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Cardiovascular effects of rivaroxaban in heart failure patients with sinus rhythm and coronary disease with and without diabetes: a retrospective international cohort study from COMMANDER-HF

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ABSTRACT

Objectives COMMANDER-HF was a randomised trial comparing rivaroxaban 2.5 mg two times a day to placebo, in addition to antiplatelet therapy, in patients hospitalised for worsening heart failure with coronary artery disease and sinus rhythm. Patients with diabetes are at increased risk of cardiovascular events and therefore have more to gain.

Methods and results In this post-hoc analysis, we evaluated the efficacy and safety of rivaroxaban in patients with (n=2052) and without diabetes (n=2970). The primary outcome was the composite of cardiovascular death, myocardial infarction (MI) or ischaemic stroke. HRs and 95% CIs with interaction analyses were used to describe event-rates and treatment effects. Patients with diabetes had a higher prevalence of cardiovascular comorbidities (eg, hypertension, obesity) and increased incidence of cardiovascular events. Adjusted HRs for events in people with versus without diabetes were 1.34 (95% CI 1.19 to 1.50) for the primary outcome, 1.21 (95% CI 0.84 to 1.75) for stroke, 1.51 (95% CI 1.14 to 1.99) for MI, 1.17 (95% CI 1.05 to 1.31) for heart failure hospitalisation and 1.06 (95% CI 0.56 to 2.01) for major bleeding. Rivaroxaban had no significant effect on event-rates in patients with and without diabetes (all interaction p values >0.05). Low-dose rivaroxaban was associated with an overall reduction in ischaemic stroke (HR 0.66; 95% CI 0.47 to 0.95), with no apparent subgroup interaction according to diabetes status (p-int=0.93).

Conclusions In COMMANDER-HF a diagnosis of diabetes conferred higher rates of cardiovascular events that, with exception of ischaemic stroke, was not substantially reduced by rivaroxaban. Rivaroxaban was associated with reduced risk of ischaemic stroke for patients with and without diabetes.

Trial registration number NCT01877915; Post-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study used a large and well-established dataset from the COMMANDER-HF (a study to assess the effectiveness and safety of rivaroxaban in reducing the risk of death, myocardial infarction or stroke in participants with heart failure and coronary artery disease following an episode of decompensated heart failure) trial, providing high-quality data for analysis.

⇒ The study examined the effect of low-dose rivaroxaban on both cardiovascular outcomes and bleeding events, providing a comprehensive overview of the safety and efficacy of low-dose rivaroxaban in people with and without diabetes.

⇒ The study was a post-hoc analysis which was not specifically powered for efficacy or safety assessments; therefore, the findings should be considered hypothesis-generating.

⇒ Diabetes mellitus was only defined by baseline medical history, which may have restricted diagnostic sensitivity and limited the ability to examine the effect of different types, durations, severities and controls of diabetes on outcomes.

INTRODUCTION

Patients with diabetes and worsening acute heart failure are at increased risk of adverse cardiovascular events and death.[1] The addition of low-dose rivaroxaban (eg, 2.5 mg two times a day) to background antiplatelet therapy has been studied as a potential therapy in various cardiovascular populations including acute coronary syndromes,[2] stable coronary artery disease,[3] peripheral artery disease[3 4] and chronic heart failure with atherosclerotic vascular disease.[5] Low-dose rivaroxaban adjunct therapy has been shown to reduce cardiovascular morbidity and mortality but increase the risk of bleeding complications in these populations.[2–5]

Recently, the COMMANDER-HF trial (a study to assess the effectiveness and safety of rivaroxaban in reducing the risk of death,

myocardial infarction, or stroke in participants with heart failure and coronary artery disease following an episode of decompensated heart failure)[5] investigated the effects of rivaroxaban 2.5 mg orally two times a day compared with placebo in patients recently hospitalised for worsening heart failure with coronary artery disease and sinus rhythm in a substantial double-blind randomised trial. The trial did not show any significant difference in the risk of the primary composite outcome of death, myocardial infarction (MI) or stroke or any other secondary and exploratory efficacy outcomes, such as heart failure and cardiovascular death. In exploratory analyses, rivaroxaban was associated with reduced risk of ischaemic stroke compared with placebo.[6–8] However, whether these secondary and exploratory treatment effects were consistent in patients with and without diabetes has not been evaluated. As a result, we aimed to evaluate differences in the efficacy and safety of low-dose rivaroxaban between patients with and without diabetes, by analysing the interaction between rivaroxaban and diabetes status in the COMMANDER-HF trial.

METHODS

Study population

This is a post-hoc analysis of the COMMANDER-HF trial that aimed to evaluate the effect of diagnosed diabetes on prespecified secondary and exploratory efficacy outcomes. The design and results of the COMMANDER-HF trial have previously been published.[9] In brief, the COMMANDER-HF trial was a stage III international multi-centre, double-blind, randomised, placebo-controlled trial funded by Janssen Research and Development (Raritan, NJ, USA). The trial enrolled 5022 patients with worsening heart failure with reduced left ventricular ejection fraction (≤40%), elevated natriuretic peptides (natriuretic peptide >200 pg/mL; N-terminal pro-brain natriuretic peptide (NT-proBNP) >800 pg/mL; protocol amendment (2 May 2014)) and coronary artery disease. Exclusion criteria were a high risk of bleeding, history of stroke, atrial fibrillation or other condition requiring anticoagulation, acute MI or percutaneous coronary intervention during the index hospitalisation, or severe diseases including but not limited to chronic kidney disease with estimated glomerular filtration rate (eGFR) <20 mL/min. Patients randomly received either rivaroxaban 2.5 mg two times a day or placebo in addition to standard therapy for heart failure and coronary artery disease. Baseline characteristics were recorded at the time of enrolment and participants were followed at weeks 4 and 12 and then every 12 weeks thereafter for a median of 21.1 months.[6 9]

Safety and efficacy outcomes

The primary efficacy outcome in COMMANDER-HF was a composite of death, non-fatal MI or non-fatal stroke. Secondary and exploratory efficacy outcomes included cardiovascular death, heart failure death, sudden cardiac death, heart failure hospitalisation, cardiovascular events requiring hospitalisation and composite outcomes including cardiovascular death with MI or stroke. In addition, to account for the competing risk of death, heart failure hospitalisation was analysed as a composite outcome with all-cause death or cardiovascular death. The primary safety outcome was a composite of fatal bleeding and bleeding into a critical space with the potential for permanent disability. Secondary safety outcomes included the International Society on Thrombosis and Haemostasis (ISTH) definition for major bleeding and bleeding requiring hospitalisation.[6] This was defined by either a decrease in haemoglobin level of ≥20 g/L, transfusion of ≥2 units of packed red cells or whole blood, or critical site bleeding.

Statistical analysis

The data analysis was conducted according to the intention-to-treat principle for all efficacy outcomes. Population data were described as numbers and percentages when categorical and as median and first and third quartiles when continuous. Safety outcome analysis was restricted to patients who took at least one dose of rivaroxaban or placebo, in accordance with the COMMANDER-HF protocol. The baseline characteristics of patients with and without diabetes were compared using p values for means, medians or proportions as appropriate.

With regards to the efficacy and safety outcomes, event-rates were computed per 100 person-years. HRs with 95% CIs with two-sided p values were also computed using Cox proportional hazard models for patients with versus without diabetes. Adjustments were made for traditional cardiovascular risk factors at baseline (ie, randomisation) to attenuate the risk of confounding. These adjustments included age, sex, race, body mass index (BMI), New York Heart Association (NYHA) class, systolic blood pressure, anaemia, eGFR, left ventricular ejection fraction, history of MI, history of stroke, history of coronary revascularisation and geographic region. The effect of treatment randomisation was assessed by conducting interaction analyses and evaluating the p value for each efficacy and safety outcome in patients with and without diabetes. In addition, the annualised absolute risk reduction per year (aARR) conferred by rivaroxaban was evaluated in patient with and without diabetes. P values <0.05 were considered significant and all statistical analyses were performed with Stata V.16 (StataCorp. 2019. College Station, TX: StataCorp).

Patient and public involvement

None.

RESULTS

Baseline characteristics

Recruitment for the COMMANDER-HF trial was between September 2013 and October 2017, and among the 5022 patients randomised, a significant number of individuals

Table 1 Baseline characteristics of patients with and without diabetes mellitus

Variable	Diabetes	No diabetes	P value
Overall, N	2052	2970	
Age groups			
Age, median (IQR)	66 (59, 74)	66 (59, 74)	0.98
<65	856 (41.7%)	1303 (43.9%)	0.13
≥65	1196 (58.3%)	1667 (56.1%)	
Sex			
Female	510 (24.9%)	640 (21.5%)	0.006
Male	1542 (75.1%)	2330 (78.5%)	
Geographic region			
Eastern Europe	1187 (57.8%)	2037 (68.6%)	<0.001
Western Europe and South Africa	232 (11.3%)	226 (7.6%)	
North America	86 (4.2%)	63 (2.1%)	
Asia Pacific	340 (16.6%)	393 (13.2%)	
Latin America	207 (10.1%)	251 (8.5%)	
Race			
Caucasian	1625 (79.2%)	2503 (84.3%)	<0.001
Black/African American	32 (1.6%)	33 (1.1%)	
Asian	343 (16.7%)	384 (12.9%)	
Other	52 (2.5%)	50 (1.7%)	
Heart failure severity			
LVEF (%), median (IQR)	34 (27, 38)	34 (28, 38)	0.024
LVEF≤35% (%)	1292 (63.0%)	1773 (59.7%)	0.020
BNP (pg/mL), median (IQR)	667 (390, 1207)	730.2 (373.5, 1303.7)	0.55
NT-proBNP (pg/mL), median (IQR)	2884 (1560, 6386)	2814 (1478, 6270)	0.51
Baseline NYHA class			
Class I–II	1037 (50.5%)	1330 (44.8%)	<0.001
Class III–IV	1014 (49.4%)	1640 (55.2%)	
Hypertension	1759 (85.7%)	2024 (68.1%)	<0.001
SBP (mm Hg), median (IQR)	121 (110, 130)	124 (112, 134)	<0.001
DBP (mm Hg), median (IQR)	73 (68, 80)	73 (68, 80)	0.46
Body weight			
BMI (kg/m^2), median (IQR)	26.5 (23.7, 29.7)	28 (25, 32.1)	<0.001
BMI group			
<25	506 (24.7%)	1096 (36.9%)	<0.001
25–29.9	804 (39.2%)	1170 (39.4%)	
≥30	740 (36.1%)	702 (23.7%)	
Cardiovascular comorbidities			
PCI or CABG	1374 (67%)	1776 (59.8%)	<0.001
Stroke	222 (10.8%)	231 (7.8%)	<0.001
Cardiac resynchronisation	44 (2.1%)	50 (1.7%)	0.24
Laboratory characteristics			
Anaemia	746 (36.4%)	796 (26.8%)	<0.001
Haemoglobin, median (IQR)	138 (126, 149)	133 (120, 145)	<0.001
Kidney function			
eGFR (mL/min/1.73m^2), median (IQR)	68.5 (54, 83.6)	63 (48.5, 80.3)	<0.001

Continued

Table 1 Continued

Variable	Diabetes	No diabetes	P value
eGFR group			
<30	100 (4.9%)	63 (2.1%)	<0.001
30–59.9	826 (40.3%)	956 (32.2%)	
60–89.9	809 (39.4%)	1429 (48.1%)	
≥90	317 (15.4%)	522 (17.6%)	
Medicines			
Beta blocker	1918 (93.5%)	2724 (91.7%)	0.021
ACEi/ARB	1883 (91.8%)	2777 (93.5%)	0.019
MRA	1511 (73.6%)	2329 (78.4%)	<0.001
ARNI	15 (0.7%)	26 (0.9%)	0.58
Digoxin	188 (9.2%)	245 (8.2%)	0.26
Diuretic	2040 (99.4%)	2959 (99.6%)	0.27
ASA	1906 (92.9%)	2769 (93.2%)	0.63
DAPT	723 (35.2%)	1023 (34.4%)	0.56
Insulin	630 (30.7%)	0 (0%)	<0.001
Rivaroxaban allocation (%)	1024 (49.9%)	1483 (49.9%)	0.98

ACEi/ARB, ACE inhibitor/angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASA, acetylsalicylic acid/aspirin; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

(N=2054, 40.6%) had a history of diagnosed diabetes (table 1). Those with diabetes compared with those without were more likely to be female (24.9% vs 21.5%) and had an increased prevalence of cardiovascular comorbidities: for example, hypertension (85.7% vs 68.1%), prior stroke (10.8% vs 7.8%), BMI ≥30 kg/m^2 (36.1% vs 23.7%), worse renal function with eGFR <60 mL/min/1.73m^2 (45.2% vs 34.3%) and anaemia (36.4% vs 26.8%). The proportion of participants with diabetes was greater in the Asia Pacific (16.6% vs 13.2%) and the Western Europe and South Africa region (11.3% vs 7.6%) whereas the proportion of participants with diabetes was less in Eastern Europe (57.8% vs 68.6%).

Heart failure severity

Heart failure severity was clinically well-balanced in people with and without diabetes; both groups had similar left ventricular ejection fractions (34% vs 34%) and median baseline values for NT-proBNP (2884 vs 2814 pg/mL). However, moderate differences were observed in functional classification. That is, 49.4% versus 55.2% of patients with and without diabetes, respectively, had an NYHA class between III and IV (ie, moderate to severe functional impairment). Nevertheless, the use of ACE inhibitors or angiotensin receptor blockers (91.8% vs 93.5%), mineralocorticoid receptor antagonists (73.6% vs 78.4%), beta-blockers (93.5% vs 91.7%), concomitant aspirin (92.9% vs 93.2%) and dual antiplatelet therapy (35.2% vs 34.4%) was similar in both groups. Data on glucagon-like-peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT-2i) use was not available as recruitment was prior to the inclusion of these therapies in the American Diabetes Association guidelines for diabetes care. Furthermore, randomisation was well-balanced as shown in table 1.

Diabetes and risk of cardiovascular and bleeding outcomes

With respect to cardiovascular outcomes, event-rates were generally higher among patients with versus without diabetes despite the moderate differences in functional classification (table 2). The adjusted HRs (aHRs) were 1.34 (95% CI 1.19 to 1.50) for the primary adjusted efficacy outcome of all-cause death, non-fatal MI or non-fatal stroke (16.23 vs 11.81 events per 100 patient-years), 1.24 (95% CI 1.13 to 1.37) for cardiovascular death or heart failure hospitalisation (27.56 vs 19.94 events per 100 patient-years), 1.51 (95% CI 1.14 to 1.99) for MI (3.03 vs 1.75 events per 100 patient-years) and 1.42 (95% CI 1.14 to 1.77) for heart failure death (4.41 vs 3.03 events per 100 patient-years). The event-rate for stroke was also numerically but not statistically significantly increased in patients with versus without diabetes: the aHR was 1.21 (95% CI 0.84 to 1.75; 1.49 vs 1.20 events per 100 patient-years). With respect to safety, there were no significant differences in ISTH defined major bleeding based on the presence or absence of diabetes (aHR 0.99; 95% CI 0.69 to 1.42).

Efficacy and safety outcomes based on randomisation

No significant interaction effects were observed when we evaluated the effect of diabetes on rivaroxaban treatment

Table 2 Efficacy and safety event-rates compared in patients with versus without diabetes mellitus

DM vs non-DM (2052 vs 2970)	DM present (event-rate per 100 persons-year)	DM absent (event-rate per 100 persons-year)	Crude HR (95% CI) DM yes vs no	Adjusted HR* (95% CI) DM yes vs no
Primary efficacy outcome†	16.23	11.81	1.36 (1.22 to 1.52)	1.34 (1.19 to 1.50)
CV death, MI, or stroke	14.30	10.23	1.38 (1.23 to 1.55)	1.38 (1.22 to 1.56)
All-cause death or HF hospitalisation	29.01	21.13	1.33 (1.21 to 1.45)	1.24 (1.13 to 1.36)
CV death or HF hospitalisation	27.56	19.94	1.33 (1.22 to 1.46)	1.24 (1.13 to 1.37)
All-cause death	13.42	9.83	1.35 (1.20 to 1.52)	1.35 (1.19 to 1.53)
CV death	11.38	8.24	1.37 (1.20 to 1.55)	1.30 (1.22 to 1.60)
MI	3.03	1.75	1.71 (1.31 to 2.24)	1.51 (1.14 to 1.99)
Stroke	1.49	1.2	1.21 (0.85 to 1.72)	1.21 (0.84 to 1.75)
Sudden cardiac death	4.70	3.76	1.24 (1.02 to 1.51)	1.35 (1.10 to 1.66)
HF death	4.41	3.03	1.43 (1.16 to 1.77)	1.42 (1.14 to 1.77)
HF hospitalisation	20.28	14.89	1.30 (1.17 to 1.45)	1.17 (1.05 to 1.31)
Non-HF CV hospitalisation	15.02	12.33	1.18 (1.05 to 1.33)	1.09 (0.96 to 1.23)
Principal safety outcome‡	0.47	0.38	1.19 (0.64 to 2.20)	1.06 (0.56 to 2.01)
ISTH major bleeding§	1.46	1.30	1.07 (0.76 to 1.52)	0.99 (0.69 to 1.42)

*Adjusted for age, sex, race, body mass index, NYHA class, blood pressure, history of myocardial infarction, history of stroke, history of coronary revascularisation, region.
†Composite outcome of all-cause death, non-fatal MI or non-fatal stroke,
‡Composite outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.
§ISTH definition: composite of fatal bleeding, or decrease in haemoglobin level of ≥20 g/L, or transfusion of ≥2 units of packed red cells or whole blood, or critical site bleeding).
CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction.

(figure 1; online supplemental table S1). With respect to the primary outcome, the risk of cardiovascular death, non-fatal MI or non-fatal stroke was similar in patients with and without diabetes (diabetes aHR 1.00, 95% CI 0.85 to 1.18; no diabetes aHR 0.90, 95% CI 0.77 to 1.04; interaction p value=0.32). Likewise, rivaroxaban was associated with reductions in ischaemic stroke in patients with and without diabetes (overall HR 0.66; 95% CI 0.47 to 0.95, diabetes aHR 0.66, 95% CI 0.38 to 1.12 (aARR 0.61%); no diabetes aHR 0.68, 95% CI 0.42 to 1.09 (aARR 0.47%); interaction p value=0.93). The p value for interaction based on the presence or absence of diabetes did not reach clinical significance for any of the remaining secondary and exploratory outcomes (eg, heart failure hospitalisation).

The absence of clinically significant interaction effects was also consistent with respect to the evaluated safety outcomes. There was no interaction between diagnosed diabetes and treatment on the principal safety outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability (diabetes aHR 0.81, 95% CI 0.32 to 2.06; no diabetes aHR 0.76, 95% CI 0.33 to 1.74; interaction p value=0.92). Similarly, the risk of major bleeding with rivaroxaban treatment as defined by the ISTH was similarly higher with and without diagnosed diabetes (diabetes aHR 1.79, 95% CI 1.03 to 3.09; no diabetes aHR 1.56, 95% CI 0.99 to 2.47; interaction p value=0.72).

DISCUSSION

In this post-hoc analysis of the COMMANDER-HF trial, 40% of patients had a previous diagnosis of diabetes which resulted in a more complex clinical presentation and increased risk of cardiovascular events. Patients with diabetes had a higher prevalence of comorbidities including hypertension, coronary revascularisation, stroke, anaemia and chronic kidney disease. The severity of heart failure seemed clinically well-balanced based on participants' left ventricular ejection fractions and circulating plasma natriuretic peptides; however, moderate to severe functional impairment was slightly less prevalent in people with diagnosed diabetes. Nevertheless, the risk of cardiovascular outcomes including the primary composite endpoint, heart failure hospitalisation and mortality were significantly increased in patients with versus without diabetes. Despite these findings, low-dose rivaroxaban did not have a modifier effect among

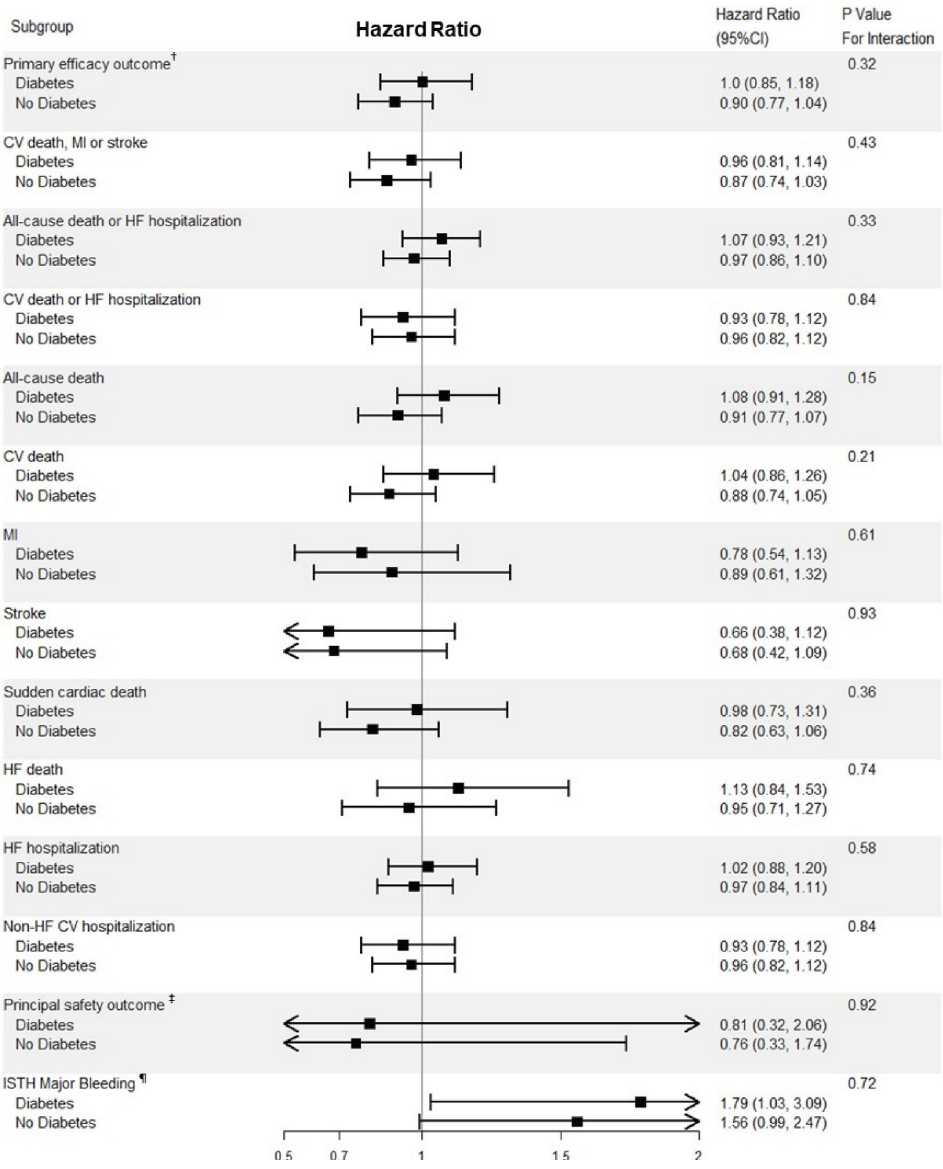

Figure 1 Forest plot for the interaction of rivaroxaban on efficacy and safety outcomes in patients with and without diabetes mellitus. All HRs are adjusted, and p values reflect the presence or absence of any interaction effects. *Adjusted for age, sex, race, body mass index, New York Heart Association class, blood pressure, history of myocardial infarction, history of stroke, history of coronary revascularisation, region. †Composite outcome of all-cause death, non-fatal MI or non-fatal stroke. ‡Composite outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. ¶ISTH definition: composite of fatal bleeding, or decrease in haemoglobin level of ≥20 g/L, or transfusion of ≥2 units of packed red cells or whole blood, or critical site bleeding. CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction.

diabetics on the composite end point. Rivaroxaban did, however, reduce the risk of ischaemic stroke in a similar manner irrespective of diabetes status.

Diabetes accelerates coronary, cerebrovascular and peripheral vascular atherosclerotic disease and increases the risk of thromboembolic events.[10–12] Diabetes is also an independent risk factor for heart failure hospitalisations and death.[13–15] The data in this analysis support these facts even though individuals diagnosed with diabetes in our analysis had a decreased prevalence of moderate and severe NYHA functional classification. Our data further demonstrated a trend towards an increased risk of ischaemic stroke in patients with versus without diabetes (crude HR 1.21, 95% CI 0.85 to 1.72; aHR 1.21, 95% CI 0.84 to 1.75). This finding is consistent with the results of larger studies that have shown prevalent diabetes is an independent risk factor for ischaemic stroke in people with heart failure.[16 17]

The beneficial therapeutic value of low-dose anticoagulation with respect to cardiovascular outcomes has been observed in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies), VOYAGER-PAD (Vascular Outcomes Study of acetylsalicylic acid Along with Rivaroxaban in Endovascular or Surgical Limb Revascularisation for Peripheral Artery Disease) and ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower

Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) trials, which suggests that there may be a coagulation mediated pathway that contributes to the risk of cardiovascular disease.

Diabetes also contributes to a pro-thrombotic state and carries some degree of residual risk despite glycaemic control and statin therapy in patients with and without heart failure.[14] Given the high risk of thrombotic events in patients with diabetes, the addition of low-dose anticoagulation may provide an effective strategy to reduce the burden of ischaemic stroke in patients with and without diabetes. Interestingly, a recent subgroup analysis of the COMPASS trial with respect to diabetes discovered that although cardiovascular absolute risk reductions (ARR) were nominally greater in patients with versus without diabetes, both subgroups derived similar relative benefit from rivaroxaban.[18] For instance, compared with placebo, rivaroxaban was associated with reduced the risk of major adverse cardioavscular in both patients with (HR 0.73, 95% CI 0.59 to 0.91, ARR 2.3%) and without (HR 0.77, 95% CI 0.64 to 0.93, ARR 1.4%) diabetes. While the COMMANDER-HF patient population is significantly different from the COMPASS patient population, the consistency in the stroke reduction highlights the possible therapeutic value of low-dose rivaroxaban in patients with diabetes and coronary artery disease. The CHA_2DS_2-VASc score, which has previously been shown to be predictive of stroke in COMMANDER-HF, might be used to identify patients who might derive the most benefit from low-dose rivaroxaban therapy.[8]

With respect to bleeding events both subgroups (ie, people with and without diabetes) were equally affected by the addition of rivaroxaban. For instance, rivaroxaban treatment increased the risk of major bleeding (according to the ISTH criteria) but did not increase the risk of severe bleeding (according to the principal safety outcome definition). It is important to highlight, however, that the COMMANDER-HF population had coronary artery disease and was thus treated with background antiplatelet therapy, which increases the risk of bleeding. The proportion of dual-antiplatelet therapy in the different arms could have influenced the results, however, the proportion of patients on dual-antiplatelet therapy was similar in patients with (35.2%) and without (34.4%) diabetes. Nevertheless, the long-term effects of antiplatelet therapy in patients with heart failure and coronary artery disease remains unclear and might warrant future research.[19 20]

This analysis includes some limitations that should be considered. First, it was a subgroup analysis that was not prespecified, and therefore not powered for efficacy or safety assessments. Therefore, any findings should be considered hypothesis generating, thus requiring further confirmation in prospective studies. Second, the definition for diabetes mellitus was only defined by baseline medical history, which may have restricted diagnostic sensitivity.[21 22] Furthermore, there was no additional data on duration, type, severity or control of diabetes mellitus that could be captured in this analysis. Third, data were not available on the use of GLP1-RA or SGLT-2i, which are now considered standard of care for patients with diabetes and cardiovascular disease. Consequently, whether the use of low-dose oral rivaroxaban has an interaction with the use of prognostic modifying agents (ie, GLP1-RA, SGLT-2i) remains unclear.[23] Finally, since the COMMANDER-HF trial only enrolled patients with reduced ejection fraction the findings may not be generalisable for patients with heart failure with preserved ejection fraction. However, this does not impact the internal validity of our findings.

CONCLUSION

This post-hoc analysis of the COMMANDER-HF trial demonstrated that in patients with worsening heart failure and underlying coronary artery disease, people with diabetes versus those without are at increased risk of cardiovascular outcomes. Moreover, the presence of diagnosed diabetes was not shown to interact with treatment to significantly modify the effects of low-dose rivaroxaban on secondary or exploratory cardiovascular events. Low-dose rivaroxaban was associated with lower risk of ischaemic stroke compared with placebo, regardless of diabetes status. Given the impact of ischaemic strokes on morbidity and mortality, future prospective trials assessing the possible therapeutic value of low-dose rivaroxaban in patients with diabetes with worsening heart failure with reduced ejection fraction may be warranted.

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REFERENCES

1 Sharma A, Zhao X, Hammill BG, *et al*. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure. *Circ Heart Failure* 2018;11:e004646.
2 Mega JL, Braunwald E, Wiviott SD, *et al*. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9–19.
3 Eikelboom JW, Connolly SJ, Bosch J, *et al*. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319–30.
4 Bonaca MP, Bauersachs RM, Hiatt WR. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020;382:1994–2004.
5 Branch KR, Probstfield JL, Eikelboom JW, *et al*. Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease. *Circulation* 2019;140:529–37.
6 Zannad F, Anker SD, Byra WM, *et al*. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018;379:1332–42.
7 Greenberg B, Neaton JD, Anker SD, *et al*. Association of rivaroxaban with thromboembolic events in patients with heart failure, coronary disease, and sinus rhythm: a post hoc analysis of the COMMANDER HF trial. *JAMA Cardiol* 2019;4:515–23.
8 Mehra MR, Vaduganathan M, Fu M, *et al*. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J* 2019;40:3593–602.
9 Zannad F, Greenberg B, Cleland JGF, *et al*. 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. *Eur J Heart Fail* 2015;17:735–42.
10 American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333–41.
11 Bhatt DL. Antiplatelet therapy following myocardial infarction in patients with diabetes. *JAMA* 2012;308:921–2.
12 Gutierrez JA, Scirica BM, Bonaca MP, *et al*. Prevalence and outcomes of polyvascular (coronary, peripheral, or cerebrovascular) disease in patients with diabetes mellitus (from the SAVOR-TIMI 53 trial). *Am J Cardiol* 2019;123:145–52.
13 Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the framingham study. *Am J Cardiol* 1974;34:29–34.
14 Dunlay SM, Givertz MM, Aguilar D, *et al*. Type 2 diabetes mellitus and heart failure: a scientific statement from the American heart association and the heart failure society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019;140:e294–324.
15 Greenberg BH, Abraham WT, Albert NM, *et al*. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF). *Am Heart J* 2007;154:277.
16 Tabata N, Yamamoto E, Hokimoto S, *et al*. Prognostic value of the $CHADS_2$ score for adverse cardiovascular events in coronary artery disease patients without atrial fibrillation-a multi-center observational cohort study. *J Am Heart Assoc* 2017;6:e006355.
17 Melgaard L, Gorst-Rasmussen A, Lane DA, *et al*. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;314:1030–8.
18 Bhatt DL, Eikelboom JW, Connolly SJ. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. *Circulation* 2020;141:1841–54.
19 Mujaj B, Zhang Z-Y, Yang W-Y, *et al*. Aspirin use is associated with increased risk for incident heart failure: a patient-level pooled analysis. *ESC Heart Fail* 2022;9:685–94.
20 Cleland JGF. Aspirin for primary and secondary prevention of cardiovascular disease: time to stop? *Thromb Haemost* 2022;122:311–4.
21 Cavagnolli G, Comerlato J, Comerlato C, *et al*. HbA(1C) measurement for the diagnosis of diabetes: is it enough? *Diabet Med* 2011;28:31–5.
22 Kramer CK, Araneta MRG, Barrett-Connor E. A1C and diabetes diagnosis: the rancho bernardo study. *Diabetes Care* 2010;33:101–3.
23 Sharma A, Pagidipati NJ, Califf RM, *et al*. Impact of regulatory guidance on evaluating cardiovascular risk of new glucose-lowering therapies to treat type 2 diabetes mellitus: lessons learned and future directions. *Circulation* 2020;141:843–62.