Anticoagulant therapy and outcomes in patients with prior or acute heart failure and acute coronary syndromes: Insights from the APixaban for PRevention of Acute ISchemic Events 2 trial

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Background Clinical outcomes and the effects of oral anticoagulants among patients with acute coronary syndrome (ACS) and either a history of or acute heart failure (HF) are largely unknown. We aimed to assess the relationship between prior HF or acute HF complicating an index ACS event and subsequent clinical outcomes and the efficacy and safety of apixaban compared with placebo in these populations.

Methods High-risk patients were randomly assigned post-ACS to apixaban 5.0 mg or placebo twice daily. Median follow-up was 8 (4-12) months. The primary outcome was cardiovascular death, myocardial infarction, or stroke. The main safety outcome was thrombolysis in myocardial infarction major bleeding.

Results Heart failure was reported in 2,995 patients (41%), either as prior HF (2,076 [28%]) or acute HF (2,028 [27%]). Patients with HF had a very high baseline risk and were more often managed medically. Heart failure was associated with a higher rate of the primary outcome (prior HF: adjusted hazard ratio [HR] 1.73, 95% CI 1.42-2.10, $P < .0001$, acute HF: adjusted HR 1.65, 95% CI 1.35-2.01, $P < .0001$) and cardiovascular death (prior HF: HR 2.54, 95% CI 1.82-3.54, acute HF: adjusted HR 2.52, 95% CI 1.82-3.50). Patients with acute HF also had significantly higher rates of thrombolysis in myocardial infarction major bleeding (prior HF: adjusted HR 1.22, 95% CI 0.65-2.27, $P = .54$, acute HF: adjusted HR 1.78, 95% CI 1.03-3.08, $P = .04$). There was no statistical evidence of a differential effect of apixaban on clinical events or bleeding in patients with or without prior HF; however, among patients with acute HF, there were numerically fewer events with apixaban than placebo (14.8 vs 19.3, HR 0.76, 95% CI 0.57-1.01, interaction $P = .13$), a trend that was not seen in patients with prior HF or no HF.

Conclusions In high-risk patients post-ACS, both prior and acute HFs are associated with an increased risk of subsequent clinical events. Apixaban did not significantly reduce clinical events and increased bleeding in patients with and without HF; however, there was a tendency toward fewer clinical events with apixaban in patients with acute HF. (Am Heart J 2015;169:531-8.)

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Recurrent ischemic events after an acute coronary syndrome (ACS) depend not only on therapeutic interventions but also on patient characteristics.[1,2] Heart failure (HF) is a frequent complication of ACS and a known risk factor for recurrent cardiovascular (CV) events and bleeding.[2-4] Both a history of HF and HF as an acute complication of ACS are common in patients with both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI).[4,5] Data regarding the relationship between a history of HF and HF complicating an ACS event and subsequent clinical outcomes are limited.[5]

Heart failure is associated with a prothrombotic, hypercoagulable state[6]; however, data from randomized trials using vitamin K antagonists in stable chronic HF do not show a clear benefit on outcomes other than ischemic

stroke.[7-9] Oral anticoagulation therapy with vitamin K antagonists reduces the incidence of recurrent ischemic events after myocardial infarction (MI) but also increases the risk of bleeding when added to aspirin or aspirin and clopidogrel.[10-12] Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines do not recommend prolonged anticoagulation beyond the acute period of an ACS.[13,14]

Apixaban, an oral, direct, selective factor Xa inhibitor, is safe and effective compared with warfarin for the prevention of thromboembolic events in patients with atrial fibrillation.[15,16] However, in high-risk patients post-ACS, the addition of apixaban to antiplatelet therapy resulted in an increase in bleeding without a meaningful reduction in recurrent ischemic events.[17] The objectives of this study are (1) to assess the relationship between HF, either a history of HF or as an acute complication of the index ACS event, and subsequent clinical outcomes in high-risk patients after an ACS event and (2) to explore the efficacy and safety of apixaban compared with placebo in patients with and without HF.

Methods

The APPRAISE-2 trial enrolled 7,392 patients between March 2009 and November 2010. In November 2010, the independent Data Monitoring Committee recommended that the trial be stopped due to an excess of clinically important bleeding among patients receiving apixaban without a counterbalancing reduction in ischemic events. Details regarding the study design, patients, outcome definitions, and results have been published.[17]

Study population

Patients were eligible if they had an ACS (STEMI, NSTEMI, or unstable angina) within 7 days characterized by symptoms of myocardial ischemia at rest lasting at least 10 minutes plus either elevated cardiac biomarkers or dynamic ST-segment depression or elevation ≥0.1 mV. Patients had completed parenteral anticoagulation therapy, were clinically stable, and were receiving standard post-ACS care including aspirin or aspirin plus any P2Y12 receptor antagonist. In addition, enrolled patients had ≥2 of the following high-risk characteristics: (1) age ≥65 years, (2) diabetes mellitus, (3) prior MI (other than the qualifying event) within 5 years, (4) ischemic cerebrovascular disease, (5) peripheral vascular disease, (6) acute clinical HF or a left ventricular ejection fraction (LVEF) <40% associated with the index ACS, (7) impaired renal function with a calculated creatinine clearance of <60 mL/min, and (8) no revascularization after the index ACS event. Important exclusion criteria were persistent severe hypertension, severe renal dysfunction with a calculated creatinine clearance of <20 mL/min, active bleeding or a high risk of bleeding (eg, active peptic ulcer disease, other gastrointestinal pathology with a raised risk of bleeding, liver cirrhosis, or malignancies with a raised risk of bleeding), known coagulopathy, ischemic stroke within 7 days, New York Heart Association (NYHA) class IV HF, and requirement of ongoing treatment with a parenteral or oral anticoagulant.

Randomization

Patients were randomized to blinded apixaban 5 mg or matching placebo twice daily. Patients with an estimated creatinine clearance of <40 mL/min at the time of randomization were randomized to apixaban 2.5 mg or matching placebo twice daily.

Heart failure assessment

The presence of a history of HF and acute HF as a complication of the index ACS event were collected at randomization in the electronic case record form. *Heart failure* was defined as a clinical diagnosis with signs and symptoms consistent with HF with physician documentation of any of the following symptoms of HF including dyspnea on light exertion; recurrent dyspnea occurring in the supine position; fluid retention; low cardiac output secondary to cardiac dysfunction; or the description of rales, jugular venous distension, or pulmonary edema. A previous hospital admission with principal diagnosis of HF is considered evidence of HF history. Patients with reduced LVEF without clinical HF were not considered to have HF in this analysis. If a history of HF was present, NYHA class was collected at the time of randomization. Heart failure was prespecified in the protocol as a planned subgroup for efficacy and safety analyses.

Clinical outcomes

The primary outcome was the composite of CV death, MI, and ischemic stroke. Secondary efficacy outcomes included the composite of CV death, MI, ischemic stroke, or unstable angina; the composite of CV death, MI, ischemic or hemorrhagic stroke, and fatal bleeding; the composite of all-cause death, MI, and ischemic or hemorrhagic stroke; the individual outcomes of CV death, MI, and ischemic stroke; unstable angina; and stent thrombosis.[17,18]

The main safety outcome was thrombolysis in myocardial infarction (TIMI) major bleeding.[19] Additional safety outcomes included TIMI major or minor bleeding and International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding. The primary and secondary outcomes were adjudicated with the use of prespecified criteria by an independent clinical events committee.

Statistical analysis

Baseline characteristics were compared among the following groups: (1) no HF (ie, no history of HF and no acute HF complicating the index ACS event), (2) a history of HF (referred to as prior HF), and (3) HF complicating the index ACS event (referred to as acute HF). Categorical

variables were presented as counts (proportions). Continuous variables were presented as medians (25th-75th percentiles). Heart failure groups 2 and 3 are not mutually exclusive (there were 1,109 patients who belonged to both the prior HF and acute HF groups). Because of these overlapping populations, statistical testing was not performed, and no *P* values are presented.

The number of events per 100 patient-years was calculated for each of the 3 HF groups for each outcome. The relationship of HF status and each outcome end point was characterized using the hazard ratio (HR) and corresponding 95% CI from a Cox proportional hazards model comparing each of the HF groups with the no (neither acute nor prior HF) HF group. Because the 2 HF groups are not mutually exclusive, 2 separate regression models were fit to make each comparison; the no-HF group was the reference group in both analyses. Both univariable and multivariable regression analyses were performed. Multivariable analyses were adjusted for the following covariates: age, female sex, race, current smoker, heart rate, diabetes, prior MI, hypertension, peripheral vascular disease, impaired renal function, enrolling MI, ST changes on presenting electrocardiogram, and revascularization for the index ACS event. Each analysis was stratified by baseline antiplatelet therapy use (mono vs dual).

The number of events per 100 patient-years was calculated by treatment group (apixaban vs placebo) for each of the 3 HF groups for each outcome. To determine whether there was a differential treatment effect among the HF groups, the interaction between treatment (apixaban vs placebo) and HF status was tested in regression models described above. The treatment effect in each HF group was characterized by the HR and corresponding 95% CI from a Cox proportional hazards model. All analyses were performed at the Duke Clinical Research Institute (Durham, NC) using SAS software version 9.3 (SAS Institute, Inc, Cary, NC). A 2-sided *P* value of .05 was regarded as statistically significant.

The APPRAISE-2 trial was funded by Bristol-Myers Squibb (Princeton, NJ) and Pfizer, Inc (New York, NY). The analyses presented here were designed by the authors, performed at the Duke Clinical Research Institute, and interpreted by the authors.

Results

Patients

Among the 7,392 patients enrolled in the APPRAISE-2 study, 2 were excluded from the analysis because of missing HF status. Heart failure was reported in 2,995 patients (41%), including 2,076 patients with prior HF and 2,028 patients with acute HF. Among patients with prior HF, 397 (19.2%) were NYHA class I, 1,260 (60.7%) were NYHA class II, 417 (20.1%) were NYHA class III, and 2 (0.1%) were NYHA class IV. By clinical trial design, all the groups had a high-risk profile (Table I). Most patients with HF were managed medically after their ACS event. Patients without HF were more likely to be treated with percutaneous coronary intervention and be on clopidogrel and statins than patients with HF. A relatively low proportion of patients with a diagnosis of HF were treated with diuretics.

Outcomes in relation to HF status

The median duration of follow-up was 8 (4-12) months. Patients with HF, either prior HF or acute HF, had worse outcomes than patients without HF (Table II). Heart failure was associated with a 1.5- to 2.0-fold increase in the primary outcome of CV death, MI, and ischemic stroke. Heart failure was also associated with a 2.0- to 3.0-fold increase in CV death and a 1.5- to 2.0-fold increase in stent thrombosis. Patients with acute HF had a numerically higher rate of major bleeding than patients without HF. This was not seen in patients with prior HF (Table II).

Outcomes in relation to randomized treatment in patients with and without HF

The effect of apixaban versus placebo among patients with no HF, prior HF, and acute HF are shown in Figure A to C, respectively. Although there was no evidence of a beneficial effect of apixaban in patients with no HF or prior HF, in patients with acute HF, apixaban, compared with placebo, resulted in numerically lower rates of the primary outcome of CV death, MI, or ischemic stroke (interaction $P = .13$); CV death (interaction $P = .15$); and stent thrombosis (interaction $P = .21$). The trend toward a benefit of apixaban seen in patients with acute HF was, if anything, even greater in the cohort of patients with acute HF but no prior history of HF (data not shown). Apixaban increased the risk of bleeding similarly in patients with no HF, prior HF, and acute HF (all interaction $P > .20$). There was no evidence that the effect of apixaban differed by NYHA class among patients with prior HF for any of the outcomes (data not shown).

Discussion

Both a history of HF and acute HF complicating the index ACS event were, by design, common in the APPRAISE-2 population. Patients with HF had an overall high baseline risk and were more often managed medically after ACS. We found that patients with prior HF or acute HF complicating the index ACS event had higher rates of adverse outcomes including CV death, MI, ischemic stroke, and stent thrombosis and generally similar rates of bleeding. Although not statistically significant, apixaban tended to have benefit in patients with acute HF complicating their index ACS event but not in patients with prior HF or those without HF. In all 3 HF groups, apixaban increased the risk of bleeding.

Table I. Baseline characteristics by HF status

	No HF (n = 4395)	Prior HF* (n = 2076)	Acute HF* (n = 2028)
Age, y	67 (59-73)	67 (58-73)	65 (56-73)
Age ≥75 y	889 (20.2)	449 (21.6)	389 (19.2)
Female sex	1358 (30.9)	754 (36.3)	653 (32.2)
Inclusion criteria risk factors			
Age ≥65 y	2695 (61.3)	1181 (56.9)	1069 (52.7)
History of diabetes mellitus	2302 (52.4)	882 (42.5)	820 (40.4)
Prior MI within 5 y	1109 (25.2)	711 (34.2)	446 (22.0)
History of cerebrovascular disease	410 (9.3)	257 (12.4)	184 (9.1)
History of PVD	846 (19.3)	361 (17.4)	308 (15.2)
History of HF or LVEF <40% associated with index event	723 (16.5)	2076 (100.0)	1496 (73.8)
History of impaired renal function	1271 (30.8)	620 (31.8)	575 (30.0)
No revascularization for index ACS event	2146 (48.8)	1512 (72.8)	1258 (62.0)
No. of inclusion criteria risk factors			
2	2138 (48.6)	564 (27.2)	566 (27.9)
3	1320 (30.0)	684 (32.9)	653 (32.2)
4+	723 (16.5)	793 (38.2)	787 (38.8)
Other medical history			
Hypertension	3358 (76.4)	1815 (87.4)	1583 (78.1)
Smoking	976 (22.2)	476 (22.9)	553 (27.3)
MI	1552 (35.3)	996 (48.0)	656 (32.3)
PCI	1101 (25.1)	456 (22.0)	328 (16.2)
CABG	382 (8.7)	223 (10.7)	142 (7.0)
AF	143 (3.3)	216 (10.4)	145 (7.1)
Renal insufficiency‡ (CrCl <60 mL/min)	1271 (30.8)	620 (31.8)	575 (30.0)
ACS index event			
NSTEMI	1950 (44.4)	884 (42.6)	676 (33.3)
STEMI	1685 (38.3)	712 (34.3)	948 (46.7)
Unstable angina	730 (16.6)	473 (22.8)	386 (19.0)
ACS management before randomization			
PCI	2220 (50.5)	557 (26.8)	761 (37.5)
CABG	32 (0.7)	7 (0.3)	9 (0.4)
Medical therapy	2146 (48.8)	1512 (72.8)	1258 (62.0)
Concomitant medications			
Aspirin	4287 (97.6)	2009 (96.8)	1969 (97.1)
Clopidogrel	3768 (85.8)	1433 (69.0)	1524 (75.1)
Dual antiplatelet therapy	3794 (86.6)	1413 (68.5)	1515 (75.1)
ACE inhibitor	2753 (62.7)	1470 (70.8)	1371 (67.6)
ARB	703 (16.0)	230 (11.1)	209 (10.3)
β-Blocker	3300 (75.2)	1663 (80.1)	1604 (79.1)
Statin	3893 (88.7)	1539 (74.1)	1539 (75.9)
Loop diuretic	533 (12.1)	762 (37.6)	667 (32.1)
Thiazide	476 (10.8)	231 (11.4)	308 (14.8)
Assigned reduced dose apixaban (CrCl <40 mL/min)	335 (8.1)	190 (9.7)	185 (9.7)

Categorical variables are given as n (%); continuous variables are given as median (25th-75th percentiles). Abbreviations: *PVD*, peripheral vascular disease; *PCI*, percutaneous coronary intervention; *CABG*, coronary bypass grafting; *AF*, atrial fibrillation; *CrCl*, creatinine clearance; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.
* Acute and prior HFs are not mutually exclusive groups of patients (1,109 patients are in both groups).
‡ Estimated by the Cockcroft-Gault equation.

High-risk population

The APPRAISE-2 trial enrolled a high-risk post-ACS population. Almost 41% of the population had HF including 28% with a history of HF and 27% with acute HF complicating their index ACS event. Importantly, there was substantial overlap between these subpopulations, as patients with a history of HF were more likely to have acute HF complicating their index ACS event. This analysis confirms that, in high-risk patients post-ACS, the presence of HF, either a history of HF or acute HF complicating the ACS event, is associated with a substantially higher risk of subsequent major adverse CV events. Most striking is the more than 2-fold increase in CV death. To a lesser extent, concomitant HF increases the risk of recurrent MI, and both prior HF and acute HF complicating the index ACS event appeared to similarly increase the risk of adverse outcomes.

The APPRAISE-2 population had a 5-fold higher frequency of HF compared with other contemporary randomized controlled trials[20,21] and a 1.5-fold higher incidence of HF than contemporary registries.[5] Both HF with reduced and preserved LVEF could be included. In

Table II. Association between HF and clinical outcomes

	No. of events (rate per 100 patient-years)			Prior HF vs no HF*		Acute HF vs no HF*	
	No HF	Prior HF	Acute HF	HR (95% CI)	P	HR (95% CI)	P
Cardiac events (during ITT period)							
CV death, MI, ischemic stroke	261 (10.8)	248 (19.2)	203 (17.0)	1.73 (1.42-2.10)	<.0001	1.65 (1.35-2.01)	<.0001
CV death, MI, ischemic stroke, UA	354 (14.8)	292 (23.0)	238 (20.3)	1.54 (1.30-1.83)	<.0001	1.47 (1.23-1.75)	<.0001
CV death	70 (2.8)	111 (8.2)	99 (8.0)	2.54 (1.82-3.54)	<.0001	2.52 (1.82-3.50)	<.0001
MI (fatal or nonfatal)	186 (7.6)	158 (12.2)	115 (9.6)	1.60 (1.27-2.03)	<.0001	1.41 (1.10-1.81)	.0065
Ischemic stroke (fatal or nonfatal)	29 (1.2)	20 (1.5)	21 (1.7)	1.34 (0.68-2.63)	.3911	1.60 (0.85-3.03)	.1471
UA	105 (4.3)	55 (4.1)	43 (3.5)	1.01 (0.71-1.46)	.9392	0.96 (0.66-1.41)	.8346
Stent thrombosis	43 (1.7)	26 (1.9)	28 (2.3)	1.80 (1.07-3.04)	.0272	1.70 (1.02-2.82)	.0412
Bleeding events (during treated period)							
TIMI major	33 (1.5)	17 (1.4)	24 (2.2)	1.22 (0.65-2.27)	.5397	1.78 (1.03-3.08)	.0387
ICH (includes stroke)	7 (0.3)	4 (0.3)	8 (0.7)	1.18 (0.32-4.38)	.7997	2.56 (0.88-7.42)	.0843
TIMI major or minor	59 (2.7)	30 (2.4)	37 (3.3)	1.04 (0.64-1.69)	.8659	1.37 (0.89-2.12)	.1569
ISTH major	80 (3.6)	34 (2.8)	44 (4.0)	0.94 (0.61-1.46)	.7941	1.29 (0.88-1.90)	.1936
ISTH major or clinically relevant nonmajor	99 (4.5)	37 (3.0)	47 (4.2)	0.84 (0.56-1.27)	.4202	1.07 (0.74-1.55)	.7338
Any non-CV death bleeding	621 (31.1)	232 (20.4)	260 (25.4)	0.85 (0.72-1.01)	.0606	1.00 (0.86-1.17)	.9901

* Hazard ratio compares the hazard of patients who had acute HF or prior HF to the hazard of patients who had no HF (ie, no acute and no prior HF). Hazard ratio (*P* value) for acute HF and prior HF come from 2 separate regression models; analysis was stratified by mono versus dual antiplatelet therapy use at baseline. Adjusted for age, sex, race (white/Asian vs other), current smoker, heart rate, diabetes, prior MI, hypertension, peripheral vascular disease, enrolling MI, and ST changes at enrollment. Abbreviations: *ITT*, intention to treat; *UA*, unstable angina; *ICH*, intracranial hemorrhage; *ISTH*, International Society on Thrombosis and Haemostasis.

the recent all-comer ACS PLATO trial, baseline characteristics such as diabetes, chronic renal insufficiency, and medical management of index ACS were much less frequently present compared with APPRAISE-2.[20] The ATLAS ACS 2 TIMI-51 study included a much lower risk population.[22] High-risk patients have a high residual risk of recurrent events and represent an important target for better secondary prevention.[23] The APPRAISE-2 investigators deliberately targeted this elderly high-risk population as a population likely to benefit from additional anticoagulation therapy. This approach may have contributed to both a high overall event rate and the higher proportion of fatal events.

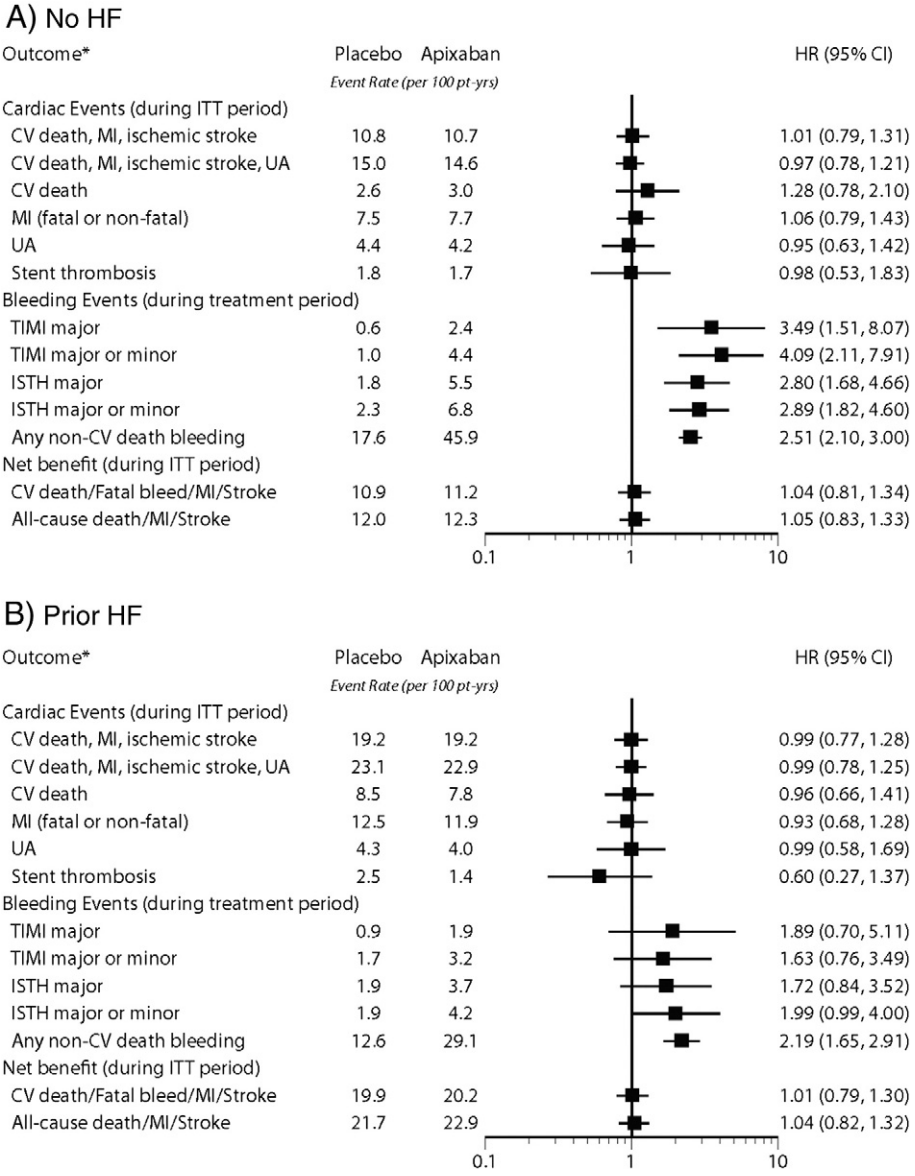
Interplay between HF and outcome

The current study includes new, in-depth insights into distinct HF subgroups that were not included in the main study publication.[17] The study population was subdivided into those with a history of HF and those with acute HF complicating their index ACS event. Despite substantial overlap, both of these subgroups are distinct and clinically relevant. We then compared each of these subgroups to patients who had no HF on a range of outcome events.

In patients with ACS, HF, both prior and acute, is associated with worse outcomes. This is different from chronic HF. In chronic HF, nonfatal MI and stroke are relatively uncommon, and CV death accounts for most adverse ischemic events.[24] In chronic HF, it has been postulated that electrical instability and/or mechanical failure, not rupture of an atherosclerotic plaque, are the main underlying causes of CV death. After a recent ACS, it is commonly assumed that atherothrombotic events are the main cause of adverse events. However, concomitant HF not only increases the risk for major adverse CV events but also may influence the distribution of events. We found that MI and CV death were the drivers of the adverse outcomes in both HF groups. Concomitant HF is indeed associated with a higher frequency of fatal events and influences the rate of recurrent MI and stroke.[5,25] This observation could be explained by enhanced vulnerability for ischemic events in the HF subset after a recent ACS. Of interest, we found that both prior HF and acute HF at the time of the index ACS event have a similar negative effect on outcomes, although we found no compelling effect in relation to bleeding. It remains unknown if the increase in risk and the relative frequency of CV death in the primary outcome do not reduce the potential to modify risk by a therapeutic intervention. In ATLAS-2, another oral factor Xa inhibitor resulted in a significant reduction in CV death in a lower risk cohort of patients with a recent ACS that was more pronounced in the subgroup of patients with a history of HF.[22,26] It is unclear from the information in the public domain as to how "a history of heart failure" was defined in ATLAS-2.[26]

Most of the APPRAISE-2 population was treated medically without revascularization.[17] Despite emphasis in guidelines on the use of invasive management for patients with NSTEMI, several reports suggest that half of them do not undergo revascularization procedures during their initial hospitalization in part probably related to their high-risk profile at baseline.[13,14,21,27,28] These medically managed patients have a higher frequency of comorbidities, and this probably influences the decision

Figure



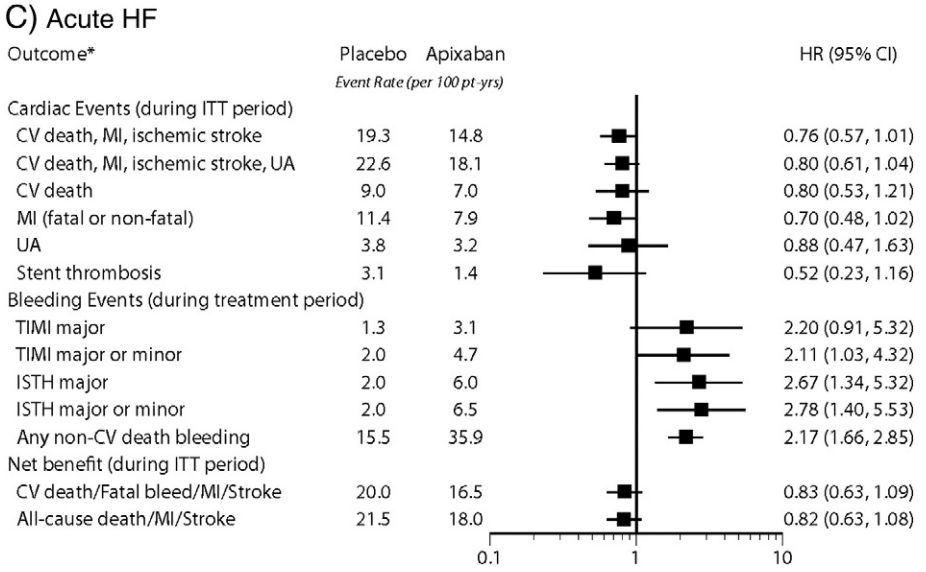
Effect of apixaban versus placebo by no HF (no prior HF and no acute HF) (**A**), prior HF (**B**), and acute HF (**C**). Adjusted for age, sex, race (white/Asian vs other), current smoker, heart rate, diabetes, prior MI, hypertension, peripheral vascular disease, impaired renal function, enrolling MI, ST changes at enrollment, and revascularization for the index ACS event.

to use a conservative strategy.[29] Demographic factors such as prior HF, older age, diabetes, and renal insufficiency are also associated with HF at the index ACS event, and therefore, these patients are less likely to undergo revascularization procedures.[24,30] The outcome of medically managed patients with ACS selected not to undergo revascularization is worse, and therapeutic interventions (eg, antiplatelet therapy) may result in a different outcome in medically managed patients compared with those who undergo revascularization.[31,32]

Outcome and anticoagulant therapy

Medical therapy after ACS has been targeted to prevent atherothrombotic events. Despite increases in the aggressive use of dual antiplatelet therapies, the residual risk of death, MI, or stroke remains high.[20] Previous studies with combined therapy of warfarin with aspirin have demonstrated a 30% reduction in nonfatal MI and a 57% reduction in the risk of ischemic stroke, if the international normalized ratio was between 2 and 3, but without an effect on mortality.[10,11] A large Danish

Figure



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observational cohort study including >40,000 patients with MI found that triple therapy, target therapeutic international normalized ratio 2 to 3, was associated with a 4-fold higher rate of bleeding without survival advantage compared with aspirin as monotherapy.[12] The newer oral anticoagulants have been tested recently in addition to evidence-based dual antiplatelet therapy.[17,22] Although not statistically significant, the current APPRAISE-2 analysis shows that, in patients with acute HF complicating their ACS event, there was a trend toward better outcomes with apixaban. Acute HF complicating an ACS event, compared with prior HF, is more likely to be related to acute coronary thrombosis. The APPRAISE-2 trial was stopped early for safety reasons (eg, excess in bleeding rate) and could be biased against demonstrating efficacy. Recently, another phase 3 randomized, placebo-controlled clinical trial has reported more favorable results with twice-daily doses of either 2.5 or 5 mg of the oral anticoagulant rivaroxaban (2- to 4-fold lower than tested in atrial fibrillation) in addition to contemporary antiplatelet therapy.[22] Similar beneficial effects of oral anticoagulation in patients with a recent ACS and concomitant HF have been demonstrated in other trials. A recent US Food and Drug Administration presentation at the Cardiovascular and Renal Drugs Advisory Committee demonstrated a larger benefit of rivaroxaban in the subgroup of patients with compared with those without a history of HF (HR 0.59, 95% CI 0.41-0.84 vs HR 0.93, 95% CI 0.78-1.11).[26] These results have not been published in the peer-reviewed literature, and it is unknown how HF was diagnosed or defined in ATLAS-2. Nevertheless, different, lower dosing of these oral anticoagulants could open new avenues to reduce thrombotic events for patients with ACS and HF. Recently, a trial with an estimated enrollment of 5,000 patients was launched to study the effectiveness and safety of rivaroxaban in reducing the risk of death, MI, or stroke in patients with HF and coronary artery disease after hospitalization for HF (COMMANDER HF Clinical Trials.gov no., NCT01877915).

Limitations

Randomization was not stratified for HF; therefore, some imbalance between the randomized groups may exist across HF subgroups. However, this was a prespecified subgroup analysis based on prespecified data acquired at randomization. Heart failure was assessed by the investigators based on clinical criteria and not centrally adjudicated independently. The premature termination of the trial due to an increase in bleeding without a reduction in ischemic events limits conclusions regarding efficacy. The current analysis represents a subgroup from a negative trial. Because of multiple comparisons, some observed differences could be due to a play of chance.

Conclusion

In high-risk patients with ACS, both a history of HF and acute HF complicating the index ACS event are associated with an increased risk of subsequent major adverse CV events and bleeding. Apixaban resulted in a nonsignificant trend toward a reduction in recurrent clinical events

among patients with acute HF complicating their index ACS event, but not in patients with prior HF or those without HF. Apixaban increased bleeding similarly in patients with and without HF. Patients with ACS complicated by acute HF represent a high-risk population that could potentially benefit from additional antithrombotic therapy and deserve further study.

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