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RESEARCH ARTICLE

Plasma D-dimer concentrations predicting stroke risk and rivaroxaban benefit in patients with heart failure and sinus rhythm: an analysis from the COMMANDER-HF trial

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Aims D-dimer is a marker of fibrin degradation that reflects intravascular coagulation. Therefore, plasma concentrations of D-dimer might predict thromboembolic risk and rivaroxaban treatment effect. The aims of this study were to investigate the association between D-dimer levels and the risk of stroke and other thrombotic, bleeding and fatal events, and whether D-dimer concentrations could predict rivaroxaban 2.5 mg twice daily (vs. placebo) effect in patients enrolled in the COMMANDER-HF trial who were in sinus rhythm, had heart failure with reduced ejection fraction and coronary artery disease.

Methods and results Survival models with treatment-by-plasma D-dimer interaction. Baseline measurement of D-dimer was available in 4107 (82%) of 5022 patients enrolled. Median (percentile$_{25-75}$) follow-up was 21 (12.9–32.8) months. The median (percentile$_{25-75}$) plasma concentration of D-dimer was 360 (215–665) ng/mL. The D-dimer tertiles were: (i) ≤255 ng/mL; (ii) 256–515 ng/mL; and (iii) >515 ng/mL. Patients within the tertile 3 were older, and had lower body mass index, blood pressure, haemoglobin, estimated glomerular filtration rate, and left ventricular ejection fraction. Higher plasma D-dimer concentrations were independently associated with higher rates of death, stroke, and venous thromboembolism. For example, the all-cause death adjusted hazard ratio (HR) (95%CI) of tertile 3 vs. tertile 1 was 1.77 [95% confidence interval (CI) 1.48–2.11; $P < 0.001$]. The effect of rivaroxaban was similar in each tertile of D-dimer for all outcomes except stroke. Patients within the tertile 3 had the greatest absolute and relative stroke reduction (tertile 1: HR 1.16, 95% CI 0.49–2.74; tertile 2: HR 1.45, 95% CI 0.77–2.73; tertile 3: HR 0.36, 95% CI 0.18–0.70; P for interaction = 0.008). The number-needed-to-treat to prevent one stroke in tertile 3 was 36.

Conclusions In COMMANDER-HF, rivaroxaban reduced the risk of stroke but the benefit may be confined to patients with D-dimer concentrations above 515 ng/mL. Prospective trials are warranted to confirm these findings.

Keywords Rivaroxaban • D-dimer • Stroke • Treatment response

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Introduction

D-dimer is a marker of intravascular fibrin degradation formed by the action of thrombin (factor IIa), factor XIIIa, and plasmin.[1,2] Low plasma D-dimer concentrations effectively rule out major thromboembolic events whilst high concentrations are associated with various conditions including deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE), atrial fibrillation, stroke, coronary artery disease (CAD),[2–4] and cancer.[5]

In the COMMANDER-HF (Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease) trial, compared to placebo, rivaroxaban 2.5 mg twice daily in addition to background antiplatelet therapy did not reduce the rate of the primary outcome [a composite of first myocardial infarction (MI), stroke, or all-cause death]. Baseline plasma concentrations of D-dimer did not show any interaction with the effect of rivaroxaban on the primary endpoint.[6] In a post-hoc analysis, rivaroxaban reduced the rate of thrombotic events, especially stroke.[7,8] Whether plasma D-dimer concentrations predict the occurrence of ischaemic stroke and other cardiovascular outcomes, and the response to rivaroxaban has not been studied. We hypothesized that D-dimer could help in identifying patients at higher risk for intravascular coagulation and thromboembolic events, and thus selecting patients more prone to benefit from rivaroxaban treatment.

This analysis investigates the association between baseline plasma D-dimer concentrations with ischaemic stroke, and other thrombotic, bleeding, and fatal events, and whether D-dimer predicts the effects of rivaroxaban.

Methods

Study populations

COMMANDER-HF was an international, double-blind, randomized trial comparing the factor Xa inhibitor rivaroxaban (2.5 mg twice daily) vs. placebo. Key inclusion criteria included history of chronic heart failure (HF) for 3 or more months, left ventricular ejection fraction (LVEF) of ≤40%, history of CAD, absence of atrial fibrillation or other indication for chronic anticoagulation, and treatment for an episode of decompensated HF (i.e. the index event) within the previous 21 days. Decompensated HF was defined by symptoms of worsening dyspnoea or fatigue, objective signs of congestion, and/or adjustment of HF medications requiring hospital admission or unscheduled parenteral diuretic.[6,9]

Investigators reported outcomes on detailed case report forms, and the sponsor's clinical operations team verified the events using source data. All participants provided written informed consent. The protocol was approved by the appropriate institutional review board or ethics committee at each site.

Based on review of patient characteristics and the blinded event rate after 1155 patients had been enrolled, the steering committee amended the enrolment criteria to require a plasma concentration of N-terminal pro brain natriuretic peptide ≥800 ng/L or brain natriuretic peptide ≥200 ng/L at any time between the index admission for decompensated HF and randomization. Simultaneous with the amendment, enrolment in the Asia-Pacific region and several additional countries began.[6,10]

Study outcomes

In COMMANDER-HF the primary efficacy outcome was the composite of death from any cause, MI, or stroke. Secondary efficacy outcomes included death from cardiovascular causes, rehospitalization for worsening HF, rehospitalization for cardiovascular events, and the composite of death from cardiovascular causes or HF rehospitalization. Rivaroxaban did not reduce the incidence of the primary efficacy outcome nor HF rehospitalization; however, the incidence of stroke was reduced.[7] The principal safety outcome was the composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. Secondary safety outcomes included bleeding events requiring hospitalization and clinically overt major bleeding events as defined by the International Society on Thrombosis and Haemostasis (ISTH) [i.e. associated with a decrease in haemoglobin level of ≥2 g/dL, transfusion of ≥2 units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome].[6,10] The median follow-up duration was 21.1 months (percentile$_{25-75}$, 12.9–32.8).

D-dimer determination

Baseline plasma D-dimer concentrations were measured at a central laboratory using frozen (−20°C) citrated plasma with Siemens Healthcare Diagnostics INNOVANCE® D-dimer reagents. The intra- and inter-assay precision is 1.5 to 7.8 and 2.2% to 7.9% coefficient of variation, respectively. Among the 5022 patients enrolled in COMMANDER-HF, D-dimer levels were available in 4107 (82%).

Statistical analysis

The baseline characteristics of the population were compared across tertiles of plasma D-dimer concentrations using a *P*-value for trend comparison of means, medians or proportions (as appropriate). We have chosen to divide the D-dimer levels in tertiles to allow the comparison of tendencies across D-dimer levels and, simultaneously, preserve power to study subgroups, particularly regarding less frequent events (such as stroke). Number and proportion of events, person-time exposures and event rates (per 100 person-years) were computed across D-dimer tertiles. The risk associated with plasma D-dimer concentrations was explored in Cox models using D-dimer tertiles (with the lower D-dimer level tertile set as referent) and also using continuous restricted cubic splines with five knots. All models were adjusted for age, sex, race, diabetes, prior MI, stroke, percutaneous coronary intervention/coronary artery bypass grafting, New York Heart Association class, body mass index, systolic blood pressure, LVEF, estimated glomerular filtration rate (eGFR), anaemia, dual antiplatelet therapy, treatment allocation (rivaroxaban or placebo) and stratified on geographic region.[6] A treatment-by-D-dimer concentration interaction was tested in the survival models. Whenever the interaction was significant, the effect of treatment was furtherly explored by subgroups of D-dimer tertiles and also using log transformed plasma D-dimer concentrations (to maintain the log-linearity assumption). Cumulative incidence rates were computed using the Nelson–Aalen method. Absolute risk reduction and number needed to treat to benefit were also assessed. The predictive capacity of D-dimer was computed using the Somers' D method and compared with that of CHA_2DS_2-VASc and with a stroke risk score for patients without atrial fibrillation who had a high-risk MI – the HRMI stroke risk score.[11] We repeated some of the models (for events such as stroke) using a

competing risk approach as described by Fine and Gray with all-cause death set as a risk competitor.[12] We have also repeated the analysis using multiple imputation by chained equations (MICE) for the missing plasma D-dimer concentrations. The analyses were repeated across 10 imputed datasets. The proportional hazards assumption was tested by plotting the Schoenfeld residuals over time; the residuals were independent of time and no evidence of proportional hazards violation was found. A 2-sided *P*-value of <0.05 was considered significant. Stata® version 16 (StataCorp LLC, College Station, TX, USA) was used for the analysis.

Results

Patient characteristics by plasma D-dimer concentrations

The comparison of the patients in whom D-dimer levels were determined ($n = 4107$) vs. those in whom the D-dimer levels were not determined ($n = 915$) is depicted in the online supplementary *Table S1*. Patients with D-dimer levels available were slightly older (67 vs. 65 years) and less often from Eastern Europe (62.5% vs. 71.7%), but the majority of the characteristics were well balanced.

Among the 4107 patients with available D-dimer, the median (percentile$_{25-75}$) plasma D-dimer concentration was 360 (215–665) ng/mL. Three similarly distributed quantiles of plasma D-dimer concentrations were created: tertile 1 with plasma D-dimer concentrations ≤255 ng/mL and 1373 patients, tertile 2 with plasma D-dimer concentrations between 256 ng/mL and 515 ng/mL and 1365 patients, and tertile 3 with plasma D-dimer concentrations >515 ng/mL and 1369 patients. Patients with higher plasma D-dimer concentrations were older, had lower body mass index, blood pressure, haemoglobin, eGFR, LVEF, were less often from Eastern Europe, and less often had a prior MI (*Table 1*).

Events and event rates

Higher plasma D-dimer concentrations were independently associated with higher rates of the primary composite outcome, and higher rates of all-cause, cardiovascular and sudden death, HF rehospitalization, stroke of any cause, ischaemic stroke, and DVT/TEP. Higher D-dimer levels were also associated with a thromboembolic composite of MI, ischaemic stroke, sudden death and DVP/TEP. Bleeding and MI rates did not significantly differ by plasma D-dimer concentrations (*Table 2*, *Figure 1*).

Rivaroxaban effect

Rivaroxaban effect was homogeneous across D-dimer tertiles for all outcomes except stroke of any cause and ischaemic stroke. Patients in the third tertile of plasma D-dimer concentrations (>515 ng/mL) benefited from treatment with rivaroxaban for reducing all strokes, whereas patients with lower plasma D-dimer concentrations did not [tertile 1: hazard ratio (HR) 1.16, 95% confidence interval (CI) 0.49–2.74; tertile 2: HR 1.45, 95% CI 0.77–2.73; tertile 3: HR 0.36, 95% CI 0.18–0.70; *P* for interaction = 0.008]. The number needed to treat for patients in the third tertile was 36 (*Tables 2* and *3*, *Figure 2*). The treatment-by-D-dimer interaction remained statistically significant with D-dimer levels as a continuous log-transformed variable (*P* for interaction = 0.012) (*Figure 3*). Using the competing risk model, multiple imputations and bootstrap replications (x1000) gave similar results (online supplementary *Table S2*). Similar results were also found when removing patients who developed atrial fibrillation during the follow-up, of whom only five had a stroke. D-dimer alone provided higher predictive accuracy for the risk of stroke than the CHA_2DS_2-VASc or the HRMI stroke risk score [C-index for D-dimer alone: 0.64 (0.58–0.69); for CHA_2DS_2-VASc: 0.59 (0.54–0.64); for the stroke risk score: 0.56 (0.50–0.62)]. Moreover, these clinical scores did not predict the response to treatment (online supplementary Tables S3 and S4).

The main findings are summarized in the *Graphical Abstract*.

Discussion

Our results confirm the independent prognostic association of plasma D-dimer concentrations with adverse outcomes, particularly for fatal events where the association rose steeply even within the lowest tertile of plasma D-dimer concentrations and stabilized at the highest risk with plasma D-dimer concentrations around 500 ng/mL. The associations for DVT/PTE and bleeding were imprecise due to the low number of events. Interestingly, D-dimer concentrations were not associated with MI risk. Importantly, only patients with higher plasma D-dimer concentrations (above ≈500 ng/mL) appeared to benefit from rivaroxaban for stroke reduction, with a substantial magnitude of relative and absolute benefit.

A D-dimer level <250 ng/mL has a high predictive value for ruling out DVT/PTE,[13] and many authors even consider a higher cut-off (up to 500 ng/mL) for ruling out DVT/PTE.[14] However, in COMMANDER-HF the risk of all-cause and cardiovascular death increased steeply with plasma D-dimer concentrations >100 ng/mL, which might have been driven by HF rehospitalizations (as discussed below). The risk increment of fatal events was linear up to 500 ng/mL, where the risk association reached a plateau. These results were different from those observed for stroke where the associations were present only at higher D-dimer levels, while no statistically significant association was observed between D-dimer concentration and MI. There were few DVT/PTE and bleeding events, and the associations were imprecise, but they suggest that higher plasma D-dimer concentrations may also be associated with the occurrence of these events. The findings above described are interesting *per se*, and may suggest different pathophysiological mechanisms for different events.

Heart failure, a condition present in all COMMANDER-HF patients is, in itself, an hypercoagulable state that may both increase D-dimer and thrombotic events.[8,15] Along with HF rehospitalization, the all-cause and cardiovascular death risk were higher even for plasma D-dimer concentrations within the 'normal' range (<250 ng/mL). HF rehospitalization was by far the most common outcome event in COMMANDER-HF and hospitalized patients

Table 1 Patient characteristics by tertiles of plasma D-dimer concentrations ($n = 4107$)

Characteristic	D-dimer tertiles (ng/mL)			*P*-value
	≤255	256–515	>515	
Patients, *n*	1373	1365	1369	
Age, years	63 (57–69)	68 (60–75)	70 (62–77)	<0.001
Age ≥65 years	596 (43.4%)	841 (61.6%)	931 (68.0%)	<0.001
Men	1088 (79.2%)	1042 (76.3%)	1029 (75.2%)	0.033
Region				
Eastern Europe	962 (70.1%)	861 (63.1%)	745 (54.4%)	<0.001
Western Europe and South Africa	72 (5.2%)	137 (10.0%)	171 (12.5%)	
North America	26 (1.9%)	42 (3.1%)	47 (3.4%)	
Asia-Pacific	213 (15.5%)	206 (15.1%)	255 (18.6%)	
Latin America	100 (7.3%)	119 (8.7%)	151 (11.0%)	
Race				
White	1134 (82.6%)	1122 (82.2%)	1062 (77.6%)	<0.001
Black	5 (0.4%)	16 (1.2%)	23 (1.7%)	
Asian	211 (15.4%)	205 (15.0%)	249 (18.2%)	
Other	23 (1.7%)	22 (1.6%)	35 (2.6%)	
Diabetes	547 (39.8%)	591 (43.3%)	559 (40.8%)	0.17
Hypertension	1024 (74.6%)	1043 (76.4%)	1027 (75.0%)	0.51
Myocardial Infarction	1081 (78.7%)	1017 (74.5%)	989 (72.2%)	<0.001
Stroke	107 (7.8%)	133 (9.7%)	140 (10.2%)	0.066
ACEi/ARB	1298 (94.5%)	1273 (93.3%)	1238 (90.4%)	<0.001
MRA	1076 (78.4%)	1035 (75.8%)	1026 (74.9%)	0.090
ARNI	6 (0.4%)	17 (1.2%)	9 (0.7%)	0.045
Beta-blocker	1287 (93.7%)	1264 (92.6%)	1234 (90.1%)	0.002
Diuretic	1364 (99.3%)	1358 (99.5%)	1366 (99.8%)	0.23
Digoxin	130 (9.5%)	123 (9.0%)	131 (9.6%)	0.87
Aspirin	1294 (94.2%)	1270 (93.0%)	1256 (91.7%)	0.037
DAPT	501 (36.5%)	478 (35.0%)	449 (32.8%)	0.17
PCI or CABG	846 (61.6%)	865 (63.4%)	858 (62.7%)	0.63
Cardiac device	9 (0.7%)	22 (1.6%)	42 (3.1%)	<0.001
NYHA class				
I	36 (2.6%)	42 (3.1%)	54 (3.9%)	0.013
II	566 (41.2%)	613 (44.9%)	639 (46.7%)	
III	709 (51.6%)	660 (48.4%)	617 (45.1%)	
IV	62 (4.5%)	50 (3.7%)	59 (4.3%)	
BMI, kg/m^2	28.2 ± 5.1	27.9 ± 5.2	26.7 ± 5.1	<0.001
BMI categories				
<25	385 (28.0%)	414 (30.4%)	577 (42.2%)	<0.001
25–29.9	540 (39.3%)	563 (41.3%)	468 (34.3%)	
≥30	448 (32.6%)	387 (28.4%)	321 (23.5%)	
SBP, mmHg	124 ± 15	123 ± 16	120 ± 16	<0.001
DBP, mmHg	75 ± 9	73 ± 9.7	72 ± 10	<0.001
D-dimer, ng/mL	180 (145–215)	360 (305–430)	880 (665–1425)	
Haemoglobin, g/dL	13.9 ± 1.6	13.4 ± 1.7	13.0 ± 1.9	<0.001
Anaemia	284 (20.7%)	447 (32.7%)	562 (41.1%)	<0.001
eGFR, mL/min/1.73 m^2	74 ± 24	67 ± 22	63 ± 23	<0.001
eGFR categories				
<30	25 (1.8%)	44 (3.2%)	65 (4.7%)	<0.001
30–59.9	362 (26.4%)	502 (36.8%)	619 (45.2%)	
60–89.9	681 (49.6%)	617 (45.2%)	513 (37.5%)	
≥90	305 (22.2%)	202 (14.8%)	172 (12.6%)	
BNP, pg/mL	552 (314–987)	722 (424–1256)	795 (445–1440)	<0.001
NT-proBNP, pg/mL	2385 (1312–4749)	2884.0 (1470.0–6360.0)	3437.0 (1865.0–7927.0)	<0.001
LVEF, %	35 (30.0–38.0)	34.0 (28.0–38.0)	32.0 (25.0–37.0)	<0.001
LVEF ≤35%	736 (53.6%)	852 (62.4%)	934 (68.2%)	<0.001
Rivaroxaban allocation	679 (49.5%)	657 (48.1%)	701 (51.2%)	0.27

The proportion of missing values was low (<1%) except for BNP and NT-proBNP that had 80% and 42% of missing values, respectively.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; DAPT, dual anti-platelet 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; SBP, systolic blood pressure.

Table 2 Events and event rates

D-dimer tertiles (ng/mL)	Events (%)	Event rate (per 100 py)	Adj. HR (95% CI)	*P*-value	Interaction *P*[*]
MI, stroke, all-cause death					
≤255 (*n* = 1373)	242 (17.6)	8.5 (7.5–9.7)	Ref.		
256–515 (*n* = 1365)	371 (27.2)	14.5 (13.1–16.0)	1.50 (1.27–1.77)	<0.001	0.41
>515 (*n* = 1369)	444 (32.4)	18.7 (17.1–20.5)	1.72 (1.46–2.02)	<0.001	
MI, stroke, CV death					
≤255 (*n* = 1373)	216 (15.7)	7.6 (6.7–8.7)	Ref.		
256–515 (*n* = 1365)	329 (24.1)	12.8 (11.5–14.3)	1.51 (1.27–1.80)	<0.001	0.44
>515 (*n* = 1369)	376 (27.5)	15.9 (14.3–17.5)	1.67 (1.40–1.99)	<0.001	
MI					
≤255 (*n* = 1373)	46 (3.4)	1.6 (1.2–2.1)	Ref.		
256–515 (*n* = 1365)	61 (4.5)	2.3 (1.8–3.0)	1.27 (0.86–1.88)	0.23	0.78
>515 (*n* = 1369)	66 (4.8)	2.7 (2.1–3.5)	1.31 (0.88–1.95)	0.88	
Stroke (all)					
≤255 (*n* = 1373)	21 (1.5)	0.7 (0.5–1.1)	Ref.		
256–515 (*n* = 1365)	39 (2.9)	1.5 (1.1–2.0)	1.99 (1.16–3.41)	0.013	0.008
>515 (*n* = 1369)	42 (3.1)	1.7 (1.3–2.4)	2.22 (1.28–3.85)	0.004	
Ischaemic stroke					
≤255 (*n* = 1373)	18 (1.3)	0.6 (0.4–1.0)	Ref.		
256–515 (*n* = 1365)	34 (2.5)	1.3 (0.9–1.8)	2.00 (1.14–3.64)	0.017	0.017
>515 (*n* = 1369)	34 (2.5)	1.4 (1.0–2.0)	2.12 (1.16–3.86)	0.014	
Haemorrhagic stroke					
≤255 (*n* = 1373)	3 (0.2)	0.1 (0.0–0.3)	Ref.		
256–515 (*n* = 1365)	5 (0.4)	0.2 (0.1–0.5)	1.60 (0.37–6.95)	0.53	0.36
>515 (*n* = 1369)	8 (0.6)	0.3 (0.2–0.7)	2.63 (0.65–10.7)	0.18	
DVT/PTE					
≤255 (*n* = 1373)	2 (0.2)	0.1 (0.0–0.3)	Ref.		
256–515 (*n* = 1365)	8 (0.6)	0.3 (0.2–0.6)	4.32 (0.91–20.6)	0.066	0.30
>515 (*n* = 1369)	16 (1.2)	0.7 (0.4–1.1)	9.46 (2.11–42.5)	0.003	
CV death					
≤255 (*n* = 1373)	174 (12.7)	6.0 (5.1–6.9)	Ref.		
256–515 (*n* = 1365)	271 (19.9)	10.2 (9.0–11.5)	1.52 (1.25–1.84)	<0.001	0.66
>515 (*n* = 1369)	322 (23.5)	13.1 (11.8–14.6)	1.73 (1.42–2.10)	<0.001	
All-cause death					
≤255 (*n* = 1373)	202 (14.7)	6.9 (6.0–8.0)	Ref.		
256–515 (*n* = 1365)	316 (23.2)	11.9 (10.6–13.2)	1.50 (1.25–1.80)	<0.001	0.64
>515 (*n* = 1369)	392 (28.6)	16.0 (14.5–17.6)	1.77 (1.48–2.11)	<0.001	
Sudden cardiac death					
≤255 (*n* = 1373)	90 (6.6)	3.1 (2.5–3.8)	Ref.		
256–515 (*n* = 1365)	128 (9.4)	4.8 (4.0–5.7)	1.53 (1.16–2.02)	0.002	0.77
>515 (*n* = 1369)	117 (8.6)	4.8 (4.0–5.7)	1.43 (1.07–1.91)	0.015	
Thrombotic composite[a]					
≤255 (*n* = 1373)	153 (11.1)	5.4 (4.6–6.3)	Ref.		
256–515 (*n* = 1365)	220 (16.1)	8.6 (7.5–9.8)	1.52 (1.24–1.88)	<0.001	0.48
>515 (*n* = 1369)	215 (15.7)	9.1 (8.0–10.4)	1.52 (1.22–1.88)	<0.001	
HF rehospitalization					
≤255 (*n* = 1373)	300 (21.9)	12.0 (10.7–13.4)	Ref.		
256–515 (*n* = 1365)	382 (28.0)	17.3 (15.7–19.2)	1.26 (1.08–1.47)	0.004	0.94
>515 (*n* = 1369)	462 (33.8)	23.9 (21.9–26.2)	1.48 (1.27–1.72)	<0.001	
Bleeding safety main					
≤255 (*n* = 1373)	10 (0.7)	0.3 (0.2–0.6)	Ref.		
256–515 (*n* = 1365)	10 (0.7)	0.4 (0.2–0.7)	0.91 (0.37–2.21)	0.82	0.95
>515 (*n* = 1369)	15 (1.1)	0.6 (0.4–1.0)	1.23 (0.52–2.91)	0.64	
Bleeding ISTH major					
≤255 (*n* = 1373)	25 (1.8)	0.9 (0.6–1.3)	Ref.		
256–515 (*n* = 1365)	36 (2.6)	1.4 (1.0–1.9)	1.25 (0.75–2.11)	0.39	0.87
>515 (*n* = 1369)	51 (3.7)	2.1 (1.6–2.8)	1.50 (0.91–2.48)	0.12	
Bleeding hospitalization					
≤255 (*n* = 1373)	18 (1.3)	0.6 (0.4–1.0)	Ref.		
256–515 (*n* = 1365)	29 (2.1)	1.1 (0.8–1.6)	1.35 (0.74–2.45)	0.33	0.34
>515 (*n* = 1369)	44 (3.2)	1.8 (1.4–2.5)	1.70 (0.95–3.03)	0.073	

CI, confidence interval; CV, cardiovascular; DVT, deep venous thrombosis; HF, heart failure; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis: major bleeding is defined by the ISTH as overt bleeding associated with a decrease in haemoglobin level of at least 2 g/dL, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome; MI, myocardial infarction; PTE, pulmonary thromboembolism; py, person-years.
[a]The thrombotic composite included a MI, ischaemic stroke, sudden/unwitnessed death, symptomatic pulmonary embolism, or symptomatic DVT as used by Greenberg *et al.*[8]
*Treatment-by-D-dimer tertile interaction term for each outcome.

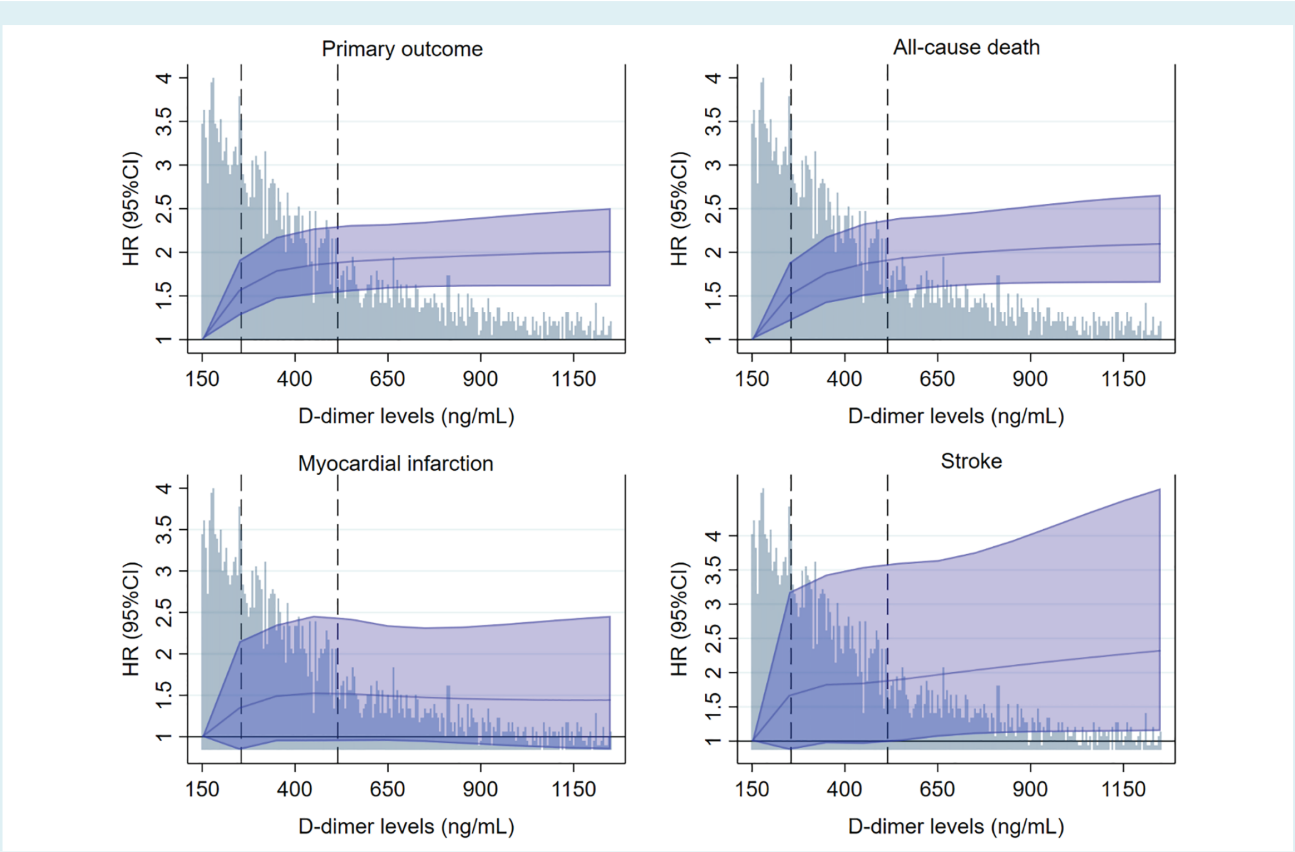

Figure 1 Continuous spline representation of the association between plasma D-dimer concentrations and the risk of various clinical outcomes. CI, confidence interval; HR, hazard ratio. The primary outcome was a composite of myocardial infarction, stroke or all-cause death. The background ('grey') histogram represents the D-dimer concentration in ng/mL. The vertical 'dashed' bars mark the values for the D-dimer tertiles.

Table 3 Treatment effect on stroke by tertiles of plasma D-dimer concentrations

D-dimer tertiles (ng/mL)	Events		HR (95% CI)	*P*-value	ARR	NNT
	Rivaroxaban	Placebo				
≤255 (n = 1373)	11 (1.6%)	10 (1.4%)	1.16 (0.49–2.74)	0.73	0.18 (−1.12 to 1.48)	558
256–515 (n = 1365)	22 (3.4%)	17 (2.4%)	1.45 (0.77–2.73)	0.26	0.95 (−0.82 to 2.73)	106
>515 (n = 1369)	12 (1.7%)	30 (4.5%)	0.36 (0.18–0.7)	0.003	−2.78 (−4.62 to −0.94)	36

The C-index of the model with D-dimer alone is 0.64 (0.58–0.69).
ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.

may present slightly elevated plasma D-dimer concentrations and have a high risk of dying, which might explain why relatively low plasma D-dimer concentrations were associated with fatal events.[15,16] In a post-hoc analysis of the ARISTOTLE trial, higher plasma D-dimer concentrations were independently associated with increased risk of stroke/systemic embolic events, all-cause and cardiovascular death, and major bleeds.[17] Higher plasma D-dimer concentrations were also associated with adverse outcomes in sub-studies of the ATLAS ACS-TIMI 46 and RE-LY trials.[4,18] Regarding stroke, in COMMANDER-HF an ischaemic event was by far the most frequent (82%) form of stroke[7], meaning that many of these patients could have undetected paroxysmal atrial fibrillation, a patent foramen ovale, or a left intraventricular (or atrial) thrombi, that increased the ischaemic stroke but not the MI risk. It is also possible that some of these patients had undiagnosed cancer or other pro-thrombotic conditions (e.g. factor V Leiden or other mutations, used certain pro-thrombotic drugs, or had low mobility) leading to a hypercoagulable state that could increase the risk of stroke and systemic embolism. It should be noted that atrial fibrillation and cancer are also conditions that can raise the plasma D-dimer concentrations way above normal and thus may explain both the high event risk and plasma

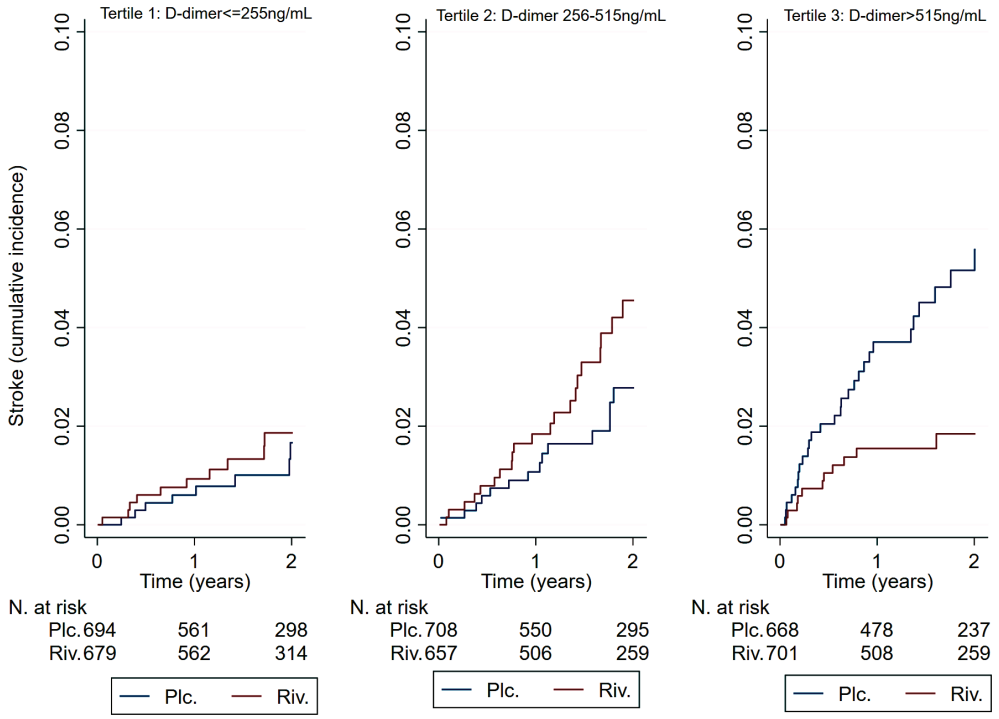

Figure 2 Treatment effect on stroke by tertiles of plasma D-dimer concentrations. Plc., placebo; Riv., rivaroxaban.

D-dimer concentrations.[5,19] Furthermore, in an observational study, plasma D-dimer concentrations were disproportionally elevated in patients with cardioembolic stroke (vs. small or large vessel occlusion and other forms of stroke) with an optimal cut-off for diagnosis around 1800 ng/mL[3], much superior than the cut-off found in our study, suggesting that patients at risk for embolic stroke may have ongoing clot formation with high fibrin turnover which may serve as substrate for the action of rivaroxaban.

Even more interesting and unique was the finding that plasma D-dimer concentrations were associated with a better response to rivaroxaban for stroke reduction. It is plausible that the interaction might be mediated by D-dimer, where higher levels could identify both patients at high risk for stroke and with a hypercoagulable state with 'fibrin-rich' clot formation serving as substrate for the action of rivaroxaban. Given the low doses used in COMMANDER-HF, the bleeding event rates were overall low and rivaroxaban effect on bleeding was not influenced by plasma D-dimer concentrations; thus, providing an optimal stroke-bleeding trade-off profile. The present results support the hypothesis that patients with CAD, HF, reduced ejection fraction and sinus rhythm may benefit from low dose rivaroxaban for stroke prevention when plasma D-dimer concentrations are elevated. In COMPASS (Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease),[20] regimens containing rivaroxaban (with or without aspirin) also reduced stroke but not MI, supporting the fibrin clot embolic hypothesis, rather than a local 'anti-thrombotic' effect. Similar analysis stratified by plasma D-dimer concentrations was not provided in COMPASS where only 12% of the patients had HF with reduced ejection fraction (HFrEF),[21] and the COMPASS results may not apply to patients with the characteristics of those in COMMANDER-HF who had symptomatic HFrEF with a recent decompensation. Thus, these hypothesis-generating data suggest that plasma D-dimer concentrations may help in better identifying patients with HF and CAD in sinus rhythm who may benefit from low-dose rivaroxaban for stroke prevention. Such a hypothesis may be worth testing in a dedicated trial.

Limitations

Several limitations should be acknowledged in this study. This is a post-hoc analysis of the COMMANDER-HF trial and the interaction by plasma D-dimer concentrations was prespecified for the primary outcome but not for stroke alone; therefore, these findings should be regarded as hypothesis-generating. Moreover, we have performed several non-prespecified interaction tests and it is possible that the significant interaction observed for stroke is a chance finding. No linear dose–response association between D-dimer levels and rivaroxaban benefit on stroke was observed, which may limit the biological plausibility of our findings. Stroke (cause-specific death and other non-fatal events) lacked formal independent adjudication by a clinical events committee and instead relied on site investigator-based event adjudication. However, data collection to support site adjudication was carefully performed. As cerebral imaging was not uniformly available, we used stroke from any cause as the main studied outcome, but the results remained similar when using only strokes classified as ischaemic. The bleeding

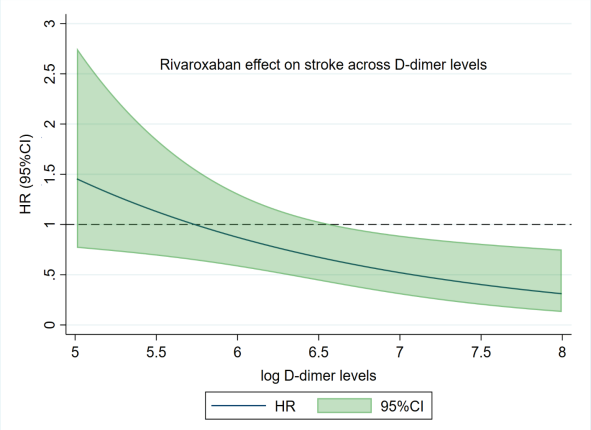

Figure 3 Association between plasma D-dimer concentration (log transformed) and the effect of rivaroxaban compared to placebo on the risk of stroke. CI, confidence interval; HR, hazard ratio. *P* for interaction with continuous log D-dimer = 0.012. The D-dimer concentration was log transformed to meet the proportional hazards assumptions. To revert the natural log to the absolute number, the exponential needs to be computed. A log D-dimer of 5.5, 6.0, 6.5, 7.0, and 7.5 is equal to a D-dimer concentration of 245, 403, 665, 1097 and 1808 ng/mL, respectively.

and DVT/PTE rates were low, which affected the precision around the association of the plasma D-dimer concentrations with these events. Despite the adjustment performed using several variables with prognostic value, we cannot eliminate residual confounding in the associations reported in this manuscript.

Conclusion

In COMMANDER-HF, rivaroxaban reduced the risk of stroke but the benefit may be confined to patients with D-dimer concentrations above 515 ng/mL. These findings are hypothesis-generating and prospective trials are warranted to confirm whether D-dimer concentrations may be used to predict the effect of rivaroxaban.

Supplementary Information

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

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Conflict of interest: J.P.F. has received consulting fees from Boheringer Ingelheim. M.R.M. reports consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, Roivant, Baim Institute for Clinical Research and Triple Gene. B.G. is co-PI of COMMANDER-HF, Consultant for Actelion, Akcea, Amgen, Bayer, EBR Sustems, Ionis, Janssen, Myokardia, Novartis, Relypsa, Rocket, Sanofi, Viking and Zensun. All other authors have nothing to disclose.

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