Reduced mortality with low-dose rivaroxaban in patients with coronary artery disease: a meta-analysis

Short title: low-dose rivaroxaban in patients with coronary artery disease.

Supplementary Material

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Search terms used for the identification of randomized controlled trials in MEDLINE

Dual pathway inhibition, novel oral anticoagulants, direct oral anticoagulants, direct oral anticoagulant AND low dose, direct oral anticoagulant AND antiplatelet therapy, rivaroxaban AND antiplatelet therapy, rivaroxaban AND low dose, rivaroxaban AND coronary artery disease, rivaroxaban AND low dose AND coronary artery disease, rivaroxaban AND low dose AND acute coronary syndrome, rivaroxaban AND low dose AND antiplatelet therapy.

Supplementary Table 1. Inclusion, exclusion criteria and primary endpoint of randomized trials included in the meta-analysis

Study	Major inclusion criteria	Major exclusion criteria	Primary endpoint	FUP in months (median or mean)
ATLAS ACS 2–TIMI 51	ACS within 48 hours before hospital presentation or while being hospitalized other reasons.	Contraindication to anticoagulant therapy, unacceptable risk of bleeding, severe concomitant disease.	Efficacy: CV death, MI, or stroke. Safety: TIMI major bleeding not CABG related.	13.1
COMMANDER HF	Significant CAD with symptomatic chronic HF for at least 3 months.	Contraindication to anticoagulant therapy, unacceptable risk of bleeding, severe concomitant disease, use of chronic anticoagulants, acute MI, prior stroke in 90 days.	Efficacy: all-cause death, MI, or stroke. Safety: fatal bleeding or bleeding into a critical space.	21.1
COMPASS CAD	CAD (myocardial infarction within 20 years, multi-vessel CAD, history of stable or unstable angina, previous multi-vessel PCI, or previous multi-vessel CABG).	High risk of bleeding, stroke within 1 month, hemorrhagic or lacunar stroke, severe CHF, eGFR< 15 mL/min, and the need for dual-antiplatelet therapy.	Efficacy: CV death, MI, or stroke. Safety: fatal bleeding, bleeding into a critical space, or bleeding leading to hospital admission	23.4
GEMINI – ACS-1	ACS (STEMI, NSTEMI with positive cardiac biomarkers and either ischemic EKG changes or an atherosclerotic culprit lesion identified during angiography; unstable angina with ischemic EKG changes, or revascularization for the index ACS event, or a (TIMI) risk score of 4 or more.	History of active bleeding, intracranial hemorrhage, or clinically significant gastrointestinal bleeding within 12 months.	TIMI non-CABG significant bleeding	10.7

H-REPLACE	ACS (STEMI, NSTEMI, unstable angina) who missed primary reperfusion window and before selective revascularization, and with an indication for short-term combination use of DAPT and enoxaparin.	Contraindication to anticoagulant therapy, increased bleeding risk, thrombolytic therapy or revascularization therapy within 12 hours, severe concomitant disease, use of chronic anticoagulants.	Efficacy: CV death, MI, revascularization or stroke. Safety: ISTH bleeding	6

ACS = acute coronary syndromes; CABG = coronary artery bypass grafting, CAD = coronary artery disease; CV = cardiovascular; DAPT = dual antiplatelet therapy; HF = heart failure; ISTH = International Society on Thrombosis and Haemostasias; MI = myocardial infarction; NA = not available; NSTEMI = non ST-segment elevation myocardial infarction; PAD = peripheral arterial disease; PCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

Supplementary Table 2. Definitions used in the component trials of the meta-analysis

	Cardiovascular death	Myocardial infarction	Major bleeding
ATLAS ACS 2–TIMI 51	All deaths unless an unequivocal non- cardiac cause could be established	**For patients with no recent revascularization.** Typical cardiac biomarker rise and fall and at least 1 of the following: chest pain ≥ 10 minutes; or ECG changes indicative of ischemia, or development of new Q waves, or pathologic findings of an acute MI. **Within 24 hours after PCI.** CK-MB 3 × ULN or pathologic finding of an acute MI. **Within 24 hours after CABG**. CK-MB 5 × ULN and at least one of the following: new Q waves in ≥ 2 contiguous leads, or increase R amplitude in V1-V3 consistent with posterior infarction, or angiographically documented new graft or native coronary occlusion, or imaging evidence of new loss of myocardium, or CK-MB 10 × ULN, or pathologic findings of an acute MI.	TIMI non-CABG major bleeding
COMMANDER HF	Any death that is not clearly non-CV	**For patients with no recent revascularization.** Elevated cardiac biomarkers (troponin I or T, or CK-MB) greater than the ULN and/or development of new pathological Q waves and/or new significant ST changes and/or new LBBB and/or autopsy confirmation **For patients with recent PCI.** Elevated cardiac biomarkers (troponin I or T, or CK-MB) >5 x ULN plus either prolonged ischemia (> 20 minutes of chest pain), ischemic ST changes or new pathological Q waves, or angiographic evidence of a flow-limiting complication, or imaging evidence of	ISTH major bleeding

		new loss of viable myocardium or new regional wall abnormality and/or development of new pathological Q waves. **For patients with recent CABG.** Elevated cardiac biomarkers (troponin I or T, or CK-MB) >10 x ULN with development of new pathological Q waves or a new LBBB on the ECG, or angiographic documented new graft.	
COMPASS CAD	All deaths unless an unequivocal non- cardiac cause could be established	Third Universal Definition	ISTH major bleeding
GEMINI – ACS-1	All deaths unless an unequivocal non- cardiac cause could be established	Third universal definition	TIMI non-CABG major bleeding
H-REPLACE	Death to a cardiovascular etiology includes acute myocardial infarction, sudden cardiac death, HF, stroke, cardiovascular procedure, cardiovascular hemorrhage, and other cardiovascular causes	Fourth universal definition	ISTH major bleeding

ACS = acute coronary syndromes; CABG = coronary artery bypass grafting; CAD = coronary artery disease; HF = heart failure; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; NA = not available; TIMI = Thrombolysis in Myocardial Infarction; ULN = upper limit normal.

Supplementary Table 3. Other definitions used in the component trials of the meta-analysis

	Stroke	MACE
ATLAS ACS 2–TIMI 51	New, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible (or results in death) within 24 hours and is not due to a readily identifiable cause. Ischemic infarction, ischemic infarction with hemorrhagic conversion, intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, uncertain (any stroke without brain imaging surgical exploration, autopsy, other documentation, or if tests are inconclusive).	Cardiovascular death, MI, stroke, or stent thrombosis.
COMMANDER HF	New, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause such as trauma, a tumor or seizure. Classified in primary ischemic infarction, primary hemorrhagic, subarachnoid hemorrhage, uncertain (no imaging or autopsy available).	Cardiovascular death, MI, stroke, venous thromboembolism, hospitalization for heart failure.
COMPASS CAD	Presence of acute focal neurological deficit of vascular origin with signs and symptoms lasting ≥ 24 hours. Classified as: ischemic stroke, hemorrhagic stroke (primary intracerebral / intraparenchymal brain hemorrhage, subarachnoid hemorrhage), uncertain or unknown stroke.	Cardiovascular death, MI, ischemic stroke, acute limb ischemia.
GEMINI – ACS-1	An acute episode of focal or global neurological dysfunction caused by vascular injury. Classified in ischemic, hemorrhagic and undetermined.	Cardiovascular death, MI, stroke, or definite stent thrombosis.
H-REPLACE	Presence of acute infarction as demonstrated by imaging or based on the persistence of symptoms. Classified in ischemic, haemorrhagic and unknown.	Cardiac death, MI, stroke, revascularization and major bleeding events.

ACS = acute coronary syndromes; CAD = coronary artery disease; CT = computed tomography; HF = heart failure; ISTH = International Society on Thrombosis and Haemostasis; MACE = major adverse cardiovascular events; MI = myocardial infarction; MRI = Magnetic Resonance Imaging; NA = not available; TIMI = Thrombolysis in Myocardial Infarction.

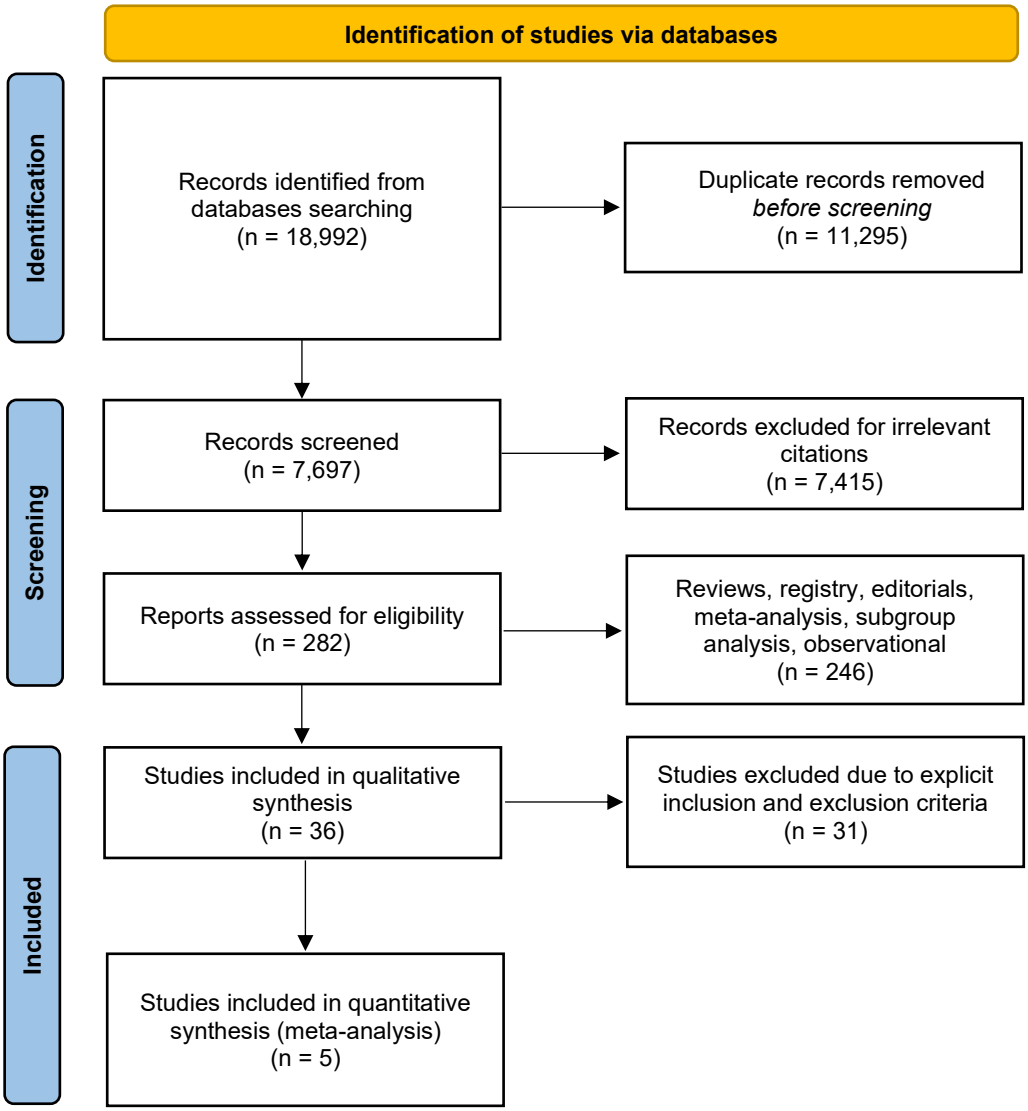
Supplementary Table 4. Clinical characteristics of patients enrolled in the randomized controlled trials included in the meta-analysis*

	Treatment arm	Age†	Male	Diabetes	Hypertension	Prior MI	ACS
ATLAS ACS 2–TIMI 51	Low-dose DOACs	61.8±9.2	74.9%	32.3%	67.1%	26.3%	100%
	Standard therapy	61.5±9.4	75.0%	31.8%	67.5%	27.3%	100%
COMMANDER HF	Low-dose DOACs	66.5±10.1	78.0%	40.8%	75.7%	76.2%	none
	Standard therapy	66.3±10.3	76.2%	40.9%	75.0%	75.2%	none
COMPASS CAD	Low-dose DOACs	69 (65-73)	79%	37%	76%	68%	none
	Standard therapy	69 (65-73)	80%	37%	75%	69%	none
GEMINI – ACS-1	Low-dose DOACs	62 (57-69)	75%	29%	71%	21%	100%
	Standard therapy	63 (57-69)	75%	30%	75%	23%	100%
H-REPLACE	Low-dose DOACs	66.2±7.8	70.7%	31.5%	61.9%	14.3%	100%
	Standard therapy	65.3±8.7	71.2%	34.0%	63.7%	16.2%	100%

ACS = acute coronary syndromes; CAD = coronary artery disease; DOAC = direct oral anticoagulant; HF = heart failure; MI = myocardial infarction; NA = not available.
*Data are provided as they appear in the original publication; †Age is provided as mean ± standard deviation or median (interquartile range).

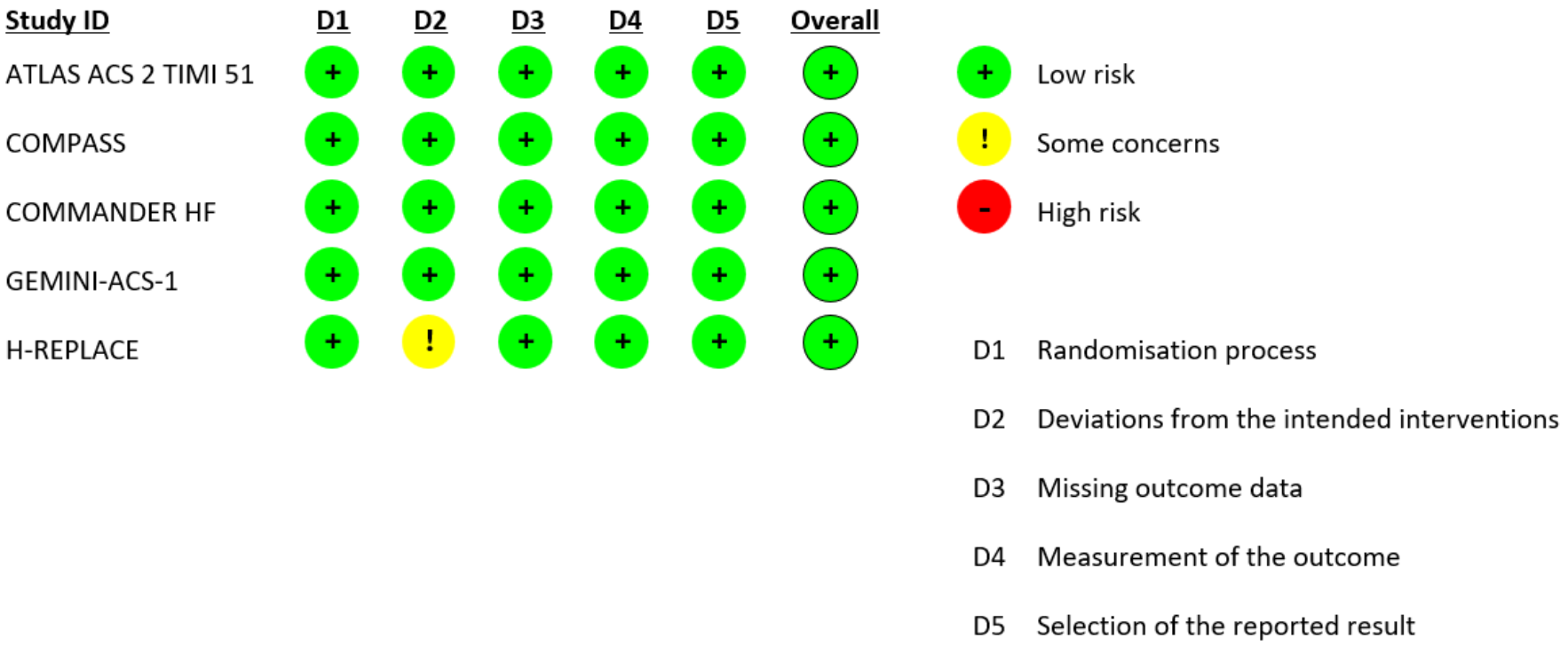
Supplementary Figure 1: Flow diagram of the study.

Of 7,697 articles initially screened, 5 trials met the inclusion criteria and were included in the meta-analysis.



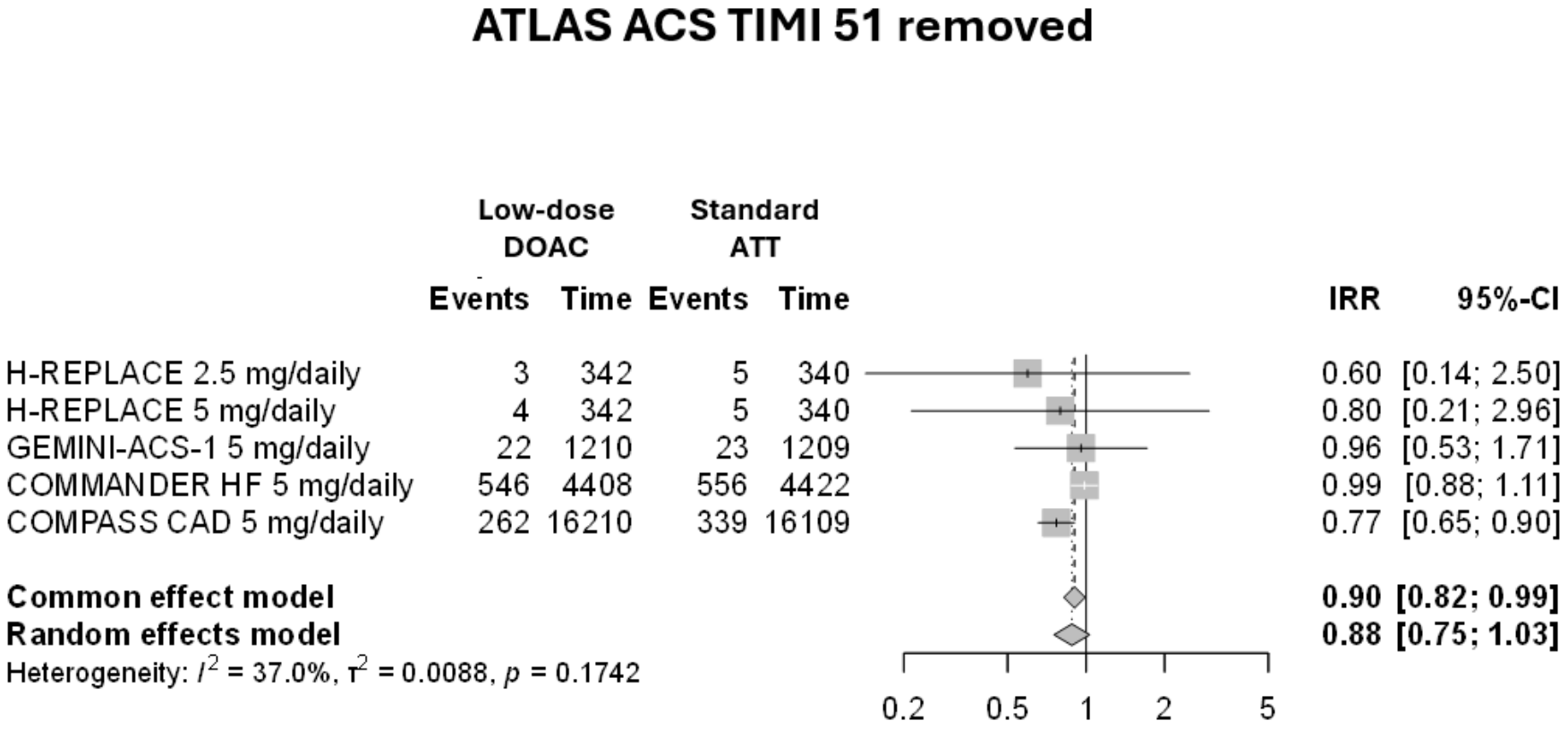
Supplementary Figure 2: Risk of bias for each trial included in the meta-analysis using the Cochrane risk of bias tool.

No major concern of bias was apparent across the trials included in the meta-analysis.

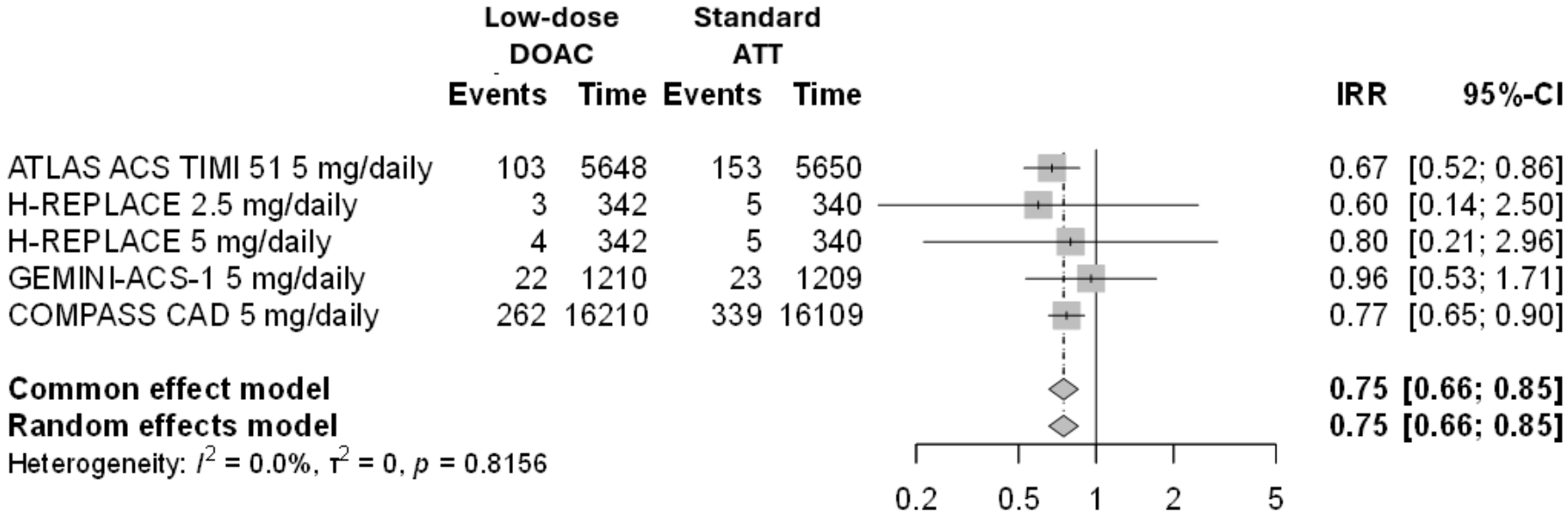


Supplementary Figure 3: Sensitivity analysis excluding component trials of the meta-analysis one at a time.

Removal of trials one at a time did not alter the direction of the treatment effect.



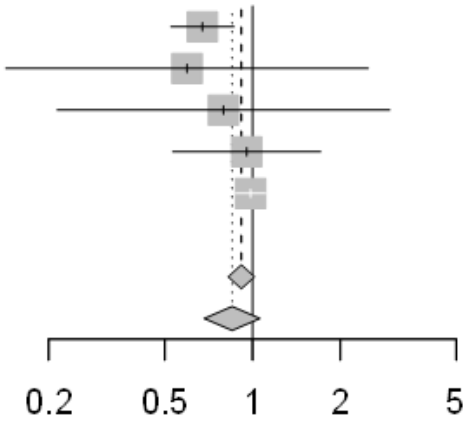
COMMANDER HF removed



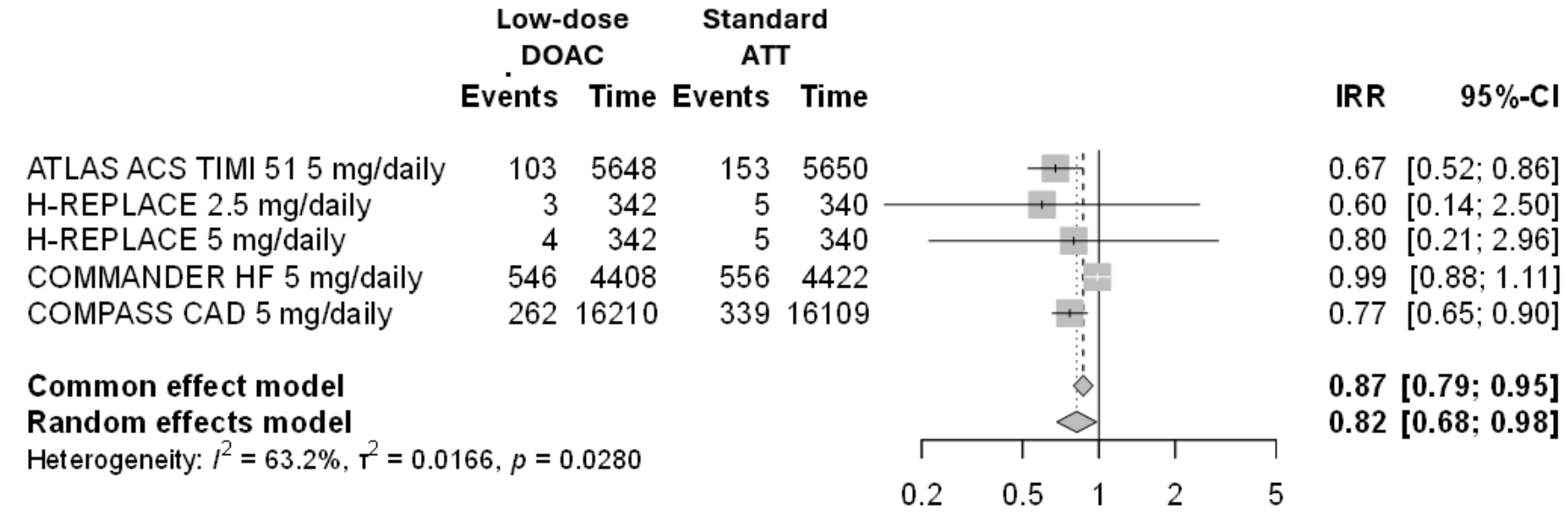
COMPASS CAD removed

	Low-dose DOAC Events	Time	Standard ATT Events	Time	IRR	95%-CI
ATLAS ACS TIMI 51 5 mg/daily	103	5648	153	5650	0.67	[0.52; 0.86]
H-REPLACE 2.5 mg/daily	3	342	5	340	0.60	[0.14; 2.50]
H-REPLACE 5 mg/daily	4	342	5	340	0.80	[0.21; 2.96]
GEMINI-ACS-1 5 mg/daily	22	1210	23	1209	0.96	[0.53; 1.71]
COMMANDER HF 5 mg/daily	546	4408	556	4422	0.99	[0.88; 1.11]
Common effect model					**0.92**	**[0.83; 1.02]**
Random effects model					**0.85**	**[0.68; 1.06]**

Heterogeneity: I^2 = 48.0%, τ^2 = 0.0194, p = 0.1035



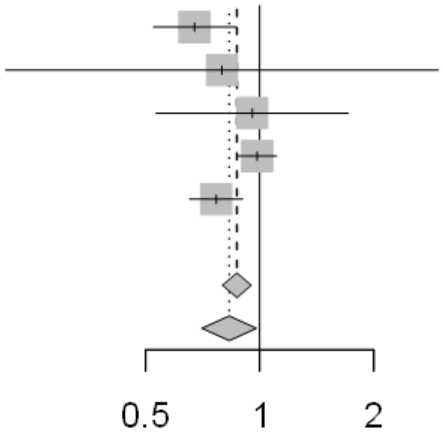
GEMINI ACS removed



H REPLACE 2.5 mg removed

	Low-dose DOAC		Standard ATT			
	Events	Time	Events	Time	IRR	95%-CI
ATLAS ACS TIMI 51 5 mg/daily	103	5648	153	5650	0.67	[0.52; 0.86]
H-REPLACE 5 mg/daily	4	342	5	340	0.80	[0.21; 2.96]
GEMINI-ACS-1 5 mg/daily	22	1210	23	1209	0.96	[0.53; 1.71]
COMMANDER HF 5 mg/daily	546	4408	556	4422	0.99	[0.88; 1.11]
COMPASS CAD 5 mg/daily	262	16210	339	16109	0.77	[0.65; 0.90]
Common effect model					**0.87**	**[0.80; 0.95]**
Random effects model					**0.83**	**[0.70; 0.98]**

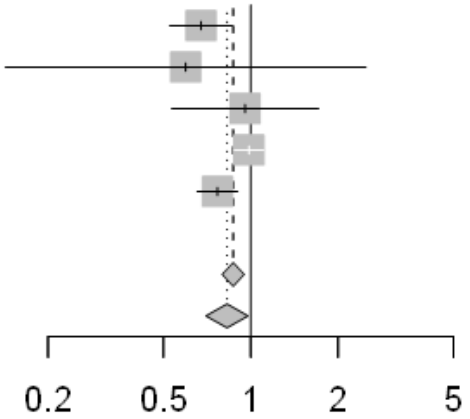
Heterogeneity: I^2 = 62.6%, τ^2 = 0.0150, p = 0.0301



H REPLACE 5 mg removed

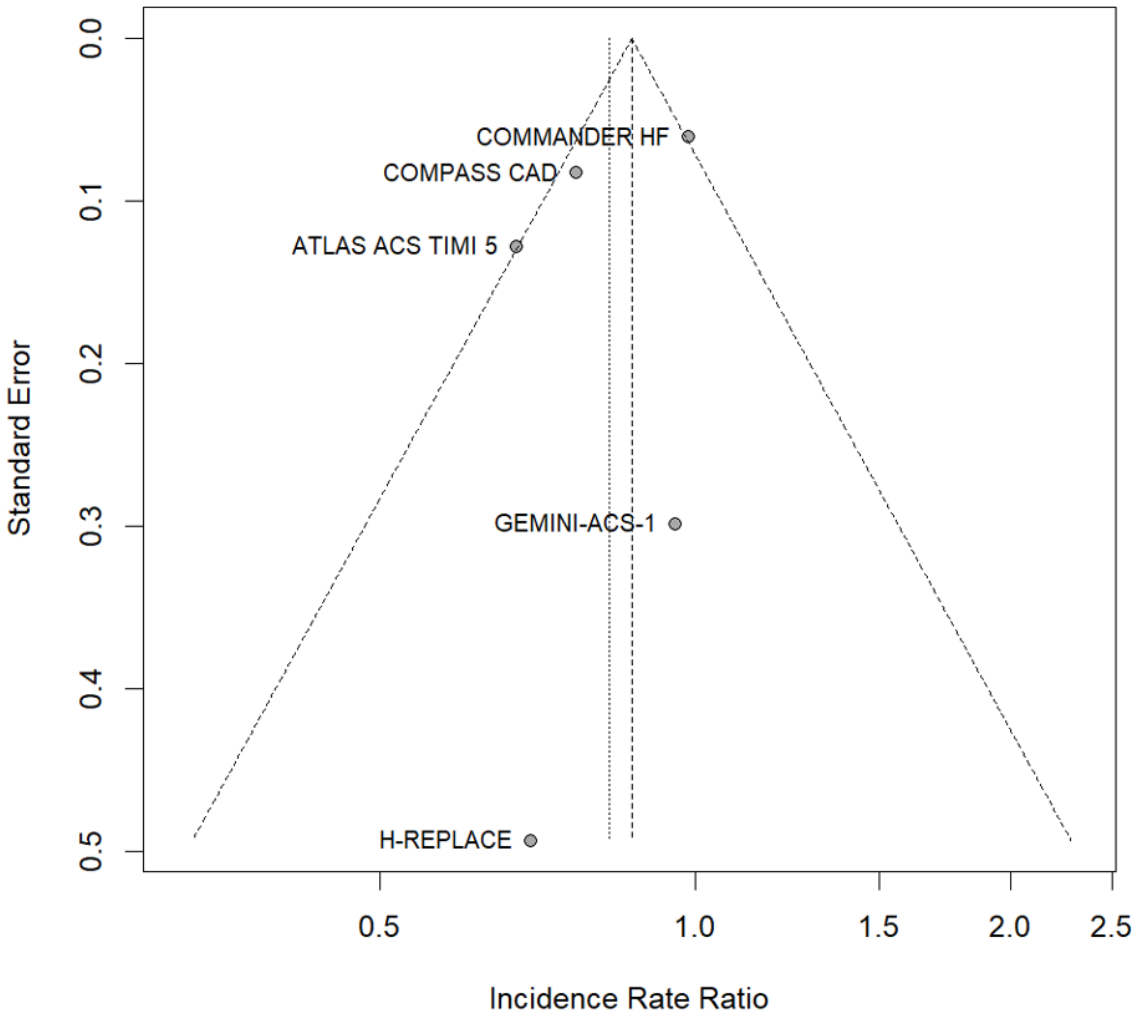
	Low-dose DOAC		Standard ATT			
	Events	Time	Events	Time	IRR	95%-CI
ATLAS ACS TIMI 51 5 mg/daily	103	5648	153	5650	0.67	[0.52; 0.86]
H-REPLACE 2.5 mg/daily	3	342	5	340	0.60	[0.14; 2.50]
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COMPASS CAD 5 mg/daily	262	16210	339	16109	0.77	[0.65; 0.90]
Common effect model					**0.87**	**[0.80; 0.95]**
Random effects model					**0.83**	**[0.70; 0.98]**

Heterogeneity: I^2 = 63.5%, τ^2 = 0.0152, p = 0.0271



Supplementary Figure 4: Funnel plot of the included studies for the risk of all-cause mortality.

No evidence of publication bias was apparent (Egger test= 0.73).



PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pages 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4: Suppl Table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4; Suppl Fig 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4; Suppl Table 2-3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4; Suppl Fig 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4-5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Suppl Fig 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Suppl Fig 2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Suppl Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl Fig 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl Fig 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 5-7; Fig 1-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 5-7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 5-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Na
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Na
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 7-9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 7-10
	23b	Discuss any limitations of the evidence included in the review.	Page 10
	23c	Discuss any limitations of the review processes used.	Page 10
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11, 13
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4

Section and Topic	Item #	Checklist item	Location where item is reported
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Na
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 5
Competing interests	26	Declare any competing interests of review authors.	Page 13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Na

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/