Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 24, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.03.039

Antithrombotic Treatment in Patients With Heart Failure and Associated Atrial Fibrillation and Vascular Disease

A Nationwide Cohort Study

Morten Lamberts, MD, PhD,* Gregory Y. H. Lip, MD,† Martin H. Ruwald, MD, PhD,* Morten Lock Hansen, MD, PhD,* Cengiz Özcan, MD,* Søren L. Kristensen, MD,* Lars Køber, MD, DMSc,‡ Christian Torp-Pedersen, MD, DMSc,§ Gunnar H. Gislason, MD, PhD*‖

Copenhagen and Aalborg, Denmark; and Birmingham, United Kingdom

Objectives The aim of this study was to investigate the impact of atrial fibrillation (AF) and antithrombotic treatment on the prognosis in patients with heart failure (HF) as well as vascular disease.

Background HF, vascular disease, and AF are pathophysiologically related, and understanding antithrombotic treatment for these conditions is crucial.

Methods In hospitalized patients with HF and coexisting vascular disease (coronary artery disease or peripheral arterial disease) followed from 1997 to 2009, AF status was categorized as prevalent AF, incident AF, or no AF. Risk of thromboembolism (TE), myocardial infarction (MI), and serious bleeding was assessed by Cox regression models (hazard ratio [HR] with 95% confidence interval [CI]) with antithrombotic therapy and AF as time-dependent variables.

Results A total of 37,464 patients were included (age, 74.5 ± 10.7 years; 36.3% females) with a mean follow-up of 3 years during which 20.7% were categorized as prevalent AF and 17.2% as incident AF. Compared with vitamin K antagonist (VKA) in prevalent AF, VKA plus antiplatelet was not associated with a decreased risk of TE (HR: 0.91; 95% CI: 0.73 to 1.12) or MI (HR: 1.11; 95% CI: 0.96 to 1.28), whereas bleeding risk was significantly increased (HR: 1.31; 95% CI: 1.09 to 1.57). Corresponding estimates for incident AF were HRs of 0.77 (95% CI: 0.56 to 1.06), 1.07 (95% CI: 0.89 to 1.28), and 2.71 (95% CI: 1.33 to 2.21) for TE, MI, and bleeding, respectively. In no AF patients, no statistical differences were seen between antithrombotic therapies in TE or MI risk, whereas bleeding risk was significantly increased for VKA with and without single-antiplatelet therapy.

Conclusions In AF patients with coexisting HF and vascular disease, adding single-antiplatelet therapy to VKA therapy is not associated with additional benefit in thromboembolic or coronary risk, but notably increased bleeding risk. (J Am Coll Cardiol 2014;63:2689–98) © 2014 by the American College of Cardiology Foundation

Although systolic heart failure (HF) is associated with increased risk of thromboembolism (TE) and death, no firm evidence exists of the benefit of antithrombotic treatment in uncomplicated HF in sinus rhythm (1–3). For example, a recent Cochrane review found no convincing evidence that oral anticoagulant therapy modified mortality or vascular events in patients with HF in sinus rhythm (4).

See page 2699

Two conditions commonly related to HF are vascular disease and atrial fibrillation (AF), with both frequently requiring the use of antithrombotic therapy with antiplatelet drugs and oral anticoagulation, respectively. In patients with coronary or peripheral artery disease, antiplatelet therapy is recommended (5–7), although the benefits of antiplatelet therapy in patients with concomitant HF are less well defined in relation to mortality and vascular events (4). In HF patients with AF, oral anticoagulation is clearly indicated (8,9).

From the *Department of Cardiology, Gentofte University Hospital, Hellerup, Copenhagen, Denmark; †University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; ‡The Heart Centre, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark; §Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark; and the ‖National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark. Dr. Gislason is supported by an independent research scholarship from the Novo Nordisk Foundation. Dr. Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi-Aventis, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim; and has been on the Speakers' Bureau of Bayer, Bristol-Myers Squibb/Pfizer. Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, and Sanofi Aventis. Dr. Torp-Pederson is a consultant for Cardiome, Merck, Sanofi-Aventis, and Daiichi Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Lip and Gislason contributed equally to this paper.

Manuscript received October 14, 2013; revised manuscript received February 22, 2014, accepted March 4, 2014.

JACC Vol. 63, No. 24, 2014
June 24, 2014:2689–98

Abbreviations and Acronyms

AF = atrial fibrillation

CHA_2DS_2-VASc = congestive heart failure, hypertension, older than 75 years of age, diabetes, stroke/thromboembolism, vascular disease, 65 to 74 years or age, female sex

CI = confidence interval

HAS-BLED = hypertension, abnormal liver/renal function, stroke, bleeding, labile international normalized ratio, elderly, drugs

HF = heart failure

HR = hazard ratio

ICD = International Classification of Diseases

INR = international normalized ratio

TE = thromboembolism

VKA = vitamin K antagonist

The use of antithrombotic therapy has to balance a reduction in TE against the potential increase in risk of bleeding (10). Bleeding while on antithrombotic therapy may have implications for subsequent adverse outcomes (11–15). Patients with HF may also be predisposed to more bleeding due to difficulties with warfarin and liver congestion (16), and in the recent WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) trial conducted in HF patients in sinus rhythm, the beneficial effects of reducing ischemic stroke were offset by an increase in major bleeding with warfarin therapy (17).

If patients with HF have both vascular disease and AF, a common practice is to concomitantly prescribe oral anticoagulation and antiplatelet therapy because such patients are considered high risk. Indeed, incident and prevalent AF may confer different risks. In general population studies, there is little evidence of a beneficial effect of such combination antithrombotic therapy on TE, given the increase in serious bleeding (11,12). Limited data are available for HF patients who have both vascular disease and AF.

In a real-life cohort of HF patients with vascular disease, our objective was to assess the relationship of incident or prevalent AF to TE and serious bleeding. Second, we also assessed the effectiveness and safety of ongoing antithrombotic treatment in such patients.

Methods

Registries. We linked information on the individual level from several nationwide databases. The National Patient Registry classifies all hospital contacts according to the International Classification of Diseases (ICD) since 1977 (with the eighth revision until 1994 and then the 10th revision.). Coding is performed for the primary diagnosis of contact, and, if appropriate, ≥1 secondary diagnoses, and when identifying diagnoses in the registries was allowed (18). Procedures performed are also coded according to Nordic Medical Statistics Committee of Surgical Procedures. From the national prescription registry, we collected information on the dose, number of tablets, and date of dispensing for each individual according to the Anatomical Therapeutic Chemical Classification system endorsed by the World Health Organization (19). Vital status and cause of death according to the ICD 10th revision were obtained from the Danish Personal Registration System and the National Causes of Death register, respectively (20). Using a unique number, we retrospectively linked this information for each individual. All ICD and Anatomical Therapeutic Chemical Classification system codes used are available in the Online Table 1.

Study population. All Danish residents with a first-time HF hospitalization between January 1, 1997 and December 31, 2009 were identified. We included patients with a previous diagnosis of myocardial infarction (MI), aortic plaque, and peripheral artery disease and having undergone procedures on coronary arteries (coronary artery bypass and coronary intervention) as markers of vascular disease. The date of study inclusion of patients with HF was the date of discharge. The presence of no AF included patients without an AF diagnosis (since 1977) before HF hospitalization, whereas prevalent AF patients had a diagnosis of AF before hospitalization for HF. During the study period, no AF patients were continuously screened for an AF diagnosis and categorized as incident AF at the date of a first-time AF admission. Hence, the study population initially comprised patients with a HF hospitalization and coexisting vascular disease with status of prevalent (known) AF or no AF. During follow-up, the status of no AF patients could subsequently change to incident AF (Fig. 1). Categorizing AF patients was predefined as the occurrence of AF (either prevalent or incident) from a first-time HF hospitalization might pose different risks (e.g., duration of AF disease burden, influencing antithrombotic treatment strategy, progression of HF).

Heart failure. The administrative discharge coding for HF classified HF as hypertensive (ICD-10 DI11.0), cardiomyopathy (ICD-10 DI42, including dilated, alcoholic, and obstructive cardiomyopathy), acute pulmonary edema (ICD-10 DJ81.9), and unspecified HF (ICD-10 DI50 including decompensated HF [ICD-10 I50.9]). To assess the severity of HF, we calculated the daily dose of loop diuretics before and after HF hospitalization: group 1 (0 to 39 mg), group 2 (40 mg to 79 mg), group 3 (80 mg to 159 mg), and group 4 (≥160 mg), as previously done (21).

Antithrombotic treatment. For each individual, all prescriptions of aspirin, clopidogrel, and vitamin K antagonists (VKA) (i.e., warfarin and phenprocoumon) were identified, and the following commonly used treatment regimens were classified: single-antiplatelet therapy (aspirin or clopidogrel), VKA, and VKA plus single-antiplatelet therapy. In no AF patients, dual-antiplatelet therapy (aspirin and clopidogrel) was also assessed for the primary outcomes. Ongoing antithrombotic treatment was determined from claimed prescriptions as previously done (11,22). Briefly, from the number of tablets dispensed and the strength of tablets, the average daily dose was defined. Patients were allowed to change group but could only be exposed to 1 treatment group at any given time and were only considered at risk when having tablets available for consumption. Subsequent antithrombotic treatment at baseline was defined as any claimed prescriptions of VKA, antiplatelet drugs, or both up to 30 days after HF discharge (11).