Received: 24 October 2018 | Revised: 15 December 2018 | Accepted: 18 December 2018

DOI: 10.1002/clc.23139

WILEY CLINICAL CARDIOLOGY

REVIEW

Clinical scores used for the prediction of negative events in patients undergoing catheter ablation for atrial fibrillation

Falco Kosich[1] | Katja Schumacher[1] | Tatjana Potpara[2] | Gregory Y. Lip[3] | Gerhard Hindricks[1] | Jelena Kornej[1,4]

[1]Department of Electrophysiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany

[2]Cardiology Clinic, Clinical Center of Serbia, School of Medicine, Belgrade University, Belgrade, Serbia

[3]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[4]Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany

Correspondence
Falco Kosich, Heart Center Leipzig, HELIOS Kliniken GmbH, Department of Electrophysiology, Struempellstrasse 39, 04289 Leipzig, Germany.
Email: falco.kosich@gmail.com

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults. Catheter ablation (CA) is one of the most important management strategies to reduce AF burden and AF-associated complications. In order to stratify the risk of adverse events and to predict treatment success in AF patients undergoing CA, several risk stratification scores had been developed during the last decade. The aim of this review is to provide an overview of the most important clinical risk scores predicting rhythm outcomes, electro-anatomical substrate and mortality in AF.

KEYWORDS

atrial fibrillation, biomarkers, mortality, electro-anatomical remodeling, recurrences, scores

1 | INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults. Catheter ablation (CA) is important management strategy to reduce AF burden and AF-associated complications.[1] In general, AF is associated with several cardio- and cerebrovascular complications, such as heart failure, stroke, and death. Furthermore, AF recurrence rates after single CA range from 30% to 50%,[2] often requiring repeated CA and leading to increased treatment costs. Pathophysiological, electrical, and structural atrial remodeling plays an important role in AF pathogenesis[3,4] and is associated with endothelial damage, inflammation, and fibrosis.[5] Several pro-fibrotic blood biomarkers[6,7] as well as electro-anatomical mapping during CA[8] and magnetic resonance imaging (MRI) techniques[9,10] had been shown to predict these remodeling processes.

In order to stratify the risk of negative outcomes in AF patients undergoing CA, several risk prediction scores had been developed. These risk scores were established on the basis of various clinical factors, such as age, gender, body mass index (BMI), AF type, left atrial (LA) size, heart failure, chronic kidney disease, and early AF recurrences (ERAF).[11–18] Clinical risk scores can be categorized by their selection of predictive factors (ie, biomarker-based or clinical variable-based risk scores). First, there are several scores, such as $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 that were originally developed to predict thromboembolic events in AF patients.[11–13] Later on, rhythm

Abbreviations: AF, atrial fibrillation; ANP, atrial natriuretic peptide; AUC, area under the curve; BMI, body mass index; BNP, B-type natriuretic peptide; CA, catheter ablation; CBA, cryoballoon ablation; EF, ejection fraction; eGFR, estimated Glomerular Filtration Rate; ERAF, early recurrence of atrial fibrillation; IDI, integrated discrimination improvement; LA, left atrium; LRAF, late recurrence of atrial fibrillation; LVA, low voltage area; MACE, major adverse cardiology event; MI, myocardial infarction; MRI, magnetic resonance imaging; NRI, net reclassification improvement; OR, odds ratio; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; ROC, receiver operating characteristics; VLRAF, very late recurrence atrial fibrillation.

Falco Kosich and Katja Schumacher contributed equally to this study.

outcome-specific prediction scores, such as ALARMEc, BASE-AF$_2$, APPLE, CAAP-AF, and MB-LATER, were introduced.[15–20] Recently, the prediction of mortality (2MACE)[21] or electro-anatomical substrate (DR-FLASH)[22] had been investigated **(Table 1)**. Furthermore, it had been shown that electro-anatomical substrate measured during CA[22,23] or through MRI,[9,10] was associated with arrhythmia recurrences after CA in AF patients.[9,22] Finally, blood biomarkers had become a promising tool for risk stratification and were included into several risk stratification tools (eg, ABC,[24–26] AEQ[27]).

The aim of this review is to provide an overview of the most important clinical risk scores predicting rhythm outcomes, electro-anatomical substrate, and mortality in AF patients undergoing CA for AF.

2 | SEARCH STRATEGY

Comprehensive electronic searches for relevant publications were performed in the PubMed database. For structural purposes, the literature research had been categorized according to different adverse events considered in this article. Major search terms were generated and combined with specific search terms for each event. The major search terms included "atrial fibrillation OR AF" AND "score OR risk OR index OR scheme OR ratio". As specific search terms the following list has been used:

1. AND "recurrence"
2. AND "LVA OR low voltage area OR substrate OR AF nest OR atrial foci OR atrial premature depolarization (APD)"
3. AND "death OR mortality"

Studies were included when they reported the prediction of an outcome in AF patients using risk assessment tools. Two authors (F.K. and J.K.) screened all retrieved publications for qualifications by title and abstract screening and full text reviewing. By applying this search strategy, we considered a number of publications and clinical scores to be relevant references for this article.

3 | SCORES (TABLE 1)

3.1 | CHADS$_2$/CHA$_2$DS$_2$-VASc

Both scores had been originally developed for stroke prediction in AF patients. The CHADS$_2$ consisted of five variables: one point for congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, and 2 points for previous stroke.[11] The scoring range is from 0 to 6 points. The predictive value for different adverse events in AF patients was tested in several studies. Congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes mellitus, previous stroke (2 points), vascular disease, age 65 to 74 years, and female sex were included to the CHA$_2$DS$_2$-VASc score.[12] The scoring range is from 0 to 9 points.

TABLE 1 Risk scores and variables

Risk scores	Age	Heart failure	Hypertension	Diabetes mellitus	Clinical history	Renal dysfunction	Biomarkers	Vascular disease	Cardiomyopathy	Sex category	AF type	LAD/ LAV	EF	MetS	BMI	ERAF	Smoking	AF duration	Antiarrhythmics failedh	BBB	LA sphericity	SHD	CHA2DS2-VASc	Stroke
2MACE	X	X			X			X						X										
ABC score	X				X		X																	
ALARMEc						X			X		X	X		X										
APPLE	X					X					X	X	X											
ATLAS	X									X	X	X					X							
BASE-AF$_2$											X				X	X	X	X						
CAAP-AF								X		X	X	X							X					
CHADS$_2$	X	X	X	X						X														X
CHA$_2$DS$_2$-VASc	X	X	X	X				X		X														X
DR-FLASH	X		X	X		X				X	X	X												
LAGO											X	X									X	X	X	
MB-LATER										X	X	X				X				X				

Abbreviations: AF, atrial fibrillation; BBB: bundle brunch block; BMI, body mass index; EF, ejection fraction; ERAF, early recurrence AF; LAD: left atrial diameter; LAV, left atrial volume; MetS, metabolic syndrome; SHD, structural heart disease.

3.2 | ALARMEc

The score was developed for the prediction of the arrhythmia recurrences after CA for AF, and ranges from 0 to 4 points[19]; AF clinical type, left atrium size, renal insufficiency, metabolic syndrome, and cardiomyopathy were considered for the ALARMEc score (1 point each).

3.3 | BASE-AF$_2$

The BASE-AF$_2$ score was developed to predict recurrences in AF patients after cryoballoon ablation (CBA).[15] BMI > 28 kg/m^2, atrial dilatation >40 mm, current smoking, early AF recurrence post-CA, duration of AF history of >6 years, and non-paroxysmal type of AF were included, each weighing 1 point.

3.4 | APPLE

The APPLE score includes age ≥ 65 years, persistent AF, impaired eGFR (<60 mL/min/1.73 m^2), LA diameter ≥ 43 mm, EF < 50% (1 point for each variable). Therefore, a maximum of five points could be achieved. The APPLE score can be used for the prediction of electro-anatomical substrate and recurrences after first and repeated CA in AF patients.[16,20]

3.5 | DR-FLASH

The DR-FLASH score was originally developed for the prediction of low voltage area (LVA). The clinical variables diabetes mellitus, renal dysfunction (assessed by using the Cockcroft-Gault formula), persistent form of AF, LA diameter > 45 mm, age > 65 years, female sex and hypertension were used in this score. Each variable scores 1 point, so the score's range is from 0 to 7 points.[22]

3.6 | CAAP-AF

This score was developed to predict AF freedom after CA and ranges from 0 to 13 points.[17] Coronary artery disease, left atrial diameter, age, presence of persistent, or long-standing AF, antiarrhythmics failed and female sex were included to CAAP-AF score.

3.7 | MB-LATER

Male sex, bundle brunch block, left atrium ≥ 47 mm, clinical type of AF, and early recurrent AF (ERAF) were included in the MB-LATER score. Each variable scores 1 point. The MB-LATER score was developed to predict very late recurrences of AF (VLRAF) >12 months after CA.[18]

3.8 | ATLAS

Age > 60 years (1 point), type of AF—non-paroxysmal (2 points), indexed left atrial volume (1 point for each 10 mL/m^2) female sex (4 points) and current smoking (7 points) were detected as independent predictors for arrhythmia recurrences after CA and they were included in the ATLAS score.[28]

3.9 | ABC death risk score

Age, heart failure in the clinical history, N-terminal pro-B-type natriuretic peptide, troponin-T, and growth differentiation factor-15 levels were included in the ABC death risk score.[24]

3.10 | 2MACE

The 2MACE scoring ranges from 0 to 7 points and it is composed of 2 points each for metabolic syndrome and age > 75 years. The remaining variables (myocardial infarction [MI]/revascularization; congestive heart failure [EF < 40%] and thromboembolic events) are rated with 1 point each.[21]

3.11 | LAGO

Five clinical items had been included to the LAGO score: AF phenotype, structural heart disease, CHA$_2$DS$_2$-Vasc score < 1, LA diameter and LA sphericity.[29] Each item scores 1 point.

4 | RHYTHM OUTCOMES AFTER CATHETER ABLATION

Arrhythmia recurrences after medical treatment (invasive or pharmacological) can be categorized into early recurrences (ERAF), late recurrences (LRAF) or very late recurrences of AF (VRLAF).[11] ERAF is defined as any atrial tachyarrhythmia occurring within 3 months after index procedure, LRAF refers to the recurrences between 3 and 12 months post-CA, and VLRAF denotes any atrial tachyarrhythmia recurrence, which occurs after 12 months after index procedure.

We identified eight risk assessment tools that had been applied for prediction of arrhythmia recurrences after radiofrequency ablation (RFA) or CBA for AF: CHADS$_2$, ALARMEc, BASE-AF$_2$, CAAP-AF, APPLE, MB-LATER, ATLAS, and LAGO **(Table 2)**.

Of note, there were substantial differences in the respective derivation cohort size among the scores. Generally, the scores developed in the large cohorts (eg, ATLAS, APPLE, and CAAP-AF) could have better generalizability than scores derived in smaller cohorts (ie, BASE-AF$_2$, ALARMEc, MB-LATER), but each score would require further validation. Although an external validation is an important quality criterion of the risk stratification tools, it was not performed for every score. Indeed, the ALARMEc, APPLE, and MB-LATER scores were the only scores that had been validated in several external cohorts.

The recurrence prediction using well-known stroke risk scores (ie, the CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$ scores) has been tested in several studies. All three scores were compared to each other and showed only modest ability to predict the arrhythmia recurrence after CA for AF.[30] However, CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$ were inferior compared to scores originally developed for arrhythmia recurrence, such as the APPLE and MB-LATER scores, for example.[16,18,20,31]

Of note, most of the arrhythmia outcomes-specific scores were developed to predict the ERAF and/or LRAF after AF CA, while the BASE-AF$_2$ and MB-LATER scores use ERAF as a variable for the LRAF/VLRAF prediction and, therefore, cannot be used at baseline,

TABLE 2 Rhythm outcome after catheter ablation

Study	Year	Participants	Scores	Results
Chao et al	2012	Overall: 238 PAF: 238	$CHADS_2$	A high CHADS2 score (cut-off ≥3) was an independent predictor for arrhythmia recurrence after CA
Wójcik et al	2013	Overall: 213PAF: 99	ALARMEc	ALARMEc demonstrated better predictive value than $CHADS_2$ and CHA_2DS_2-VASc scores for the prediction of arrhythmia recurrences after repeated catheter ablation (CBA and RFA)
Canpolat et al	2013	Overall: 236 PAF: 188	BASE-AF_2	BASE-AF_2 ≥ 3 points was an independent predictor for AF recurrences after CBA (AUC = 0.94; 95% CI: 0.89-0.97, $P < 0.001$)
Letsas et al	2014	Overall: 128 VPAF: 128	$CHADS_2$, CHA_2DS_2-VASc	$CHADS_2$ (AUC = 0.644) and CHA_2DS_2-VASc (AUC = 0.627) scores (cut-off >2) reached moderate predictive accuracy
Wójcik et al	2014	Overall: 911 PAF: 528	ALARMEc	ALARMEc score was able to predict the outcome after multiple ablation procedures. Success Rate after procedure was increased in patients with low ALARMEC
Kornej et al	2015	Overall: 1391 PAF: 710	APPLE	APPLE demonstrated better c-indices for the prediction of LRAF after RCAF than $CHADS_2$ and CHA_2DS_2-VAS
Wójcik et al	2015	Overall: 378 PAF: 320	ALARMEc	ALARMEc score could be used for the selection of patients before CBA. In patients with ≥3 points (high risk) CBA should be avoided
Jacobs et al	2015	Overall: 2179 PAF:1246	$CHADS_2$, CHA_2DS_2-VASc	Both scores can be used for recurrence prediction after first catheter ablation. CHA_2DS_2-VASc score reached slightly better results
Paylos et al	2016	Overall: 128 Only PAF	ALARMEc	Patients (PAF) with a low ALARMEc score had an excellent long-term outcome after CBA (second generation)
Winkle et al	2016	Overall:2062 PAF: 644	CAAP-AF	CAAP-AF score could be used for the prediction of AF freedom after ablation. A correlation between CAAP-AF score and amount of LA-scar (detected by magnetic resonance imaging) could be demonstrated
Kornej et al	2017	Overall: 379 PAF: 265	APPLE	APPLE score can be used for the prediction of arrhythmia recurrences after repeated catheter ablation. The APPLE score demonstrated better c-indices compared to $CHADS_2$ and CHA_2DS_2-VASc
Mujović et al	2017	Overall: 133 PAF: 92	MB-LATER	MB-LATER achieved the highest c-index for the prediction of VLRAF compared to APPLE, ALARMEc, BASE-AF_2, CHA_2DS_2-VASc, $CHADS_2$, and HATCH
Mesquita et al	2017	Overall: 1934 AF: 1488	ATLAS	ATLAS score was able to identify high-risk patients for AF-relapse after first PVI, despite of AF type. There was n't any comparison with other risk scores performed
Deng et al	2018	Overall: 1410 PAF: 1089	MB-LATER	MB-LATER was compared to six scores (HATCH, $CHADS_2$, CHA_2DS_2-VASc, BASE-AF_2, CAAP-AF, and APPLE. MB-LATER had been reached largest net reclassification improvement
Potpara et al	2018	Overall: 226 PAF: 142	MB-LATER	MB-LATER was compared with CAAP-AF, $CHADS_2$, and CHA_2DS_2-VASc. MB-LATER and CAAP-AF reached modest predictive value for LRAF
Bisbal et al	2018	Overall: 243 PAF: 160	LAGO	Different cardiovascular imaging parameters had been included to the LAGO score. The LAGO score can be used for recurrence prediction after RFA and CBA

Abbreviations: AF, atrial fibrillation; CBA, cryoballoon ablation; PAF, paroxysmal AF; PVI, pulmonary vein isolation; ERAF, early recurrence AF; LRAF, late recurrence AF; VLRAF, very late recurrence AF; RFA, radiofrequency ablation.

before index CA. Finally, the simplicity and practicality of a score are very important factors for its clinical relevance. The use of clearly defined variables, such as LA size, sex, or AF type, and easy score calculation are basic necessities. Except for the ALARMEc score, which is based on a complex calculation,[32] the introduced scores are mainly feasible.

Of note, the BASE-AF_2 score had been developed in an AF cohort undergoing CBA. The reliability of this score in the recurrence prediction after RFA is not proven so far.

4.1 | $CHADS_2$

Chao et al[11] investigated the predictive value of the $CHADS_2$ score for arrhythmia recurrences after catheter ablation. Two-hundred thirty-eight patients with paroxysmal AF undergoing radiofrequency catheter ablation had been included into analysis. This study demonstrated that LA diameter (hazard ratio [HR] 1.057, $P < 0.001$) and high $CHADS_2$ score (cut-off ≥3) (HR 1.372, $P < 0.001$) were independent predictors for arrhythmia recurrence after CA which occurred after 12 months follow-up (VLRAF).[11]

Several studies compared the $CHADS_2$ and CHA_2DS_2-VASc scores in terms of reccurrence prediction after CA. Letsas et al[33] demonstrated that the difference in receiver operating characteristics (ROC) between $CHADS_2$ (0.644) and CHA_2DS_2-VASc (0.627) did not reach significance ($P > 0.05$). However, even though their study had been based on a relatively small cohort (128 patients; median FU 16 months), both scores were able to predict recurrence after ablation effectively. In a cohort with 2179 patients (non-paroxysmal and paroxysmal), Jacobs et al had demonstrated that the CHA_2DS_2-VASc score is superior to the $CHADS_2$ score regarding the prediction of recurrence after catheter ablation.[34]

4.2 | ALARMEc

The ALARMEc score has been developed in a cohort of 213 patients (73 RFA and 140 CBA patients).[14] The authors reported the predictive value of the ALARMEc score for recurrences after repeat CA in comparison to the $CHADS_2$ and CHA_2DS_2-VASc scores. In the ROC curve analysis, ALARMEc (area under the curve [AUC] 0.657; $P < 0.001$) was superior to $CHADS_2$ (AUC 0.533; $P = 0.413$) and CHA_2DS_2-VASc (AUC 0.519; $P = 0.641$). Furthermore, the same group of authors showed in a larger cohort of 911 patients with a longer follow-up of 60 months that patients with moderate and high ALARMEc strata benefited from multiple procedures or more extensive substrate modification.[32] Of note, there are also controversial data regarding ALARMEc score showing that CBA should be avoided in patients with a high ALARMEc score (>2 points) because they have poor outcomes.[35] Interestingly, in another small study of 128 CBA patients, it was shown that a low ALARMEc score correlated with freedom from recurrent arrhythmia.[19] Although ALARMEc is the only study addressing prediction of recurrences both within 3 to 12 months and > 12 months, the results of this study are difficult to interpret because of non-standardized definitions of renal dysfunction and metabolic syndrome used in that study.[14,36]

4.3 | BASE-AF_2

The BASE-AF_2 score has been developed in a cohort of 238 patients with a follow-up of 30 months (median 20 months) after CBA. .[15] A higher BASE-AF_2 score (≥3 points) was significantly associated with AF recurrences (HR 3.34, $P = 0.001$). Since ERAF is used as an independent predictor in this score, the BASE-AF_2 score cannot be used for baseline prediction, before index CA. Similar to the ALARMEc study, some variables included in the BASE-AF_2 score such as BMI were not in accordance with current definitions.[36,37] Also, the unclear cut-off of AF duration >6 years complicates the assessment due to the fact that in some patients AF may begin with asymptomatic episodes.

4.4 | CAAP-AF

The CAAP-AF score has been developed in a large cohort of 1125 AF patients. Of 14 tested clinical variables, six factors (coronary artery disease, left atrial diameter, age, presence of persistent or long-standing AF, antiarrhythmics failed, and female sex) were significantly associated with AF recurrence after CA. A low CAAP-AF score (<4 points) was associated with a better long-term outcome after CA, while high CAAP-AF score (≥8 points) indicated LA scar and LVAs which are known to increase the recurrence risk.[17] The 2-year AF-free rates by CAAP-AF score values were as follows: 0 = 100%, 1 = 95.7%, 2 = 96.3%, 3 = 83.1%, 4 = 85.5%, 5 = 79.9%, 6 = 76.1%, 7 = 63.4%, 8 = 51.1%, 9 = 53.6%, and ≥ 10 = 29.1%. The score was internally validated in a cohort of 937 patients showing similar findings as in the development cohort. Recently, the CAAP-AF score had been externally validated and it showed a good predictive ability for LRAF.[31,38]

4.5 | APPLE

The APPLE score was originally developed to predict AF recurrences within the first year after CA.[16] The development cohort consisted of 1145 AF patients undergoing first CA. The predictive value of APPLE score was significantly superior to $CHADS_2$ and CHA_2DS_2-VASc on the ROC curve analysis (AUC 0.634 vs 0.538 and 0.542; $P < 0.001$, respectively).[16] Similar results (AUC 0.624, $P < 0.001$) were reported in an external validation cohort of 261 patients from the Vanderbilt University.

Moreover, the APPLE score has been shown to be useful for the prediction of rhythm outcome after repeat CA in The Leipzig Heart Center Ablation Registry.[20] In comparison to $CHADS_2$ (AUC 0.577, $P = 0.037$) and CHA_2DS_2-VASc (AUC 0.590, $P = 0.015$), the APPLE score showed significantly better prediction of arrhythmia recurrences (AUC 0.617, $P = 0.002$) than other scores. So far, the APPLE score has been validated in several external cohorts showing similar results as in the development cohort. The third external validation was performed by Mujović et al[18] comparing APPLE with the MB-LATER score. Both scores showed reasonably 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.

Another comparison of the APPLE, MB-LATER, and DR-FLASH scores has been published recently. Kornej et al[39] used data from two study groups: the *BioAF* cohort (Heart Center Leipzig), which consisted of 241 patients, and The Leipzig Heart Center AF Ablation Registry, which provided 873 patients for the validation cohort. Beside LVA prediction, the predictive value for LRAF had been analyzed. The APPLE score (OR 1.550; $P < 0.001$) was significantly associated with arrhythmia recurrence within 1 year after CA in the validation cohort. Of note, on multivariable analysis only the MB-LATER score (OR 1.747; $P < 0.001$) achieved slightly higher values within the validation cohort.[39]

4.6 | MB-LATER

The MB-LATER score has been introduced to predict VLRAF after RFA in 133 patients who were free from recurrent arrhythmia within first 12 months after CA.[18] After the development and internal validation (cohort of 39 patients), the score was compared to APPLE (AUC 0.716); BASE-AF_2 (AUC 0.648), ALARMEc (AUC 0.671), HATCH (AUC 0.582), $CHADS_2$ (AUC 0.555), and CHA_2DS_2-VASC (AUC 0.510) scores.[18] According to this comparison, MB-LATER showed better predictive accuracy for VLRAF (AUC 0.782, $P < 0.001$) than the other scores. Of note, the APPLE score (AUC 0.716, $P = 0.002$) showed almost similar prediction as the MB-LATER score.[18]

Recently, two external MB-LATER score validation studies have been published. First, Deng et al used a Chinese cohort of >1400 patients.[31] They compared seven risk stratification scores (HATCH, $CHADS_2$, CHA_2DS_2-VASc, BASE-AF_2, APPLE, CAAP-AF, MB-LATER) regarding their predictive ability for LRAF after CA. The MB-LATER, APPLE, BASE-AF_2, and CAAP-AF reached good predictive values with an AUC of 0.73, 0.74, 0.75, and 0.71, respectively (all $P < 0.01$). These scores were superior to HATCH (AUC 0.58, $P < 0.01$), $CHADS_2$ (AUC 0.57, $P < 0.01$), and CHA_2DS_2-VASc (AUC 0.57, $P < 0.01$). However,

the MB-LATER score had the largest net reclassification index (NRI, for 30%-82.6%) and integrated discrimination index (IDI, for 2.6%-18.6%) in comparison to other scores.

Of note, APPLE score had been mentioned as an alternative to MB-LATER.[31] It is noteworthy that a score value of ≥2 of both MB-LATER (HR 1.52,$P < 0.01$) and APPLE score (HR 1.35, $P < 0.01$) has been significantly associated with an increased risk (52.1% and 35.3%, respectively) for AF recurrences.[31] The second external validation study had been performed by Potpara et al[38] in a cohort of 226 patients. The MB-LATER score was compared to $CHADS_2$, CHA_2DS_2-VASc, and CAAP-AF scores regarding their predictive ability for LRAF. Only MB-LATER (AUC 0.62, $P = 0.003$) and CAAP-AF (0.59, $P = 0.024$) significantly predicted arrhythmia recurrences, and MB-LATER showed the largest net benefit compared to the other scores[38] In ROC analysis. In addition, also as shown in Dengs study, the MB-LATER cut-off value of ≥2 had reached the highest predictive ability for LRAF. In both external validation cohorts ERAF, which has been included in the MB-LATER score, was shown to be an independent predictor for LRAF, which may partly explain the good predictive values of the MB-LATER. Interestingly, MB-LATER included male sex as a risk factor for recurrences in contrast to the CAAP-AF[17] and ATLAS[28] scores which included female sex as a risk factor. The MB-LATER score good predictive ability for VLRAF could be partly explained by higher AF prevalence in men.[40,41]

4.7 | ATLAS

The ATLAS score has been developed in a cohort of 1934 AF patients undergoing first CA which were divided into a development and a validation cohort (50% each).[28] ATLAS score classified patients into low (<6 points), intermediate (6-10 points) and high risk (>10 points) for arrhythmia recurrences. Patients were followed-up for 4.2 ± 2.7 years, and recurrent arrhythmia occurred in 22% of patients during follow-up. In the development group, AF recurrence rates were 8, 11, and 17%/year for low (<6 points), intermediate (6-10 points) and high-risk patients (>10 points), respectively ($P < 0.001$). In the validation group, AF recurrence rates were 8, 11, and 18%/year, respectively ($P < 0.001$). There were significant differences in hazard ratio (HR) between intermediate (1.10, $P = 0.35$) and high (1.6, $P < 0.001$) risk groups. The score showed good discriminative power (censored c-statistic of 0.75 in both cohorts). Comparisons among other risk stratification scores were not performed.[28]

4.8 | LAGO

Different cardiovascular imaging parameters, such as LA sphericity had been shown to be associated with AF. Based on this knowledge, Bisbal et al[29] developed the left atrial geometry and outcome (LAGO) score in a multicenter study including 243 patients after first RFA or CBA. So far, the score is not validated in a larger cohort, further investigations are needed. Furthermore, the study cohort includes both RFA and CBA, the predictive value of the LAGO score for each ablation technique in particular is not shown.[29]

5 | PREDICTION OF LOW-VOLTAGE AREA/ELECTRO-ANATOMICAL SUBSTRATE

AF progression is related to electro-anatomical changes in atrial myocardium and indicates advanced atrial remodeling. LVA can be detected during CA and through MRI,[9]and was defined as any region with <0.5 mV[23] during electro-anatomical voltage mapping. Voltage-guided substrate modification by targeting LVA in addition to circumferential pulmonary vein isolation (PVI) is more effective than conventional PVI ablation approaches concerning arrhythmia freedom after the ablation.[42–44] Recently, Yagishita et al showed that an LA voltage cut-off of <1.1 mV for electro-anatomic voltage mapping in sinus rhythm was an independent predictor for recurrences in patients without LVA (<0.5 mV).[45] Although LVA is an important risk factor for post-procedural AF, there are no standardized methods to predict LVA non-invasively before CA.[43,44]

The predictive ability of $CHADS_2$, DR-FLASH, APPLE, and MB-LATER for LVA are discussed in this section **(Table 3)**.

5.1 | $CHADS_2$

Chao et al demonstrated that electrophysiological properties of the atrium differ between $CHADS_2$ strata, in a cohort of 247 patients with paroxysmal AF. In this study, the authors compared atrial voltage and total activation time of right and left atrium within $CHADS_2$ strata.[46] In this relatively small cohort, it could be demonstrated that a higher CHADS2 score (>3 pts.) is associated with LVA.

5.2 | DR-FLASH

The DR-FLASH score is currently the only score developed specifically for the prediction of LVA. The derivation cohort included 238 patients (153 with persistent AF). LVAs were found in 66 (28%) patients, and the score showed a good predictive ability for LVA with cut-off of 3 points (c-statistic 0.801; $P < 0.001$). The DR-FLASH score has been validated in an external cohort and showed similar results (AUC was 0.767, $P < 0.001$). Furthermore, DR-FLASH showed also a predictive ability for AF recurrence (1.3-fold increase per 1 point, $P = 0.020$) post-CA. Patients with LRAF had also a high DR-FLASH score (cut-off >3).[22] Of note, female sex—as a component of DR-FLASH score —was recently considered as a risk factor for AF substrate. Indeed, females have a 2-fold risk for LVA[47] and an almost 3-fold increased risk for AF recurrence following CA.[4] Females could present with clinical AF in a later stage of fibro-fatty infiltration, which could explain a higher presence of electro-anatomical substrate and worse rhythm outcomes after CA in female patients.[47]

5.3 | APPLE

Recently, it has been shown that the APPLE score—originally developed for arrhythmia recurrences—could be also used to predict LVA.[39] In a population of 214 patients, we showed that the APPLE score (OR 1.921, $P < 0.001$) and female sex (OR 2.283, $P = 0.005$) were independent predictors for LVA .[39] Interestingly, although atrial natriuretic peptide (NT-proANP) was an independent predictor on

TABLE 3 Low voltage area (LVA)/electro-anatomical substrate

Study	Year	Participants	Scores	Results
Chao et al	2011	Overall: 247 PAF: 247	$CHADS_2$	Higher $CHADS_2$-score is associated with LVA prediction
Kosiuk et al	2015	Overall: 902 PAF: 545	DR-FLASH	The optimal cut-off value for LVA prediction was 3 points. DR-FLASH score was also associated with the prediction of arrhythmia recurrences after PVI
Kornej et al	2018	Overall: 214 PAF: 88	APPLE	APPLE score and NT-proANP were independent predictors for LVA before catheter ablation
Kornej et al	2018	Overall:1114 PAF: 621	APPLE, DR-FLASH, MB-LATER	APPLE and DR-FLASH demonstrated robust predictive value for LVA in both study groups

Abbreviations: AF, atrial fibrillation; PAF, paroxysmal AF; PVI, pulmonary vein isolation.

univariable analysis, there was no increase in the predictive value by adding NT-proANP to the APPLE score. Importantly, the APPLE score can be used for baseline prediction of recurrent AF post-CA and contribute to an individualized AF therapy. Its components such as an impaired ejection fraction (EF) and renal dysfunction were also associated with an electro-anatomical substrate.[48,49]

This correlation had also been shown in our recent study where the APPLE, DR-FLASH, and MB-LATER scores were compared regarding their predictive ability for LVA and recurrences.[50] First, we analyzed this prediction in the BioAF cohort of 214 AF patients and then validated the results in a retrospective cohort from *The Leipzig Heart Center AF Ablation Registry*. While on univariable analysis all scores were significantly associated with LVA, on multivariable analysis only the APPLE (OR 1.789, $P < 0.001$) and DR-FLASH scores (OR 2.144, $P < 0.001$) remained significant predictors. However, the MB-LATER score (OR 1.445, $P = 0.034$) and ERAF (OR 5.078, $P < 0.001$), but not the APPLE score, were associated with LRAF on multivariable analysis.[50] All scores were significantly associated with recurrences, but ERAF was the most powerful predictor for later rhythm outcomes. In summary, on multivariable analysis the APPLE score was associated with prediction of both LVA and arrhythmia recurrences, whereas, as expected, DR-FLASH score ("a substrate score") showed the best prediction for LVA, but not for rhythm outcomes, and MB-LATER was significantly associated with rhythm outcomes, but not LVA.

6 | MACE AND DEATH

Several studies demonstrated that AF is associated with an increased risk of stroke, heart failure, or sudden cardiac death.[51,52] Consequently, AF patients have a higher mortality rate compared to patients without AF regardless of gender and age.[51,53] In addition, it had been demonstrated that an increased mortality rate in anticoagulated AF patients is mostly because of cardiovascular causes other than ischemic stroke.[54,55]

In this section, the $CHADS_2$/CHA_2DS_2-VASc, ABC death risk score and the 2MACE score **(Table 4)** are discussed in terms of their relevance for death or major adverse cardiovascular events (MACE) prediction including fatal/non-fatal myocardial infarction, cardiac revascularization, and cardiovascular death.

6.1 | $CHADS_2$/CHA_2DS_2-VASc

The value of CHA_2DS_2-VASc and $CHADS_2$ score for death and stroke prediction in AF patients after catheter ablation had been investigated by Chao et al[52] Both scores had been compared in a cohort of 565 AF patients. CHA_2DS_2-VASc score had been shown slightly better results (AUC 0.830) than the $CHADS_2$ score (AUC 0.785) in ROC analysis. However, the difference between both curves did not reach significance ($P = 0.116$).[52] Both scores had been proven their ability to predict death and thromboembolic events in AF patients after CA. Similar findings had been published by Jacobs et al[34] in 2015. The predictive ability of CHA_2DS_2-VASc and $CHADS_2$ score for death and MACE after first CA had been investigated in a cohort of 2179 AF patients. After FU of 5 years, it had been shown that CHA_2DS_2-VASc (HR 1.16; $P = 0.04$) and $CHADS_2$ (HR 1.30; $P = 0.02$) score were associated with MACE.

6.2 | 2MACE

The 2MACE score includes five clinical variables, and it has been developed for the prediction of major adverse cardiovascular events (MACE) in a derivation cohort of 1019 AF patients with oral

TABLE 4 MACE and death

Study	Year	Participants	Scores	Results
Jacobs et al	2015	Overall: 2179 PAF:1246	CHADS2, CHA2D S2- VASc	Both scores were associated with MACE prediction after catheter ablation (FU 5 years) CHA2DS2-VASc (HR 1.16; $P = 0.04$) and CHADS2 (HR 1.30; $P = 0.02$)
Pastori et.al	2016	Overall: 2108 et al PAF:n.a.	2MACE	The highest specificity and sensitivity for MACE could be reached by an value of three in the 2MACE score
Hijazi et al	2017	Overall: 23159 PAF:4115	ABC death score	ABC death score was compared to CHA2DS2-VASc score and it achieved higher c-indices. Three biomarkers (growth differentiation factor 15, high sensitivity cardiac troponin T and N-terminal pro B-type natriuretic peptide) were used in the ABC death score

Abbreviations: AF, atrial fibrillation; PAF, paroxysmal AF; MACE, major adverse cardiovascular events.

TABLE 5 Summary of clinical validations of scores

Risk scores	Number of studies	Total number of participants	Recurrences	LVA	MACE
2MACE	1[21]	2108	–	–	X
ABC death risk score	1[24]	23 951	–	–	X
ALARMEc	4 [14,19,32,35]	1630	X	–	–
APPLE	6[16,18,20,31,39,50]	4641	X	X	–
ATLAS	1[28]	1934	X	–	–
BASE-AF_2	3[15,18,21]	1779	X	–	–
CAAP-AF	3[17,31,38]	3698	X	–	–
$CHADS_2$	4[11,33,34,46]	2792	X	X	X
CHA_2DS_2-VASc	2[33,34]	2307	X	–	X
DR-FLASH	2[22,50]	2016	X	X	–
LAGO	1[29]	243	X	–	–
MB-LATER	3 [3,18,21,38]	1769	X	–	–

anticoagulation (OAK). The median follow-up was 24 months (IQR 13.9-46.3) or 2287 person-years. The MACE incidence rate was 3.4%/year (111 cases). The external validation cohort included 1089 AF patients who were treated with vitamin K antagonists. The cut-off value of 3 points in the 2MACE score showed the best combination of sensitivity and specificity to predict MACE, and the score (AUC 0.79; $P < 0.001$) was superior to $CHADS_2$ (AUC 0.660) and CHA_2DS_2-VASc (AUC 0.667). In an external validation cohort, the predictive ability of 2MACE score has been confirmed (AUC 0.66, $P < 0.001$).[21] Indeed, all three investigated scores (ie, the $CHADS_2$, CHA_2DS_2-VASc, and 2MACE) showed similar ability for the prediction of MACE. In addition, it was shown that an optimal anticoagulation level also reduced the risk of MACE.[21]

While number of participants within the study groups was relatively large, the incidence of MACE was only ~ 180 out of 1.019 patients. Therefore, the predictive value of the 2MACE score needs to be validated in further studies.

6.3 | ABC death risk score

Recently, the ABC death risk score had been introduced to predict death in AF patients without CA treatment.[24] The development (ARISTOTLE) and external validation (RE-LY trial) cohorts included over 23 000 patients. The average follow-up in derivation cohort was 1.9 years or 28 396 person-years. The external validation cohort was based on 16 794 person-years of follow-up. The incidence rate of cardiovascular death was 3.69 per 100 person-years (1047 events) in the development cohort and 3.54 per 100 person-years (594 events) in the external validation cohort.

The ABC score was compared to CHA_2DS_2-VASc score in both cohorts and different subgroups. The ABC score showed a better predictive ability for mortality risk (AUC 0.75) than CHA_2DS_2-VASc (AUC 0.58) in all cohorts and subgroups.

Presently, these are the largest analyses using blood biomarkers (ie, cardiac troponin T, growth differentiation factor-15, and NT-proBNP) in AF patients. The usefulness of biomarkers as an important tool for risk prediction was also shown in several other studies.[7,56–59] AF causes endothelial damage, inflammation, and fibrosis,[5] and such atrial remodeling can be detected by specific biomarkers.[58] Furthermore, the predictive value of biomarkers of inflammation (CRP, IL-6),[60] myocardial damage (troponin), impaired cardiac function (BNP, ANP) or renal dysfunction (cystatin C) for adverse events in AF patients has been increasingly reported.[58] Natriuretic peptides, which were used in the ABC risk score, showed a good predictive ability for adverse events in AF patients,[60–62] whereas the results for Galectin 3 were conflicting.[56,57,63,64]

The role of biomarkers in AF treatment decision-making in daily clinical practice needs to be further elucidated.

7 | CONCLUSION AND FUTURE DIRECTIONS

The major purpose of this review article was to provide an overview of the current scores for diverse negative events in AF patients undergoing catheter ablation and to discuss them critically. The development of the "ideal score" for prediction negative outcomes in AF patients still remains a clinical unmet need. Therefore, choosing only one optimal scoring system seems impossible, regarding that all of the presented scores in this review have their strengths and limitations. We therefore recommend to consider several important quality criterions for risk stratification scores: (a) size of development cohort, (b) an external validation, (c) clinical relevance, and (d) simplicity and practicality of each score. Moreover, the possibility of baseline prediction upfront the catheter ablation plays an important role due to a better feasibility **(Table 5)**.

However, there are several scores useful for the prediction of at least one adverse outcome. While DR-FLASH and APPLE scores are useful for prediction of both LVA and recurrences, the MB-LATER and APPLE scores predict recurrences within first year after ablation as well as >12 months (very late outcomes). Nevertheless, further investigations are needed to develop a universal score for patients undergoing AF catheter ablation. Biomarkers as well as cardiovascular imaging could improve the existing scores leading to better predictive values.

CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

ACKNOWLEDGMENT

We acknowledge support from the German Research Foundation (DFG) and Universität Leipzig within the program of Open Access Publishing

ORCID

Falco Kosich https://orcid.org/0000-0002-8552-8888

REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;18:1609-1678.

2. Deng H, Bai Y, Shantsila A, Fauchier L, Potpara TS, Lip GYH. Clinical scores for outcomes of rhythm control or arrhythmia progression in patients with atrial fibrillation: a systematic review. *Clin Res Cardiol*. 2017;106:813-823.
3. Xu Y, Sharma D, Li G, Liu Y. Atrial remodeling. New pathophysiological mechanism of atrial fibrillation. *Med Hypotheses*. 2013;80:53-56.
4. Nattel S, Harada M. Atrial remodeling and atrial fibrillation. Recent advances and translational perspectives. *J Am Coll Cardiol*. 2014;63:2335-2345. https://www.sciencedirect.com/science/article/pii/S0735109714013953/pdfft?md5=7a7c64d2496a20bd6819531458be00be&pid=1-s2.0-S0735109714013953-main.pdf.
5. Schumacher K, Dagres N, Hindricks G, Husser D, Bollmann A, Kornej J. Characteristics of PR interval as predictor for atrial fibrillation. Association with biomarkers and outcomes. *Clin Res Cardiol*. 2017;106:767-775.
6. Kornej J, Apostolakis S, Bollmann A, Lip GYH. The emerging role of biomarkers in atrial fibrillation. *Can J Cardiol*. 2013;29:1181-1193.
7. Kornej J, Husser D, Bollmann A, Lip GYH. Rhythm outcomes after catheter ablation of atrial fibrillation. Clinical implication of biomarkers. *Hamostaseologie*. 2014;34:9-19.
8. Koutalas E, Rolf S, Dinov B, et al. Contemporary mapping techniques of complex cardiac arrhythmias—identifying and modifying the Arrhythmogenic substrate. *Arrhythm Electrophysiol Rev*. 2015;4:19-27.
9. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation. The DECAAF study. *JAMA*. 2014;311:498-506.
10. McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. *Circ Arrhythm Electrophysiol*. 2014;7:23-30.
11. Chao T-F, Ambrose K, Tsao H-M, et al. Relationship between the CHADS(2) score and risk of very late recurrences after catheter ablation of paroxysmal atrial fibrillation. *Heart Rhythm*. 2012;9:1185-1191.
12. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272.
13. Kornej J, Hindricks G, Kosiuk J, et al. Renal dysfunction, stroke risk scores (CHADS2, CHA2DS2-VASc, and R2CHADS2), and the risk of thromboembolic events after catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2013;6:868-874.
14. Wójcik M, Berkowitsch A, Greiss H, et al. Repeated catheter ablation of atrial fibrillation: how to predict outcome? *Circulation*. 2013;77:2271-2279.
15. Canpolat U, Aytemir K, Yorgun H, Şahiner L, Kaya EB, Oto A. A proposal for a new scoring system in the prediction of catheter ablation outcomes. Promising results from the Turkish Cryoablation registry. *Int J Cardiol*. 2013;169:201-206.
16. Kornej J, Hindricks G, Shoemaker MB, et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. *Clin Res Cardiol*. 2015;104:871-876.
17. Winkle RA, Jarman JWE, Mead RH, et al. Predicting atrial fibrillation ablation outcome: the CAAP-AF score. *Heart Rhythm*. 2016;13:2119-2125.
18. Mujović N, Marinković M, Marković N, Shantsila A, Lip GYH, Potpara TS. Prediction of very late arrhythmia recurrence after radiofrequency catheter ablation of atrial fibrillation: the MB-LATER clinical score. *Sci Rep*. 2017;7:40828.
19. Paylos JM, Morales A, Azcona L, et al. Long-term evolution of patients treated for paroxysmal Atrial Fibrillation with first and second generation Cryoballoon catheter ablation with a prospective protocol guided by complete bidirectional left atrium-pulmonary veins disconnection after adenosine as Main target end point to achieved. Seven years follow-up of patients with a rough estimation profile of low ALARMEc score. a single center report. *J Atr Fibrillation*. 2016;8:1400.
20. Kornej J, Hindricks G, Arya A, Sommer P, Husser D, Bollmann A. The APPLE score - a novel score for the prediction of rhythm outcomes after repeat catheter ablation of Atrial Fibrillation. *PloS One*. 2017;12:e0169933.
21. Pastori D, Farcomeni A, Poli D, et al. Cardiovascular risk stratification in patients with non-valvular atrial fibrillation. The 2MACE score. *Intern Emerg Med*. 2016;11:199-204.
22. Kosiuk J, Dinov B, Kornej J, et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. *Heart Rhythm*. 2015;12:2207-2212.
23. Yagishita A, Gimbel JR, de OS, et al. Long-term outcome of left Atrial voltage-guided substrate ablation during Atrial Fibrillation: a novel adjunctive ablation strategy. *J Cardiovasc Electrophysiol*. 2017;28:147-155.
24. Hijazi Z, Oldgren J, Lindbäck J, et al. Wallentin L. a biomarker-based risk score to predict death in patients with atrial fibrillation : the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J*. 2017;38:477-485.
25. Hijazi Z, Lindbäck J, Alexander JH, et al. The ABC (age, biomarkers, clinical history) stroke risk score. A biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J*. 2016;37:1582-1590.
26. Hijazi Z, Oldgren J, Lindbäck J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation. A derivation and validation study. *Lancet (London, England)*. 2016;387:2302-2311.
27. Wynn GJ, Das M, Bonnett LJ, et al. A novel marker to predict early recurrence after atrial fibrillation ablation : the ablation effectiveness quotient. *J Cardiovasc Electrophysiol*. 2015;26:397-403.
28. Mesquita J, Ferreira AM, Cavaco D, et al. Development and validation of a risk score for predicting atrial fibrillation recurrence after a first catheter ablation procedure—atlas score. *Europace*. 2018;20(FI_3):f428-f435.
29. Bisbal F, Alarcón F, Ferrero-de-Loma-Osorio A, et al. Left atrial geometry and outcome of atrial fibrillation ablation: results from the multicentre LAGO-AF study. *Eur Heart J Cardiovasc Imaging*. 2018;19:1002-1009.
30. Kornej J, Hindricks G, Kosiuk J, et al. Comparison of CHADS2, R2CHADS2, and CHA2DS2-VASc scores for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation: the Leipzig heart center AF ablation registry. *Circ Arrhythm Electrophysiol*. 2014;7:281-287.
31. Deng H, Shantsila A, Xue Y, et al. Using the MB-LATER score for predicting arrhythmia outcome after catheter ablation for atrial fibrillation. The Guangzhou atrial fibrillation project. *Int J Clin Pract*. 2018;72:e13247.
32. Wójcik M, Berkowitsch A, Zaltsberg S, et al. Score associated with the outcome after multiple ablation procedures in patients with atrial fibrillation. *Pacing Clin Electrophysiol*. 2014;37:682-690.
33. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. *Eur Soc Cardiol*. 2014;16:202-207.
34. Jacobs V, May HT, Bair TL, et al. The impact of risk score (CHADS2 versus CHA2DS2-VASc) on long-term outcomes after atrial fibrillation ablation. *Heart Rhythm*. 2015;12:681-686.
35. Wójcik M, Berkowitsch A, Zaltsberg S, et al. Cryoballoon ablation of atrial fibrillation. How important is the proper selection of patients? *Cardiol J*. 2015;22:194-200.
36. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet (London, England)*. 2005;366:1059-1062.
37. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. *Circulation*. 2005;112:2735-2752.
38. Potpara TS, Mujovic N, Sivasambu B, et al. Validation of the MB-LATER score for prediction of late recurrence after catheter-ablation of atrial fibrillation. *Int J Cardiol*. 2018. Epub ahead of print.
39. Kornej J, Büttner P, Sommer P, et al. Prediction of electro-anatomical substrate using APPLE score and biomarkers. *Europace*. 2018. Epub ahead of print.
40. Mou L, Norby FL, Chen LY, et al. Lifetime risk of Atrial Fibrillation by race and socioeconomic status. ARIC study (atherosclerosis risk in communities). *Circ Arrhythm Electrophysiol*. 2018;11:e006350.
41. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts. Results from the BiomarCaRE consortium (biomarker for cardiovascular risk assessment in Europe). *Circulation*. 2017;136:1588-1597.
42. Blandino A, Bianchi F, Grossi S, et al. Left Atrial substrate modification targeting low-voltage areas for catheter ablation of Atrial Fibrillation.

A systematic review and meta-analysis. *Pacing Clin Electrophysiol*. 2017;40:199-212.
43. Kircher S, Arya A, Altmann D, et al. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation. A randomized study. *Europace*. 2017; 20:1766-1775.
44. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7:825-833.
45. Yagishita A, Sparano D, Cakulev I, et al. Identification and electrophysiological characterization of early left atrial structural remodeling as a predictor for atrial fibrillation recurrence after pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2017;28:642-650.
46. Chao T-F, Cheng C-C, Lin W-S, et al. Associations among the CHADS (2) score, atrial substrate properties, and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. *Heart Rhythm*. 2011;8: 1155-1159.
47. Huo Y, Gaspar T, Pohl M, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. *Europace*. 2017;20:956-962.
48. Akkaya M, Higuchi K, Koopmann M, et al. Higher degree of left atrial structural remodeling in patients with atrial fibrillation and left ventricular systolic dysfunction. *J Cardiovasc Electrophysiol*. 2013;24: 485-491.
49. Chao T-F, Lin Y-J, Chang S-L, et al. Associations between renal function, atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. *Circulation*. 2011;75:2326-2332.
50. Kornej J, Schumacher K, Dinov B, et al. Prediction of electroanatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. *Sci Rep*. 2018. Accessed August 15, 2018;8: 12686.
51. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998;158:229-234.
52. Chao T-F, Lin Y-J, Tsao H-M, et al. CHADS(2) and CHA(2)DS(2)-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. *J Am Coll Cardiol*. 2011;58:2380-2385.
53. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation. A global burden of disease 2010 study. *Circulation*. 2014;129:837-847.
54. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation. epidemiology, pathophysiology, and clinical outcomes. *Circ Res*. 2017; 120:1501-1517.
55. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death. Systematic review and meta-analysis. *Br Med J*. 2016;354: i4482 Accessed August 15, 2018.
56. Kornej J, Schmidl J, Ueberham L, et al. Galectin-3 in patients with atrial fibrillation undergoing radiofrequency catheter ablation. *PloS one*. 2015;10:e0123574.
57. Takemoto Y, Ramirez RJ, Yokokawa M, et al. Galectin-3 regulates atrial fibrillation remodeling and predicts catheter ablation outcomes. *JACC Basic Transl Sci*. 2016;1:143-154.
58. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation. A clinical review. *Eur Heart J*. 2013;34:1475-1480. Accessed December 15, 2017.
59. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. *J Interv Card Electrophysiol*. 2014;39:241-249.
60. Aulin J, Siegbahn A, Hijazi Z, et al. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. *Am Heart J*. 2015;170:1151-1160.
61. Silvet H, Young-Xu Y, Walleigh D, Ravid S. Brain natriuretic peptide is elevated in outpatients with atrial fibrillation. *Am J Cardiol*. 2003;92: 1124-1127.
62. Kornej J, Löbe S, Efimova E, Husser D, Hindricks G, Bollmann A. NT-proBNP in "low risk" patients with atrial fibrillation. *Int J Cardiol*. 2015; 179:493-494.
63. Yalcin MU, Gurses KM, Kocyigit D, et al. The Association of Serum Galectin-3 levels with Atrial electrical and structural remodeling. *J Cardiovasc Electrophysiol*. 2015;26:635-640.
64. Kornej J, Schmidl J, Bollmann A. Galectin-3 in Atrial Fibrillation. A novel marker of Atrial remodeling or just bystander? *Am J Cardiol*. 2015;116:163.

How to cite this article: Kosich F, Schumacher K, Potpara T, Lip GY, Hindricks G, Kornej J. Clinical scores used for the prediction of negative events in patients undergoing catheter ablation for atrial fibrillation. *Clin Cardiol*. 2019;42:320–329. https://doi.org/10.1002/clc.23139