

Burden and Prevention of Adverse Cardiac Events in Patients with Concomitant Chronic Heart Failure and Coronary Artery Disease: A Literature Review

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Keywords

Adverse cardiac events; Antithrombotics; Coronary artery disease; Heart failure.

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doi: 10.1111/1755-5922.12180

SUMMARY

Background: Chronic heart failure (HF) or coronary artery disease (CAD) confers risk for thromboembolism and secondary adverse cardiac events (ACEs) (e.g., mortality, myocardial infarction, and stroke). When HF and CAD occur concomitantly, ACE risk is reported to be elevated. We investigated ACEs, their epidemiology, and the resulting burden among patients with concomitant HF and CAD through a structured review of recent literature. Antithrombotic treatment for ACE prevention was assessed. **Methods:** Pertinent databases (PubMed, other) were searched for relevant articles published from January 2004 to March 2015. Data collected included ACE incidence, healthcare resource use, costs, change in quality of life attributed to ACEs, and treatment practice for prevention of ACEs in patients with concomitant HF and CAD. **Results:** Mortality rates for patients with both HF and CAD ranged from 4.9–12.3% at 30 days to 13.7–86% for periods between 9.9 months and 10 years. Incidence of ACEs among HF patients with CAD is, respectively, at least 82% and 15% higher than for patients without HF or without CAD, except for stroke investigated in two studies. All-cause and HF-related hospitalization is the main driver of the economic burden in patients with HF, the majority of whom had CAD origin. Despite high prevalence of ischemic complications, there is limited evidence to support the use of warfarin-type antithrombotics among HF patients. **Conclusion:** This study confirms that patients with concomitant HF and CAD are at elevated risk for ACEs and suggests the need for effective new antithrombotic treatments to further decrease ischemic complication rates in this population.

Introduction

Chronic heart failure (HF) is characterized by the inability of the heart to deliver oxygen appropriately for the needs of the body. With an incidence rate that approximates 10 per 1000 population over 65 years of age, HF affects nearly 5.8 million people in the United States, and more than 23 million people worldwide [1] translating to a prevalence of approximately 1–2% in developed countries [2]. This prevalence rises to more than 10%¹ among persons aged 85 years or older [2].

Of HF cases, at least half are systolic, referring to HF with reduced left ventricular ejection fraction (LVEF) indicative of systolic dysfunction; diastolic HF on the other hand refers to HF with diastolic dysfunction where LVEF is relatively preserved [4]. The cause of approximately two-thirds of systolic HF cases (i.e., with reduced LVEF) is coronary artery disease (CAD) [4], characterized

by angina and reduced exercise tolerance due to atherosclerotic plaque formation [5].

Few studies have focused on HF patients with concomitant stable CAD. It is known that patients with cardiovascular (CV) disease in general are at risk of developing secondary adverse cardiac events (ACE), including all-cause and CV death, nonfatal myocardial infarction (MI), nonfatal stroke, all-cause and CV hospitalization [6]. Further, several studies have reported outcomes in HF patients after an acute event (e.g., acute MI) [7–13]. However, although there is some published evidence that concomitance of HF and CAD can increase the risk of death [14], there has been no synthesis to date of information on the range of secondary ACE in patients with concomitant HF and CAD. Furthermore, beyond their clinical burden, secondary ACE can have an important economic and humanistic impact in this large population of chronic HF patients with CAD, but again, this information has not been summarized in the literature [15].

Regarding treatment for HF, despite the current therapies available, patients with HF remain subject to high mortality rates and reduced quality of life [16]. Further, patients with chronic HF are

¹As a point of comparison, the global prevalence of diabetes mellitus was estimated at 8.3% in 2013 [3].

at increased risk of thromboembolism, even in the absence of atrial fibrillation (AF) [17]. Heart failure is characterized by abnormalities in blood flow, vessel wall, and blood constituents, three prerequisites for thrombosis [17]. However, the potential benefits of antithrombotic therapy to reduce incidence of secondary ACE in HF patients, and more specifically in HF patients with CAD, remain unclear.

The overall aim of this study was to investigate secondary ACE in populations of patients with concomitant chronic HF and stable CAD within the last decade. To do so, published information related to the incidence of secondary ACE, their economic and humanistic burden, and treatment practice with antithrombotic (anticoagulant/antiplatelet) therapy for prevention of such events in this patient population were reviewed.

Methods

Disease Definitions

In this study, HF was defined as chronic HF (HF for at least 3 months) with left ventricular dysfunction (LVEF \leq 40%) in men and women aged 18 years and older.

Besides the term “coronary artery disease,” CAD was defined as: previous MI, history of coronary artery bypass graft (CABG), condition requiring coronary angiography and demonstrating at least 50% stenosis of one or more arteries, history of percutaneous coronary intervention (PCI), or in case of no documented history of MI, electrocardiogram (ECG) evidence (Q waves) with corresponding wall motion abnormality on echocardiogram.

Secondary ACE of interest include CV and all-cause death, non-fatal MI, nonfatal stroke, CV and all-cause hospitalization, and bleeding (major or minor).

Data Sources and Searches

A comprehensive literature search was performed to identify studies on the burden of secondary ACE among patients with concomitant HF and CAD. Sources of information were the National Library of Medicine’s PubMed, EMBASE, and Cochrane reviews. Searches were limited to English-language articles published between January 1, 2004, and March 31, 2015. Search terms used included a combination of the following: [prevalence, incidence, epidemiol*, burden, cost, economic evaluation, cost of illness, budget impact, resource use, quality of life, MLHFQ, MLHF, KCCQ, EQ-5D, EuroQoL, EuroQuol, SF-12, SF-36, chronic questionnaire, quality of life in severe questionnaire, patient reported outcomes, practice pattern, current practice, prescription, registry, observational, survey, secondary prevention, aspirin, clopidogrel, ticagrelor, prasugrel, factor Xa, antiplatelet, platelet aggregation inhibitor], [major ACE, major adverse CV events, death, mortality, MI, stroke, hospitalization, bleeding], and [HF, CAD, MI, CABG, PCI, coronary angiography, abnormal echocardiogram, ischemic, ischaemic].

Selection Criteria

Selected studies were limited to relevant patient populations. Study types included were as follows: observational, prospective,

historical, cohort studies; randomized controlled studies; registry-based, hospital, and claims database analyses; meta-analyses; and systematic reviews. Bibliographies of the latter two were used as sources for individual studies not captured by the primary searches. Case reports, commentaries, letters, news, withdrawn articles, and historical reports were excluded. Studies reporting data in HF patients following an acute event (e.g., acute MI) or in HF patients with AF were also excluded.

Data Extraction and Analysis

Data on the prevalence, incidence, healthcare resource use, costs, and changes in patient’s quality of life attributed to secondary ACE, as well as treatment practice patterns for prevention of secondary events in patients with HF and CAD were collected. We restricted treatment practice patterns to antiplatelets and anticoagulants in light of the potential importance of thromboembolism in patients with concomitant HF and CAD. Data on individual events and composite endpoints were extracted. Prevalence was defined as the proportion of patients who had experienced an adverse cardiac event in a given study population. Incidence was defined as the occurrence of an adverse cardiac event over a defined time period (follow-up). Data on hospital admission (rate of hospitalization and length of stay) were used to report healthcare resource utilization among HF patients with CAD. All original costs were inflated to the year 2014, then converted to Euros (€) if necessary, using a currency calculator available on <http://www.x-rate.com/>.

Results

From a total of 224 full-text articles assessed for eligibility, 20 studies were selected that reported information relevant to patients with concomitant HF and CAD that encompassed information on the incidence of ACE, their impact on healthcare resource utilization, costs, and quality of life, as well as on current practice patterns for secondary prevention of these events (Figure 1).

Incidence of Adverse Cardiac Events in Patients with HF and CAD

Our study found country-specific incidence data on ACE among patients with both HF and CAD in 11 studies, from countries including Australia [18], Canada [19,20], Czech Republic [21], Denmark [22], France [23], Italy [24], Japan [25], the United States [26,27] as well as three multinational studies [27–29]. Nine studies reported incidence rates of ACE among patients with both HF and CAD (Table 1).

All-cause mortality among patients with HF and CAD, as shown in Table 1, indicated that 30-day incidence ranged from 4.9% to 12.3% [18,19,22] with one study reporting lower rates after PCI (1.3%) or CABG (2.0%) interventions [25]. One-, three-, five-, and 10-year incidence of all-cause mortality in patients with HF and CAD was also reported (13.7–38% [18,23], 16–21% [25], 55–68% [20], and 86% [23], respectively). Three randomized controlled studies reported all-cause mortality rates of 28% [27], 36% [29], and 37% [26] after median follow-up durations of 9.9, 56,

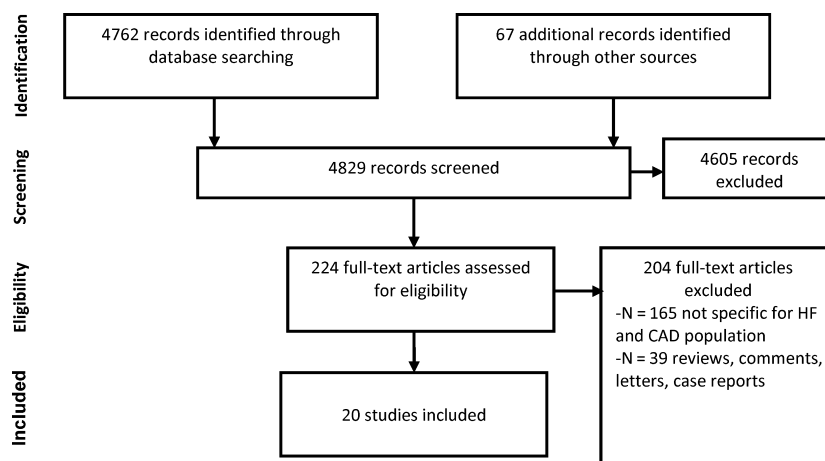


Figure 1 Search results – Prisma diagram.

and 26 months, respectively. Regarding incidence of CV death, one study reported that 7–10% of patients with HF and CAD died after 30 days [22], while figures of 21.6% [27], 28% [29], and 32% [26] were reported over longer follow-up periods in the aforementioned randomized controlled studies. Lower rates were reported at 3 years after PCI or CABG interventions (14% and 9%, respectively) [25].

The 30-day incidence of MI among patients with concomitant HF and CAD ranged from 1.5 to 4.4% [18,22] with lower rates reported after PCI (1.3%) or CABG (1.0%) interventions in another study [25]. Incidence of MI in patients with both HF and CAD was also reported at 9.9 months (2.5%) [27] and at 1 year (13.2%) [18], and after 3 years following PCI or CABG interventions (4% and 3%, respectively) [25].

For stroke in patients with both HF and CAD, very low ($\leq 0.1\%$) 30-day incidence rates were reported in a single study [22], but higher rates were reported for 30 days and 3 years after PCI (1% and 7%, respectively) or CABG (1.5% and 6%, respectively) [25] and after 9.9 months (1.7%) in another study [27]. Finally, incidence of different composites of the ACE described above was reported in three studies (Table 1).

Three studies in Table 1 reported incidence rates of various adverse cardiac events among HF patients with concomitant CAD compared with CAD patients without HF [18,19,22]. Higher rates were observed in patients with HF and CAD except for MI and stroke at 30 days [18,22]. Incidence of adverse cardiac events is at least 82% greater in patients with both HF and CAD compared with CAD patients without HF.

Four studies in Table 1 reported incidence of various ACE among HF patients with concomitant CAD compared with HF patients without CAD [20,23,26,27]. Higher rates were observed in patients with both HF and CAD, except for stroke at 9.9 months in an individual study [27]. Incidence of ACE is at least 15% greater in patients with HF and CAD than in HF patients without CAD.

Table 2 shows data from studies that reported the prognostic value of either HF in CAD patients or CAD in HF patients on the incidence of the ACE described above, expressed as hazard ratios after Cox regression analyses. Two studies reported a higher risk

of all-cause mortality in CAD patients with HF compared without HF although the effect was nonsignificant ($P = .08$) in the shorter time frame study (1 year). Compared with HF patients without CAD, patients with both HF and CAD are subject to a 1.5- to 3.8-fold increased risk of subsequent ACE including all-cause and CV death, MI, and a composite of all-cause death or CV hospitalization; this was shown for all studies except the one with a follow-up period of less than a year [27]. It was noted that patients with severe HF (NYHA III-IV and LVEF < 0.35) and CAD who also have renal impairment are at further risk of all-cause mortality (data not shown) [30].

Resource Use and Costs Associated with Adverse Cardiac Events in Patients with HF and CAD

Data on resource use associated with ACE in patients with HF (of whom the majority were of CAD origin) were found in two studies covering Canada, the UK, and the United States from the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial [31] and the multinational cohort in Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added [32] trial (Table 3). These trials enrolled HF patients of whom 72% and 62% were of CAD origin, respectively. Annual rates ranging from 38 to 89% and from 8 to 32% were reported for all-cause and HF-related hospitalizations, respectively. Lower incidence rates were reported for other causes of hospitalization such as MI and stroke in the CHARM-Added trial ($< 4\%$).

Costs associated with ACE and medications were also found in the WATCH and CHARM-Added trial reports. Specifically, annual total medical costs per patient for Canada, the UK, and the United States were reported in the first trial [31], and both hospital and total medical daily costs per patient for France, Germany, Italy, and the UK were reported in the second trial (Table 4) [32,33]. In the WATCH trial, inpatient (hospitalization) costs accounted for about 87% of total medical costs [31]. Total medical costs including hospitalizations, emergency department visits, outpatient medical procedures, and medications were higher in the United

Table 1 Incidence rates (%) of adverse cardiac events in patients with concomitant HF and CAD and patients with only HF or CAD

| Country/Study | Time frame | Patients | All-cause mortality | CV mortality | MI | Stroke | Composite 1 ^a | Composite 2 ^a | Composite 3 ^a |
|---|---------------------|-----------------------------|---------------------|-------------------|----------------------|----------|--------------------------|--------------------------|--------------------------|
| Australia/Lu et al., 2011 [18] | 30 days | HF and CAD | 4.9 ^b | NR | 4.4 | NR | 12.1 ^b | NA | NA |
| | | No HF and CAD | 1.9 | | 2.4 | | 5.9 | | |
| | 1 year | HF and CAD | 13.7 ^b | | 13.2 ^b | | 28.6 ^b | | |
| | | No HF and CAD | 3.5 | | 4.3 | | 12.6 | | |
| Canada/Ouzounian et al., 2009 [20] | 5 years | HF, no CAD | 43–58 | NR | NR | NR | NA | 68–73 | NA |
| | | HF and CAD | 55–68 ^c | | | | | 78–84 ^c | |
| Canada/Nagendran et al., 2014 [19] | 30 days | HF (LVEF ≤ 0.35) and CAD | 6.78 ^b | NR | NR | NR | NA | NA | NA |
| | | No HF (LVEF > 0.35) and CAD | 2.07 | | | | | | |
| Denmark/Andersson et al., 2014 [22] | 30 days | HF and CAD | 12.3 ^b | 7–10 ^b | 1.5–1.6 ^b | 0.02–0.1 | NA | NA | 10.0 ^b |
| | | No HF and CAD | 3.9 | 2 | 0.8–0.9 | 0.2 | NA | NA | 2.9 |
| France/Rusinaru et al., 2014 [23] | 1 year | HF, no CAD | 17 | NR | NR | NR | NA | NA | NA |
| | | HF and CAD | 38 ^c | | | | | | |
| | 10 years | HF, no CAD | 67 | | | | | | |
| | | HF and CAD | 86 ^c | | | | | | |
| Japan/Marui et al., 2014 [25] ^d | 30 days | HF and CAD (PCI) | 1.3 | NR | 1.3 | 1.0 | NA | NA | NA |
| | | HF and CAD (CABG) | 2.0 | NR | 1.0 | 1.5 | | | |
| | 3 years | HF and CAD (PCI) | 21 ^c | 14 ^c | 4 | 7 | | | |
| | | HF and CAD (CABG) | 16 | 9 | 3 | 6 | | | |
| Multinational/Mentz et al., 2013 [27] (EVEREST) | 9.9 months (median) | HF, no CAD | 23.5 | 18.1 | 0.5 | 1.6 | NA | NA | NA |
| US and Canada/Gheorghide et al., 2011 [26] (BEST) | 26 months (median) | HF and CAD | 28.1 ^c | 21.6 ^c | 2.5 ^c | 1.7 | NA | NA | NA |
| Multinational/Velazquez et al., 2011 [29] (STICH) | 56 months (median) | HF and CAD | 37 ^c | 20 | NR | NR | NA | NA | NA |
| | | HF and CAD (CABG) | 36 | 28 | NR | NR | NA | NA | NA |

BEST, Beta-Blocker Evaluation of Survival Trial; CABG, coronary artery bypass graft; CAD, coronary artery disease; CV, cardiovascular; EVEREST, Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with tolvaptan; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention; STICH, Surgical Treatment for Ischemic Heart Failure; US, United States. ^aComposite 1: death, MI, or target vessel revascularization; Composite 2: death, readmission for HF, admission for coronary events, or ischemic stroke; Composite 3: acute MI, ischemic stroke, or CV death. ^bSignificant difference between CAD patients with and without HF. ^cSignificant difference between HF patients with and without CAD. ^dComparison between PCI and CABG, no controls without CAD or without HF.

Table 2 Prognostic impact of HF or CAD on incidence of adverse cardiac events in patients with HF and CAD

| Country/Study | Time frame | Population | Hazard ratio (95% CI) | | | | | |
|---|---------------------|---|-----------------------|------------------|------------------|--------|------------------------|---------------------|
| | | | All-cause death | CV death | MI | Stroke | Composite ^a | |
| Australia/Lu et al., 2011 [18] | 1 year | Patients undergoing PCI with HF versus without | 1.7 (0.93–3.1) | NR | NR | NR | NR | NA |
| Canada/Nagendran et al., 2014 [19] | 8 years | Patients undergoing CABG with HF versus without | 2.43 (1.78–3.32) | NR | NR | NR | NR | NR |
| Czech Republic/Rosolova et al., 2005 [21] | 4 years | HF with a history of MI versus without | 2.386 (1.59–3.59) | NR | NR | NR | NR | NR |
| France/Rusinaru et al., 2014 [23] | 10 years | HF with reduced EF (<50%; mean at 35%) and CAD versus no CAD | 1.60 (1.19–2.15) | 2.01 (1.38–2.92) | 3.84 (1.16–12.7) | NR | NR | NR |
| Italy/Fumagalli et al., 2014 [24] | 27 months | HF with severe LVSD and ICD placement with CAD versus without | 1.67 (1.43–1.97) | NR | NR | NR | NR | NR |
| Multinational/Mentz et al., 2013 [27] (EVEREST) | 9.9 months (median) | Systolic CHF (EF ≤ 40%) with CAD versus without | 1.12 (0.97–1.30) | 1.15 (0.97–1.35) | NR | NR | NR | NR |
| US and Canada/Gheorghide et al., 2011 [26] (BEST) | 26 months (median) | Systolic CHF (EF ≤ 35%) with CAD versus without | 1.69 (1.47–1.95) | 1.77 (1.51–2.07) | NR | NR | NR | NR |
| Multinational/Manzano et al., 2011 [28] (SENIORS) | 21 months | HF (EF ≤ 35%) with prior MI versus without | 1.743 (1.374–2.464) | NR | NR | NR | NR | 1.545 (1.264–1.905) |

BEST, Beta-Blocker Evaluation of Survival Trial; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; EVEREST, Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with tolvaptan; HF, heart failure; ICD, implantable cardioverter defibrillator; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; US, United States. All data are from multivariate analyses. ^aComposite: all-cause mortality or cardiovascular hospital admission.

States versus Canada and were lowest in the UK. In the CHARM-Added trial, hospital costs accounted for 64–69%, 47–54%, 50–55%, and 69–73% of total medical costs (including in addition CV procedures and medications) in the candesartan and placebo arms in France, Germany, Italy, and the UK, respectively. Both hospital and total medical costs were higher for the UK, followed by France, Italy, and Germany (Table 4).

Association Between Quality of Life and Adverse Cardiac Events in Patients with HF and CAD

No studies addressing the direct effect of ACE on quality of life of patients with HF and CAD were found. However, evidence of an association between quality of life and adverse events in a group of HF patients of whom the majority had CAD was found in two studies from the UK [34,35]. Using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), one study showed that poor quality of life at baseline was associated with increased risk of mortality and hospital admissions in patients with HF (62% of CAD origin) [35]. In the other study, in which 77% of HF patients had CAD, better quality of life was associated with improved survival based on MLHFQ and EuroQoL measures. The same study showed that treatment with loop diuretics and angiotensin-converting enzyme inhibitors improved quality of life over baseline

among surviving patients (MLHFQ physical scores 18.8 ± 11.8 vs. 21.7 ± 11.2 at baseline; $P = 0.016$) [34].

Antiplatelet and Anticoagulant Practice Patterns in Patients with HF and CAD

Given the evidence above indicating that patients with HF and CAD are subject to greater incidence of secondary ACE compared with patients with HF alone, treatment practices in this population were investigated. For reference, clinical practice guidelines from both the ESC in Europe and the ACCF/AHA in the United States state that there is no evidence supporting the use of antiplatelets or anticoagulants other than aspirin to prevent ACE in patients with HF, except for patients those who suffer from AF or have experienced a prior thromboembolic event [4,36]. Prevalence of AF in patients with HF varies from 4% in NYHA class I to 40% in NYHA class IV patients [36]. For patients with stable CAD, aspirin (or clopidogrel when aspirin is contraindicated) is also recommended [5,37].

We selected observational and clinical studies reporting antiplatelet and anticoagulant use in patients with HF and CAD; these are summarized in Table 5. It should be noted that data are from populations with different comorbidities, and the percentage of patients with AF was not reported in any of these studies. The antiplatelet aspirin was used by 73–84% of patients, while clopi-

Table 3 Adverse cardiac event-related resource use (annual hospitalization rates) in WATCH and CHARM-Added trials

| Trial-Country | Population/follow-up | All-cause | HF-related | Other causes | |
|----------------------------------|--------------------------------|-------------|-------------|--------------|-------------|
| | | | | MI | Stroke |
| WATCH [31] ^a | HF, 72% CAD/1.9 years (mean) | | | | |
| Canada | | 0.38–0.50 | 0.11–0.22 | NR | NR |
| UK | | 0.43–0.47 | 0.08–0.14 | NR | NR |
| US (Veterans Administration) | | 0.60–0.89 | 0.09–0.32 | NR | NR |
| US (Non-Veterans Administration) | | 0.64–0.83 | 0.19–0.29 | NR | NR |
| CHARM-Added [32] ^b | HF, 62% CAD/41 months (median) | | | | |
| International (26 countries) | | 0.668–0.675 | 0.253–0.300 | 0.028–0.039 | 0.027–0.027 |

CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; NR, not reported; US, United States. ^aLowest and highest rates of aspirin, clopidogrel, and warfarin trial. ^bRates for candesartan and placebo arms, respectively.

Table 4 Adverse cardiac event-related hospital costs and total medical costs in WATCH and CHARM-Added trials

| Trial/Country | Hospital annual cost/patient | Total medical annual cost/patient (€2014) ^a |
|----------------------------------|--|--|
| WATCH [31] | | |
| Canada | NR | 3643–4053 |
| UK | NR | 1997–2380 |
| US (Veterans Administration) | NR | 6994–8553 |
| US (Non-Veterans Administration) | NR | 5366–6925 |
| CHARM-Added [32,33] | Hospital daily cost/patient (€2014) ^b | Total medical daily cost/patient (€2014) ^b |
| France | 14.04–16.03 | 22.04–23.21 |
| Germany | 6.76–7.71 | 14.25–14.25 |
| Italy | 9.46–10.95 | 19.10–20.00 |
| UK | 18.48–21.06 | 26.83–28.75 |

NR, not reported; UK, United Kingdom; US, United States. ^aLowest and highest cost of aspirin, clopidogrel, and warfarin trial. ^bcost for candesartan and placebo arms, respectively.

dogrel was used by 13–16% of patients in a clinical study [29] and by 55% of HF patients after MI in an observational study [38]. This higher percentage in the latter study may reflect recommendations to prescribe dual antiplatelet therapy among patients with MI [5,37]. Use of any thienopyridine and a nonaspirin antiplatelet was estimated at 25% and 6.1%, respectively, in two other studies [39,40]. The anticoagulant warfarin was used by 13–29% of patients with HF and CAD in these studies (Table 5). Because AF is a common comorbidity especially among patients with severe chronic HF, these results should be interpreted with caution.

Discussion

Coronary artery disease is the major cause of chronic systolic HF, with a prevalence of more than 60% in patients with reduced systolic function; [4] however, whether it constitutes a real thrombotic concern in patients with chronic HF is largely unknown. In the present study, we report the incidence and burden of ACE and

antithrombotic practice patterns in chronic HF patients with CAD through a structured review of the recent literature. Incidence data specific to this population showed that these patients are exposed to an increased risk of subsequent ACE compared with HF patients without CAD or CAD patients without HF. Hospitalization, mainly due to HF, occurred in 38–89% of patients and accounted for 47–87% of total medical costs; it was the main driver of the economic burden in patients with chronic HF and CAD. Finally, anticoagulant treatment was found to be used by an appreciable proportion (13–29%) of HF patients with CAD and different comorbidities.

We observed heterogeneity in incidence rates across studies within each adverse event category. Besides being due to different follow-up times, this may be explained by the heterogeneity within the CAD populations for which data were reported. Coronary artery disease defines a heterogeneous patient population, including patients with previous MI, stable or recurrent angina, patients necessitating vascular interventions such as PCI and CABG, and others (described under Methods) [5]. Heterogeneity can also exist among patients with HF due to varying severity of left ventricular systolic dysfunction. Furthermore, heterogeneity in the nature of events included in the composite endpoints makes comparison difficult between studies.

Although published information on chronic HF and CAD as separate disease states is abundant in the literature, much less information is available specifically for patients with concomitant HF and CAD, and several gaps were identified by the present study. Data on stroke, MI, and CV death are scarce in this population, and data on bleeding—one adverse cardiac event consequent to the use of antithrombotic treatment—were lacking for this HF and CAD patient population. Risk of bleeding is not necessarily a factor in patients with HF but could markedly increase in a subgroup of patients with CAD treated with antiplatelets or anticoagulants. Further, epidemiological and economic data were found for a small number of countries. Information on the impact of individual events on health-related quality of life, resource use, and medical costs was also inadequate. However, despite these limitations, this study identified an important clinical and economic burden associated with occurrence of ACE in patients with chronic HF and CAD.

As with any study that relies on literature search methodology, there are inherent limitations. Studies chosen for inclusion may

Table 5 Practice patterns of antiplatelets and anticoagulants among patients with concomitant HF and CAD

| Country/Study | Study design | Population | Observation period | Antiplatelet use, % patients | | | Anticoagulant use, % patients | |
|---|-------------------------------------|---|--------------------|------------------------------|-------------|------------------|-------------------------------|-------|
| | | | | Aspirin | Clopidogrel | Other | Warfarin | Other |
| Australia/Krum <i>et al.</i> , 2006 [38] | Multicentre | 116 patients with MI and HF | 2004–2005 | 84 | 55 | NR | 13 | |
| Canada/Ezekowitz <i>et al.</i> , 2004 [39] | Prospective cohort | 6427 patients with HF and angiographically proven CAD | NR | 73 | NR | 25 ^a | 29 | |
| US/Newby <i>et al.</i> , 2006 [40] | Retrospective registry (database) | 8914 patients with CAD and HF | 1995–2002 | 75.3 | NR | 6.1 ^b | 13 | |
| International-STICH trial (22 countries)/Velazquez <i>et al.</i> , 2011[29] | Multicenter, nonblinded, randomized | 1212 patients with CAD suitable for revascularization and LVEF ≤ 0.35 | July 2002–May 2007 | 84 | 13–16 | NR | 20–21 | |

CAD, coronary artery disease; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; STICH, Surgical Treatment for Ischemic Heart Failure; US, United States. ^aAny thienopyridine. ^bNonaspirin antiplatelet.

be subject to selection bias; to circumvent this, two of the authors screened and reviewed the relevant articles. Further, because we restricted the time frame of the search, this may have contributed to a fewer number of published studies retrieved for specific topics, as described above. However, because we were interested in recent rather than historical information, the data retrieved, although from a smaller number of studies, are likely more meaningful to present-day scenarios.

Regarding anticoagulation treatment, whether it could be useful in HF patients with CAD remains an open question. Currently, warfarin is recommended only for HF patients with AF or at increased risk of thromboembolism. Warfarin is associated with an increased risk of hemorrhage, and among a sample of patients with HF but without AF, it was associated with a reduction of stroke but no impact on survival compared with standard antiplatelet treatment [41–43]. In current practice, the present study showed that an appreciable number of HF patients with CAD and different comorbidities used anticoagulation treatment (warfarin). Whether HF patients with comorbidities such as CAD can benefit from anticoagulation treatments other than warfarin is an interesting avenue for future clinical trials. New oral anticoagulants, such as dabigatran, rivaroxaban and apixaban, have been shown to reduce the risk of stroke in patients with AF, and with or without HF [17], but their potential benefits in HF patients without AF have not been explored. Furthermore, the demonstration in the ATLAS ACS 2 TIMI 51 study that subjects with recent acute coronary syndrome (ACS) and HF showed decreased risk of primary efficacy endpoint events (composite of CV death, MI, and stroke) with the use of rivaroxaban compared with placebo [44] provides rationale for the exploration of rivaroxaban effects in similar patients with chronic HF and CAD but without a recent ACS event.

In conclusion, this study highlights the burden of ACE in patients with HF and CAD and identifies several gaps in the published literature for this specific population. The limited information available pertaining to ACE in patients with concomitant HF and CAD calls for the need to conduct large observational studies and analyses of registry-based data, especially for reporting the impact of events on resource use and costs, on patient quality of life, and regarding current practice of antiplatelet and anticoagulant treatments in this population.

Conflict of Interest Statement

Louis Lavoie, Hanane Khoury, and Sharon Welner received consultancy fees from Bayer Pharma AG to conduct the study. Jean-Baptiste Briere is an employee of Bayer Pharma AG.

Author Contributions

LL contributed to concept/design, data analysis/interpretation, drafting of the article, critical revision of the article, and data collection; HK and JBB contributed to concept/design, data analysis/interpretation, and critical revision of the article; SW contributed to concept/design, data analysis/interpretation, drafting of the article, and critical revision of the article.

Financial Support

This study was funded by Bayer HealthCare Pharmaceuticals.

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