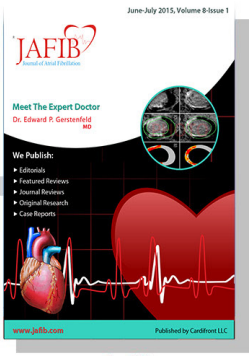
JAFIB®
Featured Review
Journal of Atrial Fibrillation



www. jafib.com

Anticoagulation in Heart Failure: a Review

Emily P. Zeitler MD, Zubin J Eapen MD, MHS

Duke Clinical Research Institute and Duke University Medical Center, Durham NC.

Abstract

Heart failure (HF) with reduced left ventricular function inflicts a large and growing burden of morbidity and mortality in the US and across the globe. One source of this burden is stroke. While it appears that HF itself may impose some risk of stroke, it is in the presence of other risk factors, like atrial fibrillation, that the greatest risks are observed. Therapeutic anticoagulation is the mainstay of risk reduction strategies in this population. While warfarin was the only available therapy for anticoagulation for many decades, there are now four direct oral anticoagulants available. In three of these four, outcomes in the specific subgroup of patients with heart failure have been examined. In this review, we provide some pathophysiologic basis for the risk of stroke in heart failure. In addition, the available therapeutic options for stroke risk prevention in heart failure are described in detail including how these options are incorporated into relevant professional society guidelines.

Introduction

The burden of heart failure (HF) continues to grow around the world. For example, current estimates of the HF burden in the US indicate that from 2009 to 2012, 5.7 million American adults have heart failure, and projections show that the prevalence will increase 46% from 2012 to 2030.[1] While HF has a considerable impact of morbidity, it also has substantial impact on mortality with 1 in 9 American deaths at least partially attributable to heart failure.[1] As such, the way in which medical therapies apply to this population are of increasing importance.

Anticoagulation in the HF population has evolved considerably over the past few decades. Never before have there been so many options for anticoagulation, but because the HF population has a unique set of potential risks and benefits, special consideration should be given to this population when considering therapeutic anticoagulation. Although HF with preserved and reduced left ventricular ejection fraction (LVEF) are often grouped together administratively and clinically, evidence based therapies for HF and preserved ejection fraction (HFpEF) are lacking. Instead, the focus for patients with HFpEF is the identification and treatment of comorbid conditions (e.g., hypertension).[2] As such, since risk factors and therapies differ for these two entities, and anticoagulation in patients with HFpEF has not been thoroughly studied, only HF with reduced ejection fraction (HFrEF) will be considered here.

Key Words:
Heart Failure, Anticoagulation, Atrial Fibrillation.

Disclosures:
Dr. Zeitler was funded by National Institutes of Health (NIH) T-32 training grant #2 T32 HL 69749-11 A1. However, no relationships exist related to the review presented. Dr. Eapen reports the following: Advisory Board – Novartis, Amgen, Cytokinetics; Consultant – Amgen; Honorarium – Janssen.

Corresponding Author:
Dr. Zubin J. Eapen, MD, MHS
Duke Clinical Research Institute
PO Box 17969
Durham, NC 27715.

Rationale for Anticoagulation in Heart Failure

Heart Failure and Sinus Rhythm

Typically, therapeutic anticoagulation is employed to achieve a reduction in risk of stroke. This risk is not trivial in the HF population.[3,4] Historically, the risk of stroke in the HF population was best explained by the elements of Virchow's triad: blood flow abnormalities, vessel wall abnormalities, and abnormal blood constituents. While all the components of Virchow's famous triad may apply to HF patients, it is the first component, blood flow abnormalities, that is presumed to play the biggest role in imparting stroke risk. Blood flow in HF is likely to be abnormal in the context of LV dysfunction (including regional areas of dyskinesis or aneurysm). Despite the plausibility of this physiologic explanation, investigation of the presumed hypercoagulable state in HF has not been confirmed in clinical trials.[5-10] The most recent, largest, and most rigorously designed of these was the Warfarin and aspirin in patients with heart failure and sinus rhythm (WARCEF) trial which was a randomized, double-blind, double-dummy study of 2305 patients worldwide.[8] WARCEF demonstrated that in patients with LVEF ≤ 35% and no existing indication for anticoagulation (e.g., atrial fibrillation) there was no difference in the primary endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause between the groups randomized to aspirin versus those randomized to warfarin. Even when clinical trial data are combined, there does not appear to be a beneficial signal for the use of anticoagulation

in HF without another risk factor (e.g., atrial fibrillation).[11,12] One possible explanation for this is an inherent increased bleeding risk in patients with HF, but this has not been confirmed empirically. The American College of Cardiology and American Heart Association (ACC/AHA) has therefore included a class IIb recommendation in the 2009 HF guidelines indicating that "the usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event".[13] The Canadian Cardiovascular Society (CCS) and The European Society of Cardiology (ESC) make similar recommendations (Table 1).[14,15]

Despite these findings and recommendations, a significant number of HF patients without another indication for anticoagulation continue to be prescribed therapeutic anticoagulation. Data spanning the last 20 years from registries and post-hoc analyses of clinical trials demonstrate that warfarin is prescribed to HF patients without another thromboembolic risk factor at a rate of between 8 and 17%.[10,16-18] However, importantly, none of the trials assessing anticoagulation in HF with sinus rhythm included direct-acting oral anticoagulants (DOACs). It remains to be seen if there is any benefit to anticoagulation with DOACs in HF and sinus rhythm, and if so, whether those benefits are balanced by acceptable bleeding risks. The COMMANDER HF study is an attempt to address this question of anticoagulation in HF with sinus rhythm in the age of DOACs.[19] This ongoing study will assess the effectiveness and safety of rivaroxaban in reducing the risk of death, myocardial infarction or stroke in patients with HF and coronary artery disease.

Heart Failure and Atrial Fibrillation

Heart rhythm abnormalities – namely atrial fibrillation – are very common in the HF population with prevalence of atrial fibrillation estimated at 13-40%.[20,21] This prevalence of documented atrial fibrillation is considerable, but the true burden of atrial fibrillation in this population and others may be even greater owing to subclinical forms.[22] The relationship between atrial fibrillation and HF is complex with both conditions acting as a risk factor and an outcome for the other. There is no doubt that HF is associated with increased risk of stroke in the presence of atrial fibrillation.[23,24] Indeed, assessment of stroke risk is conducted routinely by clinicians by using risk scores like the $CHADS_2$ and CHA_2DS_2VASc, both of which include heart failure as a risk factor.

Heart Failure and LV Thrombus

While atrial fibrillation clearly makes a large impact on stroke risk in HF, there are other stroke risk factors in HF that may be mitigated by therapeutic anticoagulation. Left ventricular dysfunction is one risk factor for the development of LV thrombus,[25-27] and acute myocardial infarction (MI) may increase risk of stroke in the post-MI period through multiple mechanisms including temporary or permanent reduction in LV function and LV thrombus development.[28] Indeed, experience has identified reduced EF following acute MI as one

Table 1: Summary of anticoagulation guidelines in heart failure

Guideline	Anticoagulation for HF + other comorbid condition			
	Atrial fibrillation	History of systemic thromboembolism	Intracardiac thrombus	Other
ACC/AHA[41]	Recommended for patients with chronic HF with permanent/persistent/ paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) (Level of Evidence: A) Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/ persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke (Level of Evidence: B)	Recommended in patients with HF who have had previous thromboembolic event (Level of Evidence: A) [13]	No formal recommendation	Not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source (Level of Evidence: B)
CCS[14]	Recommended for AF in HF patients deemed high risk for stroke unless contraindicated as per current AF guidelines, and not to coadminister with antiplatelet agents unless the latter are needed for other indications (Strong Recommendation, High-Quality Evidence).	Recommended for patients with previous systemic embolism (Weak Recommendation, Low-Quality Evidence).	Recommended for patients with demonstrated intracardiac thrombus, (Weak Recommendation, Low-Quality Evidence).	Not recommended for routine use for HF patients who are in sinus rhythm (Strong Recommendation, High-Quality Evidence) Recommended for patients after a large anterior MI (Weak recommendation, low-quality evidence)
ESC[15]	Recommended for all patients with paroxysmal or persistent/permanent AF and a CHA_2DS_2-VASc score ≥1, without contraindications, and irrespective of whether a rate- or rhythm-management strategy is used (Level of evidence: A)	Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.(Level of evidence: B)* [92] Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE (level of evidence: B)* [92]	It is recommended that patients with large, mobile thrombus protruding into the LV cavity should be anticoagulated [93] Anticoagulation should be considered in patients with large anterior wall motion abnormalities, if they are at low risk of bleeding, to prevent the development of thrombi. Consensus is that mural thrombi, once diagnosed, require oral anticoagulant therapy with vitamin K antagonists for up to 6 months [94]	Other than in HF patients with AF (both HF-REF and HF-PEF), there is no evidence that an oral anticoagulant reduces mortality–morbidity compared with placebo or aspirin
HFSA[31]	Recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing atrial fibrillation (Strength of Evidence A)	Recommended for patients with a history of systemic or pulmonary emboli, including stroke or transient ischemic attack (Strength of Evidence C)	Symptomatic or asymptomatic ischemic or non-ischemic cardiomyopathy with recent MI and LV thrombus (Strength of Evidence B) Ischemic or non-ischemic cardiomyopathy and LV thrombus depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification (Strength of evidence C)	Recent large anterior MI with symptomatic or asymptomatic ischemic cardiomyopathy (Strength of Evidence B)

*not specific to heart failure

predictor of developing LV thrombus.[26] Experience from the 2002 Warfarin, Aspirin, or Both After Myocardial Infarction (WARIS II) trial demonstrated that anticoagulation following MI reduced the risk of the composite endpoint of death, nonfatal reinfarction or thromboembolic stroke.[29] Subsequent studies have shown an inconsistent effect of post-MI anticoagulation on the risk of death, stroke, or other important endpoints outcomes[26,30] Because these results are mixed, the guidelines are as well: the Heart Failure Society of America (HFSA) recommends anticoagulation in patients with a large anterior MI with ischemic cardiomyopathy while other groups do not (Table 1).[31]

Data supporting the use of therapeutic anticoagulation in patients with a documented LV thrombus are very limited in part because most data in this area were generated before the modern era of thrombolysis for acute myocardial infarction, percutaneous coronary intervention with dual antiplatelet therapy, stroke risk assessment with modern tools (e.g., CHA_2DS_2VASc), modern imaging techniques (e.g., cardiac MRI), and certainly before DOACs were available.[27] Nonetheless, various studies have demonstrated that the incidence of LV thrombus is still considerable compared to the pre-coronary intervention era.[26,32,33] In addition, for many providers, there is a lack of equipoise in treatment strategy when an LV thrombus is documented in a patient with HF, so a randomized trial of treatment strategies for documented LV thrombus may not be possible.

Bleeding risk

The need to balance risks of thromboembolism with risks of bleeding is paramount, but this balance is complicated by the fact that risk factors for stroke and for bleeding are frequently overlapping, especially in the HF population (e.g., advanced age). Moreover, evidence suggests that risk of stroke and hemorrhage while taking warfarin increase with increasing severity of heart failure. In an analysis of >62,000 HF patients taking warfarin for atrial fibrillation, the hazard for major bleeding in patients with the most severe HF versus least severe was 3.97 after adjusting for known risk factors; risk of stroke increased with increasing HF severity as well but less dramatically.[34]

This conflict between bleeding and stroke risk is illustrated by common and validated risk scores used in clinical practice for estimating risk of stroke and bleeding, for example: $CHADS_2$ and HAS-BLED, respectively.[23,35] Both risk scores include hypertension, stroke, and advanced age. (Other elements of the HAS-BLED score include abnormal renal/liver function, bleeding history or anemia, labile INR, and concomitant drug/alcohol use.) Thus, common baseline characteristics and comorbid conditions among HF patients simultaneously confer bleeding and stroke risk making clinical decisions surrounding anticoagulation complex. However, like the HAS-BLED risk score, other bleeding risk assessment tools have not specifically assessed the impact of heart failure on bleeding risk.[36-40] Further work is needed to evaluate how these bleeding risk assessment tools perform specifically in the HF population and in the era of DOACs.

Table 2: Baseline characteristics of patients enrolled in major studies of FDA-approved direct-acting oral anticoagulants (DOACs)

Drug	Dabigatran[46]	Rivaroxaban[49]	Apixaban[48]	Edoxaban[47]
HF subgroup, n (%)	4904 (27)	9033 (63)	2736 (15)	8076 (67)
HF definition	NYHA ≥II HF symptoms <6 months screening and prior HF admission	HF history, or LVEF <40%	LVEF <40% or moderate or severe LV dysfunction	current presence or history of clinical HF Class C or D
Mean LVEF	NR		35 (30-39)	NR
LVEF ≤ 40%	44	34	NR**	NR
Mean age	68.3 ± 10.2	72 (65-78)	68 (60-74)	NR
Male %	67	61	79	NR
Nonischemic HF%	68	70	72	NR
Hypertension%	75	93	75	NR
Diabetes mellitus%	27	42	27	NR
History of stroke/TIA%	17	47	16	NR
Vascular disease%	NR	6.7	NR	NR
Mean $CHADS_2$	2.6 (1.1)	3.7(0.9)	2.22 (1.2)	NR
Efficacy	No significant interaction between treatment effect of dabigatran (110mg or 150mg) and the presence of HF.	No significant interaction between the primary efficacy endpoint and the presence of heart failure for those taking rivaroxaban versus warfarin.	No evidence of treatment heterogeneity according to the presence of heart failure.	No interaction between reduction in stroke or systemic embolism and the presence of HF.

NYHA, New York Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; NR, not reported
**55% with moderate LV dysfunction; 31% with severe LV dysfunction

Guidelines for Anticoagulation in HF

All relevant major guideline-developing groups agree on the recommendation to at least consider initiating therapeutic anticoagulation to reduce risk of systemic thromboembolism in patients with HF and atrial fibrillation (Table 1).[14,15,31,41] In addition to a decades long experience with warfarin as an anticoagulant and its proven benefit in reducing stroke risk,[42] there have been nearly 25,000 patients with HF and atrial fibrillation included in the published randomized clinical trials of the four FDA approved DOACs: dabigatran, rivaroxaban, apixaban, and edoxaban (Table 2). These agents are discussed further below.

In addition to atrial fibrillation, there are other compelling reasons to anticoagulate a patient with HF as outlined above. With varying levels of strength of recommendation, all major guideline groups recommend therapeutic anticoagulation for those patients with HF and a history of a thromboembolic event (e.g., pulmonary embolism, embolic stroke). The HFSA and the Canadian Cardiovascular Society (CCS) also provide some guideline recommendations for anticoagulation in the setting of LV thrombus.[14,31]

Options for Anticoagulation

Over the last decade there has been an explosion in the number of available anticoagulants. Until 2009, only warfarin was available for therapeutic anticoagulation. While this drug is inexpensive and effective at reducing stroke, it has significant disadvantages including the need for routine monitoring and numerous drug-drug and drug-food interactions. These reasons contribute to the relative low rates of prescription for indicated patients.[43] Moreover, the risk of serious bleeding while taking warfarin is not trivial[35] as discussed above.

Direct-Acting Oral Anticoagulants

The first DOAC to complete a phase III evaluation for nonvalvular atrial fibrillation was the direct thrombin inhibitor, ximelagatran.[44,45] However, after more than 7000 patients were randomized to

warfarin vs ximelagatran, significant hepatotoxicity was noted, and this was a primary impediment to approval by the Food and Drug Administration (FDA). In 2010, dabigatran (Pradaxa®, Boerhinger Ingelheim), a second oral direct thrombin inhibitor, was the first DOAC approved by the FDA for stroke prophylaxis in nonvalvular atrial fibrillation. Approval of dabigatran was followed by the oral Factor Xa inhibitors: rivaroxaban (Xarelto®, Bayer pharmaceuticals) in 2011, apixaban (Eliquis®, Pfizer/Bristol-Meyers Squibb) in 2012, and edoxaban (Savaysa®, Daiichi Sankyo) in 2015. Approval of these drugs represents the experience of nearly 100,000 patients in published phase III randomized studies and many more in earlier phase investigation. The phase III experience included nearly 25,000 patients with heart failure as outlined in Table 2.[46-49]

Dabigatran

FDA approval of dabigatran was supported, in part, by the non-inferiority RE-LY study of more than 18,000 patients randomized to warfarin versus two doses of dabigatran, 110 mg and 150 mg, respectively.[50] Patients with active liver disease or creatinine clearance less than 30 ml/min were excluded, and about one third of patients had HF. Ferreira and colleagues conducted a subgroup analysis to examine outcomes from RE-LY in patients with symptomatic HF.[46] The primary endpoints from the overall study were examined including: time to first occurrence of stroke or systemic embolism and time to first occurrence of major bleeding. Compared with warfarin, the hazard ratios for stroke or systemic embolism in the two dabigatran groups (110 mg twice daily and 150 mg twice daily, respectively) mirrored the results of the study overall. There was no statistically significant reduction in bleeding events in the HF subgroup taking either dose of dabigatran compared with warfarin. Importantly, there was no significant interaction between the treatment effect of either dose of dabigatran and the presence of HF in regard to the efficacy or safety endpoints. Of note, only 75 mg and 150 mg doses were approved by the FDA. Specific safety and efficacy data for the 75 mg dose are not available in the HF population but ongoing work within the FDA's Mini-Sentinel initiative may shed light on this in the future.[51]

Rivaroxaban

Patel and colleagues published ROCKET-AF in 2011 which was a multicenter, randomized double-blind, double-dummy trial at 1178 sites in 45 countries which examined safety and efficacy of warfarin versus rivaroxaban in nonvalvular atrial fibrillation.[52] Patients were at high risk for thromboembolic events and important exclusions included those patients with significant liver disease and creatinine clearance less than 30 ml/min. A subgroup analysis of the HF population in the ROCKET-AF trial was performed by van Diepen and colleagues.[49] They found no statistically significant difference in the primary efficacy or safety outcomes between HF patients randomized to rivaroxaban versus warfarin. There was no interaction observed between the primary efficacy and safety endpoints and the presence of HF. In addition, when factors contributing to risk of stroke or systemic embolism within the HF subgroup were observed in isolation (LVEF, HF with preserved versus reduced systolic function, functional class or $CHADS_2$ score), no interaction was seen suggesting that the benefit of rivaroxaban over warfarin extends to HF patients with AF over a broad range of risk.

Apixaban

In 2013, McMurray and colleagues reported on the HF subgroup from the ARISTOTLE trial[48] which was a multicenter, double-blind double-dummy trial of patients randomized to apixaban or dose-adjusted warfarin.[53] Like RE-LY and ROCKET-AF, patients with severe renal insufficiency (CrCl <25 ml/min, in this case) and active liver disease were excluded. They identified 2,736 patients from ARISTOTLE representing 19% of the total enrolled population who had an LVEF ≤ 40% or moderate or severe LV dysfunction. Patients with HF were quite different from those patients without HF who were older, less female, less ischemic, and less likely to have persistent or permanent AF as opposed to paroxysmal. HF patients in ARISTOTLE had a mean $CHADS_2$ score of 2.22 compared to 1.88 for patients without HF. Patients with HF were more likely to experience stroke, systemic embolism, major bleeding, or death from any cause (HR 1.98 95% CI 1.77-2.22, p<0.0001). In keeping with the overall results of ARISTOTLE, apixaban was superior to warfarin for stroke or systemic embolism as well as bleeding outcomes, and there was no evidence of treatment heterogeneity according to presence of HF.

Edoxaban

The primary phase III trial of edoxaban, ENGAGE AF-TIMI 48, included 8076 patients with HF defined as "current presence or history of clinical CHF class C or D".[47] Patients with renal insufficiency (CrCl <30 m/min) were excluded from enrollment. Edoxaban became the newest member of the DOAC family with FDA approval in 2015. Interestingly, and unlike its DOAC predecessors, based on higher stroke or systemic embolism rates in patients with high normal or supranormal renal function, edoxaban is contraindicated in patients with CrCl >95 ml/min. Reports of safety and efficacy in the HF subgroup have been examined by Magnani and colleagues in a 2014 abstract.[54] They showed that there was no interaction between reduction in stroke or systemic embolism and the presence of HF.

Betrixaban

A fourth oral factor Xa inhibitor, betrixaban, has been evaluated in a phase II trial for nonvalvular atrial fibrillation which demonstrated the drug to be well tolerated and safe.[55] More than a third of patients enrolled in Explore-Xa had a $CHADS_2$ score of 3 or greater, but it is not known what proportion had HF. As yet, betrixaban remains unevaluated by the FDA, and there are no phase III trials registered with clinicaltrials.gov in the atrial fibrillation population.

Summary of DOACs in HF

As noted above, in all of the modern trials of anticoagulation with direct oral anticoagulants for stroke prophylaxis in atrial fibrillation, a significant proportion of patients with HF were enrolled. In the case of all of the FDA-approved DOACs specifically studied in a heart failure population (i.e., dabigatran, rivaroxaban, and apixaban) there has been no evidence of a significant interaction between safety and/or efficacy outcomes and the presence of HF indicating that patients with HF should expect to benefit from the DOAC in a similar way as their counterparts without HF. Importantly, however, patients with significant renal and/or liver dysfunction were mostly excluded from DOAC trials, and these comorbidities are not uncommon among the heart failure population.[57-60] Indeed, in addition to the specific renal dysfunction groups excluded in each of the DOAC trials, the FDA labels indicate that edoxaban and rivaroxaban are contraindicated in patients with moderate to severe hepatic impairment, and apixaban is contraindicated in severe hepatic impairment. So, in a large portion

of the HF population, warfarin remains the only effective option for therapeutic anticoagulation to reduce stroke risk.

Other comorbidities have been evaluated in the context of the DOACs as well. Extensive work by Lega et al examined the safety and efficacy of dabigatran, rivaroxaban, and apixaban in various comorbid subgroups.[61] This group found that almost all subgroups had a treatment effect from the DOACs similar to the overall populations studied in the randomized clinical trials. It remains to be seen if these effects are borne out in clinical practice. In addition, the cardiovascular community awaits information on how HF and other important comorbid conditions impact the effects of edoxaban and betrixaban.

Role of Devices

In addition to drugs to reduce stroke risk in HF, there are device-based solutions that generally occlude or exclude the left atrial appendage (LAA). Two of the most widely known of these in the US are the Lariat® (SentreHEART, Redwood City, CA) and the Watchman® (Boston Scientific Corp, Marlborough, MA).[62,63] The Lariat enables the transcatheter ligation of the LAA via a combined transseptal and subxiphoid approach. Preliminary results which include a significant experience with HF patients demonstrate that procedural success can be high, but serious bleeding complications can occur; no long term safety and effectiveness data are available.[64] In addition, post procedural anticoagulation practices are widely variable,[65] and no unified recommendation exists. The Watchman device was recently FDA approved for occlusion of the LAA in patients with non-valvular atrial fibrillation based on two randomized non-inferiority trials in which 23 and 27% of subjects, respectively, had congestive heart failure.[62,63] In both cases the control groups were treated with adjusted-dose warfarin and noninferiority for stroke prevention was met, so the device is indicated for patients who are deemed warfarin candidates but have "an appropriate rationale" to seek a non-pharmacologic alternative.[66]

It remains unclear how these devices and others will be incorporated with anticoagulants into routine clinical practice and whether safety and/or effectiveness will differ in the HF population.

Catheter Ablation of Atrial Fibrillation

Evidence supporting AF ablation in patients with HF is limited[67-73] as are the data for post-ablation anticoagulation in this population.[74-78] Currently, based on a paucity of high quality evidence, therapeutic anticoagulation with warfarin or a DOAC is recommended indefinitely in patients at high risk for stroke which would generally include those patients with HF.[79, 80]

Conclusion

In addition to ongoing study of therapies in the traditional context, other factors including cost,[81-83] physician biases,[84,85] and patient preferences[86] and patient-centered outcomes (e.g., quality of life)[87-89] have begun to receive overdue attention. Preliminary investigation into these factors argue for nuanced, patient-specific guidance when counseling patients on anticoagulation options.

The tools available for anticoagulation in the HF population have evolved tremendously over the past 10 years, and there are additional options on the horizon in the form of ongoing clinical trials, new pharmaceuticals, and stroke prevention devices and procedures. Registries like ORBIT-AF I & II and others are designed to rigorously collect patient outcomes data in addition to patient preferences and quality of life data to further refine algorithms and guidelines for anticoagulant implementation.[90,91] These new tools for investigation and new treatment options for patients provides the best chance to date to balance stroke risk reduction with bleeding risks in a way that maximizes quality of life for all HF patients.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. Circulation 2014.
2. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA 2008;300(4):431-3.
3. Appelros P, Nydevik I, Seiger A, Terent A. Predictors of severe stroke: influence of preexisting dementia and cardiac disorders. Stroke; a journal of cerebral circulation 2002;33(10):2357-62.
4. Hays AG, Sacco RL, Rundek T, Sciacca RR, Jin Z, Liu R, et al. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. Stroke; 37(7):1715-9.
5. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;31(4):749-53.
6. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148(1):157-64.
7. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK, HELAS investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. European J Heart Fail 2006;8(4):428-32.
8. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366(20):1859-69.
9. Massie BM, Krol WF, Ammon SE, Armstrong PW, Cleland JG, Collins JF, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. Journal Card Fail 2004;10(2):101-12.
10. Mujib M, Rahman AA, Desai RV, Ahmed MI, Feller MA, Aban I, et al. Warfarin use and outcomes in patients with advanced chronic systolic heart failure without atrial fibrillation, prior thromboembolic events, or prosthetic valves. Am J Cardiol 2011;107(4):552-7.
11. Lee M, Saver JL, Hong KS, Wu HC, Ovbiagele B. Risk-benefit profile of warfarin versus aspirin in patients with heart failure and sinus rhythm: a meta-analysis. Circ Heart Fail 2013;6(2):287-92.
12. Lip GY, Shantsila E. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database Syst Rev 2014;3:CD003336.
13. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53(15):e1-e90.
14. McKelvie RS, Moe GW, Ezekowitz JA, Heckman GA, Costigan J, Ducharme A, et al. The 2012 Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure. Can J Cardiol 2013;29(2):168-81.
15. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787-847.
16. Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis

of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. Circulation 2015;131(17):1486-94.
17. Eapen ZJ, Grau-Sepulveda MV, Fonarow GC, Heidenreich PA, Peterson ED, Hernandez AF. Prescribing warfarin at discharge for heart failure patients: findings from the Get With The Guidelines-Heart Failure Registry. Int J Cardiol 2014;172(2):e322-3.
18. Hernandez AF, Hammill BG, Kociol RD, Eapen ZJ, Fonarow GC, Klaskala W, et al. Clinical effectiveness of anticoagulation therapy among older patients with heart failure and without atrial fibrillation: findings from the ADHERE registry linked to Medicare claims. J Card Fail 2013;19(6):401-7.
19. A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER HF) National Library of Medicine (US) at https://clinicaltrials.gov/ct2/show/NCT01877915?term=NCT01877915&rank=1 on April 7, 2015.
20. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009;119(18):2516-25.
21. McManus DD, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, et al. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). Am J Cardiol 2013;111(10):1460-5.
22. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366(2):120-9.
23. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110(16):2287-92.
24. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 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(2):263-72.
25. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. Heart 2012;98(23):1743-9.
26. Gianstefani S, Douiri A, Delithanasis I, Rogers T, Sen A, Kalra S, et al. Incidence and predictors of early left ventricular thrombus after ST-elevation myocardial infarction in the contemporary era of primary percutaneous coronary intervention. Am J Cardiol 2014;113(7):1111-6.
27. Lanzillo C, Di Roma M, Sciahbasi A, Minati M, Maresca L, Pendenza G, et al. Cardiac magnetic resonance detection of left ventricular thrombus in acute myocardial infarction. Acute card care 2013;15(1):11-6.
28. Witt BJ, Ballman KV, Brown RD, Jr., Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. Am J Med 2006;119(4):354 e1-9.
29. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347(13):969-74.
30. Udell JA, Wang JT, Gladstone DJ, Tu JV. Anticoagulation after anterior myocardial infarction and the risk of stroke. PloS One 2010;5(8):e12150.
31. Heart Failure Society of A, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J card fail 2010;16(6):e1-194.
32. Osherov AB, Borovik-Raz M, Aronson D, Agmon Y, Kapeliovich M, Kerner A, et al. Incidence of early left ventricular thrombus after acute anterior wall myocardial infarction in the primary coronary intervention era. Am Heart J 2009;157(6):1074-80.
33. Shacham Y, Leshem-Rubinow E, Ben Assa E, Rogowski O, Topilsky Y, Roth A, et al. Frequency and correlates of early left ventricular thrombus formation following anterior wall acute myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2013;111(5):667-70.
34. Kim E, Ozonoff A, Hylek EM, Berlowitz DR, Ash AS, Miller DR, et al. Predicting outcomes among patients with atrial fibrillation and heart failure receiving anticoagulation with warfarin. Thromb Haemost 2015;114(1).
35. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100.
36. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998;105(2):91-9.
37. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151(3):713-9.
38. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349(7):631-9.
39. Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999;159(5):457-60.
40. Hughes M, Lip GY, Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation and secondary care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. QJM 2007;100(10):599-607.
41. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-239.
42. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
43. Eapen ZJ, Mi X, Qualls LG, Hammill BG, Fonarow GC, Turakhia MP, et al. Adherence and persistence in the use of warfarin after hospital discharge among patients with heart failure and atrial fibrillation. J Card Fail 2014;20(1):23-30.
44. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293(6):690-8.
45. Olsson SB, Executive Steering Committee of the SIIII. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362(9397):1691-8.
46. Ferreira J, Ezekowitz MD, Connolly SJ, Brueckmann M, Fraessdorf M, Reilly PA, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. Eur J Heart Fail 2013;15(9):1053-61.
47. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093-104.
48. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail 2013;6(3):451-60.
49. van Diepen S, Hellkamp AS, Patel MR, Becker RC, Breithardt G, Hacke W, et al. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. Circ Heart Fail 2013;6(4):740-7.
50. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med

2009;361(12):1139-51.
51. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. N Engl J Med 2013;368(14):1272-4.
52. Patel MS, Davis MM, Lypson ML. Advancing medical education by teaching health policy. N Engl J Med 2011;364(8):695-7.
53. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
54. Magnani G, Giugliano RP, Ruff CT, Murphy SA, Nordio F, Rutman H, et al. Efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation and heart failure: Insights from engage-AF TIMI 48 [abstract]. Circulation 2014;130(Suppl 2).
55. Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, Gretler DD, Sinha U, et al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). Eur Heart J 2013;34(20):1498-505.
56. Cohen AT, Harrington R, Goldhaber SZ, Hull R, Gibson CM, Hernandez AF, et al. The design and rationale for the Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) study. Am Heart J 2014;167(3):335-41.
57. Allen LA, Felker GM, Pocock S, McMurray JJ, Pfeffer MA, Swedberg K, et al. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail 2009;11(2):170-7.
58. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109(8):1004-9.
59. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest 2012;42(2):153-63.
60. Poelzl G, Ess M, Von der Heidt A, Rudnicki M, Frick M, Ulmer H. Concomitant renal and hepatic dysfunctions in chronic heart failure: clinical implications and prognostic significance. Eur J Intern Med 2013;24(2):177-82.
61. Lega JC, Bertoletti L, Gremillet C, Chapelle C, Mismetti P, Cucherat M, et al. Consistency of safety and efficacy of new oral anticoagulants across subgroups of patients with atrial fibrillation. PloS one 2014;9(3):e91398.
62. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64(1):1-12.
63. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA 2014;312(19):1988-98.
64. Chatterjee S, Herrmann HC, Wilensky RL, Hirshfeld J, McCormick D, Frankel DS, et al. Safety and Procedural Success of Left Atrial Appendage Exclusion With the Lariat Device: A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database. JAMA Intern Med 2015.
65. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, et al. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. J Am Coll Cardiol 2014;64(6):565-72.
66. Watchman Device Summary of Safety and Effectiveness Data 2015. Accessed at http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013b.pdf on June 4, 2015.
67. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004;43(6):1004-9.
68. Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, et al. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007;18(1):9-14.
69. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008;359(17):1778-85.
70. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart 2011;97(9):740-7.
71. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;61(18):1894-903.
72. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7(1):31-8.
73. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351(23):2373-83.
74. Guiot A, Jongnarangsin K, Chugh A, Suwanagool A, Latchamsetty R, Myles JD, et al. Anticoagulant therapy and risk of cerebrovascular events after catheter ablation of atrial fibrillation in the elderly. J Cardiovasc Electrophysiol 2012;23(1):36-43.
75. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol 2008;51(8):843-9.
76. Oral H, Chugh A, Ozaydin M, Good E, Fortino J, Sankaran S, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation 2006;114(8):759-65.
77. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol 2010;55(8):735-43.
78. Karasoy D, Gislason GH, Hansen J, Johannessen A, Kober L, Hvidtfeldt M, et al. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark. Eur Heart J 2015;36(5):307-14a.
79. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: Heart Rhythm 2012;9(4):632-696 e21.
80. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31(19):2369-429.
81. Deitelzweig S, Amin A, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, et al. Medical cost reductions associated with the usage of novel oral anticoagulants vs warfarin among atrial fibrillation patients, based on the RE-LY, ROCKET-AF, and ARISTOTLE trials. J Med Econ 2012;15(4):776-85.
82. Harrington AR, Armstrong EP, Nolan PE, Jr., Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke; 2013;44(6):1676-81.
83. Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circ Cardiovasc Qual Outcomes 2013;6(6):724-31.
84. Gattellari M, Worthington J, Zwar N, Middleton S. Barriers to the use of anticoagulation for nonvalvular atrial fibrillation: a representative survey of Australian family physicians. Stroke; 2008;39(1):227-30.
85. Wutzler A, Bannehr M, Pohlmann AC, Haverkamp W. The use of direct oral

anticoagulants for stroke prevention in atrial fibrillation: a study on physicians' perspective and preferences. Int J Cardiol 2014;175(1):188-91.

86. Lahaye S, Regpala S, Lacombe S, Sharma M, Gibbens S, Ball D, et al. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. Thromb Haemost 2014;111(3):465-73.
87. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol 2013;61(17):1790-8.
88. Shaffer JA, Thompson JL, Cheng B, Ye S, Lip GY, Mann DL, et al. Association of quality of life with anticoagulant control in patients with heart failure: the Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial. Int J Cardiol 2014;177(2):715-7.
89. Wang Y, Xie F, Kong MC, Lee LH, Ng HJ, Ko Y. Patient-reported health preferences of anticoagulant-related outcomes. J Thromb Thrombolysis 2015.
90. Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J 2011;162(4):606-612 e1.
91. Steinberg BA, Blanco RG, Ollis D, Kim S, Holmes DN, Kowey PR, et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J 2014;168(2):160-7.
92. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35(43):3033-69, 3069a-3069k.
93. Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, et al. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2010;11(6):461-76.
94. Task Force on the management of ST segment elevation acute myocardial infarction of the European Society of Cardiology, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33(20):2569-619.