



HAL
open science

High risk of stroke in patients with worsening heart failure, reduced ejection fraction, coronary heart disease and sinus rhythm

Luca Monzo, Nicolas Girerd, João Pedro Ferreira, Zohra Lamiral, Stefan D. Anker, John G.F. Cleland, Toru Kondo, John J.V. McMurray, Carolyn S.P. Lam, Mandeep R. Mehra, et al.

► To cite this version:

Luca Monzo, Nicolas Girerd, João Pedro Ferreira, Zohra Lamiral, Stefan D. Anker, et al.. High risk of stroke in patients with worsening heart failure, reduced ejection fraction, coronary heart disease and sinus rhythm. *Journal of Cardiac Failure*, 2023, 10.1016/j.cardfail.2023.11.020 . hal-04361354

HAL Id: hal-04361354

<https://hal.univ-lorraine.fr/hal-04361354v1>

Submitted on 22 Dec 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

High risk of stroke in patients with worsening heart failure, reduced ejection fraction, coronary heart disease and sinus rhythm: Risk prediction score analysis from the COMMANDER-HF trial

Luca Monzo,¹ Nicolas Girerd,¹ João Pedro Ferreira,^{1,2} Zohra Lamiral,¹ Stefan D. Anker,³ John G. F. Cleland,⁴ Toru Kondo,^{4,5} John J.V. McMurray,⁴ Carolyn S. P. Lam,^{6,7} Mandeep R. Mehra,⁸ Dirk J. van Veldhuisen,⁹ Barry Greenberg,¹⁰ and Faiez Zannad¹

¹Université de Lorraine, Centre d'Investigations Cliniques Plurithématique 1433 and Inserm U1116, CHRU Nancy, FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; ²Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Portugal; ³Department of Cardiology and Berlin-Brandenburg Center for Regenerative Therapies, German Center for Cardiovascular Research partner site Berlin, Charité Universitätsmedizin Berlin, Berlin; ⁴British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK; ⁵Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; ⁶National Heart Centre Singapore, Duke-National University of Singapore, Singapore; ⁷Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁸Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; ⁹Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ¹⁰Cardiology Division, Department of Medicine, University of California, San Diego, CA, USA.

Corresponding author: Faiez Zannad, Clinical Investigation Center, INSERM, Institut Lorrain du Coeur et des Vaisseaux, F-54500, Vandoeuvre-lès-Nancy, France; email: f.zannad@chru-nancy.fr

Short title: Stroke prediction in HFrEF

Word count: 1485

A proposed tweet: Are all tools equal for predicting risk of stroke in HFrEF patients with sinus rhythm? Different clinical settings can affect the accuracy of prediction scores and possible benefit of anticoagulants @LucaMonzo @NicolasGirerd @FaiezZANNAD @lamcardio @CiCPNancy

Conflict of interest

L.M. has received lecture fees from AstraZeneca and Vifor. N.G. has received personal fees from AstraZeneca, Bayer, Boehringer, Lilly, Novartis, Roche Diagnostics, Vifor Pharma. J.P.F. has received consulting fees from Boehringer Ingelheim. S.A. has received grants and personal fees from Abbott Vascular and Vifor; and has received personal fees from Bayer, Boehringer Ingelheim, Brahms GmbH, Cardiac Dimensions, Cordio, Novartis, and Servier. J.G.F.C. has received personal fees from Janssen Research & Development LLC as a member of the steering committee of the COMMANDER HF trial; and has received grants and honoraria for speaking, committees, and advisory boards from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Medtronic, MyoKardia, Novartis, Philips Healthcare, Pharmacosmos, Pharma Nord, Sanofi, Laboratoires Servier, Stealth BioTherapeutics, Torrent Pharmaceuticals, and Vifor Pharma. T.K. has received lecture fees from Ono Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Novartis Pharma K.K., AstraZeneca K.K., Bristol-Myers Squibb Co., Abiomed Japan K.K., and Boehringer Ingelheim. J.J.V.M. has received payments through Glasgow University from work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer,

Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, DalCor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos Personal lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, Global Clinical Trial Partners (GCTP). C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder and non-executive director of eKo.ai. M.R.M. has consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, Roivant, Baim Institute for Clinical Research and Triple Gene. D.J.v.V. has received fees for serving on a steering committee and travel support from ARCA biopharma and Corvia Medical. B.G. has received personal fees from Novartis, Janssen, Sanofi, Mesoblast, Zensun, Cellular Dynamics, MyoKardia, Bayer, Actelion, Viking, Amgen, Akcea, EBR System, IONIS, and Tenaya; and was co-chair of the COMMANDER-HF steering committee. F.Z. has received personal fees from Boehringer Ingelheim, Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer, Cellprothera, CVCT and Cardiorenal. All other authors report no disclosures.

Funding

The COMMANDER-HF trial was supported by Janssen Research and Development. T.K. receives grants from the Uehara Memorial Foundation and the Japanese Heart Failure Society Tsuchiya Foundation for research activity at the University of Glasgow.

Abstract

Background Patients with heart failure, reduced ejection fraction (HFrEF) and sinus rhythm have a heightened risk of stroke. Whether anticoagulation benefits these patients is uncertain. In this post-hoc analysis of COMMANDER-HF trial we evaluated how a previously validated risk model consisting of three variables (history of prior stroke, insulin-treated diabetes, and NTproBNP) would perform, compared to plasma D-dimer, for stroke prediction and estimation of the benefit of low-dose rivaroxaban.

Methods and results Stroke risk and treatment effect were computed across risk score and plasma D-dimer tertiles. Risk score was available in 2,928 (58%) of the COMMANDER-HF population. Over a median follow-up of 512 (342-747) days, 60 patients experienced a stroke (14.6 per 1000 patient-years). The risk model did not identify patients at higher risk of stroke and showed a low overall prognostic performance (C-index=0.53). The effect of rivaroxaban on stroke was homogeneous across risk score tertiles (P-interaction=0.67). Among patients in whom the risk score was estimated, D-dimer was available in 2,343 (80%). D-dimer had an acceptable performance for stroke prediction (C-index=0.66) and higher plasma D-dimer concentrations were associated with higher rates of stroke (i.e. T3 vs. T1, HR 3.65 [95%CI 1.59-8.39], P=0.002). Treatment with low-dose rivaroxaban reduced the incidence of stroke in patients at highest risk by D-dimer levels (i.e. >515 ng/mL; HR 0.42 [95%CI 0.18-0.95], P-interaction=0.074), without any safety concern.

Conclusions In our analysis, plasma D-dimer concentrations performed better than a previously described three-variable risk score for stroke prediction in patients with HFrEF, a recent clinical worsening and sinus rhythm as enrolled in the COMMANDER-HF trial. In these patients, a raised plasma D-dimer concentration identified patients who might benefit most from rivaroxaban.

Keywords: Stroke; risk score; HFrEF; COMMANDER-HF; sinus rhythm; D-dimer

Introduction

Atrial fibrillation increases the risk of stroke in the general population and in patients with heart failure (HF). However, stroke also occurs in HF patients in sinus rhythm [1]. Blood stasis, secondary to low cardiac output, atrial and ventricular remodelling, venous dilatation, an altered haemostatic profile and atherosclerotic arterial disease fulfil the criteria for Virchow's triad in patients with HF and a reduced left ventricular ejection fraction (HFrEF) [2]. The constellation of these structural and physiological alterations lead to a prothrombotic state that heightened the risk of arterial and venous thromboembolic events, including stroke. Despite this promising rationale for the use of anticoagulant therapy in HF, low dose rivaroxaban (2.5 mg twice daily) in the COMMANDER-HF trial (N=5,022, HFrEF, coronary artery disease, and sinus rhythm) did not reduce the composite of first occurrence of death, stroke, or myocardial infarction compared to placebo over a median follow-up of 21 months [3]. In post hoc analysis, rivaroxaban significantly reduced the risk of stroke by 36% (HR 0.64, 95% CI 0.43–0.95) [4], and of all-cause stroke or TIA by 32% (HR 0.68, 95% CI 0.49–0.94) [5] compared with placebo, but at a cost of increased non-fatal bleeding. Identifying a subgroup of HFrEF patients at sufficiently high risk of stroke might provide a favourable benefit-to-risk balance for prophylactic anticoagulation. In a recent pooled patient-level cohort of the PARADIGM-HF, ATMOSPHERE, and DAPA-HF trials, including 12,751 ambulatory patients with HFrEF and sinus rhythm, Kondo et al. explored the predictive value of a simple risk model for stroke, consisting of three variables (history of prior stroke, insulin-treated diabetes, and plasma N-terminal pro-B-type natriuretic peptide level [NTproBNP]). The risk model successfully identified HF patients in sinus rhythm at higher risk of stroke (i.e. fifth quintile vs. first quintile: HR 3.73 [95% CI 2.58–5.38]), providing a good discrimination (C-index 0.84) [6]. Authors postulated that in this high-risk subgroup, prophylactic anticoagulation might have a beneficial risk/benefit ratio for stroke prevention. Our group has also demonstrated that patients from the COMMANDER-HF trial, with worsening HF, reduced ejection fraction, coronary heart disease and sinus rhythm at higher risk of stroke, defined as a D-dimer level >515 ng/mL, may

derive benefit from anticoagulation. Indeed, in this subgroup rivaroxaban significantly reduced the risk of stroke by 64% [7]. The aim of the present analysis was to evaluate how the risk model previously developed [8] and then deployed by Kondo et al. [6] would perform, compared to the D-dimer based risk score, for stroke prediction and estimation of the benefit of low-dose rivaroxaban in the COMMANDER-HF population.

Methods

Only patients with available measurement for the three components of Kondo et al's stroke risk model were included. The risk score was calculated as previously described by the equation: (history of previous stroke) \times 6.53 + (insulin-treated diabetes) \times 7.39 + [logNTproBNP (pmol/L)] \times 2.80 [8]. We divided the COMMANDER-HF population according to tertiles of risk model score and D-dimer concentration, in order to allow the comparison of trends across different groups and maintain statistical power for the analysis of non-frequent events such as stroke. Notably, we decided to mirror D-dimer tertiles' distribution as previously described by our group, where a concentration in the upper tier was associated with a higher risk of stroke but also with an increased benefit from rivaroxaban treatment [7]. The incidence rate of stroke (per 1000 patient-years) was calculated during the trial follow-up period. The overall C-index for risk model and D-dimer was estimated. Cox models were utilized to evaluate the risk of stroke across tertiles of Kondo et al's risk score and plasma D-dimer (with the lower tertile set as referent). The effect of low-dose rivaroxaban on the risk of stroke was evaluated by assessing treatment interactions across tertiles in the two risk models. A 2-sided P-value of <0.05 was considered significant. All analyses were performed using SAS version 9.4 (TS1M1) (SAS Institute Inc., Cary, N.C., USA).

Results

The set of variables needed to estimate Kondo et al's risk score was available in 2,928 (58%) of the 5,022 patients enrolled in COMMANDER-HF (main reason for exclusion was unavailability of

NTproBNP). Baseline clinical characteristics of the study population are depicted in **Table 1**. The median (percentile_{25 - 75}) risk score was 17.4 (14.9-20.7). Three similarly distributed risk score quantiles were defined: tertile 1 (T1) <15.7 (N=965); tertile 2 (T2) 15.7-19.4 (N=997); tertile 3 (T3) ≥19.5 (N=966). Over a median follow-up of 512 (342-747) days, 60 patients experienced a stroke (rate 14.6 per 1000 patient-years). Kondo et al's stroke risk model was not able to identify patients at higher risk (i.e. T3 vs. T1, HR 1.25 [95% CI 0.68-2.28]; P=0.442) and showed a low overall prognostic performance (Harrell's C-index =0.53 [95% CI 0.48-0.58]) (**Figure 1A**). The effect of rivaroxaban on stroke was homogeneous across Kondo's risk score tertiles (P for interaction = 0.67) (**Figure 1B**). The comparison of the COMMANDER-HF patients in whom Kondo et al's risk score was calculated (N = 2,928) vs. those in whom it was not possible (N = 2,094) is showed in the **Table 2**. No relevant differences were found between the two groups, although the patients in whom the risk score was computed were slightly older (67 vs. 65 years), less often treated with aspirin (92% vs. 94%) but more with dual antiplatelet therapy (36% vs. 33%) and had less frequently a history of myocardial infarction (74% vs. 78%).

Among patients in whom the Kondo's risk score was estimated, D-dimer was available in 2,343 patients (80%). No significant differences in baseline clinical characteristics were found between the population explored for Kondo et al's risk score and D-dimer score (**Table 1**). The median D-dimer level was 375 (225–675) ng/mL and tertiles were distributed as follow: T1 ≤255ng/mL (N=745); T2 256-515 ng/mL (N=793); T3 >515 ng/mL (N=805). D-dimer had an acceptable performance for stroke prediction (Harrell's C-index =0.66 [95% CI 0.64-0.68]; Δ C-index risk-score vs. D-dimer =0.12 [95% CI, 0.01 - 0.23], P =0.034) (**Figure 1A**) and higher plasma D-dimer concentrations were associated with higher rates of stroke (i.e. T3 vs. T2, HR 1.92 [95% CI 1.01-3.66], P =0.046 and T3 vs. T1, HR 3.65 [95% CI 1.59-8.39], P =0.002). This association persisted also if D-dimer levels were considered as a continuous variable (HR for every 250 ng/mL increase: 1.05 [95% CI 1.02-1.08], p<0.001). Treatment with low-dose rivaroxaban reduced the incidence of stroke vs. placebo in patients at highest risk by D-dimer levels (i.e. T3, HR 0.42 [95%

CI 0.18-0.95], P for interaction =0.074) (**Figure 1B**), without any safety concern (i.e. T3, P =0.447 for the principal safety outcome [composite of fatal bleeding or bleeding into a critical space, bleeding events requiring hospitalization and major bleeding events]).

Discussion

In this analysis we showed that the three-variable risk score validated by Kondo et al. in patients with HFrEF and sinus rhythm had a poor performance for stroke prediction in the COMMANDER-HF population, which included unique features of a recent episode of worsening HF and a history of coronary artery disease (differently from ATMOSPHERE and PARADIGM-HF, which enrolled chronic stable HF patients). In contrast, we confirmed that higher plasma D-dimer concentrations (tertile 3) identified patients with greater risk of stroke who benefited most from rivaroxaban treatment in COMMANDER-HF population. D-dimer is a simple biomarker of thrombotic risk that has predicted increases in stroke/systemic embolic events in patients with acute HF [9]. Furthermore, as demonstrated in the COMPASS trial, patients with HF and stable coronary artery disease have a higher risk of stroke than those without HF, with greater stroke prevention efficacy using low dose rivaroxaban plus aspirin [10]. Although, the stroke risk model as tested by Kondo et al. works well for outpatients with chronic HFrEF, it seems to lose its prognostic value in patients with worsening HFrEF and ischemic heart disease, such as those enrolled in COMMANDER-HF. Why this is so remains speculative, but should be noted that the Kondo risk score includes plasma NTproBNP, which may have a different prognostic significance in the acute compared to more stable clinical settings. COMMANDER-HF recruited patients after a recent episode of worsening HF and with an NTproBNP level ≥ 800 pg/mL. As a consequence, in our study the median NTproBNP at baseline was higher compared to the study by Kondo et al. [6] (i.e. 2900 pg/mL vs 1243 pg/mL), possibly impairing the stroke prediction power of this risk score. In the COMMANDER-HF population, the CHA₂DS₂-VASc risk score was also a strong predictor of stroke events, but it did not predict the effect of rivaroxaban on stroke (P for interaction >0.30) [5].

Major limitations were that these were not prespecified analyses in the original design of any of the trials, the large number of patients that did not have a measurement of NT-proBNP in COMMANDER-HF (which were collected only after a protocol amendment) [3], and differences in patient characteristics amongst different trial populations and compared to the broader population encountered in clinical practice.

Conclusion

We showed that use of plasma D-dimer concentrations may perform better than a previously described three-variable risk score for stroke prediction in patients with HFrEF and sinus rhythm with a recent clinical worsening as enrolled in the COMMANDER-HF trial. In these patients, a raised plasma D-dimer concentration identified patients who might benefit most from rivaroxaban treatment. This hypothesis warrants further investigation in a dedicated clinical trial.

References

- [1] Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. 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.
- [2] Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol*. 1999;33:1424-6.
- [3] Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghide M, et al. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med*. 2018;379:1332-42.
- [4] Greenberg B, Neaton JD, Anker SD, Byra WM, Cleland JGF, Deng H, 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.
- [5] Mehra MR, Vaduganathan M, Fu M, Ferreira JP, Anker SD, Cleland JGF, 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.
- [6] Kondo T, Abdul-Rahim AH, Talebi A, Abraham WT, Desai AS, Dickstein K, et al. Predicting stroke in heart failure and reduced ejection fraction without atrial fibrillation. *Eur Heart J*. 2022;43:4469-79.
- [7] Ferreira JP, Lam CSP, Anker SD, Mehra MR, van Veldhuisen DJ, Byra WM, et al. 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. *Eur J Heart Fail*. 2021;23:648-56.
- [8] Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della

Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. *Circulation*. 2015;131:1486-94; discussion 94.

[9] Hamatani Y, Nagai T, Nakai M, Nishimura K, Honda Y, Nakano H, et al. Elevated Plasma D-Dimer Level Is Associated With Short-Term Risk of Ischemic Stroke in Patients With Acute Heart Failure. *Stroke*. 2018;49:1737-40.

[10] Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, et al. Rivaroxaban With or Without Aspirin in Patients With Heart Failure and Chronic Coronary or Peripheral Artery Disease. *Circulation*. 2019;140:529-37.

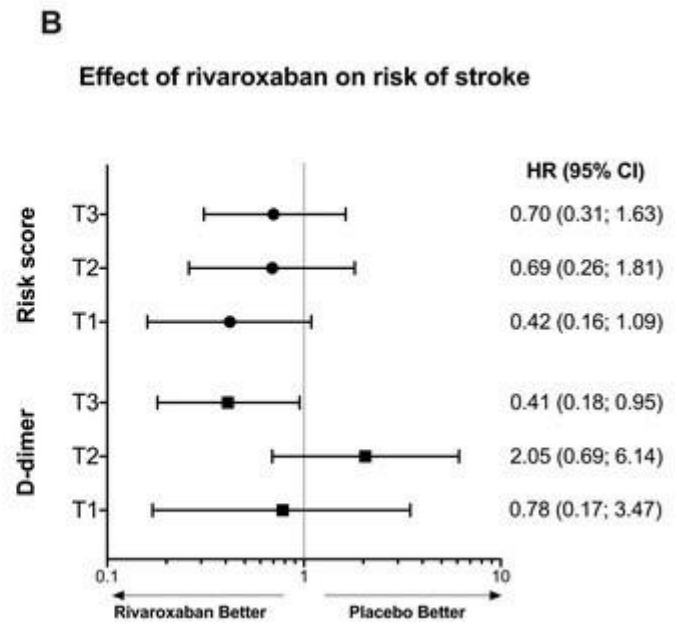
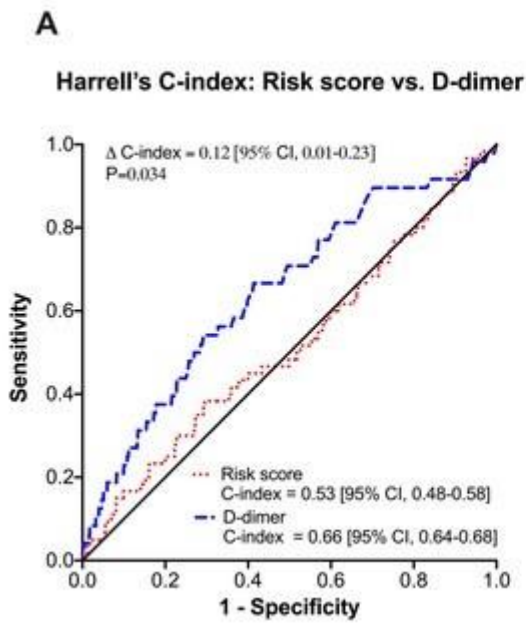


Figure legend

Figure 1. A) Harrell's C-statistic showing the prognostic performance of risk score (red line) and plasma D-dimer concentrations (blue line) on stroke risk. B) Treatment effect on stroke by tertiles of risk score and plasma D-dimer concentrations. T1, tertile 1; T2, tertile 2; T3 tertile 3.

Table 1. Baseline characteristics of the study population according to stroke risk scores

	Kondo et al. (N=2,928)	D-dimer (N=2,343)	p-value
Age, years	67 [60; 74]	67 [60; 75]	0.455
Age \geq 65 years, n. (%)	1741 (59)	1404 (59)	0.733
Men, n. (%)	2213 (76)	1771 (76)	0.996
Body Mass Index, kg/m ²	27.8 \pm 5.1	27.6 \pm 5.1	0.344
Systolic BP, mmHg	123 \pm 15	123 \pm 16	0.819
Diastolic BP, mmHg	73 \pm 9	73 \pm 9	0.788
NYHA class, n. (%)			
- I	60 (2)	55 (2)	0.747
- II	1284 (44)	1039 (44)	
- III	1471 (50)	1152 (50)	
- IV	112 (4)	97 (4)	
Previous MI, n. (%)	2177 (74)	1713 (73)	0.309
Previous stroke, n. (%)	280 (10)	234 (10)	0.606
Hypertension, n. (%)	2185 (75)	1746 (75)	0.931
Diabetes mellitus, n. (%)	1210 (41)	965 (41)	0.919
LVEF, %	32 \pm 7	32 \pm 7	0.492
LVEF \leq 35%, n. (%)	1802 (62)	1457 (62)	0.616
eGFR, mL/min/1.73 m ²	68 \pm 23	68 \pm 23	0.827
eGFR <60 mL/min/1.73m ²	1117 (38)	902 (38)	0.796
Haemoglobin, g/dL	13.4 \pm 1.7	13.4 \pm 1.7	0.658
NTproBNP, pg/mL	2850 [1505; 6288]	2872 [1518; 6310]	0.994
ACEi/ARB, n. (%)	2702 (92)	2156 (92)	0.724
ARNI, n. (%)	30 (1)	24 (1)	0.999
Aspirin, n. (%)	2707 (92)	2164 (92)	0.900
DAPT, n. (%)	1057 (36)	1057 (36)	0.877
Beta Blockers, n. (%)	2724 (93)	2174 (93)	0.729
MRA, n. (%)	2253 (77)	1808 (77)	0.851

Diuretics, n. (%)	2913 (99)	2332 (99)	0.825
Rivaroxaban allocation, n. (%)	1437 (49)	1136 (48)	0.929

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BNP, b-type natriuretic peptide BP, blood pressure; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro b-type natriuretic peptide.

Table 2. Comparison of the patients with versus without all variables to estimate Kondo et al's risk score available

Total, N=5022	With all variables available (N=2,928)	Without all variables available (N=2,094)	p-value
Age, years	67 [60; 74]	65 [58; 74]	<0.001
Age ≥65 years, n. (%)	1741 (59)	1122 (54)	<0.001
Men, n. (%)	2213 (76)	1659 (79)	0.002
Body Mass Index, kg/m ²	27.8 ± 5.1	27.6 ± 5.2	0.359
Systolic BP, mmHg	123 ± 15	122 ± 15	<0.001
Diastolic BP, mmHg	73 ± 9	73 ± 10	0.678
NYHA class, n. (%)			
- I	60 (2)	89 (4)	<0.001
- II	1284 (44)	934 (45)	
- III	1471 (50)	991 (47)	
- IV	112 (4)	80 (4)	
Previous MI, n. (%)	2177 (74)	1626 (78)	0.007
Previous stroke, n. (%)	280 (10)	173 (8)	0.111
Hypertension, n. (%)	2185 (75)	1598 (76)	0.170
Diabetes mellitus, n. (%)	1210 (41)	842 (40)	0.428
LVEF, %	32 ± 7	32 ± 7	0.997
LVEF ≤35%, n. (%)	1802 (62)	1264 (60)	0.411
eGFR, mL/min/1.73 m ²	68 ± 23	68 ± 24	0.792
eGFR <60 mL/min/1.73m ²	1117 (38)	828 (39)	0.318
Haemoglobin, g/dL	13.4 ± 1.7	13.6 ± 1.8	0.007
NTproBNP, pg/mL	2850 [1505; 6288]	-	NA
ACEi/ARB, n. (%)	2702 (92)	1958 (93)	0.096
ARNI, n. (%)	30 (1)	11 (0.5)	0.047
Aspirin, n. (%)	2707 (92)	1968 (94)	0.034
DAPT, n. (%)	1057 (36)	689 (33)	0.018

Beta Blockers, n. (%)	2724 (93)	1918 (92)	0.058
MRA, n. (%)	2253 (77)	1587 (76)	0.340
Diuretics, n. (%)	2913 (99)	2086 (99)	0.496
Rivaroxaban allocation, n. (%)	1437 (49)	1070 (51)	0.157

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BNP, b-type natriuretic peptide BP, blood pressure; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro b-type natriuretic peptide.