-to-severe aortic stenosis and no prior myocardial infarction who underwent LGE CMR, a score including clinical, biomarker, echocardiographic, and electrocardiographic variables independently associated with the presence of midwall myocardial scar/fibrosis was derived. Low risk of myocardial fibrosis was defined by a risk score of <7% whereas high risk was defined by a risk score of >57%. The prognostic value of this score was validated in two cohorts of asymptomatic patients with at least mild aortic stenosis: 127 patients from an internal cohort and 289 patients from an external cohort, resulting in 1560 patient-years. In the internal cohort, a high risk score was associated with seven-fold higher mortality rates compared with patients with low risk score (13 vs. 2.1 all-cause death/100 patient-years; P < 0.001). Similarly, in the external cohort, high-risk patients had 31.6 aortic stenosis related events (cardiovascular death, heart failure and new symptoms)/100 patient-years compared with 4.6 aortic stenosis related events/100 patient-years in the low-risk patients (P < 0.001).

Assessment of reactive diffuse myocardial fibrosis with T1 mapping techniques has permitted differentiation between hypertrophic cardiomyopathy and LV hypertrophy secondary to hypertension.[29] Native T1 times and extracellular volume fraction (ECV) reflect the amount of interstitial myocardial fibrosis. The International T1 Multicenter CMR study included 95 patients with hypertrophic cardiomyopathy, 69 patients with essential hypertension, 23 carriers of sarcomere gene mutations without LV hypertrophy and 23 healthy volunteers. Patients with hypertrophic cardiomyopathy had longer native T1 times (1169 ± 41 ms vs. 1058 ± 29 ms, P < 0.001) and higher ECV (0.31 ± 0.06 vs. 0.24 ± 0.04, P < 0.001) compared with hypertensive patients. Interestingly, sarcomere gene mutation carriers had significantly longer native T1 times as compared with healthy volunteers (1105 ± 17 ms vs. 1044 ± 18 ms, P < 0.001) but similar ECV. Therefore, T1-mapping CMR techniques permit as well early detection of structural changes in mutation carriers who have not developed yet the phenotype. Similarly, differentiation between patients with early non-ischaemic dilated cardiomyopathy and individuals with physiological adaptation to exercise ('athlete's heart') has been possible with calculation of native T1 times, ECV and T2 times.[30] Patients with early presentation of dilated cardiomyopathy displayed significantly larger native T1 times, ECV and T2 times (indicating replacement fibrosis) as compared with individuals performing aerobic exercise more than 6 h per week (**Figure 3**). These techniques have also helped to better understand the LV diastolic function of patients with heart failure and preserved LVEF. In 24 patients with heart failure

vremena T1, više vrijednosti ECV-a te produženje vremena T2 (što upućuje na reaktivnu nadomjesnu fibrozu) (**Slika 3**). Spomenutim je tehnikama omogućeno bolje razumijevanje dijastoličke funkcije LV-a u bolesnika sa ZS-om s očuvanim LVEF-om. U 24 bolesnika sa ZS-om i očuvanim LVEF-om, *Rommel i sur.*[31] upozorili su na činjenicu da je ECV neovisni prediktor invazivno mjerene konstante krutosti LV (r = 0,75; P < 0,01). Nadalje, bolesnici s vrijednostima ECV-a manjima od medijana (32,3 %) pokazali su produženo aktivno vrijeme relaksacije LV-a, dok su bolesnici s vrijednostima ECV-a višima od medijana pokazali veće vrijednosti krutosti LV-a. Uočena obilježja upućuju na razlike u patološkim mehanizmima koji uzrokuju pojavu istovrsnih simptoma. U *MyoRacer* studiji, istraživana je dijagnostička vrijednost tehnika CMR mapiranja primjenom T1 i T2 vremena u ukupno 129 ispitanika sa sumnjom na miokarditis (61 ispitanik s akutnim te 68 s kroničnim simptomima).[32] Biventrikulska endomiokardijalna biopsija rađena je u ukupno 93 % ispitanika. U grupi s akutnim simptomima nativno T1 mapiranje imalo je najveću površinu ispod krivulje (AUC) za dijagnozu miokarditisa (0,82; P = 0,002), praćeno T2 tehnikom (0,81; P = 0,001) te ECV tehnikom (0,75; P = 0,04). Sve su navedene tehnike uspoređivane s *Lake Louis* kriterijima (0,56). U ispitanika s kroničnim simptomima mapiranje s pomoću T2 omogućilo je razlikovanje između miokarditisa i urednih nalaza te mnogo veću površinu ispod krivulje (0,77), u usporedbi s tehnikom nativnog T1 mapiranja (0,53 : P

and preserved LVEF, Rommel *et al.*[31] showed that ECV was an independent predictor of invasively measured LV stiffness constant (r = 0.75; P < 0.01). Furthermore, patients with an ECV below the median (32.3%) were characterized by prolonged active LV relaxation whereas patients with an ECV above the median showed higher LV stiffness constant suggesting differences in the pathological mechanisms of symptoms. In the field of myocarditis, the MyoRacer-Trial assessed the diagnostic accuracy of T1 and T2 mapping CMR techniques in 129 patients with suspected myocarditis (61 with acute and 68 with chronic symptoms).[32] Biventricular endomyocardial biopsy was performed in 93% of patients. In the group with acute symptoms, native T1 mapping yielded the higher area under the curve to diagnose myocarditis (0.82, P = 0.002) followed by T2 mapping (0.81, P = 0.001) and ECV (0.75, P = 0.04) as compared with Lake Louise criteria (0.56). In patients with chronic symptoms, T2 mapping permitted differentiation between myocarditis and no myocarditis patients and provided a significantly higher area under the curve (0.77) compared with native T1 mapping (0.53, P = 0.004) and Lake Loiuse criteria (0.53, P = 0.002). Finally, the prognostic implications of T1 mapping CMR techniques were evaluated in a prospective multicentre study which included 637 consecutive patients with non-ischaemic cardiomyopathy.[33] During a median follow-up of 22 months, 28 patients died (22 from cardiac cause)

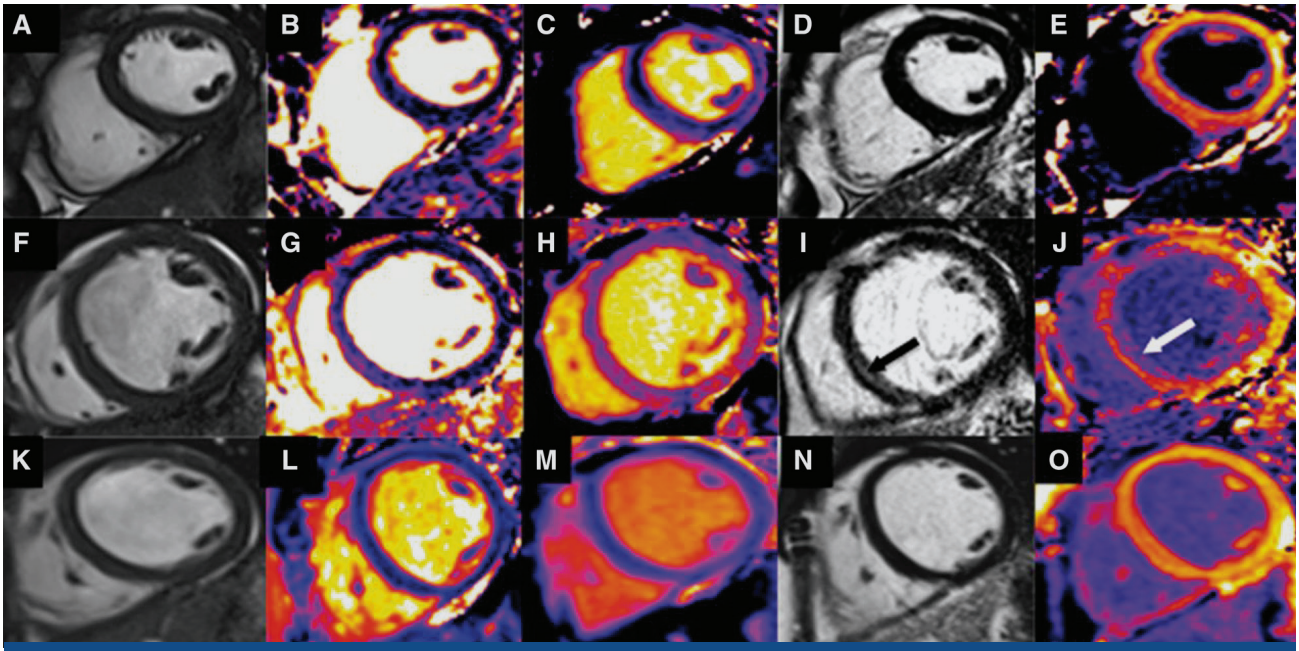

FIGURE 3. Native T1 time, extracellular volume and T2 time assessed with CMR to differentiate between the early phase of dilated cardiomyopathy and an 'athlete's heart'. CMR data acquisition in a healthy control (*panels A–E*), a patient with dilated cardiomyopathy (*panels F–J*) and an individual with 'athlete's heart' (*panels K–O*). The healthy control had normal LVEF (58%, *panel A*), the septal T2 time was 51.6 ms (*panel B*), the septal native T1 time was 924.9 ms (*panel C*) and there was no LGE (*panel D*) or diffuse fibrosis (ECV 27%, *panel E*). In contrast, the patient with dilated cardiomyopathy showed mildly reduced LVEF (48%, *panel F*), septal T2 time 59.8 ms (*panel G*), septal native T1 time 1017.8 ms (*panel H*) and midwall fibrosis in the inferoseptum (*panel I*, arrow) on LGE and significant diffuse fibrosis as reflected by an ECV of 35% (*panel J*, arrow). In the individual with 'athlete's heart', the LVEF was relatively preserved (53%, *panel K*), the septal T2 time was 50.4 ms (*panel L*), the native T1 time was 931.4 ms (*panel M*) and there was no LGE (*panel N*) and the value of ECV was similar to that of the healthy individual (28%, *panel O*). Accordingly, early stages of dilated cardiomyopathy show mildly reduced function and development of replacement fibrosis, phenomena not observed in healthy individuals or patients with 'athlete's heart'.

Reproduced with permission from Mordi *et al.*[30]

= 0,004) i *Lake Louis* kriterija (0,53; *P* = 0,002). Konačno, procjena prognostičkih implikacija T1 mapiranja s pomoću CMR tehnologije provedena je u multicentričnoj studiji koja je obuhvatila ukupno 637 ispitanika s neishemijskom kardiomiopatijom.[33] U medijanu vremena praćenja od ukupno 22 mjeseca, preminulo je 28 ispitanika (22 od srčanog uzroka), dok je 68 ispitanika dosegnuo zajedničku točku isključenja iz studije zbog ZS-a. Svako povećanje od 10 ms u vremenu T1 pokazalo se neovisno povezano s 10 % većim rizikom ukupne smrtnosti te sa 7 % povećanja rizika od ZS-a.

Učinkovitost novijih metoda transkateterske terapije mitralne regurgitacije poput *MitraClip* implantata (Abbott Vascular, Menlo Park, CA) definirana je smanjenjem stupnja mitralne regurgitacije, reverznog remodeliranja srčanih šupljina te poboljšanjem simptoma i povećanjem LVEF-a. Oslikavanje CMR-om smatra se „zlatnim standardom" pri procjeni volumena srčanih šupljina. Promatrajući ukupno 20 ispitanika s ugrađenim *MitraClip* implantatom sedam dana nakon ugradnje, procijenjeni su volumeni i funkcija lijeve i desne klijetke te cirkumferencijalna i radijalna deformacija.[34] Iako su uočeni znatno poboljšanje simptoma ZS-a te redukcija stupnja mitralne regurgitacije, nisu dokazani znatno reverzibilno remodeliranje ni poboljšanje sistoličke funkcije lijeve ili desne klijetke. Mogući je razlog prerano vrijeme ponovnoga snimanja s obzirom na trenutak ugradnje *MitraClipa*. Vrijedno je spomenuti da ugrađeni uređaj ne utječe na kvalitetu snimanja CMR-om ni na preciznost određivanja volumena klijeki.

Nuklearne metode oslikavanja

Mnogi su znanstveni radovi posvećeni boljim metodama detekcije KBS-a. *Lee i sur.*[35] proučavali su pozitronsku emisijsku tomografiju (PET) s ^{13}N-amonijem te izveli kvantitativne mjere kao što su hiperemični miokardni protok krvi, koronarna rezerva protoka te relativna rezerva protoka. Navedene su mjere uspoređivali s invazivnim FFR-om (< 0,8), koji je „zlatni standard" za detekciju funkcionalno važne stenoze koronarnih arterija. Ova je studija odredila optimalne granične vrijednosti rezultata ^{13}N-amonij PET metode za dijagnostiku značajne KBS-a, i to kao 1,99 mL/min/g za hiperemični miokardni protok krvi, 2,12 za koronarnu rezervu protoka te 0,82 za relativnu rezervu protoka. Iako su sva kvantitativna PET mjerenja bila mnogo bolja s obzirom na relativnu procjenu perfuzijskih defekata, relativna je rezerva protoka pokazala najvišu dijagnostičku preciznost za procjenu funkcijske važnosti stenoze.

U multicentričnoj klinički randomiziranoj studiji CE-MARC 2 (*Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease-2*) *Greenwood i sur.*[36] procijenili su superiornost neinvazivnoga, slikovnim prikazom vođenog postupka sa svrhom smanjenja broja nepotrebnih koronarografija (primarni ishod) s obzirom na skrb uz isti cilj preporučen u smjernicama *National Institute for Health and Care Excellence* (NICE). Nepotrebne koronarografije definirane su kao prisutnost nesignifikantnih stenoza koronarnih arterija određenih mjerenjem FFR-a > 0,8 ili stupnjem stenoze < 70 % na kvantitativnoj koronarografiji. Ukupno su 1202 simptomatska bolesnika sa sumnjom na KBS uključena i randomizirana na stres CMR-a, scintigrafiju miokardijalne perfuzije (MPS) ili na postupke definirane prema smjernicama NICE-a. Nakon razdoblja praćenja od 12 mjeseci, u skupini koja je slijedila smjernice NICE-a, završetak studije dosegnuo je 69 ispitanika (28,8 %), u skupini ispitanika pod kontrolom CMR-a mnogo manji broj od 36 (7,5 %) te 34 ispitanika (7,1 %)

and 68 composite heart failure events were recorded. Each 10 ms increase in native T1 time was independently associated with 10% increase in the risk of all-cause mortality and 7% increase in the risk of composite heart failure events.

The efficacy of new transcatheter therapies for mitral regurgitation such as the MitraClip device (Abbott Vascular, Menlo Park, CA) is defined by reduction in mitral regurgitation grade, reverse remodelling of cardiac chambers and improvement in LVEF and symptoms. Cardiovascular magnetic resonance imaging is considered the reference standard to assess cardiac chamber volumes. In 20 patients undergoing MitraClip implantation, LV and right ventricular volumes and function (including feature tracking circumferential and radial strain) were assessed at baseline and 7 days after the procedure.[34] Although there was a significant improvement in heart failure symptoms and reduction in mitral regurgitation, there was neither significant reverse remodelling nor improvement in systolic function of the LV and right ventricle. Probably, CMR was performed too early after the procedure to observe any meaningful change in ventricular volumes and function. However, the device does not affect the image quality to assess ventricular volumes.

Nuclear imaging

Various articles were dedicated to improved detection of CAD. Lee *et al.*[35] performed 13N-ammonia positron emission tomography (PET) and derived quantitative measures such as hyperaemic myocardial blood flow, coronary flow reserve, and relative flow reserve for comparison with invasive FFR (<0.8) which is considered the reference for detecting functionally significant coronary artery stenoses. This study provides optimal cut-off values for 13N-ammonia PET for the diagnosis of significant CAD, being 1.99 mL/min/g for hyperaemic myocardial blood flow, 2.12 for coronary flow reserve and 0.82 for relative flow reserve. While all quantitative PET measures performed significantly better than relative perfusion defect assessment, relative flow reserve showed the highest diagnostic accuracy to predict the functional significance of a stenosis.

In the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease-2 (CE-MARC 2) multicenter randomized clinical trial, Greenwood *et al.*[36] assessed whether non-invasive imaging-guided care is superior to National Institute for Health and Care Excellence (NICE) guidelines-directed care in reducing unnecessary angiography (primary endpoint), defined as no significant coronary artery stenosis based on FFR measurement >0.8 or <70% stenosis on quantitative coronary angiography. A total of 1202 symptomatic patients with suspected CAD were enrolled and randomized to stress CMR, myocardial perfusion scintigraphy (MPS) or NICE guidelines-directed care. Within 12 months of follow-up, the endpoint occurred in 69 (28.8%) patients in the NICE guidelines-directed care group, which was significantly reduced to 36 (7.5%) in the CMR group and to 34 (7.1%) in the MPS group (P < 0.001 for both vs. NICE, with MPS and CMR being not significantly different).

The role of nuclear imaging in heart failure was highlighted by sub-analyses of two important prospective trials: the PET and Recovery Following Revascularization (PARR-2) study and the Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF).[37-39] The PARR-2 study is the

u MPS skupini (P < 0,001) za obje metode s obzirom na NICE, dok se MPS i CMR međusobno statistički ne razlikuju).

Uloga nuklearnih metoda oslikavanja u ZS-u istaknuta je podanalizom dviju važnih prospektivnih studija: PARR-2 (*PET and Recovery Following Revascularization*) te ADMIRE-HF (*Adreview Myocardial Imaging for Risk Evaluation in Heart Failure*).[37-39] Studija PARR-2 najveća je randomizirana studija koja prati prognostičke prednosti PET tehnologije s ^{18}F-fluorodeoksiglukozom (FDG) s obzirom na uobičajeni algoritam skrbi za bolesnike s teškom disfunkcijom LV-a te KBS-a, koji su evaluirani za revaskularizaciju ili transplantaciju. Ishodi nakon 5 godina nisu pokazali razlike u učestalosti zajedničkog ishoda (srčana smrt, infarkt miokarda ili hospitalizacija povezana sa srčanom bolesti): 53 % bolesnika s PET dijagnostikom u odnosu prema 57 % sa standardnom skrbi (HR 0,82, 95 % CI 0,62 – 1,07; *P* = 0,15).[39] Ako se promatraju samo bolesnici koji su se držali preporuka snimanja PET-a s FDG-om, ishod se znatno poboljšava u skupini skrbi potpomognutoj PET snimanjem (HR 0,73, 95 % CI 0,54 – 0,99; *P* = 0,042). Navedeni rezultati upućuju na vrijednost procjene vijabilnosti miokarda pomoću PET-a u bolesnika s disfunkcijom LV-a uzrokovanom ishemijom, a koji su kandidati za revaskularizaciju.

Studija ADMIRE-HF upozorila je na vrijednost procjene simpatičke inervacije miokarda ^{123}I-jodobenzilguanidinom (mIBG) u bolesnika sa ZS-om, s pomoću koje se mogu prepoznati bolesnici s povećanim rizikom od ventrikulskih artimija i iznenadne srčane smrti.[40] U podstudiji u sklopu studije ADMIRE-HF, *Hachamovitch i sur.*[38] istražili su utjecaj ^{123}I-mIBG scintigrafije na poboljšanje ishoda i efikasnosti skrbi u bolesnika nakon ugradnje kardioverterskog defibrilatora. Od 777 bolesnika (65 % s ishemijskom bolesti srca) bez ugrađenog ICD uređaja u trenutku inicijalne scintigrafije s ^{123}I-mIBG-om, preminulo ih je 75 (9,6 %), od toga 23 (3 %) iznenadnom srčanom smrti, dok su se u njih ukupno 26 (3,3 %) razvile životno ugrožavajuće aritmije u medijanu praćenja od 17 mjeseci. Scintigrafija ^{123}I-mIBG-om pokazala se kao neovisni i inkrementalni pretkazatelj ukupne smrtnosti. Kao dodatak navedenom, u produžetku studije ADMIRE-HF (ADMIRE-HFX), na uzorku od 619 bolesnika uz 319 bolesnika bez ishemijske kardiomiopatije i s miokardijalnom perfuzijskom scintigrafijom istaknuta je prognostička relevantnost dinamike unosa ^{123}I-mIBG-a (koji reflektira miokardijalnu denervaciju) te ^{99}mTc-tetrofosmina.[37] Proširenost i ozbiljnost miokardijalne denervacije kvantificirana je udjelom zahvaćenog miokarda, a denervacijski izračun zahvaćenog segmenta dobiven je iz modela od 17 elemenata s ljestvicom od 5 bodova. Izračunano je područje razlike u unosu između ^{123}I-mIBG-a i ^{99}mTc-tetrofosmina. Smrtnost je bila veća u bolesnika s denervacijom koja je zahvaćala više od 50 % miokarda. Najveći rizik od srčane smrti za bolesnike s ishemijskom kardiomiopatijom, uočen je u ispitanika s perfuzijskim defektima koji zahvaćaju 20 – 40 % miokarda. Za usporedbu, bolesnici s neishemijskom kardiomiopatijom i manjim perfuzijskim defektima (< 20 % miokarda), ali s velikom razlikom između veličine defekta nastalih smanjenim unosom ^{123}I-mIBG-a i ^{99}mTc-tetrofosmina, imali su veću smrtnost, što čini potencijalnu prognostičku ulogu u stupnju denervacije u regijama s očuvanom miokardnom perfuzijom u bolesnika s neishemijskom kardiomiopatijom.

Ekscesivna stimulacija miokarda katekolaminima potencijalan je uzrok Tako tsubo kardiomiopatije, jedne od reverzibilnih uzroka ZS-a. Kako bi provjerili ovu hipotezu, *Christensen i sur.*[41] promatrali su i pratili 32 bolesnika s dijagnozom tako-tsubo kar-

largest randomized trial evaluating the prognostic benefit of 18F-fluorodeoxyglucose (FDG) PET-assisted management vs. standard care in patients with severe LV dysfunction and CAD considered for revascularization or transplantation; the 5-year outcome data revealed no differences in the composite event rate (cardiac death, infarction, or cardiac hospitalization): 53% in the PET arm vs. 57% in the standard care arm (HR 0.82, 95% CI 0.62–1.07; *P* = 0.15).[39] However, if only patients who adhered to the recommendation of the FDG PET scan were included, the outcome was significantly improved in PET-assisted management (HR 0.73, 95% CI 0.54–0.99; *P* = 0.042). The results suggest that evaluation of myocardial viability with PET can aid in the decision making of patients with ischaemic LV dysfunction who are considered for revascularization.

The ADMIRE-HF study demonstrated that assessment of myocardial sympathetic innervation with ^{123}I-meta-iodobenzylguanidine (mIBG) scintigraphy has incremental prognostic information in heart failure patients and may identify patients with increased risk of ventricular arrhythmias or sudden cardiac death.[40] In a sub-study of the ADMIRE-HF trial, Hachamovitch *et al.*[38] investigated whether the use of 123I-mIBG imaging to guide implantable cardioverter defibrillator (ICD) implantation will result in improved patient prognosis and efficiency of care. Of 777 patients (65% ischaemic heart disease) who did not have an ICD at the time of the index 123I-mIBG scan, 75 (9.6%) died, 23 (3%) presented with sudden cardiac death and 26 (3.3%) with life-threatening arrhythmias during a median of 17 months. Planar 123I-mIBG imaging was an independent and incremental predictor of all-cause mortality. In addition, in the extension study of the ADMIRE-HF trial (ADMIRE-HFX), the prognostic significance of patterns of 123I-mIBG uptake (reflecting myocardial denervation) and 99mTc-tetrofosmin myocardial perfusion imaging was assessed in 619 ischaemic and 319 non-ischaemic heart failure patients.[37] The extent and severity of myocardial denervation were quantified as percentage of total myocardium and the segment denervation score was calculated based on a 17-segment model using a 5-point scale. Moreover, the area of mismatch between 123I-mIBG/99mTc-tetrofosmin uptake was calculated. Mortality was higher in patients with denervation involving >50% of the myocardium. The highest cardiac mortality risk for ischaemic heart failure patients was observed with perfusion defects involving 20–40% of the myocardium. In contrast, non-ischaemic heart failure patients with smaller perfusion abnormalities (<20% of myocardium), but with a large discrepancy between 123I-mIBG and 99mTc-tetrofosmin defect sizes, were at highest risk of cardiac death, suggesting a potential prognostic role of the degree of denervation in areas with preserved myocardial perfusion in non-ischaemic heart failure patients.

An excessive catecholamine stimulation of the myocardium has been proposed as potential underlying mechanism of Tako-tsubo cardiomyopathy, a reversible cause of heart failure. To test this hypothesis, Christensen *et al.*[41] evaluated at admission and follow-up the sympathetic cardiac innervation with 123I-mIBG scintigraphy and plasma cathecolamine levels in 32 patients diagnosed with Tako-tsubo cardiomyopathy and 20 controls. At admission, Tako-tsubo cardiomyopathy patients showed lower cardiac 123I-mIBG uptake and higher levels of epinephrine compared with controls. At follow-up, cardiac 123I-mIBG uptake normalized whereas the plasma epinephrine levels remained elevated in the Tako-

diomiopatije uz 20 kontrola te procijenili simpatičku inervaciju miokarda s pomoću ^{123}I-mIBG scintigrafije i razine katekolamina u plazmi. U trenutku prijma bolesnici s dijagnozom tako-tsubo kardiomiopatije pokazali su niže razine srčanog unosa ^{123}I-mIBG-a te više razine epinefrina, u usporedbi s kontrolnom skupinom. Pri daljnjemg praćenju, srčani se unos ^{123}I-mIBG-a normalizirao, za razliku od razine katekolamina u plazmi koja je ostala povećana u skupini bolesnika s bolešću tako-tsubo. Pretpostavlja se da uočena adrenergična aktivnost ima središnju ulogu u patogenezi ove kardiomiopatije te bi zbog toga trebala imati i mjesto u kliničkome pristupu ovakvim bolesnicima.

Naposljetku, nuklearne tehnike oslikavanja omogućile su pristup važnim dijagnostičkim informacijama u bolesnika sa sumnjom na endokarditis. *Caobelli i sur.*[42] snimili su 34 ispitanika sa sumnjom na endokarditis nativnog zalistka (n = 12) i umjetnih zalistaka (n = 22), koristeći se dvostrukim izotopima: ^{111}In-om označenim leukocitima te ^{99m}Tc perfuzijskim SPECT snimanjem s pomoću kadmij-cink-telurijskog (CZT) detektora (**Slika 4**). Rezolucija visoke energije i osjetljivosti povezana s tehnologijom kamere s CZT detektorom, omogućuje simultano snimanje multiplih izotopa, čime se poboljšava detekcija molekularnih i staničnih signala. U usporedbi sa standardnom planarnom scintigrafijom s pomoću ^{111}In leukocita i SPECT-a, CZT tehnologija uz dvostruke izotope pokazuje praktičnost i dodanu dijagnostičku vrijednost jer omogućuje napredniju kvalitetu slike, povećava sigurnost pri opisivanju nalaza te povećanu preciznost temeljenu na kirurškim, odnosno Dukeovim kriterijima tijekom daljnjega praćenja.

tsubo cardiomyopathy patients. This hyperadrenergic activity may play a central role in the pathogenesis of this cardiomyopathy and may have important implications for clinical management.

Finally, nuclear imaging techniques have provided important diagnostic information in patients with suspected endocarditis. Caobelli *et al.*[42] performed dual-isotope imaging in 34 patients with suspected endocarditis of native (n = 12) or prosthetic (n = 22) valves employing 111In-labeled white blood cells (WBC) and 99mTc for perfusion imaging on a dedicated cadmium-zinc-telluride (CZT) detector equipped SPECT (**Figure 4**). The high-energy resolution and sensitivity of novel CZT detector equipped camera enable simultaneous imaging of multiple isotopes enhancing the detection of molecular/cellular signals. Compared with standard 111In-WBC planar scintigraphy and SPECT, dual-isotope CZT imaging yielded superior image quality, improved reader confidence, and improved diagnostic accuracy based on surgery or Duke Criteria during follow-up, thus demonstrating feasibility and added diagnostic value.

Hybrid imaging

It is clear that hybrid imaging (integrating two imaging modalities, mostly PET-CMR or PET-CT) is claiming a position in cardiovascular evaluations. Sometimes it is not necessary to use hybrid imaging equipment, but simple fusion of the separate images is also feasible. For example, fusion of coronary

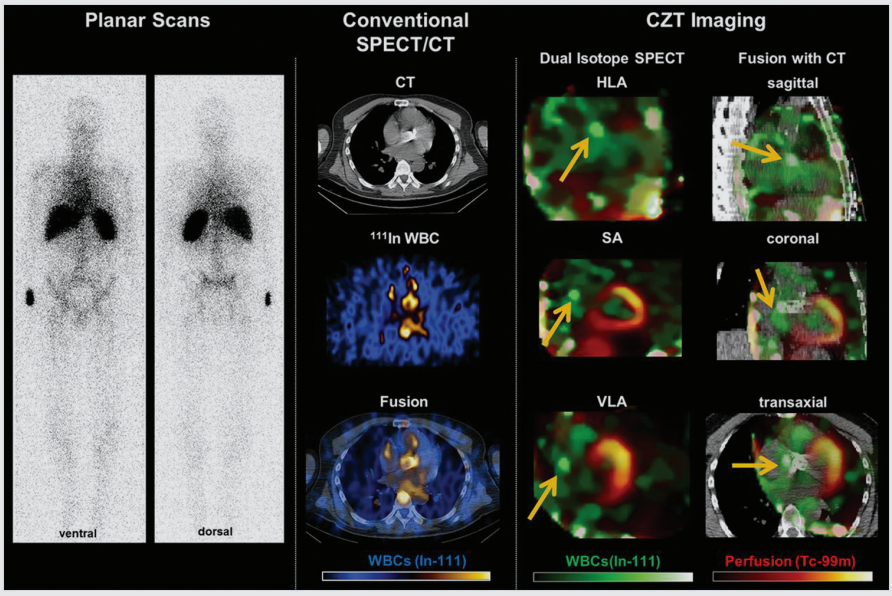

FIGURE 4. Evaluation of prosthetic valve endocarditis with nuclear imaging techniques. Representative images of a patient with suspected endocarditis of aortic valve prosthesis. From left to right, planar white blood cell scans show blood pool, with uncertainty about a valvular focus, whereas conventional SPECT/CT images suggest a potential hot spot in the region of the prosthetic valve, but with limited resolution. Dual isotope cadmium-zinc-telluride (CZT) images show reduced noise and a focal accumulation adjacent to the prosthetic valve suggesting the presence of endocarditis (arrows). During surgical aortic valve replacement, an abscess was identified under the right coronary artery ostium, matching the hot spot on the CZT scan and confirming the diagnosis of endocarditis.

HLA = horizontal long-axis; In = Indio; SA = short-axis; VLA= vertical long-axis; WBC = white blood cells.

Reproduced with permission from Caobelli *et al.*[42]

Tehnike hibridnog oslikavanja

Tehnike hibridnog oslikavanja (tehnike koje integriraju dva modaliteta oslikavanja, najčešće PET-CMR i PET-CT) počinju zauzimati sve važnije mjesto u dijagnostici KVB-a. Pokatkad nije potrebno koristiti se naprednom opremom za hibridno snimanje, već se jednostavnim spajanjem odvojenih snimaka može zadovoljiti dijagnostička svrha. Kao primjer navodi se spoj koronarne CTA i SPECT snimke, a *Nakahara i sur.*[43] dodatno su unaprijedili uobičajene tehnike spajanja i oslikavanja. Omogućili su spajanje SPECT *bull's eye* prikaza s prikazom koronarnih arterija. Usto, *Maffessanti i sur.* razvili su program za spajanje trodimenzijskih prikaza koronarne anatomije dobivenih putem CTA-a s mjerenjima longitudinalne kardijalne deformacije LV-a dobivenih trodimenzijskom ehokardiografijom, omogućujući tako vizualizaciju koronarnih stenoza zajedno s prikazom pratećih funkcijskih ispada (u obliku smanjene deformacije LV-a) (**Slika 5**).[44]

U domeni molekularnog oslikavanja hibridne se tehnike sve više primjenjuju za razumijevanje patofiziologije KBS-a, s posebnim naglaskom na prikaz nestabilnih plakova. *Bala i sur.* rabili su PET-CT i (VCAM)-1 označene s fluorom-18 (anti-VCAM-1 nanotijelo, cAbVCAM-1–5) za detekciju upale u arterijskim plakovima na modelu ateroskleroze u miša.[45] U dijelovima aorte s većim stupnjem ateroskleroze, s pomoću PET-CT-a i histologije, detektiran je povećani unos izotopa. Ovo je jedna od mnogih studija koje istražuju razlike između nestabilnih i stabilnih aterosklerotskih plakova. Potrebno je više životinjskih modela fokusiranih na koronarne arterije te s vremenom i niz translacijskih studija na ispitanicima te na kraju studija s praćenjem ishoda.

Pozitronska emisijska tomografija kombinirana s kardiovaskularnom magnetnom rezonancijom (PET-CMR) također se

CTA and SPECT images has been performed previously, but the image fusion and presentation has been further developed by Nakahara *et al.*:[43] with this approach it is possible to present the SPECT bull's eye plot overlaid with the coronary arteries. In addition, Maffessanti and colleagues developed fusion software that combines three-dimensional displays of the coronary anatomy obtained with coronary CTA with colour maps of LV longitudinal strain obtained with three-dimensional echocardiography, permitting visualization of the coronary stenosis along with its functional consequences (reduced LV strain) (**Figure 5**).[44]

Specifically in the field of molecular imaging, hybrid imaging becomes increasingly used to understand pathophysiology in CAD, with specific focus on vulnerable plaque imaging. Bala and colleagues used PET-CT and fluorine-18 labelled vascular cell adhesion molecule (VCAM)-1 (anti-VCAM-1 nanobody, cAbVCAM-1–5), to demonstrate the feasibility in a murine-atherosclerotic model to detect aortic plaque inflammation.[45] Increased tracer uptake was detected in aortic regions with increased atherosclerosis both on PET-CT and on histology. This is just one of the many studies ongoing to obtain further insight in differences between vulnerable and stable atherosclerotic plaques. In the short-term, more animal studies are needed focusing on the coronary arteries, then translational studies to patients, and finally outcome studies.

Positron emission tomography-cardiovascular magnetic resonance imaging (PET-CMR) is another modality that is increasingly used, and already some clinical studies in patients have been reported this year. Bulluck and coworkers used PET-CMR and FDG in 21 patients with ST-segment–elevation myocardial infarction (STEMI) 5 days after infarction, and follow-up scans were obtained 1 year later in 12 patients.[46]

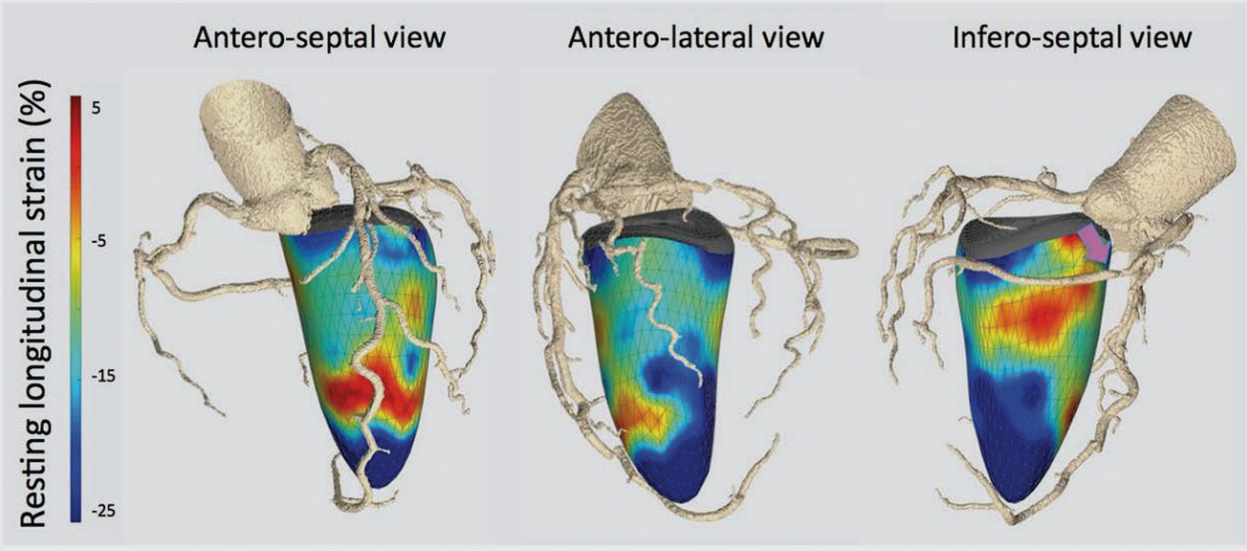

FIGURE 5. Fusion imaging of coronary CTA and three-dimensional speckle tracking echocardiography to assess the functional consequences of coronary stenosis. Combined three-dimensional displays of speckle tracking and CTA, in a patient with >70% stenosis in the mid right coronary artery (purple arrow). The infero-septal view shows reduced LV longitudinal strain in the basal segment (colour-coded in orange shades) subtended by this coronary artery. In addition, note a diffuse calcified plaque in the proximal left anterior descending coronary artery present causing reduced LV longitudinal strain in the mid-apical segments of the antero-septal view.

Reproduced with permission from Maffessanti *et al.*[44]
This Figure has been reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

sve češće uporabljuje te je u već nekoliko ovogodišnjih studija rabila kao glavna metoda oslikavanja. *Bulluck i sur.* snimili su ukupno 21 bolesnika s pomoć PET-CMR-a i FDG-a scintigrafije pet dana nakon akutnog infarkta miokarda s ST elevacijom, a godinu dana poslije ponovno je snimljeno 12 bolesnika.[46] Kardiovaskularna magnetna rezonancija rabljena je za procjenu veličine infarkta miokarda (pritom se koristeći CMR-om uz naknadno poboljšanje kontrasta) te procjene područja miokarda pod rizikom (koristeći se T2-mapiranjem). Ubrzo nakon infarkta, područje sa smanjenim unosom FDG-a bilo je znatno veće površine nego područje infarkta prikazano pomoću CMR tehnike naknadno pojačanog kontrasta (37,2 ± 11,6% vs. 22,3 ± 11,7%; P < 0,001), no slično veličini područja miokarda pod rizikom prikazanog s pomoću T2 mapiranja CMR-om (37,2 ± 11,6% *vs.* 36,3 ± 12,2%; *P* = NS). Na snimkama nakon godine dana praćenja područje smanjena unosa FDG-a bilo je mnogo manje nego na inicijalnim snimkama (19,5 [6,3 – 31,8 %] *vs.* 44,0 [21,3–55,3%]; *P* = 0,002) te je veličinom korelirao s područjem infarkta prikazanom s pomoću CMR-a s naknadnim poboljšanjem kontrasta. Spomenuta saznanja korak su naprijed u razumijevanju procesa stvaranja ožiljnoga tkiva nakon akutnog infarkta miokarda.

Rischpler i sur.[47] koristili su drugi pristup u primjeni PET-CMR tehnologije, poglavito kako bi istražili su vrijednost unosa FDG-a u području infarkta (području prikazanom uz pomoć CMR s naknadnim poboljšanjem kontrasta) kao biosignala pri procjeni funkcionalnog oporavka miokarda. PET-CMR snimke rađene su na uzorku od 49 ispitanika pet dana nakon infarkta, dok su CMR snimke (za procjenu funkcijskog oporavka) napravljene 6-9 mjeseci kasnije. Usporedbe PET-CMR snimaka s cirkulirajućim leukocitima i monocitima korištene za kvantificiranje staničnog imunološkog odgovora. Unos fluordeoksiglukoze u području infarkta nadmašio je površinu definiranu naknadnim pojačanjem gadolinija (33,2 ± 16,2 % miokarda lijeve klijetke prema 20,4 ± 10,6%; P < 0.0001), no korelirao je u području miokarda pod rizikom (r = 0,87; P < 0,0001), što je indikator uloge ranog unosa FDG-a kao biosignala ozljede miokarda. Periferni broj *CD14high/CD16+* monocita korelira s veličinom područja infarkta te veličinom područja unosa FDG-a, što podupire hipotezu da unos FDG-a reflektira ozljedu miokarda. Nadalje, unos FDG-a u oštećenom miokardu najveći je u području s transmuralnim ožiljkom te je recipročno vezan za funkcijski oporavak. Sve navedene činjenice mogle bi promijeniti pogled na postinfarktni unos FDG-a, pokazujući da unos odražava ozljedu miokarda, a ne vijabilnost.

Cardiovascular magnetic resonance imaging was used to assess the infarct size (using late contrast-enhanced CMR) and the area at risk (using T2-mapping). Immediately after infarction, the area of reduced FDG uptake was significantly larger than the infarct size on late contrast-enhanced CMR (37.2 ± 11.6% vs. 22.3 ± 11.7%; P < 0.001), but was similar to the area at risk on CMR T2-mapping (37.2 ± 11.6% vs. 36.3 ± 12.2%; *P* = NS). On the 1-year follow-up scans, the area of reduced FDG uptake was significantly smaller as compared with the acute scans (19.5 [6.3–31.8%] vs. 44.0 [21.3–55.3%]; *P* = 0.002) and correlated closely with the area of infarction on late contrast-enhanced CMR. These findings contribute to our understanding of scar formation over time after acute myocardial infarction.

Rischpler *et al.*[47] used PET-CMR from a different perspective, namely to explore the value of FDG uptake in the infarct area (defined by late contrast-enhanced CMR) as a biosignal to predict functional recovery. In 49 patients, PET-CMR was performed within 5 days after infarction, and follow-up CMR (to assess functional recovery) was performed 6–9 months later. Comparison of PET-CMR with circulating leucocytes and monocytes was performed to measure cellular innate immune response. Fluorodeoxyglucose uptake in the infarcted area exceeded late gadolinium enhancement extent (33.2 ± 16.2% LV myocardium vs. 20.4 ± 10.6%, P < 0.0001) and corresponded to the area at risk (r = 0.87, P < 0.0001), indicating that FDG uptake early after infarction may be a biosignal of myocardial injury. The peripheral blood count of CD14high/CD16+ monocytes correlated with the infarction size and FDG uptake, supporting the hypothesis that FDG uptake reflects injury. Moreover, the FDG uptake in the infarcted myocardium was highest in areas with transmural scar, and was related inversely with functional recovery. All these findings may change our view on FDG uptake early after infarction, namely that it represents myocardial injury rather than viability.

CONFLICT OF INTEREST: The Department of Cardiology of the Leiden University Medical Center received research grants from Biotronik, Boston Scientific, Edwards Lifesciences and Medtronic. Victoria Delgado received speaker fees from Abbott Vascular, outside the submitted work. Oliver Gaemperli reports personal fees from Servier, non-financial support from Amgen, outside the submitted work. Massimo Lombardi has nothing to disclose. Jeroen Bax has nothing to disclose.

LITERATURE

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37:3232-3245. https://doi.org/10.1093/eurheartj/ehw334
2. Papolos A, Narula J, Bavishi C, Chaudhry FA, Sengupta PP. U.S. hospital use of echocardiography: insights from the nationwide inpatient sample. J Am Coll Cardiol. 2016;67:502-511. https://doi.org/10.1016/j.jacc.2015.10.090
3. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Cardiovasc Imaging. 2015;16:119-146. https://doi.org/10.1093/ehjci/jeu210
4. Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. Eur Heart J. 2016;37:2097-2104. https://doi.org/10.1093/eurheartj/ehw164
5. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. Eur Heart J. 2016;37:1244-1251. https://doi.org/10.1093/eurheartj/ehv745
6. Aras MA, Teerlink JR. Lung ultrasound: a 'B-line' to the prediction of decompensated heart failure. Eur Heart J. 2016;37:1252-1254. https://doi.org/10.1093/eurheartj/ehw094
7. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J. 2016;37:1196-1207. https://doi.org/10.1093/eurheartj/ehv529
8. Kuznetsova T, Cauwenberghs N, Knez J, Yang WY, Herbots L, D'hooge J, et al. Additive prognostic value of left ventricular systolic dysfunction in a population-based cohort. Circ Cardiovasc Imaging. 2016;9:e004661. https://doi.org/10.1161/CIRCIMAGING.116.004661
9. Sengel øv M, Jørgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen T, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging. 2015;8:1351-1359. https://doi.org/10.1016/j.jcmg.2015.07.013
10. Kamperidis V, Marsan NA, Delgado V, Bax JJ. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. Eur Heart J. 2016;37:811-816. https://doi.org/10.1093/eurheartj/ehv680

11. Ben Zekry S, Freeman J, Jajoo A, He J, Little SH, Lawrie GM, et al. Patient-specific quantitation of mitral valve strain by computer analysis of threedimensional echocardiography: a Pilot Study. Circ Cardiovasc Imaging2016;9:e003254. https://doi.org/10.1161/CIRCIMAGING.115.003254
12. Thaden JJ, Nkomo VT, Suri RM, Maleszewski JJ, Soderberg DJ, Clavel MA, et al. Sex-related differences in calcific aortic stenosis: correlating clinical and echocardiographic characteristics and computed tomography aortic valve calcium score to excised aortic valve weight. Eur Heart J. 2016;37:693-699. https://doi.org/10.1093/eurheartj/ehv560
13. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol. 2016 January19;67:139-147. https://doi.org/10.1016/j.jacc.2015.10.058
14. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45. https://doi.org/10.1161/01.cir.0000437738.63853.7a
15. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College Of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66:1657-1668. https://doi.org/10.1016/j.jacc.2015.07.066
16. Mark DB, Anstrom KJ, Sheng S, Baloch KN, Daniels MR, Hoffmann U, et al. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. Circulation. 2016;133:1995-2007. https://doi.org/10.1161/CIRCULATIONAHA.115.020259
17. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J. 2016;37:1232-1243. https://doi.org/10.1093/eurheartj/ehv700
18. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ, et al. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. J Am Coll Cardiol. 2016;67:16-26. https://doi.org/10.1016/j.jacc.2015.10.045
19. Gaur S, Øvrehus KA, Dey D, Leipsic J, Bøtker HE, Jensen JM, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. Eur Heart J. 2016;37:1220-1227. https://doi.org/10.1093/eurheartj/ehv690
20. Douglas PS, De BB, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. 1-year outcomes of FFRct-guided care in patients with suspected coronary disease: the PLATFORM study. J Am Coll Cardiol. 2016;68:435-445. https://doi.org/10.1016/j.jacc.2016.05.057
21. Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37:2263-2271. https://doi.org/10.1093/eurheartj/ehv526
22. Gündüz S, Ozkan M, Kalcik M, Gursoy OM, Astarcioglu MA, Karakoyun S, et al. Sixty-four-section cardiac computed tomography in mechanical prosthetic heart valve dysfunction: thrombus or pannus. Circ Cardiovasc Imaging. 2015;8:e003246. https://doi.org/10.1161/CIRCIMAGING.115.003246
23. Suh YJ, Hong GR, Han K, Im DJ, Chang S, Hong YJ, et al. Assessment of mitral paravalvular leakage after mitral valve replacement using cardiac computed tomography: comparison with surgical findings. Circ Cardiovasc Imaging. 2016;9:e004153. https://doi.org/10.1161/CIRCIMAGING.115.004153
24. Girdauskas E, Rouman M, Disha K, Fey B, Dubslaff G, Theis B, et al. Functional aortic root parameters and expression of aortopathy in bicuspid versus tricuspid aortic valve stenosis. J Am Coll Cardiol. 2016;67:1786-1796. https://doi.org/10.1016/j.jacc.2016.02.015
25. Garcia J, Barker AJ, Murphy I, Jarvis K, Schnell S, Collins JD, et al. Four-dimensional flow magnetic resonance imaging-based characterization of aortic morphometry and haemodynamics: impact of age, aortic diameter, and valve morphology. Eur Heart J Cardiovasc Imaging. 2016;17:877-884. https://doi.org/10.1093/ehjci/jev228
26. von Knobelsdorff-Brenkenhoff F, Karunaharamoorthy A, Trauzeddel RF, Barker AJ, Blaszczyk E, Markl M, et al. Evaluation of aortic blood flow and wall shear stress in aortic stenosis and its association with left ventricular remodeling. Circ Cardiovasc Imaging. 2016;9:e004038. https://doi.org/10.1161/CIRCIMAGING.115.004038
27. Turkbey EB, Nacif MS, Guo M, McClelland RL, Teixeira PB, Bild DE, et al. Prevalence and correlates of myocardial scar in a US cohort. JAMA. 2015;314:1945-1954. https://doi.org/10.1001/jama.2015.14849
28. Chin CW, Messika-Zeitoun D, Shah AS, Lefevre G, Bailleul S, Yeung EN, et al. A clinical risk score of myocardial fibrosis predicts adverse outcomes in aortic stenosis. Eur Heart J. 2016;37:713-723. https://doi.org/10.1093/eurheartj/ehv525
29. Hinojar R, Varma N, Child N, Goodman B, Jabbour A, Yu CY, et al. T1 Mapping in Discrimination of Hypertrophic Phenotypes: Hypertensive Heart Disease and Hypertrophic Cardiomyopathy: Findings From the International T1 Multicenter Cardiovascular Magnetic Resonance Study. Circ Cardiovasc Imaging. 2015;8:e003285. https://doi.org/10.1161/CIRCIMAGING.115.003285
30. Mordi I, Carrick D, Bezerra H, Tzemos NT. T1 and T2 mapping for early diagnosis of dilated non-ischaemic cardiomyopathy in middle-aged patients and differentiation from normal physiological adaptation. Eur Heart J Cardiovasc Imaging. 2016;17:797-803. https://doi.org/10.1093/ehjci/jev216
31. Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, et al. Extracellular volume fraction for characterization of patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2016;67:1815-1825. https://doi.org/10.1016/j.jacc.2016.02.018
32. Lurz P, Luecke C, Eitel I, Fohrenbach F, Frank C, Grothoff M, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-Trial. J Am Coll Cardiol. 2016;67:1800-1811. https://doi.org/10.1016/j.jacc.2016.02.013
33. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, et al. T1-Mapping and outcome in nonischemic cardiomyopathy: all-cause mortality and heart failure. JACC Cardiovasc Imaging. 2016;9:40-50. https://doi.org/10.1016/j.jcmg.2015.12.001
34. Lurz P, Serpytis R, Blazek S, Seeburger J, Mangner N, Noack T, et al. Assessment of acute changes in ventricular volumes, function, and strain after interventional edge-to-edge repair of mitral regurgitation using cardiac magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2015;16:1399-1404. https://doi.org/10.1093/ehjci/jev115
35. Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, et al. Integrated myocardial perfusion imaging diagnostics improve detection of functionally significant coronary artery stenosis by 13N-ammonia positron emission tomography. Circ Cardiovasc Imaging. 2016;9:e004768. https://doi.org/10.1161/CIRCIMAGING.116.004768
36. Greenwood JP, Ripley DP, Berry C, McCann GP, Plein S, Bucciarelli-Ducci C, et al; CE-MARC 2 Investigators. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: The CE-MARC 2 randomized clinical trial. JAMA. 2016;316:1051-1060. https://doi.org/10.1001/jama.2016.12680
37. Clements IP, Kelkar AA, Garcia EV, Butler J, Chen J, Folks R, et al. Prognostic significance of (123)I-mIBG SPECT myocardial imaging in heart failure: differences between patients with ischaemic and non-ischaemic heart failure. Eur Heart J Cardiovasc Imaging. 2016;17:384-390. https://doi.org/10.1093/ehjci/jev295
38. Hachamovitch R, Nutter B, Menon V, Cerqueira MD. Predicting risk versus predicting potential survival benefit using 123I-mIBG imaging in patients with systolic dysfunction eligible for implantable cardiac defibrillator implantation: analysis of data from the prospective ADMIRE-HF study. Circ Cardiovasc Imaging. 2015;8:e003110. https://doi.org/10.1161/CIRCIMAGING.114.003110
39. Mc Ardle B, Shukla T, Nichol G, deKemp RA, Bernick J, Guo A, et al; PARR-2 Investigators. Long-term follow-up of outcomes with F-18-fluorodeoxyglucose positron emission tomography imagingassisted management of patients with severe left ventricular dysfunction secondary to coronary disease. Circ Cardiovasc Imaging. 2016;9:e004331. https://doi.org/10.1161/CIRCIMAGING.115.004331
40. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al; ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55:2212-2221. https://doi.org/10.1016/j.jacc.2010.01.014

41. Christensen TE, Bang LE, Holmvang L, Skovgaard DC, Oturai DB, Soholm H, et al. (123)IMIBG scintigraphy in the subacute state of Takotsubo cardiomyopathy. JACC Cardiovasc Imaging. 2016;9:982-990. https://doi.org/10.1016/j.jcmg.2016.01.028
42. Caobelli F, Wollenweber T, Bavendiek U, Kuhn C, Schutze C, Geworski L, et al. Simultaneous dual-isotope solid-state detector SPECT for improved tracking of white blood cells in suspected endocarditis. Eur Heart J. 2017;38:436-443. https://doi.org/10.1093/eurheartj/ehw231
43. Nakahara T, Iwabuchi Y, Murakami K. Diagnostic performance of 3D bull's eye display of SPECT and coronary CTA fusion. JACC Cardiovasc Imaging. 2016;9:703-711. https://doi.org/10.1016/j.jcmg.2015.09.024
44. Maffessanti F, Patel AR, Patel MB, Walter JJ, Mediratta A, Medvedofsky D, et al. Non-invasive assessment of the haemodynamic significance of coronary stenosis using fusion of cardiac computed tomography and 3D echocardiography. Eur Heart J Cardiovasc Imaging. 2017 Jun 1;18(6):670-680. https://doi.org/10.1093/ehjci/jew147
45. Bala G, Blykers A, Xavier C, Descamps B, Broisat A, Ghezzi C, et al. Targeting of vascular cell adhesion molecule-1 by 18F-labelled nanobodies for PET/CT imaging of inflamed atherosclerotic plaques. Eur Heart J Cardiovasc Imaging. 2016;17:1001-1008. https://doi.org/10.1093/ehjci/jev346
46. Bulluck H, White SK, Frohlich GM, Casson SG, O'meara C, Newton A, et al. Quantifying the area at risk in reperfused ST-segment-elevation myocardial infarction patients using hybrid cardiac positron emission tomography-magnetic resonance imaging. Circ Cardiovasc Imaging. 2016;9:e003900. https://doi.org/10.1161/CIRCIMAGING.115.003900
47. Rischpler C, Dirschinger RJ, Nekolla SG, Kossmann H, Nicolosi S, Hanus F, et al. Prospective evaluation of 18F-Fluorodeoxyglucose uptake in postischemic myocardium by simultaneous positron emission tomography/magnetic resonance imaging as a prognostic marker of functional outcome. Circ Cardiovasc Imaging. 2016;9:e004316. https://doi.org/10.1161/CIRCIMAGING.115.004316