

# Relative impact of bleedings over ischaemic events in patients with heart failure: insights from the CARDIONOR registry

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## Abstract

**Aims** Major bleeding events in heart failure (HF) patients are poorly described. We sought to investigate the importance of major bleeding and its impact on outcomes in HF patients.

**Methods and results** We analysed incident bleeding and ischaemic events during a 3 year follow-up in 2910 HF outpatients included in a prospective multicentre registry. Major bleeding was defined as a Type  $\geq 3$  bleed using the Bleeding Academic Research Consortium definition. Ischaemic event was a composite of ischaemic stroke and myocardial infarction. Events were adjudicated by a blinded committee. At inclusion, most patients (89%) received at least one antithrombotic: anticoagulation (53.9%) and/or antiplatelet therapy (46.2%). Bleeding occurred in 111 patients {3 year cumulative incidence: 3.6% [95% confidence interval (CI) 3.0–4.3]} and ischaemic events in 102 patients [3 year cumulative incidence: 3.3% (95% CI 2.7–4.0)]. Most bleedings were Bleeding Academic Research Consortium 3a (32.5%) or 3b (31.5%). Most frequent sites of bleeding were gastrointestinal (40.6%) and intracranial (27.9%). Variables associated with bleeding were atrial fibrillation [hazard ratio (HR) = 2.63 (95% CI 1.66–4.19),  $P < 0.0001$ ], diabetes [HR = 1.62 (95% CI 1.11–2.38),  $P = 0.012$ ], and older age [HR = 1.19 per 10 year increase (95% CI 1.00–1.41),  $P = 0.049$ ]. Anticoagulation use was associated with a two-fold increase in the bleeding risk. Bleeding events as well as ischaemic events were strongly associated with subsequent mortality [adjusted HRs: 5.67 (4.41–7.29),  $P < 0.0001$  and 4.29 (3.18–5.78),  $P < 0.0001$ , respectively].

**Conclusions** In HF outpatients, antithrombotics are widely used. Bleeding occurs at a stable rate of 1.2% annually (as frequent as ischaemic events) and is associated with a dramatic increase in mortality (at least as severe as ischaemic events). Most events occurred in patients receiving anticoagulation. Knowledge of these findings may help physicians to manage antithrombotics in HF patients.

**Keywords** Heart failure; Major bleeding; Anticoagulation; Myocardial infarction; Stroke

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## Introduction

There has been a considerable interest in the recent literature for bleeding events that occur in patients with cardiovascular diseases. Studies performed in patients with acute or chronic manifestations of coronary artery disease (CAD),<sup>1–3</sup> patients undergoing percutaneous coronary

revascularization,<sup>4,5</sup> or patients with atrial fibrillation (AF)<sup>6</sup> have demonstrated that bleeding events are both relatively frequent and associated with adverse outcomes. Balancing bleeding and thrombotic risks is thus an integral part of management for these patients, and specific recommendations regarding antithrombotic management are part of international guidelines.<sup>7–9</sup>

In contrast, to the best of our knowledge, there has been no specific study to evaluate the risk and the consequences of bleeding events (especially their relative impact on outcomes as compared with ischaemic events) in a population of outpatients with chronic heart failure (HF). Thus, this risk may be underestimated in daily practice. The clinical characteristics of HF patients—advanced age, common use of anti-thrombotic medications due to associated and/or causal diseases such as CAD, AF, or the presence of left ventricular thrombus<sup>10–12</sup>—would however argue for a significant risk of bleeding. In addition, the prognostic implications of major bleeding may be magnified when occurring in already high-risk patients. The number of HF outpatients is growing constantly,<sup>13</sup> and an improved knowledge on bleeding events in this population would be of value.

We therefore designed the present study to assess the importance of bleeding and its relative impact on outcomes as compared with ischaemic events in HF patients. We analysed the data of 2910 HF outpatients included in the CARDIONOR (*Suivi d'une cohorte de patients présentant une pathologie CARDIaque en régiOn NORd-pas-de-Calais*) registry,<sup>12</sup> in which CAD and AF, as well as antithrombotic use, were systematically indexed at inclusion. We report the incidence, source, determinants, and association with subsequent mortality of major bleeding events and ischaemic events occurring during the 3year follow-up of the study.

## Methods

### Study population

The CARDIONOR registry is a prospective multicentre study that enrolled, between January 2013 and May 2015, 10 517 consecutive outpatients with a diagnosis of CAD, AF, and/or HF.<sup>12</sup> As previously described, the patients were included by 81 cardiologists from the French Region of Nord-Pas-de-Calais during outpatient visits. A case record form, which contained information regarding demographic and clinical details of the patients, including current medications, was prospectively completed at the initial visit by the investigator (i.e. the cardiologist). In case of bleeding, antithrombotic management was also retrospectively collected at time of bleeding in all cases. Documented CAD was defined as history of myocardial infarction (MI), coronary revascularization, and/or the presence of coronary stenosis >50% on coronary angiogram. Documented AF was defined as history of AF, even if in sinus rhythm at inclusion. Documented HF was defined as history of hospitalization for HF and/or history of symptoms and signs of HF associated with echocardiographic evidence of systolic dysfunction, left ventricular hypertrophy, left atrial enlargement, or diastolic dysfunction. The left ventricular ejection fraction (LVEF) was the most recent

echocardiographic assessment. Preserved, mid-range, and reduced LVEF were defined as LVEF  $\geq$  50%, 40–49%, and <40%, respectively.<sup>11</sup> The sole exclusion criterion was age < 18 years. Among the 10 517 outpatients included in the CARDIONOR registry, 2910 had documented HF at inclusion and are the subject of the present analysis.

This study was approved by the French medical data protection committee and authorized by the Commission Nationale de l'Informatique et des Libertés for the treatment of personal health data. All patients consented to the study after being informed in writing of the study's objectives and treatment of the data, as well as on their rights to object, of access, and of rectification. The investigation conforms with the principles outlined in the 'Declaration of Helsinki'.

### Follow-up, definitions, and endpoints

The patients were followed up by their treating cardiologists. The treating cardiologists then followed up with the patients, with the number of outpatient visits at clinician discretion. Protocol-specified follow-up was performed at 3years using a standardized case record form to report clinical events. In the case of missing information, general practitioners and/or patients were contacted by a research technician. The identification of patients with events for adjudication was based on interviews with patients/relatives during outpatient visits, on discharge summaries for hospitalizations during follow-up, and on information obtained by the research technician. The events reported by the patients were systematically confirmed from the medical reports.

All clinical endpoints were adjudicated according to prespecified definitions by two investigators, with a third opinion in cases of disagreement. The cause of death was determined after a detailed review of the circumstances of death and classified as cardiovascular or non-cardiovascular as previously defined.<sup>14</sup> Bleeding events were classified using the Bleeding Academic Research Consortium (BARC) definitions.<sup>15</sup> BARC Types 1 and 2 bleeds were not collected in our registry. For the purpose of this study, we defined major bleeding as all BARC Type  $\geq$ 3 events. MI was defined according to the universal definition.<sup>16</sup> Ischaemic stroke was defined as a sudden onset of focal neurological symptoms with the presence of cerebral infarction in the appropriate territory on brain imaging (computed tomography or magnetic resonance imaging), regardless of the duration of symptoms (less than or more than 24 h).<sup>17</sup>

### Statistical analysis

Continuous variables are described as mean  $\pm$  standard deviation. Categorical variables are presented as absolute numbers and/or percentages. The incidence of bleeding and

ischaemic (MI and ischaemic stroke) events was estimated with the cumulative incidence function, with death as the competing event. The assessments of baseline variables associated with incident bleeding were performed with the use of a cause-specific hazard model.<sup>18,19</sup> For multivariable analysis, a stepwise approach was used with forward selection ( $P = 0.05$  for entering into the model). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The proportional hazard assumption was tested and satisfied for all variables. Collinearity was excluded by constructing a correlation matrix between candidate predictors. The associations between incident bleeding, incident ischaemic events, and mortality were assessed with Cox analyses, in which incident bleeding and incident ischaemic events were modelled as time-dependent variables. HRs and 95% CIs were calculated. All statistical analyses were performed using STATA 14.2 software (STATA Corporation, College Station, TX). Significance was assumed at  $P < 0.05$ .

## Results

### Study population

A clinical follow-up was obtained at a median of 3.2 [interquartile range (IQR): 2.5–3.5] years in 2902 (99%) of the 2910 HF outpatients included in the CARDIONOR registry. As shown in *Table 1*, most patients were male (61.8%) with

a mean age of  $71.6 \pm 12.8$  years. The mean LVEF was  $48 \pm 13\%$  with proportions being 50.4% for preserved LVEF, 23.9% for mid-range LVEF, and 25.7% for reduced LVEF. Altogether, 45% of the patients had a history of CAD. The New York Heart Association (NYHA) class was  $\geq 3$  in 22.8% of the cases. There was a high prevalence of AF at inclusion (57.3%).

There was a high prescription of HF medications (i.e. beta-blockers, angiotensin system antagonists, and diuretics). Antiplatelet therapy (APT) was used in 46.2% of the patients and oral anticoagulation (OAC) in 53.9% [vitamin K antagonists (VKA), 44.2%; direct oral anticoagulant (DOAC), 9.7%]. Supporting Information, *Figure S1* provides a detailed description of antithrombotic management at inclusion in the registry. Most patients received at least one antithrombotic treatment (88.9%). OAC was prescribed in 86.5% of the patients with AF at inclusion (among these with OAC, VKA and DOAC were used in 80.8% and 19.2%, respectively).

### Incident bleeding and ischaemic events

At follow-up, there were 856 deaths (cardiovascular deaths:  $n = 469$ ) in the 2902 patients with HF. There were 111 major bleeding events during the follow-up period with cumulative incidences, including death as the competing event, of 1.4% (95% CI 1.1–1.9), 2.5% (95% CI 1.9–3.1), and 3.6% (95% CI 3.0–4.3) at 1, 2, and 3 years, respectively (1.2% per year) (*Figure 1*). As shown in Supporting Information, *Table S1*, most events were BARC Type 3a or 3b bleeds. There were

**Table 1** Baseline characteristics of the study population and correlates of major bleeding according to univariable analysis

	All HF patients with follow-up ( $n = 2902$ )	No major bleeding ( $n = 2791$ )	Major bleeding ( $n = 111$ )	HR (95% CI)	$P$ value
Age, years	$71.6 \pm 12.8$	$71.5 \pm 12.9$	$74.1 \pm 11.3$	1.03 (1.01–1.04)	0.002
Women	38.2	38.2	37.8	0.99 (0.67–1.45)	0.943
Diabetes mellitus	31.7	31.4	40.5	1.52 (1.04–2.22)	0.030
History of hypertension	61.7	61.4	69.4	1.52 (1.02–2.28)	0.041
History of CAD	45.1	45.0	46.0	1.07 (0.74–1.55)	0.729
History of MI	26.1	26.1	25.2	0.97 (0.63–1.48)	0.878
History of coronary revascularization	34.7	34.8	32.4	0.91 (0.61–1.35)	0.639
Atrial fibrillation	57.3	56.5	78.4	2.90 (1.84–4.56)	<0.0001
History of stroke	7.7	7.7	7.2	1.02 (0.49–2.09)	0.966
NYHA Classes 3–4	22.8	22.6	27.0	1.51 (0.99–1.02)	0.055
LVEF, %	$48 \pm 13$	$48 \pm 13$	$49 \pm 14$	1.01 (0.99–1.02)	0.355
ICD	12.5	12.6	11.7	0.90 (0.50–1.60)	0.713
CRT	2.7	2.7	2.7	0.94 (0.30–2.98)	0.922
Medications at inclusion					
ACE-I or ARB	82.8	82.9	80.2	0.77 (0.48–1.22)	0.266
Beta-blocker	83.1	83.3	80.2	0.72 (0.45–1.15)	0.174
MRA	22.1	22.4	15.3	0.59 (0.35–0.99)	0.045
Diuretic	73.1	72.8	80.2	1.65 (1.04–2.64)	0.035
Statin	62.5	62.6	59.5	0.87 (0.59–1.26)	0.455
Antiplatelet drug	46.2	46.7	35.1	0.64 (0.44–0.95)	0.026
Oral anticoagulant	53.9	53.2	71.2	2.16 (1.43–3.25)	<0.0001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralo-receptor antagonist; NYHA, New York Heart Association. Data are mean  $\pm$  standard deviation or percentages.

21 fatal bleeds (Type 5). In most of the cases, the site of bleeding was gastrointestinal (40.6%) or intracranial (27.9%). The site of fatal bleeding was intracranial in 13 patients, gastrointestinal in 4 patients, retroperitoneal in 2 patients, and pulmonary in 2 patients. Over the same time period, there were 102 ischaemic events (ischaemic stroke,  $n = 64$  and MI,  $n = 38$ ) with cumulative incidences, including death as the competing event, of 1.1% (95% CI 0.8–1.5), 2.2% (95% CI 1.7–2.7), and 3.3% (95% CI 2.7–4.0) at 1, 2, and 3 years, respectively (1.1% per year) (Figure 1 and Supporting Information, Table S1).

### Correlates of incident bleeding events

The patients who experienced major bleeding were older and more frequently had diabetes mellitus, history of hypertension, and AF (Table 1). Figure 2 illustrates cumulative incidences of major bleeding according to baseline LVEF, NYHA class, history of CAD, and the presence/absence of AF. Of note, the incidence of bleeding was similar in HF with preserved, mid-range, or reduced LVEF, in patients with mild or severe HF symptoms, and in patients with or without CAD. By multivariable analysis, three clinical variables emerged as independent predictors of major bleeding: AF (HR = 2.63; 95% CI 1.66–4.19), diabetes mellitus (HR = 1.62; 95% CI 1.11–2.38), and age (HR = 1.19 per 10 year increase; 95% CI 1.00–1.41) (Table 2).

The use of OAC at inclusion was associated with a two-fold increase in the risk of major bleeding during follow-up (Table 1). Three year cumulative incidences of major bleeding were 1.8% (95% CI 1.1–3.0), 3.9% (95% CI 1.8–7.2), 4.7% (95% CI 3.6–6.0), and 4.4% (95% CI 2.5–7.0) in patients with single APT, dual APT, OAC alone, and the combination of OAC and

APT, at inclusion in the registry, respectively. Table 3 provides a detailed description of the antithrombotic regimen in all patients who experienced a major bleeding during follow-up, both at time of inclusion in the registry and at time of major bleeding. Almost all patients (91.9%) received at least one antithrombotic treatment, and most patients (71.2%) received OAC at inclusion. Among them, 14.4% of the patients received the combination of an OAC with APT at inclusion. Antithrombotic treatments were overall similar at time of bleeding, although there were numerically (but not significantly) more patients under the combination of OAC with APT at time of bleeding ( $n = 16$  at inclusion vs.  $n = 24$  at time of bleeding).

### Outcome after incident bleeding and incident ischaemic events

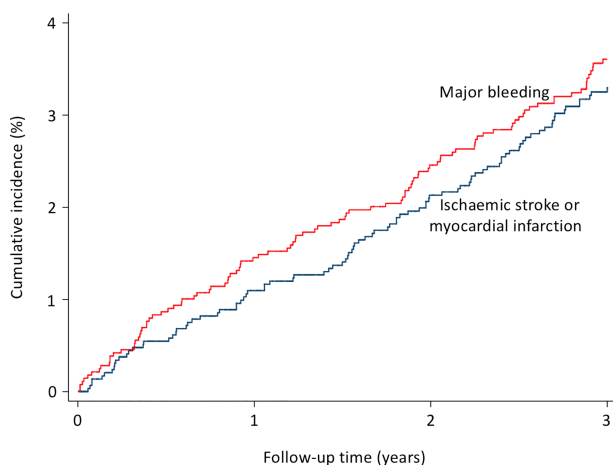
During the follow-up period, a total of 68 deaths occurred in the 111 patients with incident bleeding, and 47 deaths occurred in the 102 patients with incident ischaemic events. The median follow-up of event-free patients after bleeding was 479days (IQR: 147–834). The median time interval between the bleeding event and death was 2days (IQR: 1–7) for the 21 patients with BARC Type 5 bleeding and 188days (IQR: 63–637) in the 47 patients who died after BARC Type 3 or 4 bleeding. The median follow-up of event-free patients after ischaemic events was 566days (IQR: 298–888). The median time interval between the incident ischaemic event and death was 31days (IQR: 9–218).

When analysed as a time-dependent variable, incident bleeding during follow-up was associated with a major increase in mortality (HR = 6.73; 95% CI 5.24–8.65;  $P < 0.0001$ ). Unadjusted 1year mortality rates were 8.9% (95% CI 7.9–10.0) for patients without bleeding and 51.2% (95% CI 42.0–61.2) after incident bleeding. In an analysis taking into account the site of major bleeding, gastrointestinal, intracranial, and all other bleedings were each associated with increased mortality (HR = 4.97; 95% CI 3.33–7.43;  $P < 0.0001$ ; HR = 9.72; 95% CI 6.22–15.19;  $P < 0.0001$ ; HR = 7.11; 95% CI 4.69–10.78;  $P < 0.0001$ , respectively; patients without bleeding as reference).

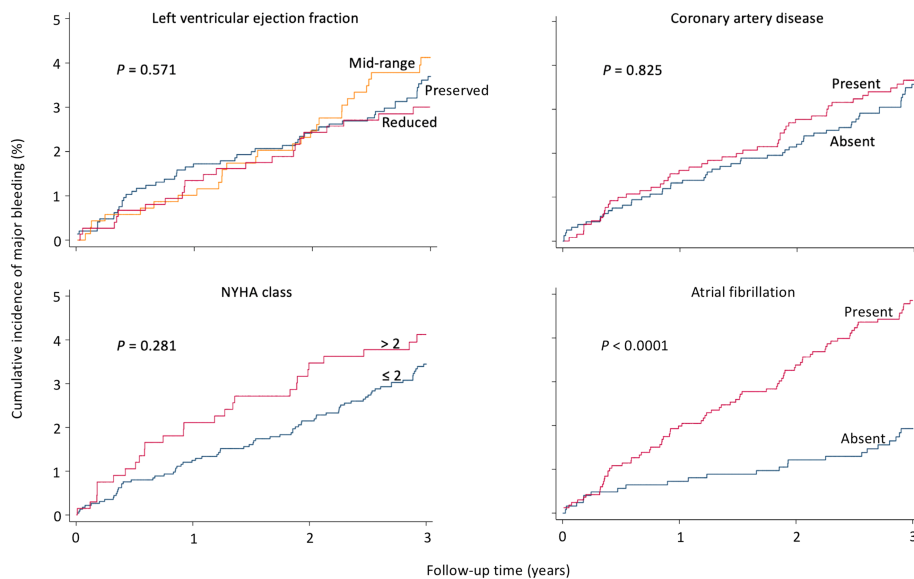
When analysed as a time-dependent variable, incident ischaemic event during follow-up was associated with an increase in mortality (HR = 4.36; 95% CI 3.24–5.86;  $P < 0.0001$ ). Unadjusted 1year mortality rates were 9.2% (95% CI 8.2–10.3) for patients without incident ischaemic event and 41.3% (95% CI 32.0–52.1) after incident ischaemic event.

In a multivariable model, both incident bleeding (HR = 5.67; 95% CI 4.41–7.29;  $P < 0.0001$ ) and incident ischaemic events (HR = 4.29; 95% CI 3.18–5.78;  $P < 0.0001$ ) were independently and strongly associated with mortality (Figure

**Figure 1** Incidence of major bleeding and ischaemic events over time in the overall heart failure population. Cumulative incidence functions are shown (death as the competing event).



**Figure 2** Incidence of major bleeding in subgroups of interest. Cumulative incidence of major bleeding during the follow-up period (death as the competing event) according to left ventricular ejection fraction, New York Heart Association (NYHA) class, coronary artery disease, and atrial fibrillation.



3). Other variables independently associated with mortality were age, NYHA class, gender, diabetes mellitus, and LVEF.

## Discussion

Although previous studies have failed to demonstrate a benefit of antithrombotic strategies in HF per se,<sup>20,21</sup> antiplatelet and/or anticoagulant medications are in daily practice largely used in HF patients as a result of associated and/or causal diseases such as AF, CAD, or the presence of left ventricular thrombus.<sup>10,11</sup> The present study indeed documents an extensive use of antithrombotic medications with nearly 90% of HF patients receiving  $\geq 1$  antithrombotic drug, including  $>50\%$  who received an OAC, which was so far poorly reported. In this context, the risk of bleeding and its relative

impact as compared with ischaemic events appears as a matter of concern. A recent letter especially highlighted the high theoretical risk of bleeding events of such patients included in the EURObservational Research Program (EORP) registry.<sup>22</sup> However, to the best of our knowledge, there has been no prior study to specifically evaluate the incidence and the consequences of major bleeding events as compared with ischaemic events in a large unselected population of HF patients.

Our results show that a major (BARC Type  $\geq 3$ ) bleeding is not a rare event in these patients and occurred continuously and linearly over time (1.2%/patient-year). Of note, it occurred at the same rate as the one observed for ischaemic events (1.1%/patient-year) in our population including almost 60% of patients with AF and 45% of patients with history of CAD. The most frequent sites of bleeding were gastrointestinal (41%) and intracranial (28%). While major bleeding is by

**Table 2** Correlates of incident bleeding according to multivariable analysis

	HR (95% CI)	P value
Atrial fibrillation	2.63 (1.66–4.19)	$<0.0001$
Diabetes mellitus	1.62 (1.11–2.38)	0.012
Age (per 10 year increase)	1.19 (1.00–1.41)	0.049

CI, confidence interval; HR, hazard ratio.

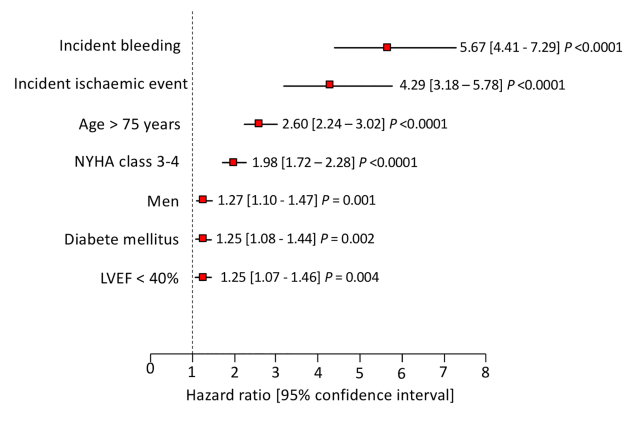
The variables included in the model were age, gender, diabetes mellitus, history of hypertension, history of coronary artery disease, history of myocardial infarction, history of coronary revascularization, atrial fibrillation, history of stroke, implantable cardioverter defibrillator, cardiac resynchronization therapy, New York Heart Association class, and left ventricular ejection fraction. A stepwise approach was used with forward selection (the P value for entering into the stepwise model was set at 0.05).

**Table 3** Antithrombotic treatment at time of inclusion and at time of incident bleeding ( $n = 111$ )

	At time of inclusion	At time of bleeding
None	9 (8.1)	5 (4.5)
Any antiplatelet therapy	39 (35.1)	39 (35.1)
Any oral anticoagulant	79 (71.2)	91 (82)
Single antiplatelet therapy	15 (13.5)	15 (13.5)
Dual antiplatelet therapy	8 (7.2)	0
Direct oral anticoagulant alone	9 (8.1)	12 (10.8)
Vitamin K antagonist alone	54 (48.7)	55 (49.6)
Direct oral anticoagulant + antiplatelet therapy	2 (1.8)	0
Vitamin K antagonist + antiplatelet therapy	14 (12.6)	24 (21.6)

Data are  $n$  (%).

**Figure 3** Association of incident bleeding and ischaemic events with subsequent mortality. Variables independently associated with all-cause mortality by multivariable analysis. The variables included in the model were age, gender, diabetes mellitus, history of hypertension, history of coronary artery disease, history of myocardial infarction, history of coronary revascularization, atrial fibrillation, history of stroke, implantable cardioverter defibrillator, cardiac resynchronization therapy, New York Heart Association (NYHA) class, and left ventricular ejection fraction (LVEF). Incident bleeding and incident ischaemic events were modelled as time-dependent variables.



definition a severe event, its prognostic implications may be magnified when occurring in already high-risk individuals such as HF patients. This was indeed the case in our study because >50% of the patients who experienced a major bleeding died within 1 year. Importantly, incident bleeding provided strong independent prognostic information when adjusted for common determinants of mortality of HF patients. In our study, bleeding events were associated with a numerically higher risk of death as compared with ischaemic events. A bleeding event should thus be considered as an important warning sign for clinicians. In addition, it is important to note that the prognostic implications of major bleedings were not limited to intracranial events. Indeed, although intracranial bleedings were associated with the greatest risk of mortality, other major bleedings had also a considerable impact on prognosis. In accordance with our results, a recent analysis focusing on the impact of gastrointestinal bleeding in HF patients showed that the occurrence of gastrointestinal bleeding was associated with a two-fold increase in cardiac events and three-fold increase in all-cause death.<sup>23</sup>

The strongest determinant of major bleeding was the presence of AF at inclusion. It is important to point out that this result applies to HF patients recruited in an outpatient setting, irrespective of the level of LVEF. Our study population was characterized by an old age and a high number of patients with preserved LVEF. Although some previous studies reported lower frequency of AF (around 35–40%) in HF patients,<sup>24–26</sup> the high prevalence of AF at inclusion (57%) in our cohort is however concordant with the data recently reported by the Swedish Heart Failure Registry investigators

in a large cohort of consecutive HF patients ( $n = 41\,446$ —AF in 57.3% in the total population and up to 65% in patients with preserved LVEF).<sup>27</sup> In our study, more than 85% of HF patients with AF received OAC; similar proportions have been reported in recent AF registries.<sup>28</sup> Diabetes mellitus and older age were also associated with a higher risk of bleeding as previously reported in other categories of patients with cardiovascular diseases.<sup>1,3</sup> In contrast, the lack of association with LVEF should be emphasized, and the risk of bleeding should be considered as well in HF patients with preserved, mid-range, or reduced LVEF. The same applies to NYHA class with a similar risk of bleeding in HF patients with mild symptoms as compared with those with severe symptoms.

Physicians in charge of HF patients should take into account the risk of major bleeding and its dramatic consequences. Our results are not a claim for stopping antithrombotics in HF patients who require them for a specific indication but rather a warning for optimizing the antithrombotic strategy in an attempt to reduce the risk of bleeding. Firstly, the rate of DOAC use was still quite low in our population (1/5 of AF patients) showing that there is some room for treatment improvement. When indicated, the use of DOAC should indeed be promoted in HF patients because they have shown a lower risk of intracranial bleeding as compared with VKA overall and a good benefit/risk ratio in HF patients.<sup>29–31</sup> Secondly, the relative risks and benefits of antithrombotic associations should be periodically reassessed in HF patients combining AF and CAD. Finally, because the most frequent site of major bleeding in HF patients was gastrointestinal, then the co-prescription of proton-pump inhibitors should be considered in the higher risk patients.

## Strengths and limitations

Our study has several strengths. We studied consecutive HF outpatients who were managed in a real-life contemporary practice with a high level of recommended treatment prescription. The follow-up rate was extremely high. Bleeding events as well as ischaemic events were all centrally adjudicated and classified using the internationally recommended definitions. To our knowledge, our study is the first to analyse in the same cohort the relative impact of bleeding as compared with ischaemic events in HF patients. Finally, because the mortality in our population was high, we estimated the risk of major bleeding and ischaemic events with the cumulative incidence function, with death as the competing event. Indeed, the inappropriate censoring of competing events may cause the Kaplan–Meier estimator to overestimate the cumulative incidence in the presence of competing risks especially if the competing risk is frequent.<sup>18,19</sup>

In contrast, there are also some limitations to our study that should be acknowledged. Firstly, as for all observational registries, biases may have occurred, and our results may

have been affected by unmeasured confounders. Secondly, we lack longitudinal information on patient medications in the overall cohort over the 3-year follow-up; however, major changes during the follow-up period are unlikely, given that all patients had been stable at inclusion, with their cardiologists confirming continuing treatments at inclusion. In addition, as shown in *Table 3*, antithrombotic management did not change significantly in those patients who experienced a major bleeding between inclusion time and bleeding events. Nonetheless, this remains a limitation of our study. Thirdly, our data reflect the practice in a regional area, and we do not know whether these findings are generalizable for practices in other parts of the world. Fourthly, some unknown or sudden deaths may have been related to either bleeding (especially intracranial) or ischaemic events. This may have led to an underestimation of both the number and the severity of incident events. However, this does not modify our principal conclusion, which is that a major bleeding occurrence is a critical warning sign in HF patients. Finally, the rate of major bleeding was numerically lower in patients with the combination of OAC and APT (4.4%) as compared with patients with OAC alone (4.7%). This unusual finding may be related to the fact that this subgroup of patients was small in size ( $n = 327$ , 11.2% of the total population). This result should therefore be taken with caution.

## Conclusions

Antithrombotic prescription is extremely common, and major bleeding is not rare in HF outpatients. The risk of bleeding is constant over time (1.2% per year) and similar in HF with preserved, mid-range, or reduced LVEF and in patients with mild or severe HF symptoms. Most bleeding events occurred in patients receiving OAC. Bleeding events are at least as frequent as ischaemic events in this population. When occurring in HF patients, major bleeding is a dramatic event with an extremely high associated mortality, numerically higher than the one observed after an ischaemic event in our study. Knowledge of these findings may help physicians to manage antithrombotic therapies in HF patients.

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## Conflict of interest

Dr G.L. reported personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier, and The Medicine Company. Dr N.L. reported personal fees from Actelion, Akcea, Amicus Therapeutics, Bayer, Novartis, MSD, Pfizer, Sanofi-Aventis, and travel grants from Amgen and Bristol Myers Squibb. Dr P.d.G. reported personal fees from Actelion, Amgen, Bayer, MSD, Novartis, and Servier. Drs S. N., G.S., and C.B. had nothing to disclose.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Description of major bleeding and ischemic events during the 3-year follow-up period.

**Figure S1.** Antithrombotic use at inclusion in consecutive outpatients with heart failure ( $N = 2,902$ ). SAPT, single-antiplatelet therapy; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant therapy; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; APT, antiplatelet therapy.

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