Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

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MB-LATER skor kao koristan predictor ponovne pojave aritmija posle radiofrekventne kateter ablacija atrijalne fibrilacije - klinička primena

MB-LATER score as a useful tool for prediction of arrhythmia recurrence after radiofrequency catheter ablation of atrial fibrillation – clinical application

„Prave“ bifurkacije koronarnih arterija u akutnom koronarnom sindromu su povezane sa dužinom trajanja perkutane koronarne intervencije, ali ne utiču na klinički ishod

„True“ coronary artery bifurcations in acute coronary syndrome are associated with longer PCI, but do not influence clinical outcome

The year in cardiology: cardiovascular prevention

The year in cardiology: imaging

Volumen 38 Broj 4
2019. godina

U ovom broju se nalazi radovi nagrađenih autora na XXII Kongresu Udruženja kardiologa Srbije, Zlatibor 17-20 oktobar, 2019. godine.

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MB-LATER score as a useful tool for prediction of arrhythmia recurrence after radiofrequency catheter ablation of atrial fibrillation – clinical application

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Abstract Atrial fibrillation (AF) is most frequent sustained cardiac arrhythmia in general population. It is well established that crucial task for management of these patients is prevention of AF-related complications. One of the most important management strategies represents catheter ablation in order to reduce AF burden, to achieve symptomatic and functional improvement, and in some patient (e.g. heart failure) to reduce overall mortality. Several prognostic scores were developed for AF recurrence prediction after catheter ablation of AF. Role of these scores might be better optimization of long-term follow-up and deciding on discontinuation of oral anticoagulant therapy and stopping of antiarrhythmic drugs after the procedure, thus identification of patients at risk for arrhythmia recurrence may be extremely important. Numerous clinical factors are associated with arrhythmia recurrence and some of those are used for developing rhythm-outcome specific scores. MB-LATER score was retrospectively derived for prediction of arrhythmia recurrence after catheter ablation of AF, and in this article, we are going to discuss its utilization in clinical practice.

Key words atrial fibrillation, catheter ablation, prognostic scores, arrhythmia recurrence

Introduction

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in general population and is associated with increased morbidity and mortality.[1] Radiofrequency catheter ablation (RFA) represents well established and effective method for invasive treatment of AF, that provides better quality of life compared to antiarrhythmic therapy.[2] Today we have more data on the importance of RFA of in AF patients with heart failure (HF), where it significantly contributes to the reduction of the risk of rehospitalization due to HF, HF progression and reduction of overall mortality.[3] Furthermore, it seems that RFA of AF might have important role in risk reduction for thromboembolic events in patients with AF shown in some observational studies, but we currently lack randomized studies powered to prove this.[4-6] Given these potential benefits, approach to invasive treatment must be balanced due to potential complication of the procedure and relatively high arrhythmia recurrence rate after RFA of AF that ranges from 20-40%.[1]

Identification of patients at risk for arrhythmia recurrence may be extremely important in terms of anticoagulant therapy and appropriate rhythm monitoring strategy after RFA. Numerous clinical factors are associated with arrhythmia recurrence after RFA of AF, most commonly older age, non-paroxysmal AF, left atrial (LA) size, gender, coronary artery disease (CAD), hypertension (HTA), diabetes mellitus (DM), metabolic syndrome (MS), chronic kidney disease (CKD), HF and early recurrence of AF (ERAF) after procedure.7 Several prognostic scores have been developed to predict individual risk of recurrence of AF after catheter ablation.[8] Some of them are rhythm-outcome specific scores like: ALARMEc, BASE-AF$_2$, APPLE, CAAP-AF, and MB-LATER.[9-14] MB-LATER score is derived by our group and validated in several external cohorts.[15] We found that our score has significant clinical implications, since it was initially developed to predict very late recurrences of AF - VLRAF (more than 12 months post AF ablation), but also it has been externally validated and showed a significant but modest predictive ability for late recurrence of AF (more than 3 months post-AF ablation).[12,15] Therefore MB-LATER score could be used for adequate discussion of the expected results of RFA before procedure with our patients as well as to develop an adequate follow-up strategy for these patients after the procedure.

The purpose of this paper is to summarize available tools for risk stratification for arrhythmia recurrence after RFA

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of AF. Here we discuss the clinical implementation of MB-LATER score in two cases from our practice and so far, published data on other rhythm-outcome specific scores for the purpose of more comprehensive understanding and adequate managing of these patients.

Case presentation

CASE 1. A 68 year-old Caucasian male with history of HTA was evaluated at our department for highly symptomatic palpitations. First episode of arrhythmia was registered three years before admission to our department, at that time he was examined at emergency room and 12-lead ECG showed AF with fast ventricular response. Rhythm control was achieved by administration of propafenone i.v. (1.5 mg/kg). Propafenone was advised for long-term rhythm control, and also dabigatran (150 mg, bid) was introduced for stroke prevention (CHA_2DS_2-VASc = 2). Further, coronary angiography was performed and revealed no significant coronary artery disease. Propafenone was transiently effective, and in the past 12 months before the procedure he had 4 episodes of AF, longest duration up to 12 hours.

Physical examination at admission revealed normal findings. Echocardiography showed no structural heart disease; LA diameter was 45 mm and ejection fraction (EF) was preserved. Chest X-ray was unremarkable. Baseline laboratory investigations including serum electrolytes, complete blood count, liver and renal function tests were normal, except dyslipidaemia. There was a history of smoking up to 20 cigarettes per day and no history of alcohol or drug abuse. Family history revealed that his brother suffered from stroke of unknown cause.

Given the previous history of the disease, resistance to medical therapy and highly symptomatic episodes of AF catheter ablation was performed. Propafenone was discontinued ≥5 half-lives before the procedure. Dabigatran was omitted 24 hours before the procedure. RF catheter ablation was performed under conscious sedation. The quadripolar catheter was inserted into the distal coronary sinus as electroanatomical landmark. Via the right femoral vein three sheets were introduced, transseptal puncture (TSP) was carried out with a long needle and sheath (BRK1/BRK1-XS, Swartz SL0/SL1, St Jude Medical, MN, USA) and navigation of the ablation catheter was performed with a long steerable sheath (8.5 Fr Agilis NXT, St Jude Medical, MN, USA). Pulmonary vein (PV) activity was assessed with a circular 20-polar catheter inserted through the long non-steerable sheath. Anatomical LA map was created, and fusion with the CT scan was performed (Ensite Precision, St Jude Medical). Ablation was performed using RF energy (TactiCath Quartz catheter, 7 Fr, St Jude Medical, MN, USA). Strategy of ablation was ipsilateral circumferential antral pulmonary vein isolation (PVI, Figure 1A). RF application were delivered 1–2 cm outside from the ipsilateral PV ostia (30W, 43C, flow rate 17 ml/min). Electrical PVI was achieved as endpoint of this procedure, and patient was observed in the lab for the 30 min after the last RF application (standard protocol in our electrophysiology lab as previously published).[12] Patient was discharged two days later, without any post-procedural complications during hospital stay.

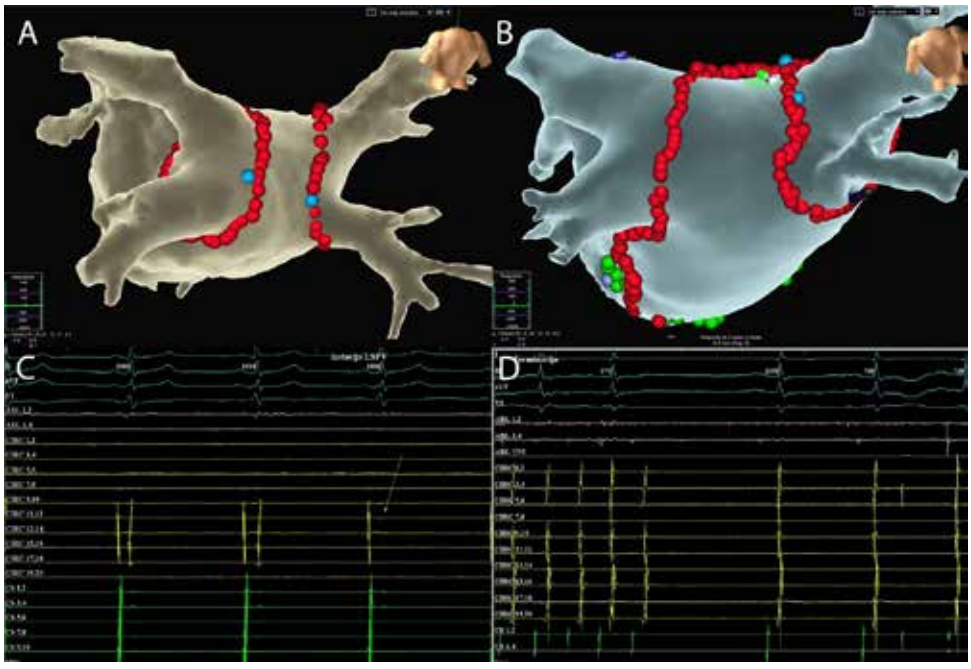

Figure 1. Panel A displays PVI ablation lesion set as ablation strategy in patient presented as Case 1 (PV isolation circumferential lines, encircling the ipsilateral PV pairs). Panel B displays ablation lesion set as ablation strategy in patient presented as Case 2 (PVI + additional substrate ablation). Panels A and B showing the posterolateral and posterior view of the LA model fused with computed tomography image. Radiofrequency lesions were tagged as the 4-mm diameter red balls. On panel B additional substrate ablation is presented (roof line connects the most cranial points of the left-sided and right-sided PVI circles; mitral line extends from the lateral mitral annulus to anteroinferior segment of left PVI, adjacent to left inferior PV ostium). Panel C presents the intracardial signals and a moment of left sided PVI (yellow arrow) in patient presented as Case 1. Panel D points the moment of AF termination during procedure in patient presented in Case 2.

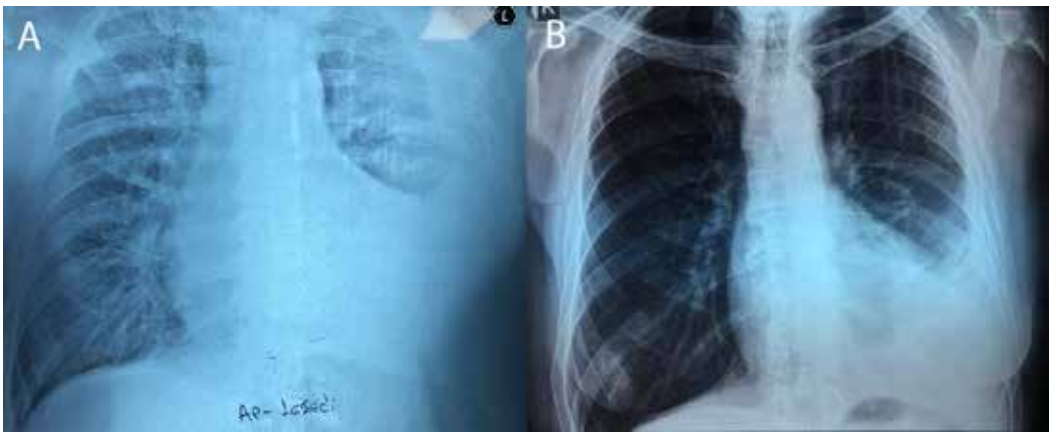

Figure 2. Chest X-ray of patient presented as Case 2. A – on admission before therapy; B – at discharge after correction of medical therapy and RF ablation of atrial fibrillation

MB-LATER score for this patient was 1 (for male gender). During the first three months after RFA therapy with propafenone and dabigatran was continued and thereafter stopped. Patient had scheduled follow-up visits consisting of physical examination, 12-lead ECG and 24-hour Holter-recording at discharge, 1, 3 and 6 months after the procedure, and every 6 months thereafter. During two years of follow-up no arrhythmia recurrence was registered, patient was symptom and drug free during that time, which could be expected based on the predictive ability of MB-LATER score.

CASE 2. A 71-year-old woman with a history of paroxysmal AF was admitted at our department due to first episode of congestive HF. She complained of reduced exercise tolerance over the past two months. ECG at admission showed AF with ventricular response of 120 bpm and presence of left bundle brunch block (LBBB) as new finding. Baseline laboratory findings were normal except slightly elevated liver and renal parameters. Thyroid hormones were in reference range.
The physical examination revealed a continuous arrhythmia, silent heart sounds, bilateral pretibial edema. The X-ray showed enlargement of the heart with a reduced transparency of lung parenchyma and left sided pleural effusion, **Figure 2**. Echocardiogram revealed LV dilatation (EDD=59 mm, ESD=44 mm) with global hypokinesia (EF=35%) and markedly enlarged LA=51 mm. Immediately intensive parenteral therapy was started after admission including digitalis, beta blocker, amiodarone and diuretics. Likewise, low molecular weight heparin was induced instead of warfarin and anti-Xa level was monitored. After initial clinical improvement CAD was excluded after coronary angiography. Despite comprehensive therapy, patient remains symptomatic and decision was made to refer for RF catheter ablation of persistent AF during same hospitalization.
Catheter ablation was performed in the same fashion as previously described except that in this patient, after the isolation of the PV, additional ablation of the substrate was performed. Endocardial LA roof and mitral isthmus ablation was performed using 30 W, with the applications lasting 60–120 s in the same location. Endpoint that involved achieving linear conduction block on both lines and PV isolation was reached (Figure 1B – lesion set during RF ablation). Patient was discharged on amiodarone as adjuvant therapy.
One month after the procedure ERAF was registered on scheduled Holter ECG monitoring (persistent AF). We performed electrical cardioversion due to ERAF during "blanking" period. Considering clinical characteristic of this patient we realize that this patient had the value of MB-LATER score of 4 (persistent AF, LBBB, LA>47 mm, ERAF), which does not necessarily mean failure of interventional treatment but in these situations, we are committed to discuss success rate and potential risk with the patient, and also to closely monitor these patients. Three months after the procedure patient reported significant symptomatic and functional capacity improvement. Echocardiogram confirmed reduction of LV dimensions (EDD=56 mm, ESD=39 mm) and increase of EF=50%. At the end of the first year of follow-up amiodarone induced hyperthyroidism was established, so amiodarone was suspended. Two months later she suffered from late recurrence of AF, which is why the procedure was repeated. In the redo procedure reconnection of left PVs was found, and PVs were reisolated. During additional two years of follow-up there were no registered episodes of AF.

Discussion

In this paper, we have presented two cases from our clinical practice that reflect the applicability of the MB-LATER score in everyday clinical work. Our experience and available data indicate that the application of such scores could be important in the treatment of these patients.
PVI represents a cornerstone of RFA for AF. The main limitations of procedure are its invasive nature with potential serious complications and the achievement of durable PVI lesion. PVI alone may be insufficient for successful rhythm control in approximately a third of patients who underwent CA of AF. As a result, relatively high rate of recurrent atrial arrhythmias post-CA is registered and repeat CA procedures are often necessary to achieve optimal treatment success.[1,16] The reliable application of prediction models of post-ablation AF recurrence might improve the pre-procedural selection of patients which are the most suitable candidates for CA and planning of the optimal rhythm monitoring strategy

Table 1. The score components included in prediction model

	HF*	HTA	AGE	DM	CVA	CAD	Enlarged LA	AF type/ history	ERAF	SEX	COPD/ Smoking	CKD	Metabolic sy/ BMI	AADs
Rhythm specific scores														
BASE-AF$_2$							✓	✓	✓		✓		✓	
ALARMc	✓						✓	✓				✓	✓	
APPLE	✓		✓				✓	✓				✓		
CAAP-AF			✓			✓	✓	✓		✓				✓
MB-LATER	✓						✓	✓	✓	✓				

HF, heart failure; HTA, hypertension; DM, diabetes mellitus; CVA, cerebrovascular accident; CAD, coronary artery disease; LBBB, left bundle branch block; LA, left atrium; AF, atrial fibrillation; ERAF, early recurrence of atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; BMI, body mass index; AAD, antiarrhythmic drug;

* HF included cardiomyopathy, congestive HF, reduced left ventricular ejection fraction and LBBB.

and drug therapy during post-CA follow-up.[16] These models should not represent limiting factor for the treatment of these patients, but should indicate what to expect from the intervention and how to monitor and manage these patients during follow-up after RF ablation.

To our knowledge, so far five rhythm specific scores are identified (ALARMEc, BASE-AF$_2$, APPLE, CAAP-AF, and MB-LATER score). Each of these scores encompasses components which are significantly associated with increased risk of arrhythmia recurrence after RF ablation of AF (Table 1).

The ALARMEc score (NPAF, normalized LA area >10.25, eGFR <68 ml/min, metabolic syndrome and cardiomyopathy) had a good predictive ability of AF recurrence during a 2-year follow-up after redo procedure (AUC: 0.657)[17]. Original score included a nonstandard definition of NPAF, renal failure, metabolic syndrome and LA enlargement, and was applied to the patients undergoing the first RF ablation. Further studies added presence of cardiomyopathy to this score, and externally validated the score.[18] All four studies found that arrhythmia recurrence rate is increased with higher ALARMc score. The main remark was related to the normalized LA area cut-off.[18-21]

The BASE-AF2 score was derived to predict recurrences in AF patients after cryoballoon ablation. A BASE-AF$_2$ score ≥3 points was significantly associated with AF recurrences (AUC: 0.94). Variables included in the score were: BMI > 28 kg/m^2, LA diameter >40 mm, current smoking, early AF recurrence post-CA, duration of AF history of >6 years, and non-paroxysmal type of AF. One of the objections is the use of ERAF as a score component, bearing in mind that ERAF is post festum phenomenon, and therefore cannot be used for baseline assessment.[9]

The APPLE score includes age ≥ 65 years, persistent AF, impaired eGFR (<60 mL/min/1.73 m^2), LA diameter ≥ 43 mm, EF < 50%. This score was derived and validated for first (AUC: 0.634) end repeated procedure (AUC: 0.557).[10,14] It has been shown that the score not only predicts arrhythmia recurrence but also can provide additional information about the presence of low-voltage areas in the LA, as a valuable marker of negative electrophysiological remodeling as substrate for AF initiation and perpetuation.[22] APPLE score has been validated in several external cohorts showing similar results. In one external validation APPLE score was compared with the MB-LATER score, and both scores showed good predictive ability in the ROC curve analysis (AUC 0.716, $P = 0.002$ vs AUC 0.782, $P < 0.001$) for the prediction of VLRAF.12

The CAAP-AF score was developed to predict AF freedom after RF ablation of AF. CAD, LA diameter, age, presence of persistent, or long-standing persistent AF, antiarrhythmics failed and female sex were included in to this predictive model. Score was initially derived in large cohort of patient (n=1125) of which majority was referred for first RFA. The score is than internally validated (n=937), with similar results as in the derivation cohort (2-year Kaplan-Meier AF-free rates by CAAP-AF scores were as follows: 0 = 100%, 1 = 87.0%, 2 = 89.0%, 3 = 91.6%, 4 = 90.5%, 5 = 84.4%, 6 = 70.1%, 7 = 71.0%, 8 = 60.7%, 9 = 68.9%, and ≥10 = 51.3%)(11). The score has been recently evaluated in two external cohorts, and it showed a good predictive ability for LRAF.[15,23]

The MB-LATER score has been developed to predict VLRAF after CA. Male sex, bundle brunch block, LA diameter ≥47 mm, clinical type of AF (0 point for paroxysmal, 1 point for persistent, and 2 points for longstanding persistent AF), and early recurrent AF (ERAF) were included in the MB-LATER score. Each variable except clinical type of arrhythmia scores 1 point (maximum points is 6).[12] The MB-LATER score showed good predictive ability for VLRAF (AUC = 0.782, p < 0.001. MB-LATER score of ≥2 had the best predictive value for VLRAF with 75.0% sensitivity, 72.6% specificity.[12] After derivation, the score has been validated in an internal cohort of patients and compared to other scores providing better predictive accuracy for VLRAF than the other scores. The score was externally validated in four studies, and MB-LATER showed the largest net benefit compared to the other scores.[15,21,23,24] MB-LATER is the first score specifically designed for patients free of arrhythmia recurrence at 1 year after ablation. Those patients are often subjected to a less intensive clinical follow-up beyond 1-year post ablation, and some of them are at increased risk for cardiovascular events, most commonly due to discontinuation of anticoagulant therapy.

Important component of MB-LATER score is ERAF, which was found to be independent predictor for LRAF also in external validation cohorts.[15,23] Although ERAF is not suitable for baseline risk stratification due to postprocedural appearance, MB-LATER score is very suitable in routine clinical practice because of its simplicity owning to readily available variables.[12,15,16]

Besides ERAF, some of the MB-LATER score components, such as AF clinical type and LA enlargement, have been already identified as independent predictors of AF recurrence following ablation and were incorporated in other scoring models.[9,10,18,25-27] HF is also one of the most common components of these clinical scores (Table 1). This does not mean that these patients are not good candidates for RF ablation of AF, on the contrary those patients might have significant benefit from the procedure.(3) Simplicity is what each prediction model should provide with the aim to facilitate implementation in everyday practice. Some components of other scores (for example normalized LA volume) require additional preprocedural work-up (CT, appropriate software and complex mathematical model for calculation), thus limiting its applicability.[12,16]

These clinical scores have also significant role reflected in decision-making regarding the use of anticoagulant and antiarrhythmic therapy. Although recurrence of the arrhythmia carries only nonsignificant trend for increased thromboembolic risk,[28] current recommendations suggest to continue long-term oral anticoagulation therapy in all patients with CHA_2DS_2-VASc ≥2, regardless of the AF ablation outcome.[1] Interestingly, in one observational retrospective multicenter study has been observed that that all thromboembolic events following AF ablation occur in patients who experienced arrhythmia recurrence in contrast to patients who did not have arrhythmia recurrence (4% vs. 0%, $p < 0.001$).[29]

Conclusion

Despite we have interesting tools for risk stratification for AF recurrence after RF ablation, one should make final decision about procedure in agreement with patient after consideration of all potential benefits and harms of the procedure. Adequate patient selection for the procedure is of great importance considering high arrhythmia recurrence rate after ablation, significant costs, availability of medical care, long radiation exposure time and potentially serious complications that may occur during AF ablation procedure.

Since the strategy of AF ablation and follow-up management differ significantly among EP centers,[1] we need additional studies to prospectively validate and compare all these scores in independent external cohorts in order to determine their relative predictive ability for post-CA recurrence and achieve clinical utility.

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Conflict of interest: None declared.

Sažetak

MB-LATER skor kao koristan predictor ponovne pojave aritmija posle radiofrekventne kateter ablacija atrijalne fibrilacije - klinička primena

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Atrijalna fibrilacija (AF) je najčešća dugotrajna aritmija u opštoj populaciji. Dobro je poznato da je jedan od osnovnih zadataka u lečenju bolesnika sa AF prevencija komplikacija povezanih sa aritmijom. Kateterska ablacija AF predstavlja važnu strategiju u lečenju ovih bolesnika sa ciljem eliminacije aritmije, odnosno redukcije vremena provedenog u aritmiji. Nakon intervencije kod značajnog broja bolesnika se registruje unapređenje simptomatskog i funkcionalnog statusa, a u podgurpi bolesnika sa srčanom insuficijencijom dolazi i do redukcije ukupnog mortaliteta. Razvijeno je nekoliko prognostičkih skoring sistema za predikciju pojave recidiva aritmije nakon kateterske ablacije AF. Uloga ovih modela je u eventualnoj boljoj optimizaciji dugoročnog praćenja ovih bolesnika kao i odlučivanju vezanom za obustavljanje antikoagulantne i antiaritmijske terapije nakon intervencije. Brojni faktori su definisani do sada kao prediktori recidiva aritmije, a neki od njih su korišćeni za razvoj skorova specifičnih predikciju recidiva aritmije nakon kateterske ablacije. MB-LATER skor je kreiran u retrospektivnoj studiji sa ciljem predikcije recidiva aritmije nakon kateterske ablacije AF. U ovom radu ćemo prikazati njegovu primenu u kliničkoj praksi.

Ključne reči: atrijalna fibrilacija, radiofrekventna kateter ablacija, prognostički skor, recidiv aritmija

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„True“ coronary artery bifurcations in acute coronary syndrome are associated with longer PCI, but do not influence clinical outcome

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Abstract

Introduction: Percutaneous coronary interventions (PCI) in bifurcation lesions with more than 50% stenosis of both main and side branch remain challenging. These “true” bifurcation lesions (TBL) causing acute coronary syndrome (ACS) could pose an additional challenge for adequate treatment since there are no recommended strategies. We investigated the influence of the presence of TBLs as culprit lesions for ACS on the clinical outcomes after PCI.

Methods: The study was retrospective and conducted in a high-volume university PCI centre. Study included 256 consecutive patients with native coronary artery bifurcation lesions causing an ACS. Patients with ACS caused by stent thrombosis were not included in the study. All patients underwent PCI of the culprit bifurcation lesion and afterwards were treated according to the appropriate guidelines.

Results: Most of the bifurcations were located in left anterior descending 152/256 (59.3%), then in circumflex 66/256 (25.9%) and right coronary artery 38/256 (14.8%). The initial clinical presentation was STEMI in 144/256 (56.2%), then NSTEMI 59/256 (23.1%) and unstable angina in 53/256 (20.7%) patients. TBLs were present in 146/256 (57.0%) patients. TBLs were associated with longer PCI procedural time 48±24min vs. 31±28min ($p<0.05$) and greater contrast volume 177±73 vs. 149±48 ml ($p=0.01$), but not with larger myocardial infarction in terms of magnitude of troponin I release 47.35±73.73 vs 31.07±38.05 ng/ml ($p=0.164$) and LVEF 40±13 vs 42±13% ($p=0.439$), as compared to other bifurcations. The patients were followed for 405±377 days. MACCE (major adverse cardio-cerebral events: death, myocardial infarction, repeated revascularization and stroke) occurred in 55/256 (21.5%) patients. In univariate regression analysis, provisional PCI strategy was associated with fewer MACCE [OR 0.283 (95 % CI 0.089–0.898)]. However, in the multivariate regression analysis, that included recognized predictors of MACCE (diabetes, LVEF, chronic kidney disease, multivessel disease, provisional PCI strategy, use of ticagrelor, TBLs) only the presence of the multi-vessel coronary artery disease remained an independent predictor of MACCE [OR 5.147 (95 % CI 1.859–14.248)].

Conclusions: TBL in acute coronary syndrome are associated with longer PCI duration, but were not associated with larger myocardial infarction and adverse cardiovascular outcomes. The extent of the CAD at presentation is associated with future cardiovascular events.

Key words true bifurcation lesion, acute coronary syndrome, percutaneous coronary intervention

Introduction

A bifurcation lesion (BL) is an atherosclerotic lesion formed at or near the junction of two significant epicardial coronary arteries[1] ,,True'' coronary bifurcation (TBL) includes stenosis more than 50% of both main branch (MB) and side branch (SB). Medina classification is based on lesion greater than 50% in bifurcation branches, while TBL have a significant narrowing of both MB and SB[2-4]. The complex morphology of TBL is manifested in MB and SB diameters' difference, angle between the arteries and plaque characteristics (calcification, presence of the inflammatory cells and lipid content)[5]. Atherosclerosis frequently develops in areas adjacent to branching points of coronary arteries. Almost 15-20% of patients undergoing a percutaneous coronary intervention (PCI) have BL as a target lesion. PCI procedures involving TBL are complex and challenging for

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interventional cardiologists. They are frequently associated with complications such as restenosis, stent thrombosis and worse clinical outcomes.[6-8]. Data on clinical outcomes of TBLs in the acute coronary syndrome (ACS) are limited. TBLs are usually treated with provisional stenting strategy that includes MB stent implantation across the ostium of the SB. SB should be treated in a case of unfavourable angulation of SB or its significant stenosis leading to critical ischemia after MB stent implantation. These procedures carry potential high risk of residual myocardial ischemia. The clinical success of PCI depends mainly on the optimal treatment of MB, which should be the main goal of PCI in any bifurcation lesion including TBL.[9] Since there are no recommended strategies for TBL causing ACS, they could pose an additional challenge for adequate treatment. In this study we have investigated the influence of TBLs compared to other bifurcation, causing an ACS on the clinical outcomes after PCI.

Methods

This was a retrospective, observational study conducted at Department of Cardiology, University Clinical Hospital Centre Zemun, Belgrade, Serbia. A total of 256 consecutive patients with native coronary artery BL causing an ACS, admitted to our hospital between December 2016 and September 2018, were included in the study. Patients with ACS caused by stent thrombosis, previously revascularized and patients in cardiogenic shock were excluded from the study. Coronary angiograms were visually assessed for coronary lesions in two orthogonal planes by an experienced interventional cardiologist blinded to all other data. TBL were assessed by a Medina classification and based on the presence of a lesion> 50% on both MB and SB. All patients underwent PCI procedure of the BL using a technique selected according to the operator's preference, and afterwards were treated in accordance with current recommendations. The choice of a vascular approach, guiding catheters, coronary guidewires, balloons and stents was left to the interventional cardiologist who performed the intervention. Second generation drug eluting stents were implanted according to the catheterization laboratory shelf availability. Puncture site haemostasis was done manually or using a haemostatic device. Patients were followed using telephone interview or an office visit and the clinical status, occurrence of major adverse cardiovascular and cerebral events (MACCE) and use of dual antiplatelet therapy (DAPT) were recorded. The study was approved by the Institutional Ethics Committee.

Statistical analysis

Continuous data were expressed as means with standard deviations and compared between groups using unpaired and paired T-test. Categorical data were summarized by proportions and compared by using a Chi square and Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to determine patient's and procedural characteristics associated with outcomes – cardiovascular events. The multivariable regression model was done using "stepwise selection model". The stepwise selection iteratively selected the most significant variable with multivariate p-value <0.25, to start the model. At each step, another significant variable is added and after running the model, a check was performed to remove the variable with a multivariate p-value >0.10. This was repeated with the complete set of variables until no more variables could be entered and no variables could be dropped. All statistical tests were two-tailed, and p value <0.05 was considered significant. Statistical analysis was performed using PASW Statistics software version 19 (SPSS, Inc., Chicago, IL).

Results

The study included 256 consecutive patients with ACS caused by a bifurcation coronary artery lesion, of which 146 were TBL (57.0%). Characteristics of the study population are summarized in **Table 1.** Patients with TBL were more frequently male, had a higher body mass index (BMI) and more frequently underwent previous PCI. Traditional risk factors for cardiovascular disease were present in both groups at similar rates. Most of the bifurcations were in left anterior descending 152/256 (59.3%), then in circumflex 66/256 (25.9%) and right coronary artery 38/256 (14.8%), while the most common clinical presentation was ST elevation myocardial infarction in both groups (**Table 2**). TBLs were associated with longer PCI duration 48±24min vs. 31±28min (p<0.05) and contrast agent consumption 177±73 vs. 149±48 ml (p=0.01), but not with greater myocardial infarction in terms of magnitude of troponin I release 47.35±73.73 vs 31.07±38.05 ng/ml (p=0.164) and LVEF 40±13 vs 42±13% (p=0.439), as compared to other bifurcation lesions. Patients were followed for 405±377 days by either office visit or telephone contact. MACCE (Major adverse cardiocerebral events: death, myocardial infarction, repeated revascularization and stroke) were noted in 58/256

Table 1. Clinical characteristics of patients

Variable	,,True bifurcation'' n = 146	Other bifurcation n = 110	p
Age (years)	61±10	57±16	0.070
Male sex (%)	73.9	85.4	0.050
Family history of CAD (%)	46.6	49.1	0.750
Smoking (%)	59.6	60.9	0.878
Hypertension (%)	88.3	77.2	0.049
Dyslipidemia (%)	75.3	71.8	0.605
Diabetes mellitus (%)	25.3	29.1	0.605
PAD (%)	4.8	0.0	0.193
Previous IM	26.1	14.5	0.129
Previous CVI (%)	4.1	1.8	0.676
Previous PCI (%)	34.2	16.3	0.005
BMI (kg/m^2)	27±4	26±3	0.028
CKD (%)	7.5	16.3	0.170

BMI - body mass index; CVA - cerebrovascular event; CKD – chronic kidney disease IM - myocardial infarction; PAD - peripheral arterial disease; PCI - percutaneous coronary intervention

Table 2. Clinical and angiographic characteristics

Variable	,,True'' bifurcation	Other bifurcation	p
	n = 146	n = 110	
Location (%)			
LAD–D	83 (56.8)	67 (61.0)	0.645
Cx–OM	38 (26.0)	26 (23.6)	0.862
RCA PD–PL	25 (17.2)	17 (15.4)	1.000
Medina class. n (%)			
1.0.1	19 (13.1)	0 (0)	-----
0.1.1	25 (17.1)	0 (0)	-----
1.1.1	102 (69.8)	0 (0)	-----
0.0.1	0 (0)	6 (5.5)	-----
1.0.0	0 (0)	49 (44.5)	-----
0.1.0	0 (0)	55 (50)	-----
STEMI (%)	79 (54.1)	71 (64.5)	0.368
NSTEMI (%)	39 (26.7)	14 (12.7)	0.086
Unstable angina (%)	28 (19.2)	25 (22.8)	0.700

LAD – left anterior descending artery; D - diagonal artery; Cx - circumflex coronary artery; OM - obtuse marginal artery; RCA - right coronary artery; PD – posterior descending artery; PL – posterior olateral artery; STEMI - ST elevation myocardial infarction; NSTEMI – non ST elevation myocardial infarction

(22.6%) patients. Patients with TBL had a higher incidence of angina symptoms and recurrent percutaneous revascularization, but the overall incidence of MACCE was similar in the study groups (**Table 3**). In univariate regression analysis, only ,,provisional'' PCI strategy was associated with lower MACCE [OR 0.283 (95% CI 0.089–0.898)], while in the multivariate regression analysis, including recognized predictors of MACCE (diabetes, LVEF, chronic kidney disease, multivessel disease, ,,provisional'' PCI strategy, use of ticagrelor, TBLs), only presence of multivessel coronary artery disease remained an independent predictor of cardiovascular events [OR 5.147 (95 % CI 1.859–14.248)]. (**Table 4**)

Discussion

In this study, we have investigated the association of true bifurcation lesion causing an acute coronary syndrome with PCI complications and significant adverse cardiovascular events. Our study demonstrated that the presence

Table 3. Incidence of outcomes

Variable	"True" bifurcations n = 146	Other bifurcations n = 110	p
Death n (%)	11 (7.5)	8 (7.2)	1.000
Myocardial infarction n (%)	3 (2.1)	1 (0.9)	0.561
Repeated PCI n (%)	21 (14.3)	6 (5.4)	0.862
CABG n (%)	0 (0)	0 (0)	-----
CVA n (%)	5 (3.4)	2 (1.8)	1.000
Angina pectoris n (%)	32 (21.9)	12 (10.9)	0.146
MACCE n (%)	41 (28.1)	17 (15.4)	0.238

CABG- coronary artery bypass grafting; CVA – cerebrovascular event; MACCE - major adverse cardiovascular and cerebral events; PCI – percutaneous coronary intervention

of TBL responsible for ACS, has been associated with a longer duration of the PCI procedure, as well as an increased amount of contrast given during the intervention. However, the presence of TBL was not associated with a decrease in left ventricular systolic function (LVEF) and the size of the myocardial infarction measured as troponin I release compared to uncomplicated BL responsible for the development of ACS. After approximately one year follow-up period, association between the presence of TBL and the occurrence of adverse cardiovascular events was not found in by a multivariate regression analysis. On the other hand, multivessel coronary artery disease has been shown to be strongly associated with adverse cardiovascular events. [7]

The presence of TBL involving significant lesions of both MB and SB is associated with the higher occurrence of PCI complications, especially if more than one stent was implanted or complex interventional strategy was employed[4,10,11]. At the same time, the interventional treatment of a BL in ACS presents an additional challenge[12]. In our study, the presence of diabetes and decreased LVEF were not associated with the occurrence of adverse cardiovascular events. On the other hand, large registries of BL, as well as acute myocardial infarction, identified these clinical features as significant predictors of adverse clinical outcomes[11,13,14]. The potential reason for this finding could be a small sample size in our study. A favourable signal could be the univariate association

Table 4. Univariable and multivariable predictors of MACCE

	Univariable		Multivariable	
	OR [95% CI]	P value	OR [95% CI]	P value
Diabetes mellitus	1.287 [0.596 – 2.782]	0.521	- - -	- - -
LVEF	0.965 [0.940 – 0.992]	0.010	0.977 [0.948 – 1.007]	0.139
Multivessel disease	6.821 [2.536 – 18.346]	<0.001	5.551 [2.004 – 15.376]	0.001
„Provisional" PCI strategy	0.283 [0.089 – 0.898]	0.032	2.543 [0.736 – 8.778]	0.140
CKD	2.333 [0.854 – 6.375]	0.098	0.556 [0.183 – 1.692]	0.556
„True" bifurcation	1.745 [0.747 – 4.079]	0.199	- - -	- - -
Ticagrelor in DAPT	1.893 [0.897 – 3.994]	0.094	1.865 [0.825 – 4.218]	0.134

CI – confidence interval; CKD - chronic kidney disease; DAPT – dual antiplatelet therapy; LVEF – left ventricular ejection fraction; OR – probability ratio; PCI – percutaneus coronary intervention.

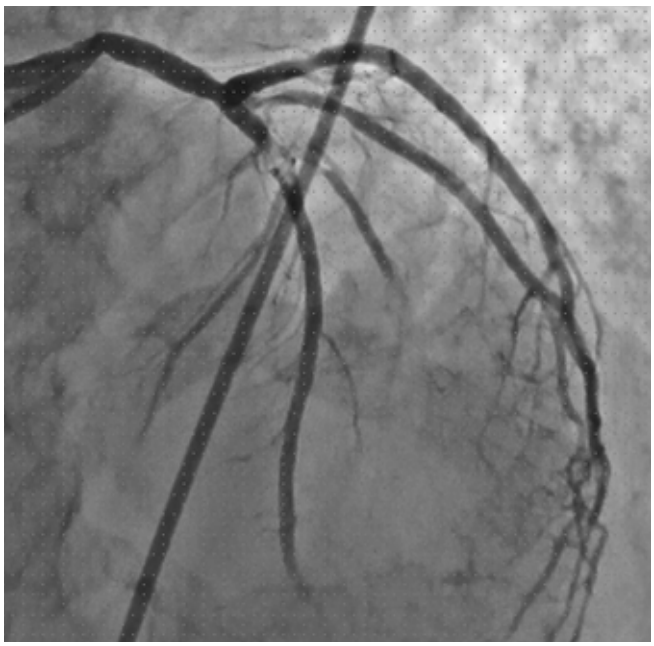

Figure 1. True coronary artery bifurcation in LAD-D territory with large thrombus burden causing an acute coronary syndrome is presented.

of LVEF with adverse cardiovascular outcomes, which did not stand comparison to multivessel coronary artery disease in multivariable analysis. On the other hand, our study included only patients with ACS, in contrast to previously mentioned registries of BL, which may also affect clinical outcomes.

The presence of a TBL was not significantly associated with adverse cardiovascular outcomes, and this is in accordance with a study by Zimarino et al. which included more than 5,000 treated BL[14]. The reason for this finding could be sought primarily in the presence of strong clinical predictors of outcomes like multivessel coronary artery disease, LVEF, diabetes and ACS that might obscure the potential effect of TBL on cardiovascular events. Importantly, most patients, regardless of the presence of TB, were treated with a "provisional" strategy - implantation of stent in the bifurcation's MB - which "equalizes" the treatment of TBL and other bifurcations, thus bringing them into similar position in relation to outcomes. This conclusion stems from studies that have shown that complex strategies with implantation of two stents were associated with increased incidence of adverse cardiovascular events[14,15]. Our study showed that the "provisional" stent implantation strategy was associated with better outcomes in univariate analysis, but this was not maintained in multivariable model. We've demonstrated that TBLs are associated with a longer PCI duration and greater contrast consumption, which pointed towards the complexity of the procedure. The reason for this should be sought in several features of a bifurcation lesion with significant disease of the SB where an operator could experience difficulty to pass the coronary gudewire into the SB. Also, a suboptimal result in the SB after stent implantation in the MB could be the reason to perform additional procedures like SB ostial angioplasty, stent implantation and/or repeated postdilatation of the stent implanted in the MB (proximal optimization - POT). All this could lead to increased procedural time and use of contrast[16]. Multivessel coronary artery disease is a relatively common finding in patients with ACS and is associated with greater cardiovascular events rate in the first year after initial hospitalization[17]. Large registry of BL showed that the multivessel disease was an important clinical predictor of adverse cardiovascular events[14,17]. Our study also showed that the presence of multivessel disease was associated with adverse cardiovascular events. The reasons for this finding should be sought in the prevalence of coronary artery disease, which is growing despite interventions and drug therapy[17,18,19]. On the other hand, complex interventional treatment which includes BL, carries the risk of specific manifestations of coronary artery disease like stent thrombosis and in-stent restenosis[15].

Study limitations

Our study is limited by its single centre, retrospective, observational design. Further, data on angiographic findings and interventions were obtained from the registry instead directly from the angiograms. Finally, in some cases, patient's data were obtained by telephone and patient's self-assessment of their own health and prescribed medications which may cause certain inaccuracy in reporting.

Conclusion

True bifurcation lesions responsible for an acute coronary syndrome are associated with prolonged PCI procedures, but were not associated with larger myocardial infarctions and adverse cardiovascular outcomes compared to uncomplicated ones. The extent of CAD at presentation remains one of the most important clinical factors in prediction of the future cardiovascular events.

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Sažetak

„Prave“ bifurkacije koronarnih arterija u akutnom koronarnom sindromu su povezane sa dužinom trajanja perkutane koronarne intervencije, ali ne utiču na klinički ishod

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Uvod: *Perkutane koronarne intervencije (PKI) na bifurkacionim lezijama (BL) sa suženjem glavne i bočne grane većim od 50 % predstavljaju izazov. Ove ,,prave“ bifurkacione lezije (PBL) predstavljaju dodatni izazov kada su uzrok akutnog koronarnog sindroma (AKS), zato što nema preporuka za njihovo adekvatno lečenje. Cilj studije je ispitati uticaj PBL odgovorne za AKS na klinički ishod nakon PKI.*

Metode: *Studija je retrospektivna, sprovedena u univerzitetskom centru i uključila je 256 konsekutivnih pacijenata sa AKS uzrokovanim BL na nativnoj koronarnoj arteriji. Pacijenti sa AKS usled stent tromboze nisu uključeni u studiju. Svi pacijenti su podvrgnuti PKI odgovorne arterije, a zatim lečeni prema odgovarajućim preporukama.*

Rezultati: *BL su najzastupljenije na prednjoj descedentnoj grani leve koronarne arterije 152/256 (59.3%), zatim na cirkumfleksnoj 66/256 (25.9%) i desnoj koronarnoj arteriji 38/256 (14.8%). Klinička prezentacija bila je STEMI kod 144/256 (56.2%) , zatim NSTEMI 59/256 (23.1%) i nestabilna angina pektoris kod 53/256 (20.7%) pacijenata. PBL su nađene kod 146/256 (57.0%) pacijenata. PBL su povezane sa dužim trajanjem PKI 48±24 min naspram 31±28 min (p<0.05), većom potrošnjom kontrasta 177±73 naspram 149±48 ml (p=0.01), ali ne i većim infarktom prema nivou troponina I 47.35±73.73 naspram 31.07±38.05 ng/ml (p=0.164), i vrednostima ejekcione frakcije leve komore (LVEF) 40±13 naspram 42±13% (p=0.439). Pacijenti su praćeni 405±377 dana. Neželjeni kardiovaskularni događaji (smrt, infarkt miokarda, ponovna revaskularizacija, moždani udar) registrovani su kod 55/256 (21,5%) pacijenata. U univarijantnoj regresionoj analizi, ,,provizorna'' strategija PKI je povezana sa manjom učestalošću kardiovaskularnih događaja [OR 0.283 (95 % CI 0.089–0.898)]. U multivarijantnoj regresionoj analizi koja uključuje poznate prediktora za značajne kardiovaskularne događaje (dijabetes, LVEF, hronična bubrežna insuficijencija, višesudovna koronarna bolest (VKB), ,,provizorna'' strategija PKI, upotreba tikagrelora, prisustvo PBL), utvrđeno je da je samo VKB nezavisni prediktor nastanka kardiovaskularnih događaja [OR 5.551 (95 % CI 2,004–15,376)].*

Zaključak: *,,Prave” bifurkacione lezije u akutnom koronarnom sindromu su povezane sa dužim trajanjem PKI i većom potrošnjom kontrasta, ali ne i sa veličinom infarkta i kardiovaskularnim događajima. Opsežnost koronarne bolesti predstavlja najbolji prediktor budućih kardiovaskularnih događaja.*

Ključne reči: bifurkaciona lezija, akutni koronarni sindrom, perkutana koronarna intervencija

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Current Opinion

The year in cardiology 2019

The year in cardiology: cardiovascular prevention

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Preamble

Advances in genomics, understanding of the effects of cumulative exposure and various environmental risk factors have moved us closer to better models of care focused at early risk assessment and treatment to prevent cardiovascular (CV) disease. We review relevant contributions in 2019 to the field of CV disease prevention, with a focus on epidemiology, lipids, diabetes, and hypertension.

Evolving concepts in prevention

Current concepts for risk assessment for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) are based on assessments of multiple risk factors and global risk when one high-risk condition such as diabetes, genetic dyslipidaemia, or hypertension is absent. These are usually measured at a specific time point and predict short-term risk (10 years) upon which life-long interventions including lifestyle and pharmacotherapy are then based. Advances in genomics may help identify individuals with genetic vulnerability to ASCVD and the recognition of the importance of duration of exposure to risk factors such as low-density lipoprotein (LDL)-cholesterol (LDL-C), blood pressure[1] or number of cigarettes (pack-years) are helping to reshape the paradigm of risk assessment with greater precision (*Take home figure*). These are likely to move the approach of health systems from ones treating disease to ones which aim to preserve health (*Figure 1*). Central to this aim is the move from shortterm risk assessment to lifetime risk and earlier implementation of preventive strategies.[2] In this article, we highlight some of the key scientific observations in the field of prevention in 2019 from risk assessment, epidemiology with an additional focus on lipids, diabetes, and hypertension.

A recurring observation is that conventional risk assessment is imprecise and the addition of information from imaging consistently helps to correctly reclassify individuals. As a result, the use of imaging and in particular coronary artery calcification (CAC) has been shown to be superior to other modalities and is therefore encouraged among those at intermediate risk and the presence of subclinical atherosclerotic disease supports earlier and more targeted CV prevention strategies in the new ESC/EAS and ESC/EASD 2019 guidelines.[3,4] Moreover, absence of CAC may also reclassify risk down and that should be considered in a shared decision environment. Imaging modalities which lend themselves to machine learning such as evaluation of perivascular fat in cardiac computer tomography may well allow imaging to be scaled up, become reproducible and cost-effective as part of the risk assessment tool.[5]

Whilst imaging is clearly important its use is likely to be useful after decades of exposure to risk factors and still provides assessment for shortto intermediate-term risk. Recently, a lifetime-perspective CardioVascular Disease (LIFE-CVD) model for the estimation of treatment-effects of cholesterol-lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people has been developed. This freely accessible on line calculator (www.U-Prevent.com) estimates risk and treatment-effects in terms of improved 10-year risk, lifetime risk, and life-expectancy free of CVD and is designed to facilitate doctor–patient communication.[6]

Large trials of pharmacological intervention assessing outcomes over a time horizon of 50 years will never occur. However, the importance of early and sustained reduction in risk factors notably LDL-C and blood pressure were highlighted in analyses from UK Biobank where a 1 mmol/L lower LDL-C and a 10 mmHg lower blood pressure were associated with an 80% lower risk of CV disease.[1] Put more simply small differences maintained over

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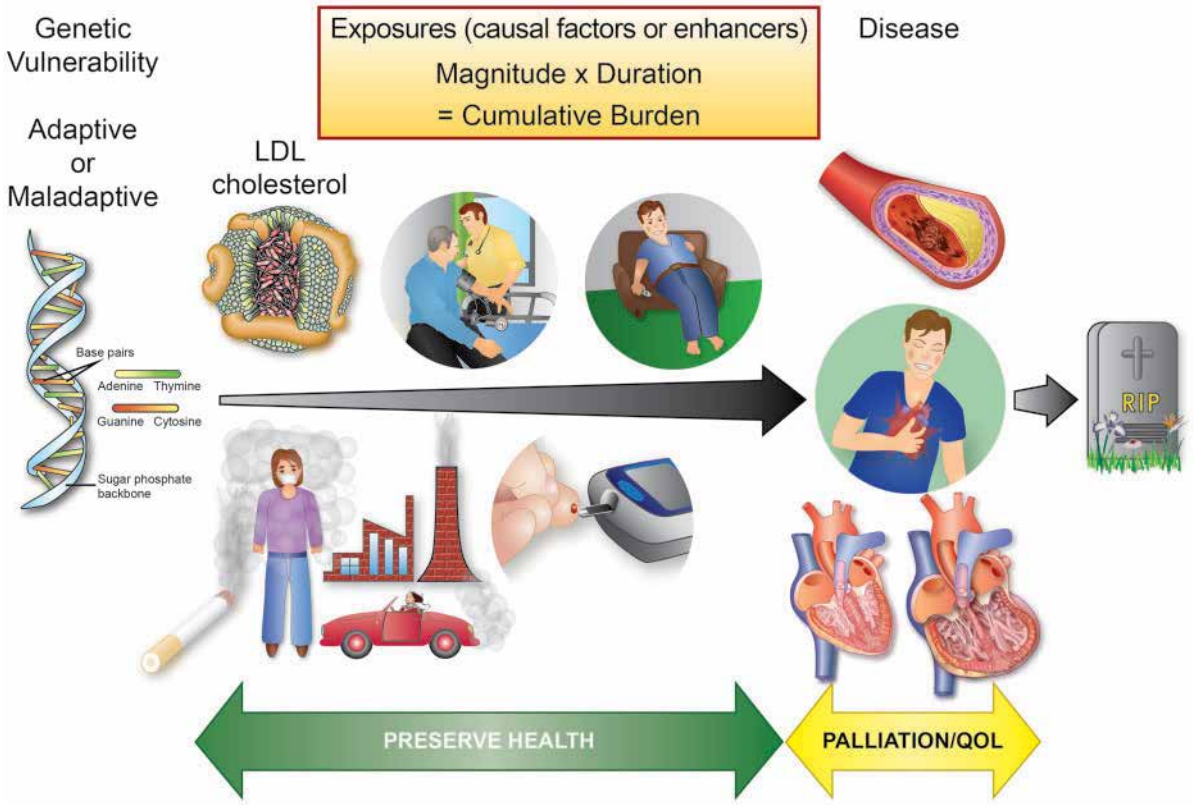

Take home figure Life time trajectory of gene-environment interactions towards cardiovascular disease and death. The figure illustrates the impact of life time exposure to both genetic and life style/environmental causal risk factors that determine the development and clinical course of cardiovascular disease. A better understanding of opportunities for a more effective preservation of health is described in the article that is gaining an increasing attention.QOL, quality of life.

a long time produce cumulative benefits.[1] Moreover, higher levels of CV risk factors are associated with worse brain health across grey and white matter macrostructure and microstructure in relatively healthy middle and older age individuals suggesting that common risk factor modification could improve a current health burden in late-life namely dementia.[7] Digital health technology is rapidly advancing and sensors may allow earlier detection of conditions associated with increased CV risk, such as atrial fibrillation (AF). Whilst compelling evidence for their effectiveness is largely lacking, large scale studies have been initiated. The HEARTLIVE study enrolling ~150 000 participants (>65 years of age) is assessing whether earlier detection of AF by a smartwatch sensing technology reduces the risk of CV events. However, there are also concerns that widespread use of such approaches, particularly in the low risk, younger populations using such devices, may lead to unnecessary medical consultations,[9] making an assessment of studies such as HEARTLIVE in appropriate populations important.

Behaviour and environmental factors

Genetics

Considerable amounts of data have emerged from UK Biobank. However data is needed on non-European populations as ~ 10 000 of the 500 000 cohort are from south Asian or Afrocarribean ancestry.

Behaviour may, in part, have a genetic basis. In a Mendelian randomization analysis from UK Biobank genetic variants known to affect educational attainment were associated with health-conscious lifestyle later in life and which in turn may subsequently affect the risk of coronary artery disease.[10]

Nutrition

Red meat

Data are conflicting with different recommendations regarding red meat consumption. Observational studies suggested potential carcinogenic effects of processed meat.[11] Four systematic reviews on the health effects of red meat and one systematic review on individual health-related values and preferences regarding meat consumption have been published,[12] where the magnitudes of any effect weresmall. Additionally, these studies report only very low to low certainty for any association of unprocessed or processed red meat intake with CV mortality, diabetes, or cancer. The authors conclude that individuals continue their current consumption of both processed and unprocessed meat, albeit with a weak recommendation because of the low certainty around the evidence.[12] Of note, a recent randomized dietary study suggests that chronic dietary red meat consumption increases systemic levels of trimethylamine N-oxide (TMAO), a microbiome-dependent metabolite, that has been associated with increased CV risk[13] but larger studies are needed.

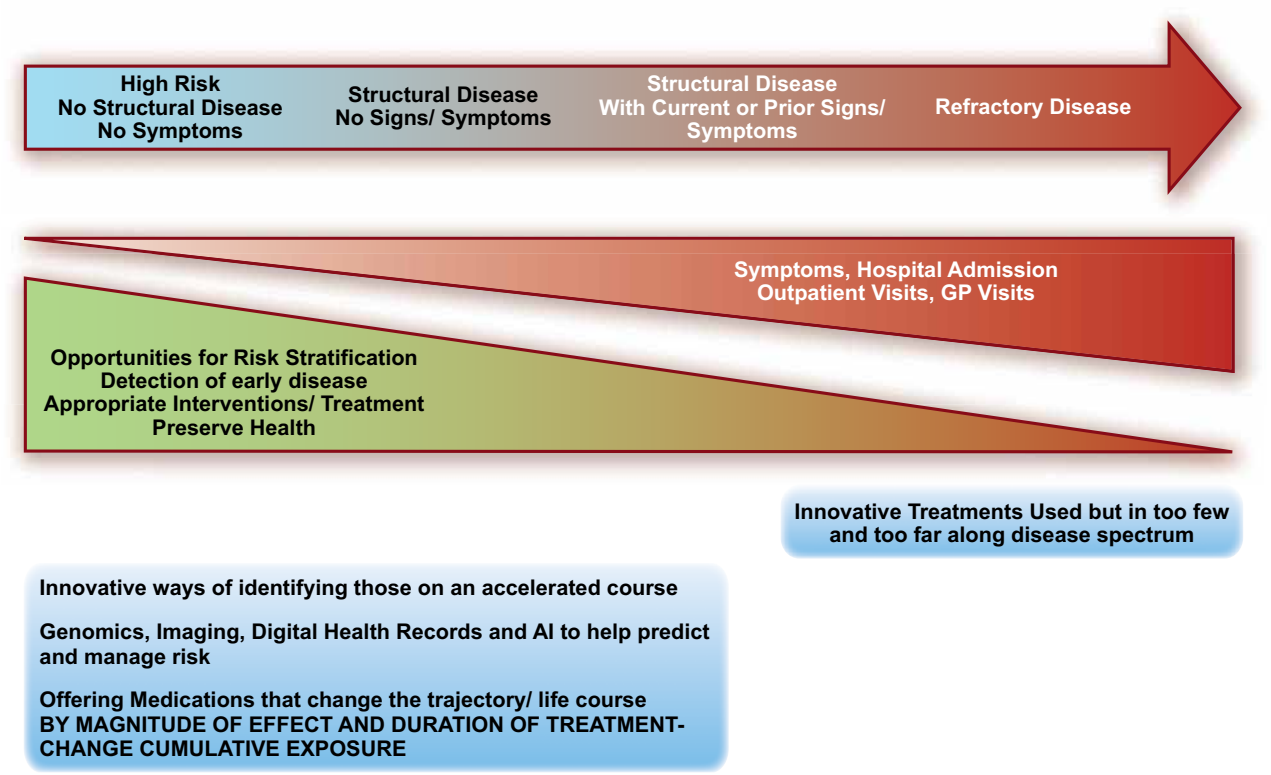

Figure 1 Missed OPPORTUNITIES in reducing the health care burden, improving quality of life, delaying death—exemplar for common conditions. The figure shows potential opportunities formore effective prevention strategies during the course of subclinical and clinical cardiovascular disease development; e.g. atherosclerotic cardiovascular disease develops and progresses over several decades providing numerous opportunities for prevention before clinical manifestations of the disease.

Carbohydrates

Conflicting data on the role of carbohydrates for ASCVD risk have led to different recommendations. For example, the large Prospective Urban Rural Epidemiology (PURE) study reported that high carbohydrate intake was associated with higher risk of total mortality[14] In contrast, a recent analysis of the National Health and Nutrition Examination Survey (NHANES; 1999–2010) suggests exactly the opposite with low carbohydrate diets associated with excess overall and cause-specific mortality.[15] Nutritional epidemiology carries the risk of confounding by social and economic factors. The underlying causal association (if any) of behaviour, such as 'skipping breakfast', with ASCVD may be unrelated to discussions about the benefit of fat vs. carbohydrates,[16] therefore, the evidence to support population-level interventions such as increasing the price of high sugar snacks appears incomplete, especially since this would differentially affect low-income individuals.[17] More recently, the totality of the literature of this topic was summarized by a U-shaped relationship between carbohydrate intake and mortality.[18] The authors conclude that 'taking all the studies into account, the message of moderation is perhaps the most convincing one of all —diets that focus too heavily on a single macronutrient, whether extreme protein, carbohydrate, or fat intake, may adversely impact health —the best advice seems to be to select whole foods from a variety of sources and avoid dietary extremism. For now, for carbohydrates, everything in moderation seems to carry the day'.[18]

Body weight

The notion that the effect of any diet on body weight is in turn proportional to risk of ASCVD may be over-simplistic.[19] In the Women's Health Initiative, during a median of 17.9 years of followup, whole body fat mass was not associated with incident ASCVD among normal weight post-menopausal women. Interestingly, the distribution of fat was; with higher trunk fat associated with higher risk of ASCVD, while higher leg fat predicted lower risk.[20] These data suggest an adverse fat distribution and risk can be characterized by increased (unfavourable) abdominal/visceral (trunk) and decreased (beneficial) lower body (leg) fat that is independent of body fat mass. Future research should address potential mechanisms for the development of adverse fat distribution and how it is may be linked to atherosclerosis.[19,20]

Sleep duration

Data from the Prospective Urban Rural Epidemiology (PURE) study on 116 632 with follow-up of 7.8 years that show that estimated total sleep duration of 6–8 h per day is associated with the lowest risk of deaths and major CV events.[21] Interestingly, a neuro-immune axis that links sleep to haematopoiesis and atherosclerosis has been identified and provides a mechanistic rationale for disturbed sleep and increased CV risk.[22]

Smoking

Recent data from the Framingham Heart Study provide quantitative information on the positive health effects of smoking cessation based on >25 years of follow-up showing that quitting within 5 years was associated with 39% lower risk of incident CVD compared with current smokers. Also, among heavy smokers, smoking cessation was associated with lower risk of CVD relative to current smokers.[23] The health effects of e-cigarettes (so-called 'vaping ') are still uncertain, recent case reports suggest potential emerging clinical syndromes that are not yet completely understood.[24]

Exercise

Increased physical activity, at any intensity and less time spent sedentary, is associated with substantially reduced risk for premature mortality.[25] However, translation into patient care and individualized training recommendations remain a challenge. A randomized controlled trial showed that endurance and interval training but not resistance training-induced effects on circulating blood cells that are important for cellular senescence and regenerative capacity showing that different training modalities exert differential cellular and vascular effects contributing to vascular health.[26]

Noise, pollution, and workplace

There is increasing awareness of associations between our environment and health. For instance, ambient air pollution has been linked to an excess annual mortality rate of 659 000 in the European Union (EU-28), with the majority attributable to CV causes.[27] Estimates put attributable per capita annual mortality rate in Europe at 133/ 100 000, but considerable uncertainty around this estimate remain.[27] In this regard, a nationwide cohort study from Switzerland modelled long-term exposure to noise levels as well as environmental pollutants for each address of four million adults.[28] The data suggest that road traffic, aircraft, and railway noise are each associated with excess mortality from myocardial infarction (MI), independent of air pollution. The authors suggest that air pollution studies not adequately adjusting for noise exposure may overestimate the attributable burden of risk from air pollution.[28,29]

Finally, large cohort studies from Sweden and Denmark reveal that 9% reported being bullied at work and 13% recorded exposure to workplace violence during the preceding year. After adjustment, being bullied at work was associated 59% increased risk of ASCVD. The population attributable risk was dose-dependent and overall 5.0% for workplace bullying and 3.1% for workplace violence.[30]

Dyslipidaemia and lipids

Several clinical trial programmes have studied novel treatment options for modification of lipoprotein-related risk of ASCVD that are described below, e.g. new options for lowering LDL-cholesterol and triglyceride-rich lipoproteins. These novel therapeutic approaches will allow a more effective and targeted strategy for management of lipoprotein-related risk in the future (*Figure 2*).

Low-density lipoprotein-cholesterol

ATP citrate lyase is an enzyme in the cholesterol-biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the target of statins. Genetic variants that mimic the effect of ATP citrate lyase inhibitors and statins appeared to lower plasma LDL-cholesterol levels by the same mechanism of action and were associated with similar effects on the risk of CV disease per unit decrease in the LDL-cholesterol level.[31] Bempedoic acid, an inhibitor of ATP citrate lyase, reduced levels of LDL cholesterol by 16.5% when added to maximally tolerated statin therapy,[32] and a clinical outcomes study is ongoing.

Recent data from trials of ezetemibe and PCSK9 monoclonal antibodies demonstrating consistent evidence of benefit with the achievement of lower risk among patients with lower LDL-C levels have now been incorporated into the new ESC/EAS treatment guidelines in 2019 with 55 mg/ dL the new goal for very high-risk patients.[3]

Triglyceride-rich lipoproteins

In a genetic study, it was observed that triglyceride-lowering lipoprotein lipase variants and LDL-C-lowering LDL-receptor variants were associated with a similar lower risk of coronary heart disease per unit difference in ApoB, suggesting that the clinical benefit of lipid lowering *per se* is proportional to the absolute change in ApoB.[33] Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowered triglyceride levels, and reduced ischaemic events by 26% in the recent REDUCE-IT trial in patients with elevated triglyceride levels compared to mineral oil.[34] The magnitude of benefit was greater than that expected by ApoB changes alone suggesting mechanisms beyond ApoB lowering.[34,35]

Lipoprotein (a)

A recent analysis of > 65 000 subjects suggested that lipoprotein(a) levels >93 mg/dL (199 nmol/L; 96th–100th percentiles) vs. <10 mg/ dL (18 nmol/L; 1st–50th percentiles) was associated with a 50% excess risk for CV mortality and of 20% for all-cause mortality.[36] The authors hypothesize that elevated lipoprotein(a), (through corresponding low LPA KIV-2 number of repeats) rather than through Lp(a) cholesterol content were the drivers of this excess risk.[36]

Hypertension

Epidemiology

Hypertension is a very important risk factor for CV disease and five decades of trials have demonstrated the benefits of pharmacotherapy in reducing CV morbidity and mortality. However, contemporary data reinforce the need for improvement in hypertension healthcare

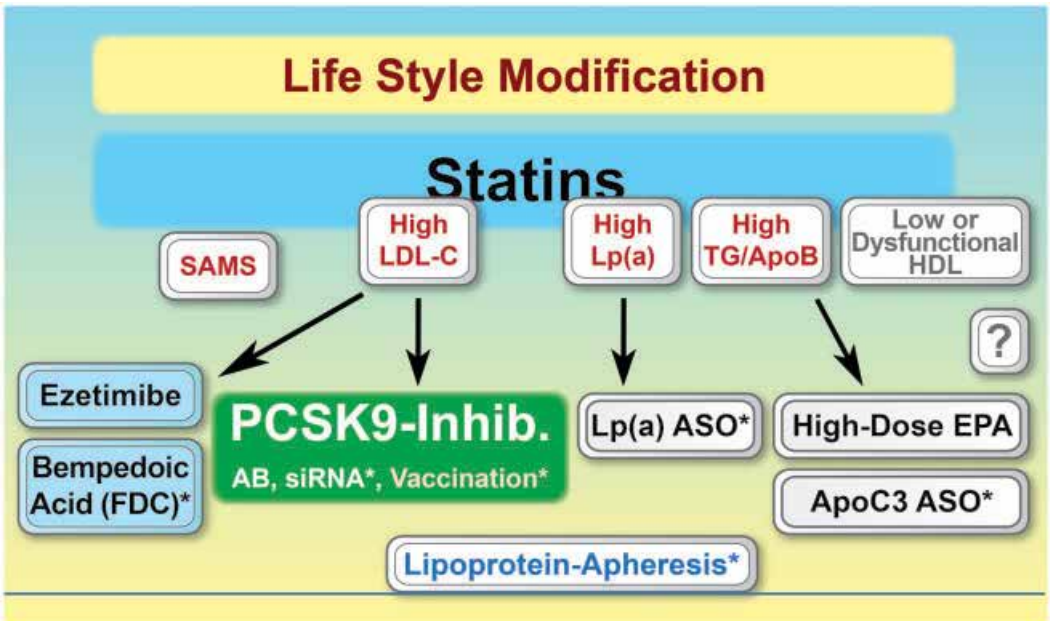

Figure 2 Developments in lipid-targeted therapies. Genetic studies have provided important insights into causal genes and related lipoproteins for development and progression of atherosclerotic vascular disease. Whereas initial management steps will remain life style optimization and statin ther- apy, a more focused treatment depending on the lipoprotein profile is currently being developed in addition to these treatment options, focusing on low-density lipoprotein-cholesterol-related risk, lipoprotein(a), and triglyceride-rich lipoproteins. *no outcomes data available. AB, antibody; ASO, anti sense oligonuceotide; EPA; eicosapentanoeic acid; FDC, fixed dose combination; SAMS, statin associated muscle symptoms; si, small interfering.

globally. In 12 high-income countries, data from more than half a million participants indicated greatly improved hypertension awareness, treatment, and control since the 1980s but substantial variations in hypertension prevalence and treatment across countries.[37] Control rates have plateaued in recent decades with rates of treatment coverage ~80% and control ~70% in best performing countries. Conversely, in 44 low-income and middle-income countries, only 40% of those with hypertension were diagnosed, with 30% receiving antihypertensive medication, and 10% controlled with disparity across countries and sub-Saharan Africa performing the worst.[38]

Blood pressure measurement

A study from 1.3 million North American patients has shown that both systolic blood pressure (SBP) and diastolic blood pressure (DBP) independently predicted MI, ischaemic/haemorrhagic stroke with a greater effect of systolic hypertension.[39] Importantly, the relationship between SBP, DBP, and events is independent of treatment threshold (>_ 140/90 vs. >_ 130/80 mmHg) supporting the more proactive management of hypertension in high-risk individuals in recent guidelines.[40–42] The IDACO investigators observed in a study of 11 135 adults, that higher 24-h and night-time SBP were significantly associated with greater risks of death and CV events even after adjusting for other office-based or ambulatory BP measurements,[43] reinforcing recent guidelines, recommending the routine use of ambulatory BP monitoring (ABPM) for BP assessment.

Treatment

Pharmacotherapy

Whilst there have been no developments in novel therapies for hypertension, an increasing focus is use of multidrug combinations, even as an initial step in treatment. Most recently, the WHO added fixed dose combination antihypertensive medications to the Essential Medicines List with the aim of addressing inequalities in treatment and control in low to middle income countries (LMIC).[44] This approach has already demonstrated cost-effectiveness in patients in Sri Lanka with mild-moderate hypertension treated with a triple pill strategy vs. usual care; providing the first economic evaluation of a triple-pill approach.[45]

Evidence is accumulating to support nocturnal dosing of antihypertensive medication, with the Hygia Chronotherapy trial, the first ABPM-based outcome study providing evidence that bed-time dosing of >_ 1 antihypertensive drug, vs. morning, results in better ambulatory BP control lower sleep-time BP and improved nocturnal dipper status.[46] Despite modest differences in BP,[46] there was a disproportionate reduction in CVD morbidity and mortality with bedtime dosing with no safety signal noted. Whether this is real requires independent confirmation.

Device therapy

Endovascular renal denervation (RDN) aims to achieve durable hypertension control through interruption of renal sympathetic nervous system signalling. The open label, single arm Global Symplicity Registry have reported significant and sustained reductions in ambulatory and office BP (-16.5 ± 28.6 and -8.0 ± 20.0 mmHg, re-

spectively) 3 years post-radiofrequency ablation with no safety signal and preserved renal function in 1742 patients.[47] Furthermore, the RADIANCE-HTN SOLO investigators have now shown that the effects of endovascular ultrasound RDN in patients with mildmoderate hypertension are preserved at 6 months with less medication burden compared with sham control.[13,48] It is unclear which, if any, of the technologies to achieve RDN is superior: radiofrequency (RF) vs. ultrasound (US) vs. alcohol chemical ablation. However the RADIOSOUND-HTN investigators have shown in patients with resistant hypertension, endovascular US-based RDN achieved similar BP reduction to RF ablation of the main arteries, accessories, and side branches but was superior to RF ablation of the main renal arteries only.[49] Furthermore, whilst the search for marker of procedural success and predictors of response to RDN is on-going, the SPYRAL HTN-OFF MED investigators have demonstrated that RF RDN in patients with mild-moderate hypertension resulted in significant heart rate reduction compared to sham and that hypertensive patients with higher heart rates may be more likely to respond.[48]

Diabetes

The prevalence of diabetes is increasing, with >425 million already affected globally potentially growing to 629 million by 2045.[4] As diabetes doubles the risk of CVD, the increase in prevalence will increase the population attributable risk disproportionately in lowmiddle income countries where the disposable income and economic growth coupled with sedentary lifestyle are seeing the greatest rise in diabetes prevalence. Novel therapeutic options now offer a chance to move away from prior glucose centric approaches in diabetes care to those aimed at preventing cardio-renal complications as evidenced by the 2019 ESC guidelines on diabetes, prediabetes, and CV diseases developed in collaboration with the European Association for the Study of Diabetes (EASD).[4] A key premise of these is the classification of absolute CV risk as the first step, into *Very high*, *High, and Moderate risk.* Based on the results of recent trials, using both GLP1RAs and SGLT2 inhibitors, in the 2019 guidelines, these drug classes are recommended as first-line therapy in patients with T2DM and established ASCVD or at high/very high CV risk, such as those with target-organ damage or multiple risk factors instead of metformin.[4] Among those already on metformin GLP1-RAs and SGLT2 inhibitors should be added for CV risk reduction with the aim of moving away from a HbA1c centric approach to one which prevents CV disease.

Notable contributions from several large trials in 2019 include the REWIND trial[50] assessing the effect of once weekly subcutaneous dulaglutide vs. placebo on three-point major adverse cardiac events (MACE) in 9901 patients with T2DM, who had either a previous CV event or multiple risk factors. Over 5.4 years of follow-up, the primary composite outcome occurred in 12.0% of participants in the dulaglutide group and in 13.4% in the placebo group reflecting a significant 12% relative risk reduction. The DECLARE-TIMI 58 trial[51] investigated the effect of dapagliflozin vs. placebo in 17 160 patients with DM and established CVD or multiple risk factors. After 4.2 years of follow-up, the pre-specified criterion for non-inferiority for the composite MACE was met by dapagliflozin compared with placebo. In two primary efficacy analyses, dapagliflozin did not significantly reduce 3P-MACE but resulted in a lower rate of the combined endpoint of CV death or HF hospitalization by 17% (4.9 vs. 5.8% absolute difference). The benefit on heart failure was similar in patients with CVD as well as those with multiple risk factors only. A recent meta-analysis of the SGLT2i trials suggested consistent benefits on reducing the composite of HF hospitalization or CV death, as well as on the progression of kidney disease, regardless of presence of established CVD, while the reduction in MACE was only apparent in ASCVD patients.[52] Previous CVOTs with SGLT2 inhibitors demonstrated renal benefit as a secondary endpoint, but the CREDENCE trial[53] was the first dedicated study assessing renal preservation with SGLT2i in chronic kidney disease and diabetes (estimated glomerular filtration rate 30 to <90 mL/min/1.73 m^2). Individuals randomized to canagliflozin had a relative reduction in the primary renal outcome of 30% compared to placebo. In addition, canagliflozin significantly reduced the prespecified secondary CV outcomes of 3P-MACE by 20% and hospitalization for heart failure by 29% compared with placebo. More recently, there is now compelling evidence that SGLT2 inhibition reduces heart failure in populations with heart failure and reduced ejection fraction equally among those with or without diabetes in the DAPA CHF trial.[54]

Inflammation and thrombosis

The CANTOS trial provided the first evidence that targeting inflammation reduced CV outcomes in those with established disease. Ultimately cost, questions regarding duration of therapy and efficacy vs. safety 'trade off ' with increased infections have not seen the development of IL-1beta antagonism. Targeting inflammation indirectly, with low-cost safe alternatives have been sought with methotrexate showing no benefit. Among patients with a recent MI low-dose colchicine reduced a broad composite CV endpoint including revascularization by 23% (1.6% absolute benefit) in the COLCOT trial.[55] Colchicine use was associated with an absolute excess of 0.8% in diarrhoea (NS) and 0.5% in pneumonia ($P = 0.03$).

Finally, aspirin clearly has net benefit (more CV events voided than significant bleeds caused) in the setting of established CV disease or secondary prevention. However, the observation that in over 100 000 patients in primary prevention trials of aspirin demonstrated an excess of about 2.5 excess major bleeds for each non-fatal MI averted and no mortality benefit over 5 years.[56] As such aspirin is not routinely recommended in the ESC guidelines in the setting of primary prevention.[57]

Summary and conclusions

The present article summarizes important advances in the field of CV prevention in 2019. We have highlighted

the increasing role of considering lifetime CV risk for maintaining CV health, as well as the need for risk assessment in patients with established ASCVD or diabetes, for which novel and more targeted preventive therapies have been developed and proven effective.

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Current Opinion

The year in cardiology 2019

The year in cardiology: imaging

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Introduction

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

This year, artificial intelligence and machine learning applied to cardiac imaging has been one of the main novelties. Other advances innon-invasive cardiac imaging published in 2019 are summarized inthis Year in Cardiology review article (*Take home figure*).

Echocardiography

Early detection of left ventricular (LV) dysfunction in various populations has been the focus of numerous publications in 2019. Left ventricular diastolic function usually precedes LV systolic dysfunctionand is associated with cardiovascular morbidity and mortality. Fromthe Copenhagen City Heart Study, a population-based study including 6238 individuals, Lassen *et al.*[3] evaluated the association between LV filling pressures measured on tissue Doppler imaging (E/E^0)and speckle tracking echocardiography (E/E^0sr) with the occurrenceof cardiovascular death, admission for incident heart failure or myocardial infarction (MI). Of 1238 participants, 140 (11.3%) reached the primary endpoint during a median follow-up of 11 years. After adjusting for various clinical and echocardiographic parameters, E/E^0sr was independently associated with the endpoint [hazard ratio (HR) 1.08,95% confidence interval (CI) 1.02–1.13 per each 10 cm increase;$P = 0.003$] whereas E/E^0 was not. In addition, E/E^0sr provided incremental prognostic value over the SCORE risk chart, currently usedto evaluate the risk of cardiovascular morbidity and mortality in thegeneral population. Increased LV filling pressures may reflect the ageing process of the heart characterized by increased fibrosis. This fibrosis may lead to conduction abnormalities that influence the contractile function of the LV. Modin *et al.*[4] evaluated in 1138 participants of the Copenhagen City Heart Study the prognostic value ofLV mechanical dispersion which is measured as the standard deviation from time to peak longitudinal strain of the three LV apical views. The mean value of LV mechanical dispersion in the generalpopulation was 45 ± 38 ms and increased with age, hypertension, body mass index, and presence of MI. Large LV mechanical dispersion was associated with worse LV systolic and diastolic function. Each10 ms increase in LV mechanical dispersion was independently associated with increased risk of cardiovascular death (HR 1.04, 95% CI1.01–1.06; $P = 0.004$).

Despite the growing evidence on the diagnostic and prognostic
value of strain derived measures of LV systolic and diastolic function,LV ejection fraction (EF) remains the mainstay parameter for risk stratification in clinical practice. The association between physicianreported LVEF and sur-

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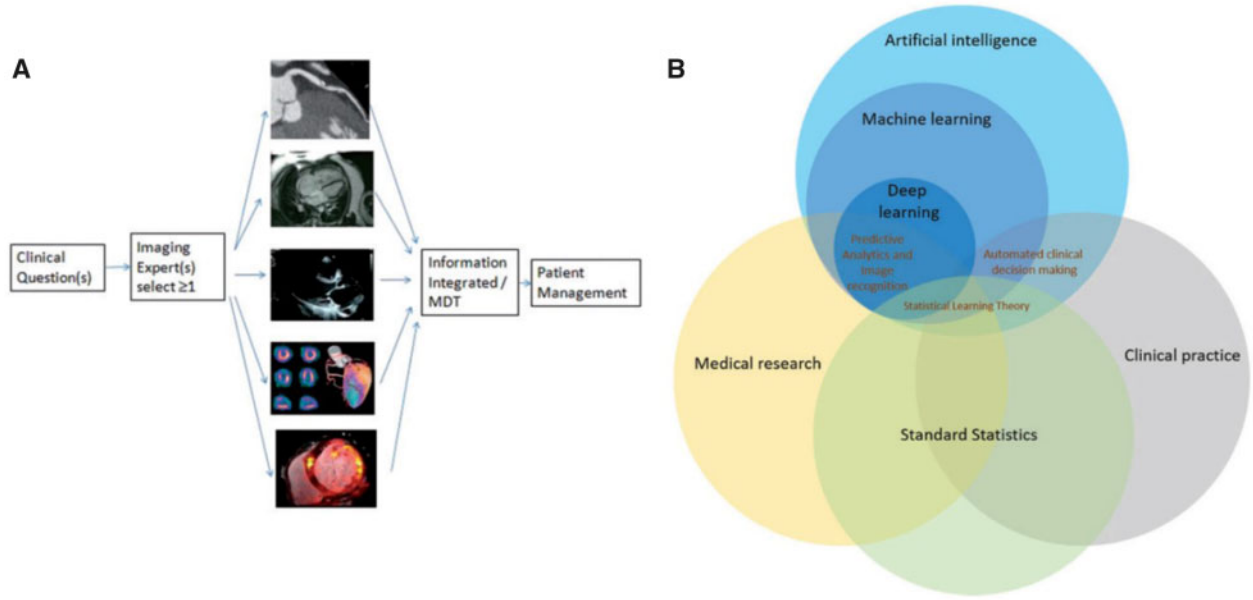

Take home figure Multimodality imaging and artificial intelligence in cardiac imaging. The use of the different imaging modalities should be based on a clinical question. Selecting the most appropriate imaging techniques and integrate them to answer that specific question will be key to improve the outcomes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

vival was assessed in 403 977 echocardiograms performed in 203 135 patients from USA.[5] Fifty percent of the population had an LVEF between 55% and 65%. Over a median follow-up of 4 years, 23% of patients died. A U-shaped relationship between LVEF and all-cause mortality was observed with the nadir atthe 60–65% LVEF category. These results were reproduced in an independent dataset from New Zealand including 45 531 echocardiograms from 35 976 patients. The U-shaped relationship was also observed in men and women, inpatients and outpatients with heartfailure, and deviations from LVEF of 60–65% were associated withgreater multiplicative increase in risk for younger patients as compared to old patients.

Left ventricular ejection fraction is also the parameter to classifyheart failure patients. Ten to 20% of patients with heart failure withreduced LVEF (≤40%) may improve in LVEF. However, the evidence on the frequency and outcomes of patients with heart failure and recovered LVEF is based on selected cohort of patients or randomized clinical trials. Of 3124 heart failure patients with reduced LVEF atbaseline treated with contemporary heart failure medications, 37.6% presented improvement in LVEF from 26% to 46% over a medianfollow-up of 17 months.[6] Patients with heart failure and recovered LVEF had lower rates for all-cause mortality, all-cause hospitalizations, cardiac transplantation, or LV assist device implantation thanthe patients who remained with reduced LVEF. Not less important isthe characterization of the right ventricular (RV) remodelling in heartfailure patients. In 271 patients with heart failure and preserved LVEF(HFpEF), RV fractional area change reduced by 10% and RV diastolicarea increased by 21% over a median follow-up of 4 years.[7] These changes exceeded the corresponding changes in the LV. In addition,the prevalence of tricuspid regurgitation increased by 45%. Atrial fibrillation, higher body weight, coronary artery disease, higher pulmonary pressures and LV filling pressures and RV dilation were associatedwith development of RV dysfunction (*Figure 1*).[7] Patients with HFpEF developing RV dysfunction had two-fold increased risk of death. Inthis group of heart failure patients, assessment of left atrial functionhas provided important new insights. In 308 patients with HFpEF, Freed *et al.*[8] showed that impaired left atrial reservoir strain (stiff leftatrium) was associated with increased pulmonary vascular resistanceand decreased peak oxygen consumption and was independently associated with the composite outcome of cardiovascular hospitalization or death. It should be noted that the study did not correct the association between left atrial reservoir strain and the composite outcome for neuro-hormonal markers and as acknowledged by the authors, the studies stablishing the reference values of normal leftatrial strain values across the echocardiographic systems and analysisplatforms are scarce.

In patients with asymptomatic severe aortic stenosis and preserved LVEF, LV global longitudinal strain (GLS) on speckle trackingechocardiography is more sensitive than LVEF to identify early changes in LV systolic function during the follow-up. An LV GLS of >-18.2% (more impaired) is associated with higher risk of developing symptoms and needing aortic valve intervention as compared to more preserved values of LV GLS (≤-18.2%).[9] Echocardiography is the imaging technique of first choice to assess valvular heart disease.Secondary mitral regurgitation quantification remains challenging. In423 heart failure patients, Bartko *et al.*[10] developed a unifying algorithm combining effective regurgitant orifice area (EROA), regurgitant volume, and regurgitant fraction that had better discrimina-

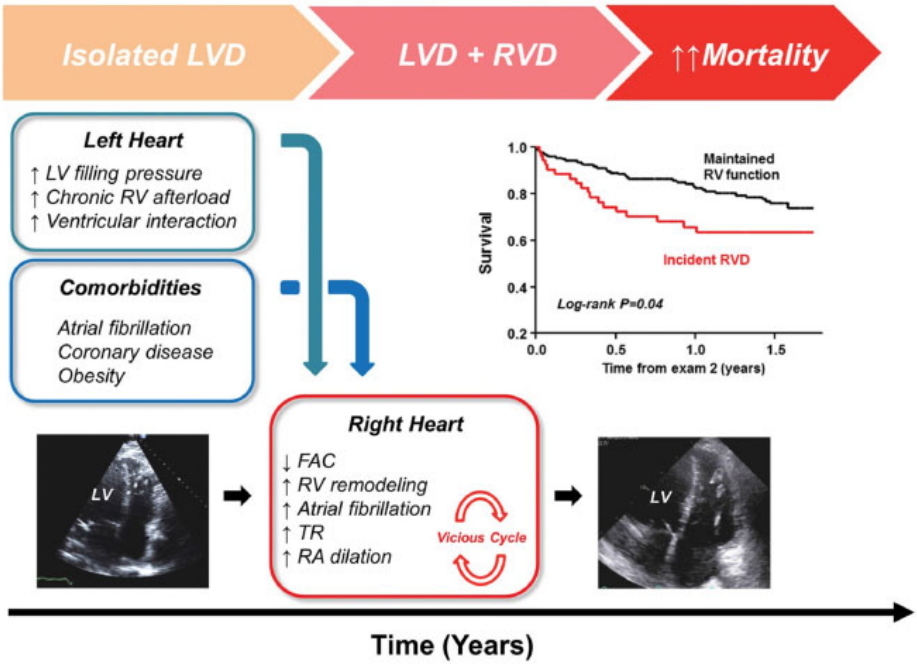

Figure 1 Development of right ventricular dysfunction (RVD) over time in patients with heart failure and preserved ejection fraction. Increased left ventricular (LV) filling pressures and associated comorbidities characterize the initial phase of isolated left ventricular dysfunction (LVD) and lead to right ventricular (RV) remodelling, right ventricular dysfunction. Patients with incident right ventricular dysfunction have worse outcome as compared to patients with preserved RV function. Reproduced with permission fromObokata et al.[7]

tionpower to identify patients with increased mortality risk than currentguideline-based definitions. Low-risk patients were characterized byan EROA of <20 mm^2 and a regurgitant volume of <30mL whereashigh-risk patients were defined by an EROA of ≥30 mm^2 and a regurgitant volume of ≥45 mL. Intermediate-risk patients (with an EROA between 20 and 29 mm^2 and a regurgitant volume of 30– 44 mL) were reclassified as high risk if the regurgitant fraction was ≥50%. However, this algorithm had a rather modest discrimination power (area under the curve 0.63).

The use of transthoracic focused cardiac ultrasound (FoCUS) isgaining popularity at the emergency department and intensive careunits. Among 839 patients with suspected acute aortic syndrome, an aortic dissection detection risk score of ≤1 and a negative FoCUS could rule out an acute aortic syndrome with a sensitivity of 94% anda failure rate of 1.9%.[11]

Finally, elevated carotid artery wave intensity measured on DuplexDoppler ultrasound was independently associated with faster cognitive decline among 3191 individuals enrolled in the Whitehall II study,[12] highlighting the relevance of ultrasound imaging outside theheart.

Cardiovascular magnetic resonance

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

In the second report from the ICELAND-MI trial, Acharya *et al.*[14] report on the long-term predictive value of unrecognized MI (UMI) inan elderly cohort of 935 subjects aged 67–93 years. Previous reportshave suggested a poor short-term prognosis but this study extendsfollow-up to 13.3 years. The authors showed that all-cause mortality in UMI patents was lower than recognized MI for at least 5 years, butsimilar at 10 years. At all time-points UMI had a higher mortality thanpatients with no MI. It is not known whether secondary preventionwould be useful in UMI patients.

Cardiovascular magnetic resonance has made an enormous contribution to the diagnosis and management of the cardiomyopathies through the presence and patterns of myocardial fibrosis from LGE imaging, tissue characterization through T1, T2, and T2* mapping, and accurate measures of ventricular function and mass.Gutman *et al.*[15] studied 452 patients with non-ischaemic dilated cardiomyopathy (DCM) stratified by the presence or absence of non-ischaemic myocardial fibrosis by LGE. In patients with fibrosis, the mortality was reduced by an implantable cardioverter-defibrillator (ICD) with HR 0.45 (P = 0.003), but in patients without fibrosis there was no improvement in mortality with ICD (HR 1.22,P = 0.64). The authors conclude that in non-ischaemic DCM, the presence of fibrosis may allow for improved selection of patients requiring ICD. Galan-Arriola *et al.*[16] used serial CMR to identify the early stages of anthracycline-induced cardiotoxicity in a pig study. The earliest detectable abnormality was increased T2 relaxation which was correlated on histology with intramyocyte oedema, with-

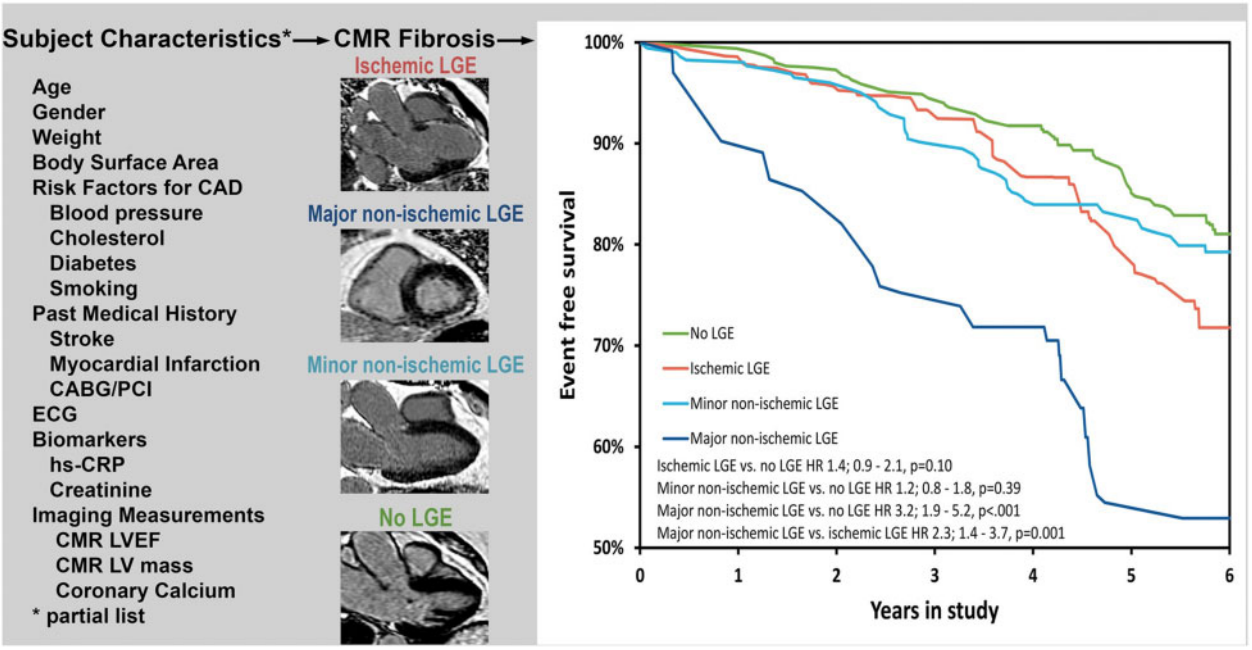

Figure 2 Inverse propensity adjusted prognosis of ischaemic and non-ischaemic myocardial fibrosis. Reproduced with permission from Shanbhag et al.[13]

out change in the extracellular space. Changes in T1 and the extracellular volume on T1 mapping occurred much laterand coincided with wall motion abnormalities. Stopping doxorubicin upon detection of T2 abnormality resolved intramyocyte vacuolization, indicating that the early T2 findings are at a stage when reversibility is still possible. These findings have important clinical implications for cancer therapy. Scally *et al.*[17]studied 55 patients with takotsubo cardiomyopathy using CMR including ultrasmall paramagnetic particles of iron oxide (USPIO) which localize in inflammatory macrophages. During the acute presentation, USPIO signal was reduced in the ballooning zone by27% ($P < 0.001$) as compared to non-ballooning zone (19%$P = 0.02$). No enhancement was visible in either zone at 5 months. The authors conclude that takotsubo cardiomyopathy is characterized by an acute myocardial macrophage inflammatory infiltrate, most marked in the ballooning zone. Aung *et al.*[18] report on3920 subjects from the UK Biobank study who were free of overtcardiovascular disease but had chronic exposure to ambient air pollutants including particulates and nitrogen dioxide. There was an incremental increase in LV and RV end-diastolic and LV endsystolic volumes with increasing exposure to particulates with a diameter of <2.5 lm. Likewise, biventricular volumes were increased with higher nitrogen dioxide exposure. The authors conclude that air pollution is an under-recognized cardiac risk factor that may contribute to heart failure.

Diffusion tensor (DT) CMR is a new technique that images the asymmetry of water diffusion to define tissue architecture. Tissuessuch as neurons and the myocardium can be interrogated because oftheir longitudinal grain. The technique has recently become possible*in vivo* in humans and has been well validated. The three-dimensional(3D) architecture of the layers of the heart is now well described and is preserved across mammalian species suggesting that the observedstructure has functional importance. Khalique *et al.*[19] report the firstseries of patients in whom the 3D architecture is deranged, thesebeing those with situs inversus totalis (SIT, dextrocardia). The normalepicardial left-handed myocyte helix was switched to right handed at the base with a return to left handed at the apex. The endocardiumwas likewise inverted at the base, with variable derangement moreapically. There was reduced strain in the SIT hearts. The long-termconsequences of these findings are not yet known, but it could behypothesized that SIT patients may be more susceptible to heart failure from a second insult such as hypertension or infarction. Ariga*et al.*[20] used DT-CMR to examine 50 patients with hypertrophic cardiomyopathy and report a reduction in the diffusion parameter calledfractional anisotropy (FA) in patients with ventricular arrhythmias[odds ratio (OR) 2.5, $P = 0.015$]. Fractional anisotropy reflects packing of the myocytes and could therefore be reduced in myocardialdisarray. Whilst there is no direct evidence of this from histology, theauthors conclude that connection of reduced FA with arrhythmiasmight reflect disarray. Further work is needed to validate this intriguing study.

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

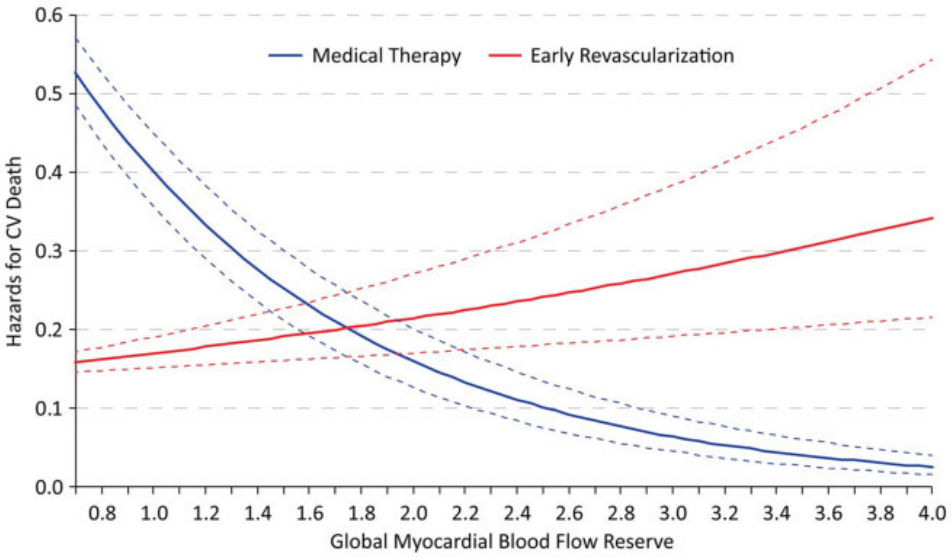

Figure 3 Hazards for cardiac death with early revascularization compared to medical therapy based on global myocardial blood flow reserve by positron emission tomography myocardial perfusion imaging. Reproduced with permission fromPatel et al.[26]

Nuclear imaging

The current limitation of coronary computed tomography angiography (CCTA) is its suboptimal positive predictive value for the identification of myocardial ischaemia. Myocardial perfusion imaging (MPI)using CT could solve that limitation. Alessio *et al.*[23] performed a dynamic contrast-enhanced cardiac CT and ^{82}rubidium positron emission tomography (PET) imaging in 34 high-risk patients. The CTderived global myocardial blood flow values correlated highly withthose measured on PET (r = 0.92; P < 0.001). In addition, the mean global myocardial blood flow values estimated on CT vs. PET werecomparable (0.9 ± 0.3 vs. 1.0 ± 0.2 mL/min/g at rest and 2.1 ± 0.7 vs. 2.0 ± 0.8 mL/min/g during stress, respectively). However, myocardialblood flow estimates on CT contained substantial individual variance with a standard error of the estimate of 0.44 mL/min/g. The results are promising but further development is needed to improve reliability of the methodology at individual level as well. Furthermore, thestudy measured only global perfusion, while regional values would bemore clinically meaningful. Another novel method to determine whether a coronary lesion is functionally significant is transluminal attenuation gradient (TAG) that can be measured using standard CCTA data. In the presence of significant coronary stenosis, luminalattenuation will decrease rapidly on CCTA and can be measured with TAG. In the study by Bom *et al.*[24] Transluminal attenuation gradient was compared against quantitative PET perfusion imaging andinvasive fractional flow reserve (FFR) and demonstrated that TAGdid not discriminate between vessels with or without ischaemia as defined by either PET or FFR. The lack of diagnostic value of TAGwas related to the large variability of coronary luminal dimensions.

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

While the diagnostic and prognostic power of MPI has been wellcharacterized, there is little evidence on how this information shouldguide patient management. Patel *et al.*[26] examined a cohort of 12 594patients with suspected or known CAD undergoing PET MPI. Thepatients were followed-up for 3.2 years. As expected, the low global perfusion reserve was associated with greater hazard of all-cause death. More interestingly, the patients with global perfusion reserve ≤1.8 had a survival benefit with early revascularization, regardless of the level of regional ischaemia. However, the patients with preservedperfusion reserve had no benefit of revascularization over medicaltherapy (*Figure 3*).[26] The results are concordant with earlier findingsshowing that large ischaemia justifies revascularization[27,28] and extend this notion also to global myocardial perfusion reserve.

^{18}F-fluoride PET imaging is gaining increasing interest in variousconditions as an indicator of tissue microcalcification, which is occurring in atherosclerosis. Creager *et al.*[29] investigated in an *ex vivo* studyif ^{18}F-fluoride accumulation on atherosclerotic plaques are related tothe development of microcalcifications that are not visible on CT. Inthis complex study, ^{18}F-fluoride signal in tissue analysis of human andmouse specimens was found to be clearly linked with small microcalcifications, which were not detected on CT. These results confirmthat plaque mineralization is an active process and that ^{18}F-fluoride PET imaging detects coronary and carotid plaques with high-risk features.

In the study by Cartlidge *et al.*,[30] the degeneration of bio-

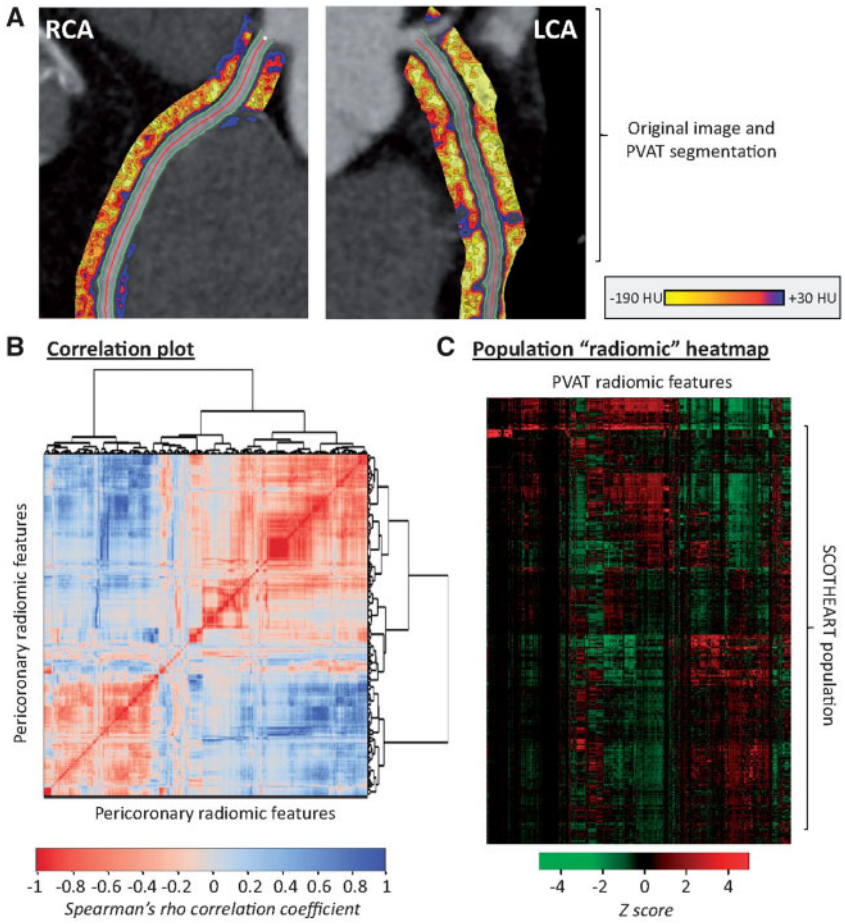

Figure 4 Radiomic phenotyping of coronary perivascular adipose tissue. (A) The perivascular adipose tissue (PVAT) of the right (RCA) and left (LCA) coronary was segmented and used to calculate a number of shape-, attenuation-, and texture-related statistics. (B) Correlation plot of all 1391 stable radiomic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

prostheticaortic valve was investigated using ^{18}F-fluoride PET. In *ex vivo* analyses,the ^{18}F-fluoride uptake colocalized with tissue degeneration on histology. In patients with aortic bioprostheses, increased valve ^{18}F-fluoride uptake in PET imaging was associated with more rapid deterioration in valve function at 2-year follow-up. Aortic bioprosthesis dysfunction was detected in 10 patients and all of them showed^{18}F-fluoride uptake at baseline when still the valve haemodynamicswere normal. On multivariable analysis, ^{18}F-fluoride uptake was theonly independent predictor of future bioprosthetic dysfunction. Although a larger patient cohort is needed, ^{18}F-fluoride PET imaging appears promising method in predicting dysfunction of bioprostheticvalves.

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

Another challenging population is patients with suspected infectionof cardiac implantable electronic devices. In a study by Calais *et al.*,[32]the diagnostic positive and negative predictive values were 80% and91% for FDG PET and 100% and 85% for white blood cell SPECT, respectively. A prolonged antibiotic therapy before imaging tended todecrease the sensitivity for both techniques. As FDG is not specificfor inflammation but for glucose uptake, more specific imaging agentsfor infection are being developed.

Computed tomography

Cardiac computed tomography has evolved into a one-stop-shop imaging tool that can provide valuable diagnostic and prognostic information in patients with suspected or known CAD. Assessment of coronary artery calcium (CAC) score on CT can be used as a riskmodifier and may guide statin therapy. Mitchel *et al.*[33] assessed therelative impact of statins on adverse cardiovascular events stratifiedby CAC scores in 13 644 patients (mean age 50 years; 71% men)who were followed-up for a median of 9.4 years. Patients without CAC had an excellent prognosis irrespective of statin therapy whereas in patients

with CAC > 0 statin therapy was associated withreduced risk of major adverse cardiovascular events (adjusted subHR 0.76; 95% CI 0.60–0.95; *P* = 0.015). The effect of statin use on major adverse cardiovascular events was significantly related to theseverity of CAC (*P* < 0.0001 for interaction), with a number needed to treat to prevent 1 initial major adverse cardiovascular events over10 years ranging from 100 (when CAC was 1–100) to 12 (if CAC >100). A recent *post hoc* analysis of the SCOT-HEART trial demonstrated that coronary heart disease death or non-fatal MI was threetimes more frequent in patients with high-risk plaque features (positive remodelling or low attenuation plaque) and was twice as frequent in those with obstructive CAD.[34] However, these associationswere not independent of CAC score, a surrogate measure of atherosclerosis burden.

The investigators of the PROMISE Trial assessed the prevalenceand clinical predictors of high-risk CAD (defined as left main stenosisor either ≥50% stenosis or ≥70% stenosis of 3 vessels or 2-vessel CAD involving the proximal left anterior descending artery).[35] Highrisk CAD was identified in 6.6% (≥50% stenosis) and 2.4% (≥70% stenosis) of patients. Variables predictive of high-risk CAD included family history of premature CAD, age, male sex, lower glomerular filtration rate, diabetes mellitus, elevated systolic blood pressure, andangina. High-risk CAD was associated with more frequent invasiveinterventions and adverse events as compared to non-high-risk CAD.

An intriguing study has investigated the prognostic value of combined information of lesion-specific ischaemia (FFR) and adverse plaque features by CCTA.[36] The authors evaluated 772 vessels (299 patients) by both CCTA and invasive FFR measurement.Interestingly, the presence of ≥3 high-risk plaque features was independently associated with clinical events in the FFR > 0.80 group, butnot in the FFR ≤0.80 group. It seems that the integration of both lesion-specific ischaemia and CT plaque features may provide betterprognostic stratification than either individual component alone, especially in patients with *n* FFR >0.80.

Using computational fluid dynamics simulations CT is now capable to provide non-invasive FFR measurements. A study by Norgaard *et al.*[37] assessed real-world clinical outcomes following a diagnostic strategy including first-line coronary CTA with selective FFR_{CT} testing. The study reviewed the results of 3674 consecutive patients with stable chest pain evaluated with CTA and FFR_{CT} testing. The presence of intermediate-range CAD and FFR_{CT} >0.80 was associated with favourable clinical outcomes similar to the prognosis in patients without or with minimal evidence of CAD. Beyond FFR_{CT} simulation stress CT perfusion has emerged as a potential strategy to acquire anatomic and functional evaluation of CAD. Whole heart coverage CT scanners have become readily available, which allow a more robust stress CT MPI (CTP). The diagnostic accuracy of latest scanner generation was tested by Pontone *et al.*[38] in 100 intermediateto high-risk symptomatic patients with suspected CAD. CCTA alone demonstrated a sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83%, respectively. Combining CCTA with stress CTP, these values were 91%, 94%, 96%, 86%, and 93%, respectively, with a significant improvement in specificity, positive predictive value, and accuracy. The mean effective radiation dose for CCTA and stress CTP were 2.8 ± 1.4 mSv and 2.5 ± 1.1 mSv. Patients with diabetes are a high-risk patient cohort for adversecardiovascular outcomes. The PROMISE Trial investigators assessedwhether a diagnostic strategy based on CCTA is superior to functional stress testing in reducing cardiovascular death or MI amongsymptomatic patients with diabetes [*n* = 1908 (21%)] vs. patients without diabetes [*n* = 7058 (79%)].[39] Patients with diabetes who underwent CCTA had a lower risk of cardiovascular death or MI compared with functional stress testing [CCTA: 1.1% (10 of 936) vs.stress testing: 2.6% (25 of 972); adjusted HR 0.38; 95% CI 0.18–0.79; *P* = 0.01]. Another study including also individuals with diabetes,investigated the rate and extent of plaque progression, changes in plaque features, and clinical predictors of plaque progression.[40] A totalof 1602 patients who underwent serial CCTA (median scan interval 3.8 years) were enrolled and analysed from the PARADIGM (Progression of Atherosclerotic Plaque Determined by ComputedTomographic Angiography Imaging) trial.[41] Diabetes was an independent risk factor for plaque progression (OR 1.526, 95% CI 1.100–2.118; *P*=0.011).

A more precise risk assessment that incorporates the detection ofcoronary inflammation would allow personalized medical interventions. Novel analytical techniques such perivascular fat attenuationindex or plaque-based radiomics may facilitate the detection and quantification of pericoronary inflammation and atherosclerotic plaque activity.[42,43] An innovative study by Oikonomou *et al.*[44] demonstrated that artificial intelligence powered pericoronary fat radiomicprofile (FRP) analysis significantly improved major adverse cardiovascular events prediction beyond traditional risk stratification that included risk factors, CAC, coronary stenosis, and high-risk plaquefeatures on CCTA in the SCOT-HEART trial (*Figure 4*). The authors conclude that FRP leads to a significant improvement of cardiac riskprediction over and above the current state-of-the-art, which mighthelp to identify patients with elevated residual risk for cardiovascularevents.

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

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

Ramos *et al.*[45] used an animal (mice) model to study myocardialhealing after infarction using serial imaging (7

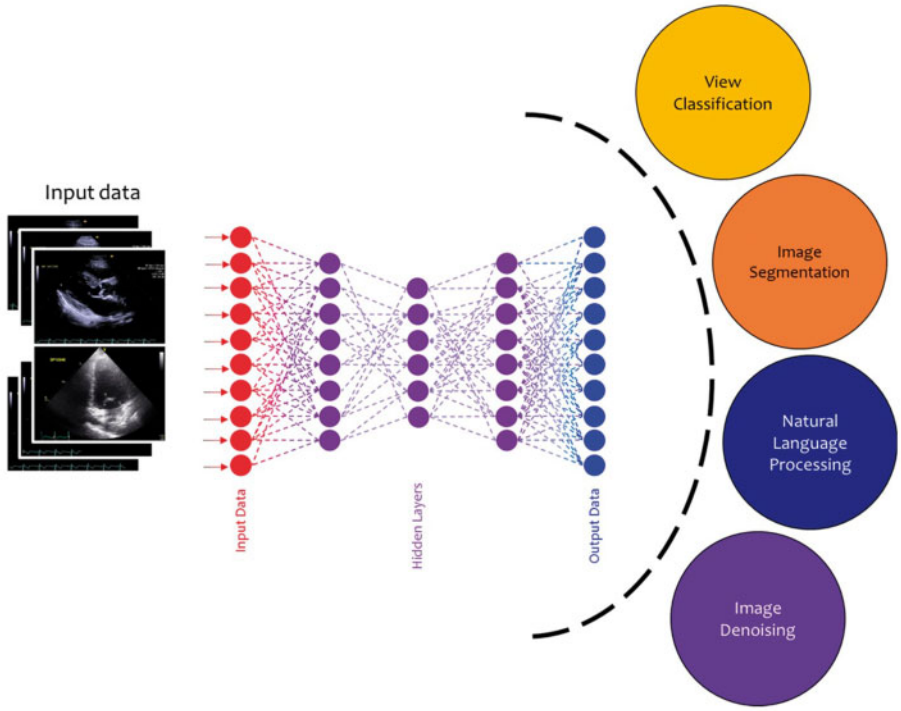

Figure 5 Machine learning algorithms applied to echocardiography. Echocardiographic data are post-processed to automate many processes performed in clinical practice by cardiologists and sonographers such as view classification and image segmentation that will lead to the interpretation of the data and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

days and 21 days postinfarction) with 3 T magnetic resonance imaging (MRI) and a 19F/1Hsurface coil. Injected 19F-perfluorocarbon nanoparticles were usedto evaluate recruitment of inflammatory cells (e.g. macrophages), and an injected gadolinium-based elastin-binding contrast agent was usedto assess elastin content. The combination of these imaging techniques enabled assessing the time course of the remodelling and healing process, as well as scar development.

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

Several articles in the field of multimodality and fusion imaging are worth to highlight. Mitral annular calcification is observed in patients with mitral regurgitation/stenosis and is important when transcatheter valve replacement is considered. To better understand pathophysiology, Massera *et al.*[47] performed CT calcium score of the mitral annulus, as well as PET with ^{18}F-fluoride (calcification activity) and ^{18}F-FDG (inflammation activity) in 104 patients. Mitral annular calcification was noted in 35 patients who exhibited increased ^{18}F-fluoride uptake and FDG uptake, suggesting increased local calcification and inflammation. Fernandez-Friera *et al.*[48] used hybrid FDG PET/MRI to assess arterial vascular plaques in middle-aged individuals (n = 755). With this sophisticated imaging technology, the authors evaluated multiterritorial atherosclerosis (carotid, aortic, and ilio-femoral arteries);plaques were present on MRI in 90.1% (73.9% femorals, 55.8% iliacs,and 53.1% carotids), whereas inflammation was observed on PET in48.2% of individuals (24.4% femorals, 19.3% aorta, 15.8% carotids,and 9.3% iliacs). The authors concluded that arterial inflammation isnoted in 50% of arterial plaques in middle-aged individuals.

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

Another excellent review was published by Krittanawong *et al.*[2]providing further insight in deep learning. This is a branch of artificialintelligence, which combines computer science, statistics and decision theory to discover patterns in complex and big data. CasaclangVerzosa *et al.*[50] applied machine learning to advanced network analysis to demonstrate automated assessment of LV (hypertrophy) inresponse to aortic valve stenosis from echocardiographic images. Finally, Zhang *et al.*[51] published original research on the use of deeplearning to analyse echocardiographic data (n = 14 035 echocardiograms), in a fully automated fashion, including (i) view identifica-

tion, (ii) image segmentation, (iii) quantification of structure and function,and (iv) disease detection. Specifically, convolutional neural networkswere trained to detect hypertrophic cardiomyopathy, cardiac amyloidosis, and pulmonary arterial hypertension with respective C statistics of 0.93, 0.87, and 0.85.

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▼ Ovaj lijek je predmet dodatnog praćenja/nadzora. Ovo će omogućiti da se nove bezbjedonosne informacije o lijeku pribave u što kraćem vremenu. Od zdravstvenih stručnjaka se traži da prijave svaku sumnju na neželjeno dejstvo predmetnog lijeka. **Sastav:** *Xarelto 15 mg:* Svaka film tableta sadrži 15 mg rivaroksabana. Svaka film tableta sadrži 24,13 mg laktoze (u obliku monohidrata). *Xarelto 20 mg:* Svaka film tableta sadrži 20 mg rivaroksabana. Svaka film tableta sadrži 21,76 mg laktoze (u obliku monohidrata). **Indikacije:** Prevencija inzulta i sistemske embolije kod odraslih pacijenata sa ne-valvularnom fibrilacijom atrija, sa jednim ili više faktora rizika, kao što su kongestivno zatajenje srca, hipertenzija, starost ≥ 75 godina, diabetes mellitus, raniji inzult ili prolazni ishemijski atak. Tretman duboke venske tromboze (DVT) i plućne embolije (PE), te prevencija rekurentne DVT i PE kod odraslih osoba. **Kontraindikacije:** Preosjetljivost na aktivnu supstancu ili bilo koju pomoćnu supstancu.; Aktivno klinički značajno krvarenje.; Lezija ili stanje, ukoliko se smatra da je značajan rizik za veliko krvarenje. Ovo može uključivati trenutnu ili nedavnu gastrointestinalnu ulceraciju, prisustvo malignih neoplazmi sa povećanim rizikom od krvarenja, nedavnu ozljedu mozga ili kičmene moždine, nedavni hirurški zahvat na mozgu, kičmenoj moždini ili oku, nedavno intrakranijalno krvarenje, ukoliko se zna ili se sumnja na varikozitete jednjaka, arteriovenske malformacije, vaskularne aneurizme ili velike intraspinalne ili intracerebralne vaskularne abnormalnosti.; Istovremeno liječenje sa nekim drugim antikoagulansima, npr. nefrakcioniranim heparinom (UFH), niskomolekularnim heparinima (enoksaparinom, dalteparinom, itd.), derivatima heparina (fondaparinuksom, itd.), oralnim antikoagulansima (varfarinom, dabigatran eteksilatom, apiksabanom, itd.), osim u specifičnim uslovima kada se mijenja antikoagulansna terapija ili kada je nefrakcionirani heparin (UFH) primijenjen u dozama potrebnim za održavanje otvorenog centralnog venskog ili arterijskog katetera.; Bolest jetre povezana sa koagulopatijom i klinički značajnim rizikom od krvarenja uključujući pacijente sa cirozom sa Child Pugh B i C.; Trudnoća i dojenje. **Doziranje:** *Prevencija inzulta i sistemske embolije:* Preporučena doza je 20 mg jednom dnevno, što je također i preporučena maksimalna doza. *Tretman DVT, tretman PE i prevencija rekurentne DVT i PE:* Preporučena doza za početno liječenje akutne DVT ili PE je 15 mg dva puta dnevno tokom prve tri sedmice, nakon čega slijedi 20 mg jednom dnevno za nastavak liječenja i prevencije rekurentne DVT i PE. Kada je indicirana produžena prevencija rekurentne DVT i PE (nakon završetka najmanje 6 mjeseci terapije za DVT ili PE) preporučena doza je 10 mg jednom dnevno. Kod pacijenata kod kojih se rizik od rekurentne DVT ili PE smatra velikim, kao što su oni sa komplikovanim komorbiditetima ili kod kojih je rekurentna DVT ili PE nastala tokom produžene prevencije sa lijekom Xarelto u dozi od 10 mg jednom dnevno, potrebno je razmotriti lijek Xarelto u dozi od 20 mg jednom dnevno. *Pacijenti koji se podvrgavaju kardioverziji:* Liječenje sa lijekom Xarelto se može započeti ili nastaviti kod pacijenata kod kojih može biti potrebna kardioverzija. Za kardioverziju vođenu transezofagealnim ehokardiogramom (TEE) kod pacijenata koji prethodno nisu liječeni sa antikoagulansima, liječenje sa lijekom Xarelto treba započeti najmanje 4 sata prije kardioverzije kako bi se osigurala odgovarajuća antikoagulacija. Za sve pacijente, prije kardioverzije mora se zatražiti potvrda da je pacijent uzimao lijek Xarelto kako mu je bilo propisano. Prilikom odluke o započinjanju i trajanju liječenja moraju se uzeti u obzir preporuke iz važeće smjernice za antikoagulacijsko liječenje kod pacijenata koji se podvrgavaju kardioverziji. *Pacijenti sa ne-valvularnom fibrilacijom atrija koji se podvrgavaju perkutanoj koronarnoj intervenciji (PCI), eng. percutaneous coronary intervention) sa postavljanjem stenta:* Postoji ograničeno iskustvo sa smanjenom dozom lijeka Xarelto 15 mg jednom dnevno (ili lijeka Xarelto 10 mg jednom dnevno za pacijente sa umjerenim oštećenjem funkcije bubrega [klirens kreatinina 30 – 49 ml/min]), dodatno uz P2Y12 inhibitor tokom najviše 12 mjeseci kod pacijenata sa ne-valvularnom fibrilacijom atrija kojima je potrebna oralna antikoagulacija i koji se podvrgavaju perkutanoj koronarnoj intervenciji sa postavljanjem stenta. **Način primjene:** Za oralnu primjenu. Tablete lijeka Xarelto treba uzeti sa hranom. Za pacijente koji ne mogu progutati cijele tablete, tableta lijeka Xarelto se može zdrobiti i pomiješati sa vodom ili kašom od jabuke neposredno prije primjene i primijeniti oralno. Nakon primjene zdrobljenih film tableta lijeka Xarelto 15 mg ili 20 mg, za dozom treba odmah uslijediti hrana. Zdrobljena tableta lijeka Xarelto se također može dati kroz želučanu sondu nakon potvrde da je sonda ispravno postavljena u želudac. Zdrobljena tableta se putem želučane sonde mora primijeniti u maloj količini vode, nakon čega se sonda treba isprati sa vodom. Nakon primjene zdrobljenih film tableta lijeka Xarelto 15 mg ili 20 mg, za dozom treba odmah uslijediti enteralna prehrana. **Posebna upozorenja i mjere opreza:** Preporučuje se kliničko praćenje u skladu sa praksom antikoagulacije tokom perioda liječenja. *Rizik od krvarenja:* Kao i sa drugim antikoagulansima, pacijenti koji uzimaju lijek Xarelto se moraju pažljivo pratiti na znakove krvarenja. Preporučuje se da se koristi sa oprezom u stanjima sa povećanim rizikom od krvarenja. Primjena lijeka Xarelto se mora prekinuti ukoliko se pojavi teško krvarenje. U kliničkim ispitivanjima, krvarenja iz sluznice (tj. epistaksa, krvarenje desni, gastrointestinalno i genitourinarno krvarenje, uključujući abnormalno vaginalno ili povećano menstrualno krvarenje) i anemija su zabilježeni češće tokom dugotrajnog liječenja sa rivaroksabanom u poređenju sa liječenjem sa antagonistima vitamina K (VKA). Stoga, pored odgovarajućeg kliničkog praćenja, laboratorijsko određivanje hemoglobina/hematokrita može biti od značaja za otkrivanje okultnog krvarenja i određivanje kliničkog značaja vidljivog krvarenja, ukoliko se procijeni potrebnim. Nekoliko podgrupa pacijenata imaju povećani rizik od krvarenja. Ovi pacijenti se moraju pažljivo pratiti na znakove i simptome komplikacija krvarenja i anemije nakon početka liječenja. Pri svakom neobjašnjivom padu hemoglobina ili krvnog pritiska mora se potražiti mjesto krvarenja. Premda liječenje sa rivaroksabanom ne zahtijeva rutinsko praćenje izloženosti, mjerenje koncentracija rivaroksabana sa kalibriranim kvantitativnim anti-faktor Xa testom može biti korisno u izuzetnim situacijama u kojima poznavanje izloženosti rivaroksabanu može pomoći kao informacija u kliničkim odlukama, npr. pri predoziranju i hitnom hirurškom zahvatu. *Oštećenje funkcije bubrega:* Kod pacijenata sa teškim oštećenjem funkcije bubrega (klirens kreatinina < 30 ml/min) koncentracije rivaroksabana u plazmi mogu biti značajno povećane (1,6 puta u prosjeku), što može dovesti do povećanog rizika od krvarenja. Lijek Xarelto je potrebno koristiti sa oprezom kod pacijenata sa klirensom kreatinina 15–29 ml/min. Ne preporučuje se primjena kod pacijenata sa klirensom kreatinina < 15 ml/min. Kod pacijenata sa oštećenjem funkcije bubrega koji istovremeno uzimaju druge lijekove koji povećavaju koncentracije rivaroksabana u plazmi, lijek Xarelto je potrebno koristiti sa oprezom. *Interakcija sa drugim lijekovima:* Primjena lijeka Xarelto se ne preporučuje kod pacijenata koji istovremeno sistemski uzimaju azolne antimikotike (kao što su ketokonazol, itrakonazol, vorikonazol i posakonazol) ili inhibitore HIV proteaze (npr. ritonavir). Ove aktivne supstance su jaki inhibitori oba enzima i CYP3A4 i P-gp i stoga mogu povećati koncentracije rivaroksabana u plazmi do kliničkí značajnog stepena (2,6 puta u prosjeku), što može dovesti do povećanog rizika od krvarenja. Potrebno je obratiti pažnju ukoliko se pacijenti istovremeno liječe sa lijekovima koji utječu na hemostazu, kao što su nesteroidni antiinflamatorni lijekovi (NSAIDs), acetilsalicilna kiselina i inhibitori agregacije trombocita ili selektivni inhibitori ponovne pohrane serotonina (SSRIs) i inhibitori ponovne pohrane serotonina i noradrenalina (SNRIs). Za pacijente koji imaju rizik od ulcerozne gastrointestinalne bolesti može se razmotriti odgovarajuće profilaktičko liječenje. *Drugi faktori rizika od krvarenja:* Kao i sa drugim antitromboticima, rivaroksaban se ne preporučuje kod pacijenata sa povećanim rizikom od krvarenja kao što su: kongenitalni ili stečeni poremećaji krvarenja; teška arterijska hipertenzija koja nije kontrolisana; druga gastrointestinalna bolest bez aktivnih ulceracija, koja potencijalno može dovesti do komplikacija sa krvarenjem (npr. upalna bolest crijeva, ezofagitis, gastritis i gastroezofagealna refluksna bolest); vaskularna retinopatija; bronhiektazije ili anamneza plućnog krvarenja. *Pacijenti sa vještačkim valvulama:* Sigurnost i učinkovitost lijeka Xarelto nisu ispitivani kod pacijenata sa vještačkim srčanim valvulama; stoga, nema podataka koji podržavaju da lijek Xarelto pruža odgovarajuću antikoagulaciju kod ove populacije pacijenata. Liječenje sa lijekom Xarelto se ne preporučuje kod ovih pacijenata. *Pacijenti sa ne-valvularnom fibrilacijom atrija koji se podvrgavaju perkutanoj koronarnoj intervenciji (PCI) sa postavljanjem stenta:* Klinički podaci su dostupni iz intervencijskog ispitivanja sa primarnim ciljem procjene sigurnosti kod pacijenata sa ne-valvularnom fibrilacijom atrija koji se podvrgavaju perkutanoj koronarnoj intervenciji sa postavljanjem stenta. Podaci o učinkovitosti kod ove populacije su ograničeni. Nisu dostupni podaci za takve pacijente sa historijom moždanog udara/tranzitornog ishemijskog ataka. *Hemodinamski nestabilni pacijenti sa plućnom embolijom ili pacijenti koji zahtijevaju trombolizu ili plućnu embolektomiju:* Lijek Xarelto se ne preporučuje kao alternativa nefrakcioniranom heparinu kod pacijenata sa plućnom embolijom koji su hemodinamski nestabilni ili mogu primati trombolizu ili plućnu embolektomiju, pošto sigurnost i učinkovitost lijeka Xarelto nisu utvrđeni u ovim kliničkim situacijama. *Spinalna/epiduralna anestezija ili punkcija:* Prilikom izvođenja neuroaksijalne anestezije (spinalne/epiduralne anestezije) ili spinalne/epiduralne punkcije, pacijenti koji su liječeni sa antitrombotskim agensima za prevenciju tromboembolijskih komplikacija izloženi su riziku od razvoja epiduralnog ili spinalnog hematoma, koji može rezultirati dugotrajnom ili trajnom paralizom. Rizik od ovih događaja se može povećati postoperativnim korištenjem trajnih epiduralnih katetera ili istovremenom primjenom lijekova koji utječu na hemostazu. Rizik se također može povećati traumatskom ili ponovljenom epiduralnom ili spinalnom punkcijom. Pacijenti se moraju učestalo pratiti na znakove i simptome neurološkog oštećenja (npr. utrnulost ili slabost u nogama, disfunkcija crijeva ili mokraćnog mjehura). Ukoliko se primijeti neurološki poremećaj, potrebna je hitna dijagnostička obrada i liječenje. Prije neuroaksijalne intervencije ljekar mora razmotriti potencijalnu korist u odnosu na rizik kod pacijenata koji primaju antikoagulanse ili kod pacijenata koji će primati antikoagulanse za tromboprofilaksu. Nema kliničkog iskustva sa primjenom 15 mg rivaroksabana u ovakvim situacijama. Kako bi se smanjio mogući rizik od krvarenja povezan sa istovremenom primjenom rivaroksabana i neuroaksijalne anestezije (spinalne/epiduralne anestezije) ili spinalne punkcije, potrebno je razmotriti farmakokinetički profil rivaroksabana. Postavljanje ili uklanjanje epiduralnog katetera ili lumbalna punkcija najbolje se provode kada je antikoagulansni učinak rivaroksabana procijenjen kao nizak. Međutim, tačno vrijeme potrebno za postizanje dovoljno niskog antikoagulansnog učinka kod svakog pacijenta nije poznato. Za uklanjanje epiduralnog katetera i na temelju opštih farmakokinetičkih karakteristika mora proći najmanje dvostruko poluvrijeme, odnosno najmanje 18 sati kod mladih pacijenata i 26 sati kod starijih pacijenata od posljednje primjene rivaroksabana (vidjeti poglavlje 5.2). Nakon uklanjanja katetera, najmanje 6 sati mora proći prije primjene slijedeće doze rivaroksabana. Ukoliko se dogodi traumatska punkcija, primjena rivaroksabana se mora odložiti za 24 sata. *Preporuke za doziranje prije i nakon invazivnih postupaka i hirurških intervencija:* Ukoliko je potreban invazivni postupak ili hirurška intervencija, lijek Xarelto 15 mg ili 20 mg se mora prestati uzimati najmanje 24 sata prije intervencije, ukoliko je moguće i na temelju kliničke procjene ljekara. Ukoliko se postupak ne može odložiti, mora se procijeniti povećani rizik od krvarenja u odnosu na hitnost intervencije. Lijek Xarelto se mora što prije ponovo početi uzimati nakon invazivnog postupka ili hirurške intervencije, pod uslovom da to dozvoljava klinička situacija i da je uspostavljena odgovarajuća hemostaza prema ocjeni nadležnog ljekara. *Starija populacija:* S povećanjem dobi može se povećati rizik od krvarenja. *Dermatološke reakcije:* Ozbiljne kožne reakcije, uključujući Stevens-Johnsonov sindrom/toksičnu epidermalnu nekrolizu i DRESS sindrom, zabilježene su tokom praćenja nakon stavljanja lijeka u promet u vezi sa primjenom rivaroksabana. Izgleda da su pacijenti u najvećem riziku od ovih reakcija na početku terapije: do početka reakcije u većini slučajeva dolazi unutar prvih sedmica liječenja. Primjena rivaroksabana se treba prekinuti pri prvoj pojavi teškog kožnog osipa (npr. osipa koji se širi, intenzivan je i/ili je praćen stvaranjem mjehurića) ili bilo kojeg drugog znaka preosjetljivosti u vezi sa lezijama sluznice. *Informacije o pomoćnim supstancama:* Lijek Xarelto sadrži laktozu. Pacijenti sa rijetkim nasljednim poremećajem nepodnošenja galaktoze, nedostatkom "*Lapp laktaze*" ili glukoza-galaktoza malapsorpcijom ne bi trebali uzimati ovaj lijek. **Neželjeni efekti:** *Česti neželjeni efekti:* anemija, vrtoglavica, glavobolja, krvarenje u oku (uključujući krvarenje u konjunktivu), hipotenzija, hematom, epistaksa, hemoptiza, gingivalno krvarenje, krvarenje u gastrointestinalnom traktu (uključujući rektalno krvarenje), gastrointestinalni i abdominalni bol, dispepsija, nauzeja, konstipacija, dijareja, povraćanje, povećane transaminaze, pruritus (uključujući manje česte slučajeve generaliziranog pruritusa), osip, ekhimoza, kožno i potkožno krvarenje, bol u ekstremitetima, krvarenje u urogenitalni trakt (uključujući hematuriju i menoragiju), oštećenje funkcije bubrega (uključujući povećani kreatinin u krvi, povećanu ureu u krvi), vrućica, periferni edemi, smanjena opšta snaga i energija (uključujući umor i asteniju), postproceduralno krvarenje (uključujući postoperativnu anemiju i krvarenje iz rane), kontuzija, sekrecija iz rane. *Manje česti neželjeni efekti:* trombocitoza (uključujući povećani broj trombocita), trombocitopenija, alergijska reakcija, alergijski dermatitis, angioedem i alergijski edem, cerebralno i intrakranijalno krvarenje, sinkopa, tahikardija, suha usta, oštećenje funkcije jetre, povećani bilirubin, povećana alkalna fosfataza u krvi, povećani GGT, urtikarija, hemartroza, loše osjećanje (uključujući malaksalost), povećani LDH, povećana lipaza, povećana amilaza. **Način izdavanja lijeka:** Lijek se izdaje na ljekarski recept. **Nosilac dozvole za stavljanje gotovog lijeka u promet:** Bayer d.o.o., Trg solidarnosti 2a, Sarajevo. **Broj i datum rješenja o dozvoli za stavljanje gotovog lijeka u promet:** *Xarelto 15 mg:* 04-07.3-2-7287/16 od 23.3.2017.; *Xarelto 20 mg:* 04-07.3-2- 7288/16 od 23.3.2017.

Reference:
1. Xarelto®(rivaroxaban). SmPC odobren od ALMBiH

PP-XAR-BA-0030-1
14 Mar 2019

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Brzo i efikasno do cilja

INDIKACIJE:

Liječenje hiperholesterolemije	Prevencija kardiovaskularnih događaja
Početna doza: 5-10 mg jednom dnevno Maksimalna doza: 40 mg jednom dnevno	20 mg jednom dnevno

- **efikasan u terapiji hiperholesterolemije i prevencije KV događaja**
- **kada je potreban snažan i pouzdan efekat na LDL holesterol**
  - prosječan procenat smanjenja LDL holesterola preko 40% već sa dozom od 5 mg
  - najveći procenat prosječnog smanjenja LDL holesterola među statinima
- **kada je potrebno efikasno povećanje HDL holesterola**
  - najveći procenat povećanja HDL holesterola u svim doznim segmentima
  - efikasniji od ostalih statina u nižim terapijskim dozama
- **za više pacijenata sa dostignutim ciljnim vrijednostima lipida**
- **za primarnu prevenciju (kod pacijenata sa visokim rizikom značajno smanjuje broj velikih KV događaja: infarkt miokarda, moždani udar i KV smrt)**
- **u visokoj dozi (40 mg) kod pacijenata sa uznapredovalom koronarnom bolešću dovodi do značajne regresije ateroskleroze**

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