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Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.1946

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Mulder, B. A., van Veldhuisen, D. J., & Rienstra, M. (2020). What should the C ('congestive heart failure') represent in the CHA(2)DS(2)-VASc score? European Journal of Heart Failure, 22(8), 1294-1297. https://doi.org/10.1002/ejhf.1946

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What should the C (‘congestive heart failure’) represent in the CHA\textsubscript{2}DS\textsubscript{2}-VASc score?

Bart A. Mulder*, Dirk J. van Veldhuisen, and Michiel Rienstra

University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Introduction

Patients with atrial fibrillation (AF) require anticoagulation therapy when at least two clinical risk factors for stroke or thromboembolism are present, as defined in the CHA\textsubscript{2}DS\textsubscript{2}-VASc score. In this score the C stands for ‘congestive heart failure’ and nowadays the criteria to qualify for a C in clinical practice are more or less synonymous to the presence of signs/symptoms of heart failure. The criteria for the CHA\textsubscript{2}DS\textsubscript{2}-VASc score were, however, defined and developed at a time when heart failure was more or less restricted to patients who had left ventricular systolic dysfunction [or reduced left ventricular ejection fraction (LVEF)]. Whether these criteria also apply to patients who have heart failure with preserved ejection fraction [HFrEF] remains challenging as compared to diagnosing a heart failure with reduced (LVEF <40%), mid-range (40–49%) and preserved (>50%). In the first description of the CHADS\textsubscript{2} score, the precursor of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, the C was classified as recent (i.e. in the last 100 days in one of the studies) congestive heart failure exacerbation (without a LVEF criterium). The CHA\textsubscript{2}DS\textsubscript{2}-VASc score is based on the CHADS\textsubscript{2} score and uses the same definitions. In the first paper by Lip et al. proposing the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, the Euro Heart Survey was used as a validation cohort, where congestive heart failure was classified as ‘heart failure’ or ‘left ventricular ejection below 35%’. The group ‘heart failure’ in that study is possibly reflecting patients with symptoms of heart failure, with and without reduced ejection fraction, so it may be suggested that also HFrEF patients were included, although these data are not reported.

Stroke prediction risk scores in atrial fibrillation

The CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores were not the first (and not the last) attempts for a reliable stroke prediction risk score in AF. The CHADS\textsubscript{2} score was the result of previous risk scoring models, namely the Atrial Fibrillation Investigators (AFI) scheme and the Stroke Prevention and Atrial Fibrillation (SPAF) scheme. In the AFI risk scheme, data were collected from five other trials: (i) the Atrial Fibrillation, Aspirin, Anticoagulation Study from Copenhagen, Denmark (AFASAK), (ii) the Stroke Prevention in Atrial Fibrillation (SPAF) study, (iii) the Boston Area Anticoagulation Trial in Atrial Fibrillation (BAATAF), (iv) the Canadian Atrial Fibrillation Anticoagulation (CAFA) study, and (v) the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) study. Congestive heart failure was considered as a risk factor, but was not qualified similarly amongst the studies (see Table 1 for an overview of the studies). For example, in the AFASAK trial only...
patients with symptomatic moderate and severe heart failure were considered to have congestive heart failure.\textsuperscript{10} Notably, no data on LVEF were provided in any of these trials and it is uncertain what type of heart failure these patients really had (reduced, mid ranged or preserved LVEF). It appears, however, that from a historical perspective, many of these patients must have been HFrEF patients.\textsuperscript{3} In conclusion, in the original cohorts, predominantly HFrEF patients were included as HFpEF was not acknowledged at that time. Therefore, the C of congestive heart failure, appears to be primarily driven by HFrEF.

### Pathophysiology of atrial fibrillation-related stroke in heart failure with preserved and reduced ejection fraction

For HFpEF and HFrEF the same pathophysiology processes are contributing to Virchow’s pre-requisites for thrombosis: abnormal blood flow, abnormalities in the blood vessel wall, and abnormal blood constituents (Figure 1).\textsuperscript{11,12} Constituent abnormalities are present in the form of abnormal platelets and increased levels of pro-thrombotic markers.\textsuperscript{11} While the level of many circulating biomarkers increases with severity or worsening of heart failure, as is the case for e.g. the level of plasminogen activator inhibitor and tissue plasminogen activator antigen, both markers of fibrinolysis are elevated in heart failure patients across a wide range of LVEF, and regardless of LVEF.\textsuperscript{11,13}

### Stroke risk in heart failure regardless of left ventricular ejection fraction

The risk of stroke is significantly increased in patients with any reduction in LVEF and increases with a high \(\text{CHA}_2\text{DS}_2\text{-VASc} \) score.\textsuperscript{14} The influence of LVEF on stroke risk appears to be substantial.\textsuperscript{13,15} Recent data, however, suggest that the stroke risk is similarly increased in patients with reduced and preserved LVEF.\textsuperscript{16} A sub-analysis of patients (from the non-oral anticoagulation arm) participating in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trials who also had heart failure were categorized as having preserved vs. reduced ejection fraction.\textsuperscript{16} Data from this study showed that the stroke risk was comparable between the two groups: 4.3% (in patients with HFpEF) and 4.4% (in HFrEF) per 100 person-years.\textsuperscript{16} In addition, a meta-analysis incorporating seven studies with a total of 33,773 patients with heart failure showed that for patients with HFrEF and HFpEF who also had AF the rate of stroke risk was similar at 1.6% in HFrEF and 1.3% in HFpEF (relative risk 0.85, \( P = 0.094 \)).\textsuperscript{15}

### Prevention of atrial fibrillation-related stroke in heart failure regardless of left ventricular ejection fraction

The most recent AF guidelines do not further differentiate the C (congestive heart failure) in the \(\text{CHA}_2\text{DS}_2\text{-VASc} \) score, and score the ‘C’ when patients have signs/symptoms of heart failure or objective evidence of reduced LVEF. Indeed, there is no mention of HFpEF with regard to stroke prevention and as a result patients with HFpEF possibly must have more symptoms to receive anticoagulation (since they do not qualify with the LVEF criterium) than those with HFrEF. In the most recent heart failure guidelines it is stated that patients with heart failure (non-specified) and in New York Heart Association (NYHA) functional class II–IV should be considered for anticoagulation, if eligible, as assessed by the \(\text{CHA}_2\text{DS}_2\text{-VASc} \) score. Data on efficacy and safety of anticoagulation in heart failure patients have been published in several post-hoc analyses of the landmark novel oral anticoagulant (NOAC) trials.\textsuperscript{17–19} In the heart failure substudy of the ROCKET-AF trial, heart failure was defined as a history of heart failure (non-specified) or a LVEF <40%.\textsuperscript{17} In the ARISTOTLE heart failure substudy, two groups of heart failure were defined. Patients with left ventricular systolic dysfunction (defined as LVEF <40%, or a documentation of moderate or severe left ventricular systolic dysfunction) with or without symptomatic heart failure. Or the second group which were heart failure patients who had

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Hypothesis generating figure of the relation of stroke and heart failure. Illustrating that heart failure with preserved (HFpEF) and reduced ejection fraction (HFrEF) share similar risk factors for stroke using Virchow’s triad. BMI, body mass index; RAAS, renin–angiotensin–aldosterone system.

Figure 2 Percentages of stroke in heart failure patients in the four major novel oral anticoagulant trials. HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction.

symptomatic heart failure and LVEF >40%, normal left ventricular function, or mild left ventricular systolic dysfunction, grouped as HFpEF. In the RE-LY trial, heart failure was defined as the presence of NYHA class II or higher in the 6 months before screening, in patients with a history of previous admission for congestive heart failure. Information about LVEF was available in only 2889 patients with heart failure (58.9%). A total 43.5% of the heart failure patients had a LVEF <40%, which may suggest that 56.5% of patients in the RE-LY heart failure group had HFpEF (or that no measurement was available). In the ENGAGE AF-TIMI 48 study, heart failure was defined as current presence or history of heart failure class C or D according to the American Heart Association/American College of Cardiology definition. In this study, 49% of patients had LVEF <50%, implying that half of the heart failure patients were HFpEF (of which many were classified as severe heart failure). Figure 2 shows the percentages of stroke in the heart failure groups and illustrates that in the heart failure population a significant proportion of patients had HFpEF. Overall the conclusions of these post-hoc NOAC papers were that the effect of NOACs in patients with heart failure and AF is similar, both for efficacy as well as for safety outcomes as compared to AF patients without heart failure. Although one should be cautious to draw strong conclusions from the above studies in patients with HFpEF, these recommendations have in fact been made (from the historical data) for patients with HFrEF.17–20
Summary

Given the recent increase in HFrEF and the fact that the CHA2DS2-VASc is (mainly) based on HFrEF, criteria for anticoagulation for AF and HFrEF are in reality lacking. This is remarkable, given the fact that AF is more common in patients with HFrEF. However, as long as there are no trials performed specifically in this HFrEF population and there is no pathophysiological reason why data would be different in HFrEF, we believe that given the available data, anticoagulation must be seriously considered in many patients with AF and HFrEF. Indeed, recommendations for anticoagulation in AF/HFrEF patients may possibly be similar to those for HFrEF.

Conflict of interest: none declared.

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