European Journal of Heart Failure (2015) **17**, 735–742
doi:10.1002/ejhf.266

Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

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Received 23 January 2015; revised 4 March 2015; accepted 11 March 2015; online publish-ahead-of-print 27 April 2015

[Correction added on 29 May 2015, after first online publication: Stefan D. Anker has significantly contributed to the article and has now been added to the Authorship.]

Aims Thrombin is a critical element of crosstalk between pathways contributing to worsening of established heart failure (HF). The aim of this study is to explore the efficacy and safety of rivaroxaban 2.5 mg bid compared with placebo (with standard care) after an exacerbation of HF in patients with reduced ejection fraction (HF-rEF) and documented coronary artery disease.

Methods This is an international prospective, multicentre, randomized, double-blind, placebo-controlled, event-driven study of approximately 5000 patients for a targeted 984 events. Patients must have a recent symptomatic exacerbation of HF, increased plasma concentrations of natriuretic peptides (B-type natriuretic peptide ≥200 pg/mL or *N*-terminal pro–B-type natriuretic peptide ≥800 pg/mL), with left ventricular ejection fraction ≤40% and coronary artery disease. Patients requiring anticoagulation for atrial fibrillation or other conditions will be excluded. After an index event (overnight hospitalization, emergency department or observation unit admission, or unscheduled outpatient parenteral treatment for worsening HF), patients will be randomized 1:1 to rivaroxaban or placebo (with standard of care). The primary efficacy outcome event is a composite of all-cause mortality, myocardial infarction or stroke.

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The principal safety outcome events are the composite of fatal bleeding or bleeding into a critical space with potential permanent disability, bleeding events requiring hospitalization and major bleeding events according to International Society on Thrombosis and Haemostasis bleeding criteria.

Conclusion COMMANDER HF is the first prospective study of a target-specific oral antithrombotic agent in HF. It will provide important information regarding rivaroxaban use following an HF event in an HF-rEF patient population with coronary artery disease.

Keywords rivaroxaban • thrombin • antithrombotic • heart failure • coronary artery disease

Introduction

The prevalence of heart failure (HF) has increased progressively over the past several decades owing primarily to a reduction in myocardial infarction (MI) mortality and a steady ageing of the population around the world.[1] Heart failure with reduced ejection fraction (HF-rEF) is a final common pathway for many cardiovascular diseases, notably coronary artery disease (CAD).[2] Once established, HF-rEF progresses through activation of a variety of pathways that adversely affect cardiac structure and function.

Currently, the most effective pharmacological therapies for HF-rEF target the activation of the renin–angiotensin–aldosterone system and the β-adrenergic sympathetic nervous system that occurs in HF.[3,4] However, even with these treatments, morbidity and mortality remain unacceptably high and increase further after episodes of acute decompensation.[5–7]

Because thrombotic events are increased in HF patients,[8,9] clinical and observational studies have explored chronic oral antithrombotic treatment strategies. A recent comprehensive review of warfarin anticoagulation in HF patients in normal sinus rhythm[10] that included both the WASH[11] and HELAS[12] randomized trials found 'no convincing evidence that oral anticoagulant therapy modifies mortality or vascular events in patients with HF and sinus rhythm.' In addition, the WARCEF trial,[13] which compared the effects of warfarin vs. aspirin on a composite endpoint of ischaemic stroke, intracerebral haemorrhage or death from any cause, showed no significant differences in outcome. A reduction in ischaemic stroke risk with warfarin was balanced by increased risk of bleeding.

Nonetheless, thrombin plays a critical role in multiple pathophysiological processes that occur in CAD patients with recent symptomatic decompensation of HF-rEF.[14] Targeted reduction of thrombin generation with rivaroxaban, a Factor Xa inhibitor, rather than non-selective depletion of multiple vitamin K–dependent clotting factors with warfarin, may hold promise. Supporting this concept, analysis of 5284 patients with chronic HF from Val-HeFT and GISSI-HF trials demonstrated the clinical importance of ongoing myocardial injury in HF.[15] Increased plasma cardiac troponin T detected by high-sensitivity assay (hs-cTnT) predicted increased all-cause mortality (ACM) after adjustment for conventional risk factors and baseline hs-cTnT and *N*-terminal pro–B-type natriuretic peptide (NT-proBNP; 59% increase in Val-HeFT and 88% increase in GISSI-HF). Recognition of the importance of troponin elevations[16–18] in HF has drawn attention to the thrombin-related pathways that may be associated with ongoing myocyte injury, including inflammation, endothelial dysfunction and microvascular thrombosis.[14,16,19,20] A growing body of evidence suggests that thrombin provides a common element of 'crosstalk' that links these pathways.[19] However, the potential benefits of antithrombotic therapy in HF patients remain unclear.[21]

Inflammation

Heart failure is intricately linked to elevation in pro-inflammatory cytokines and abnormalities in circulating lymphocyte subsets.[22] In more than 1700 patients with HF in the Val-HeFT trial, increasing plasma concentrations of growth differentiation factor (GDF)-15 (evidence of inflammation) over 12 months were independently associated with higher future morbidity and mortality, supporting a role for heightened inflammatory activity in the progression of HF.[23]

Endothelial dysfunction

The presence and importance of endothelial dysfunction in patients with CAD is well documented.[24] In 259 subjects with New York Heart Association II–IV HF and a median follow-up of just over 1 year, Katz *et al.*[25] demonstrated that decreased brachial arterial flow-mediated dilation (FMD) and decreased exhaled NO production were associated with increased risk of death or urgent transplantation after adjustment for other known HF prognostic factors (age, aetiology of HF, functional class, left ventricular ejection fraction). In a study of 245 patients with stable HF and impaired FMD, optimal medical therapy for 6 months failed to reverse impaired FMD in 53% (130 patients), and persistently impaired FMD increased the 3-year risk for cardiac events by threefold.[26]

Thrombosis

Evidence for increased thrombin activity and microvascular thrombosis in HF and an association with increased mortality continues to accumulate. Patients with HF have increased thrombin activity (D-dimer, thrombin-antithrombin complexes) compared with controls.[27,28] A study of 174 patients with systolic HF demonstrated that elevated thrombin activity (D-dimer >1435 ng/mL) was associated with greater than threefold increase in mortality.[29]

Thus, a growing body of evidence provides the clinical rationale for modulation of thrombin generation in HF-rEF. In contrast,

inhibition of Factor Xa with rivaroxaban is associated with an increased risk of bleeding. The COMMANDER HF trial was designed to test the hypothesis that rivaroxaban could reduce the composite of ACM, stroke and MI in patients with HF-rEF and documented CAD who had experienced a recent acute decompensation of their condition with an acceptable risk of bleeding.

Rivaroxaban

Rivaroxaban is a specific inhibitor of activated Factor X (Factor Xa or FXa). In the clotting cascade, exposure of blood to tissue factor (TF) activates circulating Factor VII. Factor VII complexes with Factor X, and the complex initiates formation of the prothrombinase complex that includes FXa, Factor Va, and calcium. The prothrombinase complex cleaves prothrombin to generate thrombin. Because FXa activation leads to an amplifying burst of thrombin generation,[30] specifically targeting FXa may offer a new approach to interrupt the negative feedback cycles associated with increased thrombin generation in HF-rEF.

In 12 healthy volunteers receiving single doses of rivaroxaban (5 mg or 30 mg) or placebo, both doses of rivaroxaban potently inhibited thrombin generation for 24 h.[31] In 51 patients who had undergone elective hip or knee replacement 6–8 h before receiving either dalteparin (2500–5000 U QD) or rivaroxaban (10 mg QD), effective inhibition of *ex vivo* thrombin generation was consistently achieved with rivaroxaban, and inhibition was greater than with dalteparin.[32] In 18 HF patients receiving rivaroxaban 10 mg QD or placebo, thrombin generation after 7 days (as measured by prothrombin fragment 1.2) was reduced with rivaroxaban.[33] These data demonstrate that rivaroxaban effectively inhibits thrombin generation across a wide spectrum of doses.

In the ATLAS-2 trial,[34] both rivaroxaban 5 mg bid and rivaroxaban 2.5 mg bid reduced the composite efficacy endpoint; however, the 2.5 mg bid dose was associated with fewer episodes of major bleeding. In addition, an unpublished subgroup analysis of ATLAS-2 (Janssen Research & Development, LLC, Raritan, NJ, USA; data on file), although subject to all the limitations of retrospective *ad hoc* subgroup analysis, showed that in patients clinically diagnosed as having HF at the time of their acute coronary syndrome (ACS) event, rivaroxaban 2.5 mg bid reduced the primary outcome event of cardiovascular death, MI or stroke after a mean follow-up of 13 months from 18.6% with placebo to 11.6% with rivaroxaban 2.5 mg bid ($P < 0.001$), reduced cardiovascular death from 10.4% with placebo to 5.2% with rivaroxaban 2.5 mg bid ($P < 0.001$), and reduced death from any cause from 11.1% with placebo to 5.3% with rivaroxaban 2.5 mg bid ($P < 0.001$). In this subgroup, major bleeding, according to Thrombolysis In Myocardial Infarction (TIMI) criteria, occurred in slightly fewer patients receiving rivaroxaban 2.5 mg bid than placebo (0.4% vs. 0.7%).

Rivaroxaban 2.5 mg bid is approved in Europe for the treatment of biomarker-positive patients after an ACS, and is undergoing additional study in the USA. Based on the data and the considerations above, a dose of rivaroxaban 2.5 mg bid was chosen for the COMMANDER HF trial as the most likely to offer an optimal combination of safety and efficacy.

Study design

Study objectives and outcome events

The primary efficacy objective is to demonstrate that rivaroxaban is superior to placebo in subjects with HF and significant CAD, who are receiving standard care, in reducing the risk of the composite of ACM, MI or stroke following a recent exacerbation of HF. The primary efficacy outcome event is the composite of ACM, MI or stroke. The principal safety outcome event is the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability.

Major secondary efficacy outcomes include the composite of cardiovascular mortality and rehospitalization for worsening of HF, and the separate outcomes of cardiovascular mortality, rehospitalization for worsening of HF, and rehospitalization for cardiovascular events. Additional bleeding outcomes are bleeding events requiring hospitalization and major bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria.[35]

Prespecified exploratory analyses will evaluate symptomatic deep vein thrombosis, symptomatic pulmonary embolism and benefit–risk balance.

Design

COMMANDER HF (ClinicalTrials.gov Identifier: NCT01877915) is an international prospective, randomized, double-blind, placebo-controlled, event-driven, parallel-group comparison between rivaroxaban and placebo (*Figure 1*). The study includes a screening phase, a double-blind treatment phase and follow-up after the sponsor-announced global treatment end date (GTED, defined as the date when 984 primary efficacy outcome events are predicted to have occurred). Subjects will be followed for a minimum of approximately 7 months and a maximum of 31 months.

Ethics approval

COMMANDER HF will be conducted in keeping with Good Clinical Practice guidelines, the principles outlined in the Declaration of Helsinki, and applicable local laws and regulations. All participating centres/countries must obtain approval from appropriate independent ethics committees or institutional review boards, and patients must give written informed consent.

Patient population

The COMMANDER HF study will enroll adult (≥18 years old) patients, who are clinically stable up to 30 days after a symptomatic index event, defined as an exacerbation of HF symptoms requiring: (1) hospitalization, emergency room or observation unit admission capable of treating with intravenous medications, or (2) an unscheduled outpatient visit requiring parenteral therapy. Patients must have HF documented by a level of NT-proBNP ≥800 pg/mL or B-type natriuretic peptide (BNP) ≥200 pg/mL (obtained between the onset of the index event and randomization), must have left

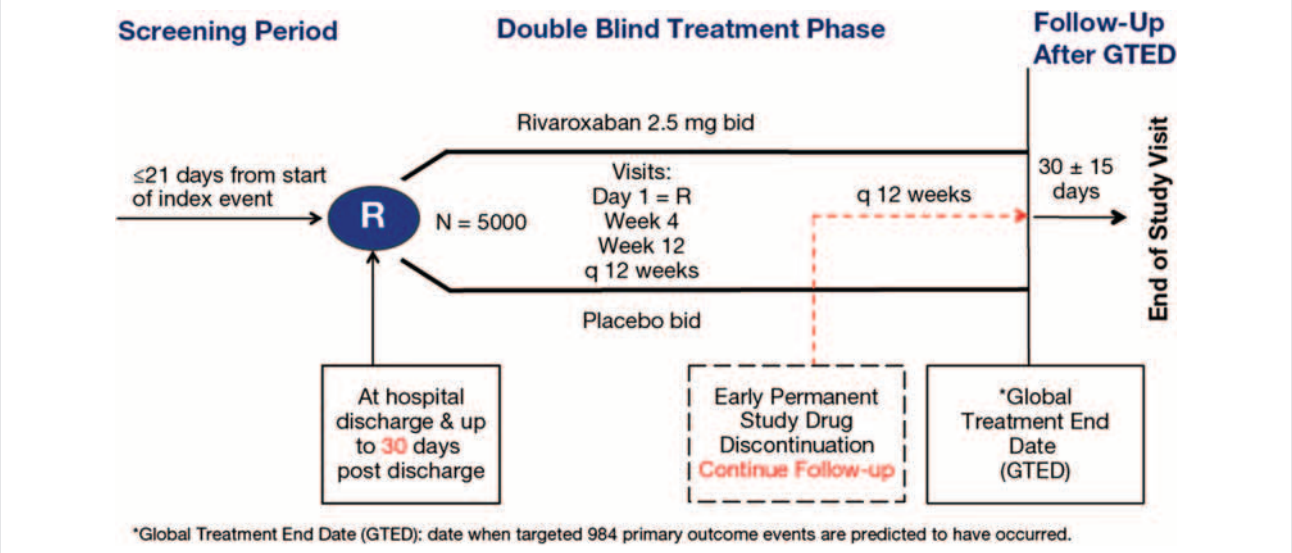

Figure 1 Study design. GTED, global treatment end date; R, randomization; HF, heart failure; HF-rEF, heart failure with reduced ejection fraction; CAD, coronary artery disease.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
18 years of age or older	Bleeding risk or any severe concomitant disease (e.g. atrial fibrillation or acute MI during index hospitalization)
Documented symptomatic HF for ≥3 months before screening with a minimum of an overnight stay (i.e. staying past midnight) in a hospital, emergency department or medical facility and a documented LVEF of ≤40% within 1 year before randomization or during index hospitalization, and evidence of significant CAD	Planned cardiac surgery within 28 days before or after randomization, excluding PCIs and electrophysiological devices
	History of severe valvular disease, chronic episodes of ventricular tachycardia, severe peptic ulcer disease, or HIV
Medically stable in terms of HF clinical status (ambulatory and receiving no IV medications) at randomization, receiving appropriate HF treatment at the appropriate dosing per guidelines, and receiving appropriate CAD treatment per guidelines	Stroke within 90 days of randomization
	HF caused by postpartum, infection, substance abuse, alcohol, infiltrative disease, or transient reversible condition
	Cardiogenic shock at randomization
Completed all prophylactic anticoagulation before randomization	eGFR <20 mL/min
Signed informed consent	Anticipated life expectancy <6 months
≥200 pg/mL BNP or ≥800 pg/mL NT-proBNP during their index hospitalization, or after discharge from index hospitalization but before randomization	Acute endocarditis
	Currently on haemofiltration or dialysis or known significant liver disease
	Anaemia (Hb <8 g/dL) or severe thrombocytopenia (platelets <50 000/μL) at screening
	Hospitalized >21 days during index hospitalization
	Planned IV intermittent outpatient positive inotropic drug treatment

HF, heart failure; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; BNP, B-type natriuretic peptide; NT-proBNP, *N*-terminal pro–B-type natriuretic peptide; MI, myocardial infarction; PCI, percutaneous coronary intervention; HIV, human immunodeficiency virus; eGFR, estimated glomerular filtration rate; Hb, haemoglobin.

ventricular ejection fraction ≤40%, and must have documented significant CAD according to predefined criteria (*Table 1*).

Patients with significant valvular heart disease or atrial fibrillation before randomization will be excluded, as will those with other indications for chronic anticoagulation (*Table 1*).

Patients will have follow-up visits at week 4, week 12, and every 12 weeks for assessment of outcome events and safety. When it is estimated that 984 primary outcome events have occurred, the investigator sites will be notified of the GTED, and patients will be required to have a final visit within 30 days of the GTED. Patients who discontinue study drug prematurely will continue follow-up with the investigator every 12 weeks until GTED.

Study drug

Patients randomized to rivaroxaban will receive rivaroxaban 2.5 mg orally twice daily without adjustment for renal function, consistent with the dose approved in the European Union for post-ACS

management. Subjects are advised to take the study drug at approximately the same times each day.

Concurrent interventions

The use of strong inhibitors of both cytochrome P450 3A4 and P-glycoprotein (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, or human immunodeficiency virus protease inhibitors), Factor IIa inhibitors, low molecular weight heparin, or unfractionated heparin is prohibited. Strong inducers of cytochrome P450 3A4 are prohibited within 4 days before randomization or during the study. Patients who are receiving concomitant non-steroidal anti-inflammatory drugs, platelet aggregation inhibitors, or other antithrombotic agents should be monitored carefully. Patients at risk for ulcerative gastrointestinal disease or gastrointestinal bleeding can receive prophylactic treatment with proton pump inhibitors (except omeprazole or esomeprazole) at the investigator's discretion. These medications will be captured as concomitant medications on the electronic case report form.

Outcome definitions

Primary efficacy outcome

The primary efficacy outcome is the composite of ACM, MI or stroke. Outcome events will be as reported by the investigator and will not be independently adjudicated.

All-cause death and cardiovascular death

Deaths are assigned by the investigator to either cardiovascular (e.g. stroke, MI or haemorrhage) or non-cardiovascular (e.g. malignancy, infectious disease or trauma) causes. Instances of sudden cardiac death, involving cardiac arrest, accompanied by symptoms of myocardial ischaemia, abnormal electrocardiographic findings, and/or evidence of fresh thrombus by coronary angiography and/or autopsy (i.e. fatal MI) will be classified as cardiovascular.

Myocardial infarction

In the absence of percutaneous coronary intervention or coronary artery bypass graft, cases involving rise and/or fall of cardiac biomarkers (preferably troponin) with $\geq$1 value above the 99th percentile of the upper reference limit will be classified as MI if accompanied by myocardial ischaemia, demonstrated by $\geq$1 of the following: ischaemic signs, development of pathological Q waves or changes indicative of new ischaemia (i.e. new ST-T changes or new left bundle branch block) on electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality. The definition of MI as a clinical outcome event also includes criteria for periprocedural biomarker elevations around percutaneous coronary intervention or coronary artery bypass graft.

Stroke

Stroke is defined as an abrupt onset of a focal neurological deficit that is not initiated by an identifiable non-vascular cause (i.e. brain tumour or trauma) and that either is associated with symptoms lasting >24 h or results in death within 24 h of symptom onset. Computed tomography and/or magnetic resonance imaging will be used to subclassify strokes (ischaemic, haemorrhagic or subarachnoid). Subdural and epidural haematoma will be considered intracranial haemorrhages, but will not be classified as a haemorrhagic stroke. Cases in which imaging is unavailable or inconclusive will be classified as stroke of uncertain cause. Instances of stroke thought to be the primary cause of or directly leading to death (i.e. fatal stroke) will be classified as cardiovascular death.

Secondary efficacy outcomes

Secondary efficacy outcomes include the composite of cardiovascular mortality and rehospitalization for worsening of HF, and the separate outcomes of cardiovascular mortality, rehospitalization for worsening of HF, and rehospitalization for cardiovascular events.

Safety evaluations

An independent data monitoring committee (IDMC) will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives.

Major bleeding

Major bleeding events will be defined according to the ISTH criteria[35]: clinically overt bleeding that leads to a transfusion of $\geq$2 units of packed red blood cells or whole blood, or that is associated with a fatal outcome or involves a critical site. Intracranial bleeding will be classified as either a haemorrhagic stroke, subarachnoid haemorrhage, or subdural or epidural haemorrhage.

Non-major bleeding

Non-major bleeding events are defined as overt bleeding not meeting the criteria for major bleeding.

Sample size and statistical methods

This study aims to observe occurrences of the primary efficacy event in 984 unique randomized subjects, on or before the GTED to have 90% power to detect a 20% relative risk reduction (RRR) in the composite of ACM, MI or stroke at a 5%, 2-sided statistical significance level. GTED is defined as the date when 984 primary efficacy outcome events are predicted to have occurred. Approximately 5000 subjects will be randomized.

The IDMC reviews unblinded safety data periodically. If necessary, or requested by the IDMC, subject-level unblinded data may be provided to the IDMC. In addition, the IDMC will review results of an interim analysis after approximately 500 subjects have experienced primary efficacy events and will recommend whether the study should be terminated prematurely because of overwhelming benefit or futility.

The primary statistical hypothesis will be tested using a log-rank test, stratified by country.

The primary analysis will be based on the analysis set defined by the intention-to-treat subject population and the up-to-GTED observational period (up to the cut-off date to be specified for the interim analysis).

The RRR will be estimated using a Cox proportional hazards model, stratified by country, with treatment (as randomized) as the only covariate. The point estimate and corresponding 95% confidence interval (CI) for the hazard ratio (HR; rivaroxaban to placebo) will be reported.

If superiority of rivaroxaban over placebo in reducing the risk of the primary efficacy outcome event is established, treatment effects in secondary outcome events will be tested subsequently in the following hierarchical order: (1) composite of cardiovascular mortality or rehospitalization for worsening of HF; (2) cardiovascular mortality; (3) rehospitalization for worsening of HF; (4) rehospitalization for cardiovascular events.

Statistical significance is required before testing the next hypothesis in the hierarchical test procedure. These secondary outcome events will be analysed using time-to-event analysis, as described above for the primary outcome event.

Homogeneity of treatment effects, both in RRR and direction, in the following prespecified subgroups will be assessed: age, sex, left ventricular ejection fraction, estimated glomerular filtration rate, baseline troponin, history of diabetes, stroke, MI and hypertension, body mass index, aspirin use, race and geographic region.

The principal safety evaluation outcome event is the composite of fatal bleeding, or bleeding into a critical space with potential for permanent disability. Time to the first occurrence of the principal safety outcome events will be compared using a Cox proportional hazards model, stratified by country, with treatment as the only covariate. The analysis will be conducted for the analysis set defined by the on-treatment observational period and the safety population. Subjects will be analysed according to study drug received. If a subject receives both drugs, the subject will be analysed as randomized.

Discussion

COMMANDER HF has several key elements among its inclusion criteria, such as the requirements for documented CAD, for an 'index event' with clinical decompensation of HF, and for qualifying plasma concentrations of natriuretic peptides.

The requirement for CAD reflected a consensus among the investigators that evidence for the contribution of thrombotic mechanisms to adverse outcomes in patients with CAD was stronger than for non-ischaemic aetiologies of HF.[22,36] Requiring a recent worsening HF event and increased plasma concentrations of natriuretic peptides confirms that the patients have HF, that their needs were unmet by previous therapy, and identifies patients at increased risk of further events.[6,7,37] In response to changing patterns of care for HF patients, the definition of an index event was modified in a protocol amendment that eliminated the requirement of an overnight stay for treatment, and the window for randomization after the index event was extended to 30 days.

COMMANDER HF is limited to subjects with HF-rEF because of the uncertainties surrounding the diagnostic criteria, management, and event rates for HF-pEF.

As ACM is expected to be the primary driver of the efficacy outcome event, the sponsor and steering committee agreed that a complex and expensive adjudication process would not be required for this trial.

Importantly, COMMANDER HF is not another trial of oral anticoagulation in HF but rather an intervention to modulate thrombin-mediated crosstalk, a potential driver of multiple negative feedback cycles, including inflammation, endothelial dysfunction, and thrombosis, in patients with HF-rEF and CAD.

The COMMANDER HF study will be the first double-blind, placebo-controlled, randomized clinical trial designed to provide statistically robust results that explore the role of a targeted antithrombin strategy in patients with a recent exacerbation of HF-rEF and coexisting CAD.

Acknowledgements

The authors acknowledge all members of the COMMANDER HF Steering Committee: Stefan D. Anker, John G. F. Cleland, Mihai Gheorghiade, Barry Greenberg (co-chairman), Barry M. Massie, Mandeep R. Mehra, Dirk J. van Veldhuisen and Faiez Zannad (co-chairman). The authors also acknowledge the members of the independent data monitoring committee (IDMC): W. Douglas Weaver (chairman), Stuart Pocock, Henry Dargie, Marc Klapholz, Bertram Pitt and Yoshihiko Seino. In addition, Lloyd Haskell of Janssen Research & Development, LLC, has provided scientific support for this study in a variety of roles over many years, and the authors wish to acknowledge his enthusiasm. Editorial assistance was provided by Ashley O'Dunne of MedErgy.

Funding

This work was supported by Janssen Research & Development, LLC.

Conflicts of interest

F.Z. reports the following: grants to institution from Roche Diagnostics; membership of steering committees of Bayer, Boston Scientific, Janssen, Novartis, Pfizer, ResMed, and Takeda; consultant/scientific advisory board membership of Air Liquide, Amgen, CVRx, Servier, St Jude, Stealth Peptide; and speaker fees from Mitsubishi; stocks in CardioRenal Diagnostics and CVCT. B.G. reports consulting fees from Novartis, Celladon, Teva, AstraZeneca, MAST, Zensun and Janssen, and speaker's fees from Otsuka. J.G.F.C. received an honorarium for work in support of the COMMANDER HF study design and delivery. M.G. received support from Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma AG, Cardiorentis Ltd, Corthera, Cytokinetics, CytoPherx, Inc., Debiopharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, INC, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Pharmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein

Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals North America, Inc. and Trevena Therapeutics, and has received significant (>$10 000) support from Bayer Schering Pharma AG, Debiopharm S.A., Medtronic, Novartis Pharma AG, Otsuka Pharmaceuticals, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT and Takeda Pharmaceuticals North America, Inc. M.R.M. reports consulting fees from Johnson & Johnson, Boston Scientific, St Judes, Thoratec, Stealth Biopeptides, NIH-NHLBI, and the American Board of Internal Medicine. W.M.B. and R.M.M. are full-time employees of Janssen Research & Development, LLC. M.F. is a full-time employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder. D.J.v.V. received board membership fees from Janssen Research & Development, LLC, for the COMMANDER HF study. S.D.A. has received fees for steering committee work for COMMANDER-HF from Janssen Research, and fees for consultancy from Bayer.

[Correction added on 29 May 2015 after first online publication: The conflict of interest statement for Stefan D. Anker has been added to the text.]

References

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;**8:**30–41.
2. Francis GS, Cogswell R, Thenappan T. The heterogeneity of heart failure: will enhanced phenotyping be necessary for future clinical trial success? *J Am Coll Cardiol* 2014;**64:**1775–1776.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128:**e240–e327.
4. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33:**1787–1847.
5. Allen LA, O'Connor CM. Management of acute decompensated heart failure. *CMAJ* 2007;**176:**797–805.
6. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49:**1943–1950.
7. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, Paulus WJ, Voors AA, Hillege HL. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol* 2013;**61:**1498–1506.
8. Gurbel PA, Tantry US. Antiplatelet and anticoagulant agents in heart failure: current status and future perspectives. *JACC Heart Fail* 2014; **2:**1–14.
9. Gheorghiade M, Vaduganathan M, Fonarow GC, Greene SJ, Greenberg BH, Liu PP, Massie BM, Mehra MR, Metra M, Zannad F, Cleland JG, van Veldhuisen DJ, Shah AN, Butler J. Anticoagulation in heart failure: current status and future direction. *Heart Fail Rev* 2013;**18:**797–813.
10. Lip GY, Shantsila E. Anticoagulation versus placebo for heart failure in sinus rhythm. *Cochrane Database Syst Rev* 2014;**3:**CD003336.
11. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148:**157–164.
12. Cokkinos DV, Toutouzas PK. Antithrombotic therapy in heart failure: a randomized comparison of warfarin vs. aspirin (HELAS). *Eur J Heart Fail* 1999;**1:**419–423.
13. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366:**1859–1869.
14. Zannad F, Stough WG, Regnault V, Gheorghiade M, Deliargyris E, Gibson CM, Agewall S, Berkowitz SD, Burton P, Calvo G, Goldstein S, Verheugt FW, Koglin J, O'Connor CM. Is thrombosis a contributor to heart failure pathophysiology? Possible mechanisms, therapeutic opportunities, and clinical investigation challenges. *Int J Cardiol* 2013;**167:**1772–1782.
15. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F, Maggioni AP, Tavazzi L, Tognoni G, Cohn JN, Latini R. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation* 2012;**125:**280–288.
16. Omland T, Rosjo H, Giannitsis E, Agewall S. Troponins in heart failure. *Clin Chem Acta* 2014;**443:**78–84.
17. de Antonio M, Lupon J, Galan A, Vila J, Urrutia A, Bayes-Genis A. Combined use of high-sensitivity cardiac troponin T and *N*-terminal pro-B type natriuretic peptide improves measurements of performance over established mortality risk factors in chronic heart failure. *Am Heart J* 2012;**163:**821–828.
18. Egstrup M, Schou M, Tuxen CD, Kistorp CN, Hildebrandt PR, Gustafsson F, Faber J, Goetze JP, Gustafsson I. Prediction of outcome by highly sensitive troponin T in outpatients with chronic systolic left ventricular heart failure. *Am J Cardiol* 2012;**110:**552–557.
19. Borissoff JI, Spronk HM, Heeneman S, ten CH. Is thrombin a key player in the 'coagulation-atherogenesis' maze? *Cardiovasc Res* 2009;**82:**392–403.
20. Danckwardt S, Hentze MW, Kulozik AE. Pathologies at the nexus of blood coagulation and inflammation: thrombin in hemostasis, cancer, and beyond. *J Mol Med (Berl)* 2013;**91:**1257–1271.
21. Van Gelder IC, van Veldhuisen DJ, Lip GYH. New oral anticoagulants in heart failure. *Eur J Heart Fail* 2013;**15:**966–973.
22. Ueland T, Nymo SH, Latini R, McMurray JJ, Kjekshus J, Yndestad A, Fucili A, Grosu A, Masson S, Maggioni AP, Gullestad L, Aukrust P. CCL21 is associated with fatal outcomes in chronic heart failure: data from CORONA and GISSI-HF trials. *Eur J Heart Fail* 2013;**15:**747–755.
23. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H, Wollert KC. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation* 2010;**122:**1387–1395.
24. Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, Saito Y, Kawabata K, Sano K, Kobayashi T, Yano T, Nakamura K, Kugiyama K. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. *J Am Coll Cardiol* 2009;**53:**323–330.
25. Katz SD, Hryniewicz K, Hriljac I, Balidemaj K, Dimayuga C, Hudaihed A, Yasskiy A. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. *Circulation* 2005;**111:**310–314.
26. Takishima I, Nakamura T, Hirano M, Kitta Y, Kobayashi T, Fujioka D, Saito Y, Watanabe K, Watanabe Y, Mishina H, Obata JE, Kawabata K, Tamaru S, Kugiyama K. Predictive value of serial assessment of endothelial function in chronic heart failure. *Int J Cardiol* 2012;**158:**417–422.
27. Cugno M, Mari D, Meroni PL, Gronda E, Vicari F, Frigerio M, Coppola R, Bottasso B, Borghi MO, Gregorini L. Haemostatic and inflammatory biomarkers in advanced chronic heart failure: role of oral anticoagulants and successful heart transplantation. *Br J Haematol* 2004;**126:**85–92.
28. Marcucci R, Gori AM, Giannotti F, Baldi M, Verdiani V, Del PS, Nozzoli C, Abbate R. Markers of hypercoagulability and inflammation predict mortality in patients with heart failure. *J Thromb Haemost* 2006;**4:**1017–1022.
29. Zorlu A, Yilmaz MB, Yucel H, Bektasoglu G, Refiker EM, Tandogan I. Increased d-dimer levels predict cardiovascular mortality in patients with systolic heart failure. *J Thromb Thrombolysis* 2012;**33:**322–328.
30. Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. *Arterioscler Thromb Vasc Biol* 2003;**23:**17–25.
31. Graff J, von Hentig N, Misselwitz F, Kubitza D, Becka M, Breddin HK, Harder S. Effects of the oral, direct factor xa inhibitor rivaroxaban on platelet-induced thrombin generation and prothrombinase activity. *J Clin Pharmacol* 2007;**47:**1398–1407.
32. Green L, Lawrie AS, Patel S, Hossain F, Chitolie A, Mackie IJ, Haddad FS, Machin SJ. The impact of elective knee/hip replacement surgery and thromboprophylaxis with rivaroxaban or dalteparin on thrombin generation. *Br J Haematol* 2010; **151:**469–476.
33. Gheorghiade M, Thyssen A, Zolynas R, Nadar VK, Greenberg BH, Mehra M, Sun X, Tian H, Plotnikov AN, Burton P. Pharmacokinetics and pharmacodynamics of rivaroxaban and its effect on biomarkers of hypercoagulability in patients with chronic heart failure. *J Heart Lung Transplant* 2011;**30:**218–226.

34. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366:**9–19.
35. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3:**692–694.
36. Gheorghiade M, Flaherty JD, Fonarow GC, Desai RV, Lee R, McGiffin D, Love TE, Aban I, Eichhorn EJ, Bonow RO, Ahmed A. Coronary artery disease, coronary revascularization, and outcomes in chronic advanced systolic heart failure. *Int J Cardiol* 2011;**151:**69–75.
37. Januzzi JL Jr. The role of natriuretic peptide testing in guiding chronic heart failure management: review of available data and recommendations for use. *Arch Cardiovasc Dis* 2012;**105:**40–50.