

Supplemental Online Content

Coyle M, Lynch A, Higgins M, et al. Risk of intracranial hemorrhage associated with direct oral anticoagulation vs antiplatelet therapy: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7(12):e2449017.
doi:10.1001/jamanetworkopen.2024.49017

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Search strategy

Studies were searched through February 7th 2024.

Search terms were as follows:

Rivaroxaban *OR* Edoxaban *OR* Apixaban *OR* Dabigatran

AND

Aspirin *OR* Clopidogrel *OR* Triflusal *OR* Ticagrelor *OR* Prasugrel *OR* Dipyridamole *OR* Cilostazol

AND

Randomized controlled trial *OR* Randomized controlled trial *OR* Controlled clinical trial *OR* Randomized *OR* Randomized *OR* placebo *OR* Drug therapy *OR* Randomly *OR* Trial *OR* Groups

NOT

Animals *NOT* Humans

The search was conducted through Pubmed and EMBASE.

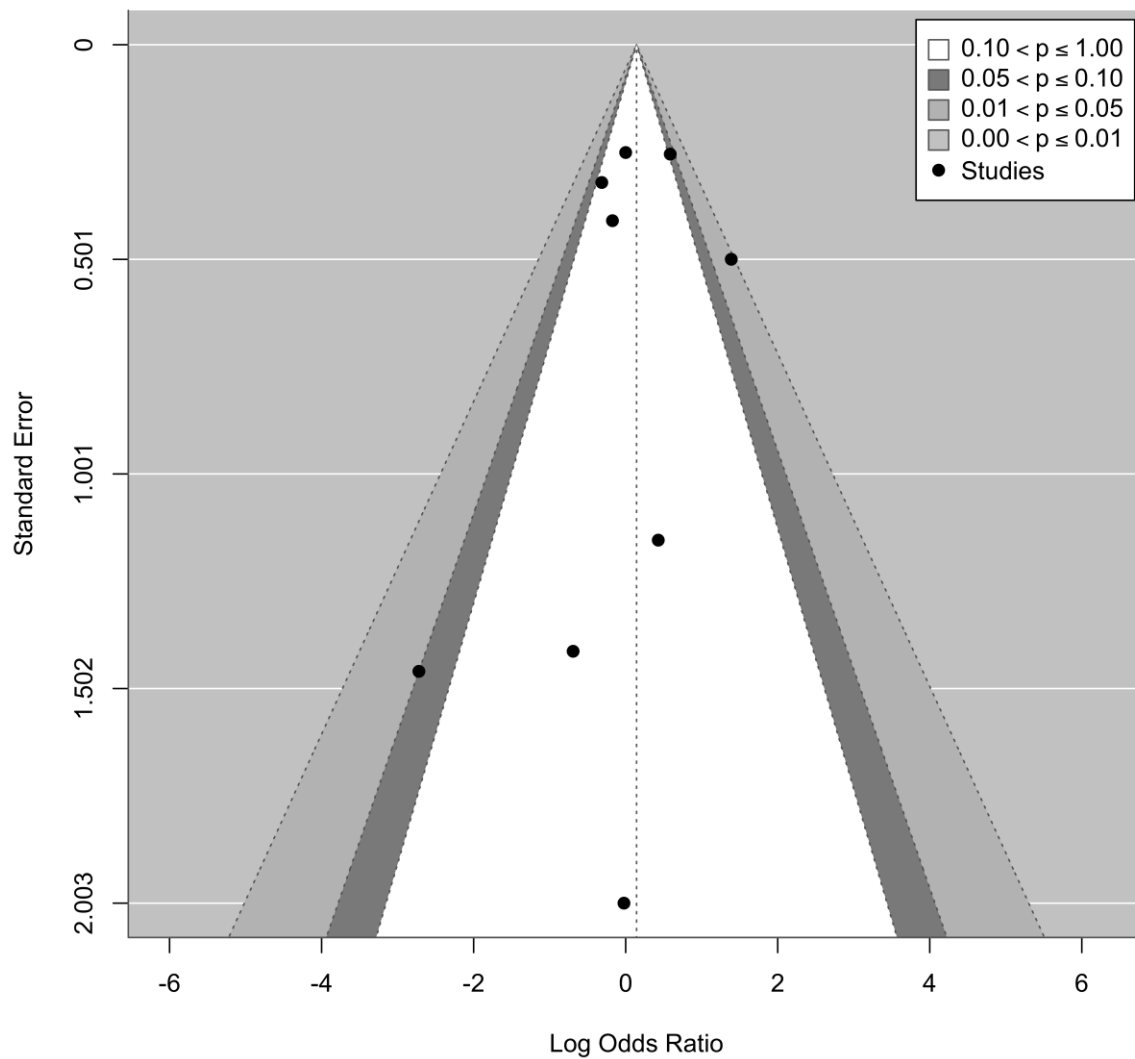
eTable 1. Reported outcomes of individual trials

Trial	Outcome						
	Intracranial haemorrhage	Major haemorrhage	Fatal haemorrhage	Gastrointestinal haemorrhage	All haemorrhage	Ischaemic stroke	Cardiovascular mortality
ATTICUS 2023	√	√	√	√	√	√	√
ARCADIA 2024	√	√				√	
ARTESIA 2023	√	√	√	√		√	√
DATAS II 2020*		√	√		√	√	√
RE-SPECT ESUS 2019	√	√	√	√	√	√	√
NAVIGATE ESUS 2018	√	√	√	√	√	√	√
EINSTEIN CHOICE 2017	√	√	√	√	√	√	
COMPASS 2017	√	√	√	√	√	√	√
AVERROES 2011	√	√	√	√	√	√	√
*Symptomatic haemorrhagic transformation was not considered as primary intracranial haemorrhage							

eTable 2. Definition of major haemorrhage of individual trials

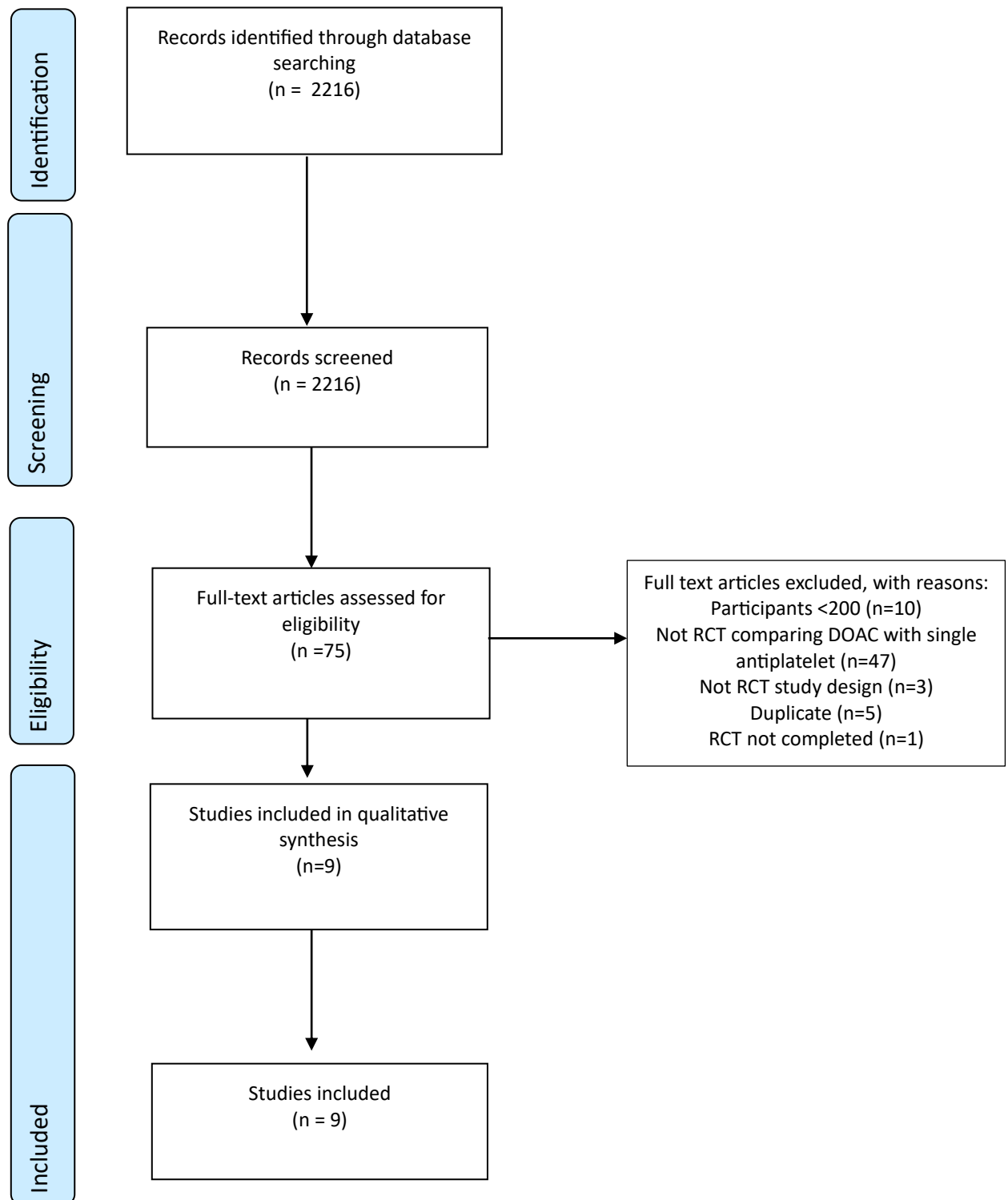
Trial	Major haemorrhage definition
ATTICUS 2023	ISTH definition for major bleeding*
ARCADIA 2024	Clinically overt bleeding accompanied by a 2-g/dL or greater decrease in the hemoglobin level during a 24-hour period, transfusion of 2 units or more of whole blood or red blood cells, involvement of a critical non-intracranial site (intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or death.
ARTESIA 2023	ISTH definition for major bleeding*
DATAS II 2020	Definition not reported
RE-SPECT ESUS 2019	ISTH definition for major bleeding*
NAVIGATE ESUS 2018	ISTH definition for major bleeding*
EINSTEIN CHOICE 2017	ISTH definition for major bleeding*
COMPASS 2017	All bleeding leading to presentation to an acute care facility or hospital
AVERROES 2011	Clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding
*ISTH definition = Fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 gL ⁻¹ (1.24 mmolL ⁻¹) or more, or leading to transfusion of two or more units of whole blood or red cells ¹⁵	

eFigure 1. Funnel plot






eFigure 1 – Contour enhanced funnel plot for the primary outcome; intracranial haemorrhage. Different levels of statistical significance for studies are indicated by the shaded regions, detailed within the figure. The grey vertical line represents the summary estimate for the association of DOAC therapy compared to antiplatelet therapy with intracranial haemorrhage outcome.

eFigure 2. PRISMA flow diagram

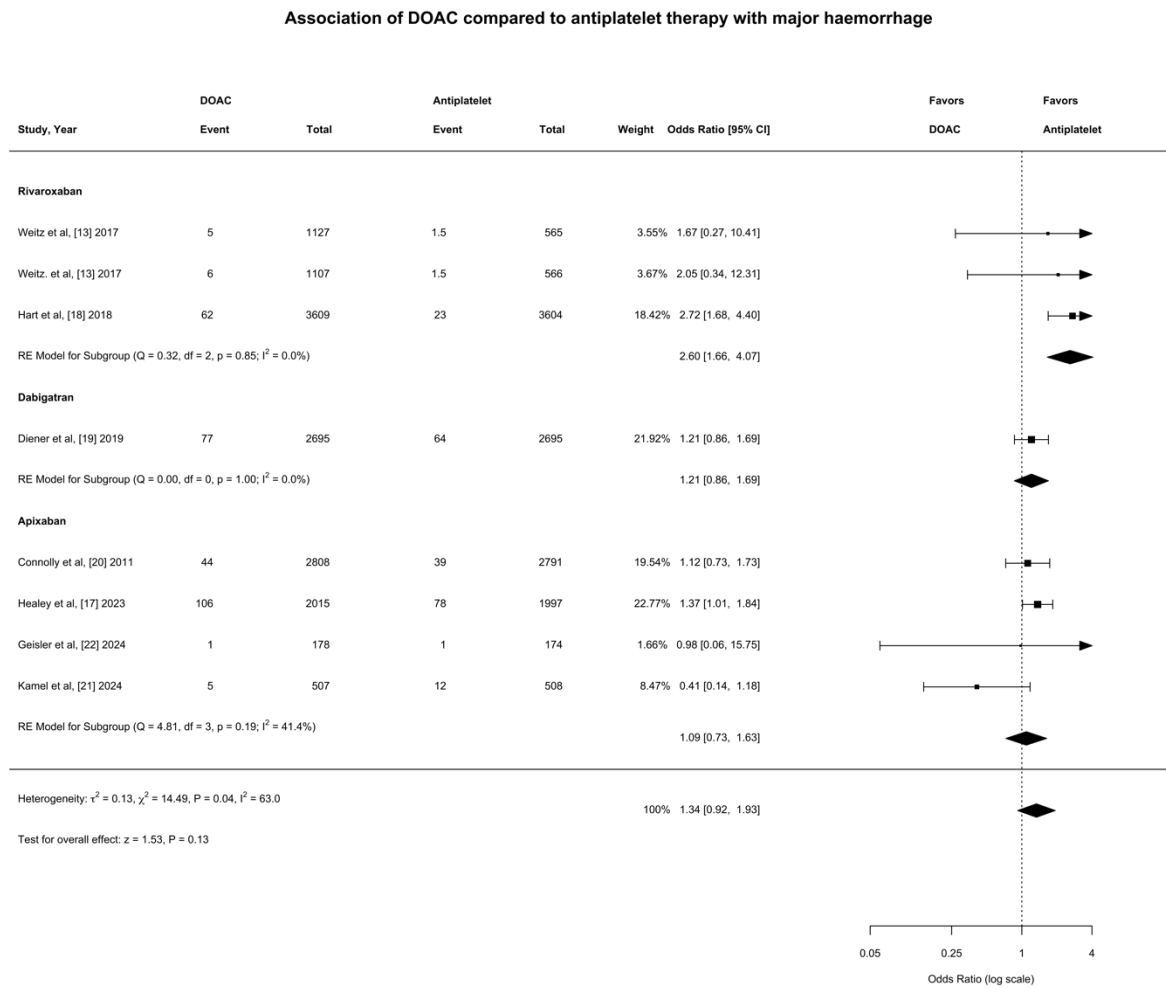


eFigure 3. Risk of bias 2 assessment

<u>StudyID</u>	<u>Experimental</u>	<u>Comparator</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>	
NAVIGATE ESUS	Rivaroxaban	Aspirin	+	+	+	+	+	+	+
RESPECT ESUS	Dabigatran	Aspirin	+	+	+	+	+	+	+
EINSTEIN CHOICE	Rivaroxaban	Aspirin	+	+	+	+	+	+	+
DATAS II	Dabigatran	Aspirin	+	!	+	+	+	+	+
AVERROES	Apixaban	Aspirin	+	+	+	+	+	+	+
ARTESIA	Apixaban	Aspirin	+	+	+	+	+	+	+
COMPASS	Rivaroxaban	Aspirin	+	+	+	+	+	+	+
ARCADIA	Apixaban	Aspirin	+	+	+	+	+	+	+
ATTICUS	Apixaban	Aspirin	+	+	+	+	+	+	+

	Low risk		
	Some concerns		
	High risk		
	D1	Randomisation process	
	D2	Deviations from the intended interventions	
	D3	Missing outcome data	
	D4	Measurement of the outcome	
	D5	Selection of the reported result	

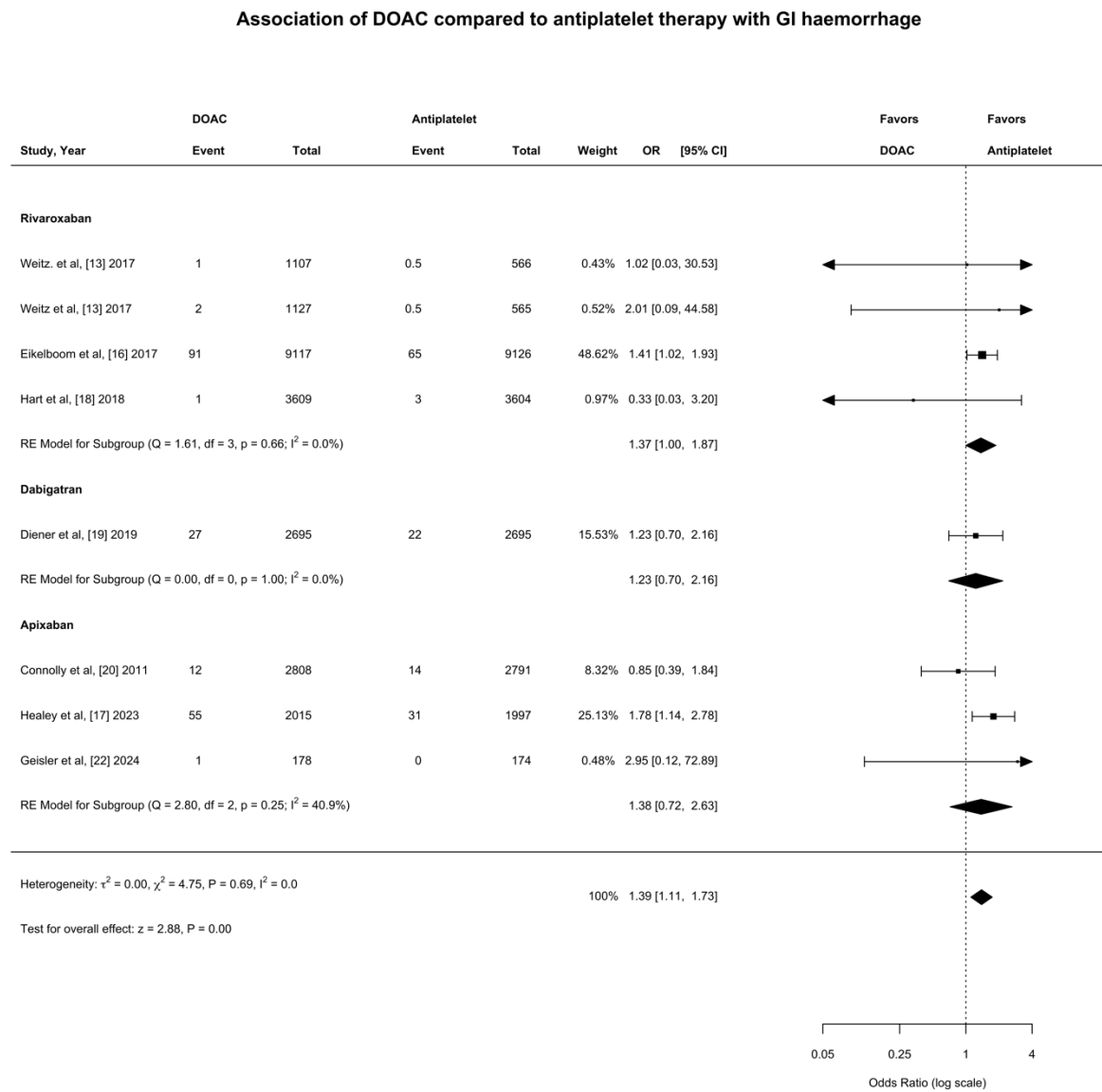
eFigure 4. Association of DOAC compared to antiplatelet therapy with ISTH defined major haemorrhage



eFigure 4 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with major haemorrhage according to the ISTH definition for major haemorrhage. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

DOAC- Direct oral anticoagulation, CI-Confidence Interval, ISTH-International Society on Thrombosis and Haemostasis.

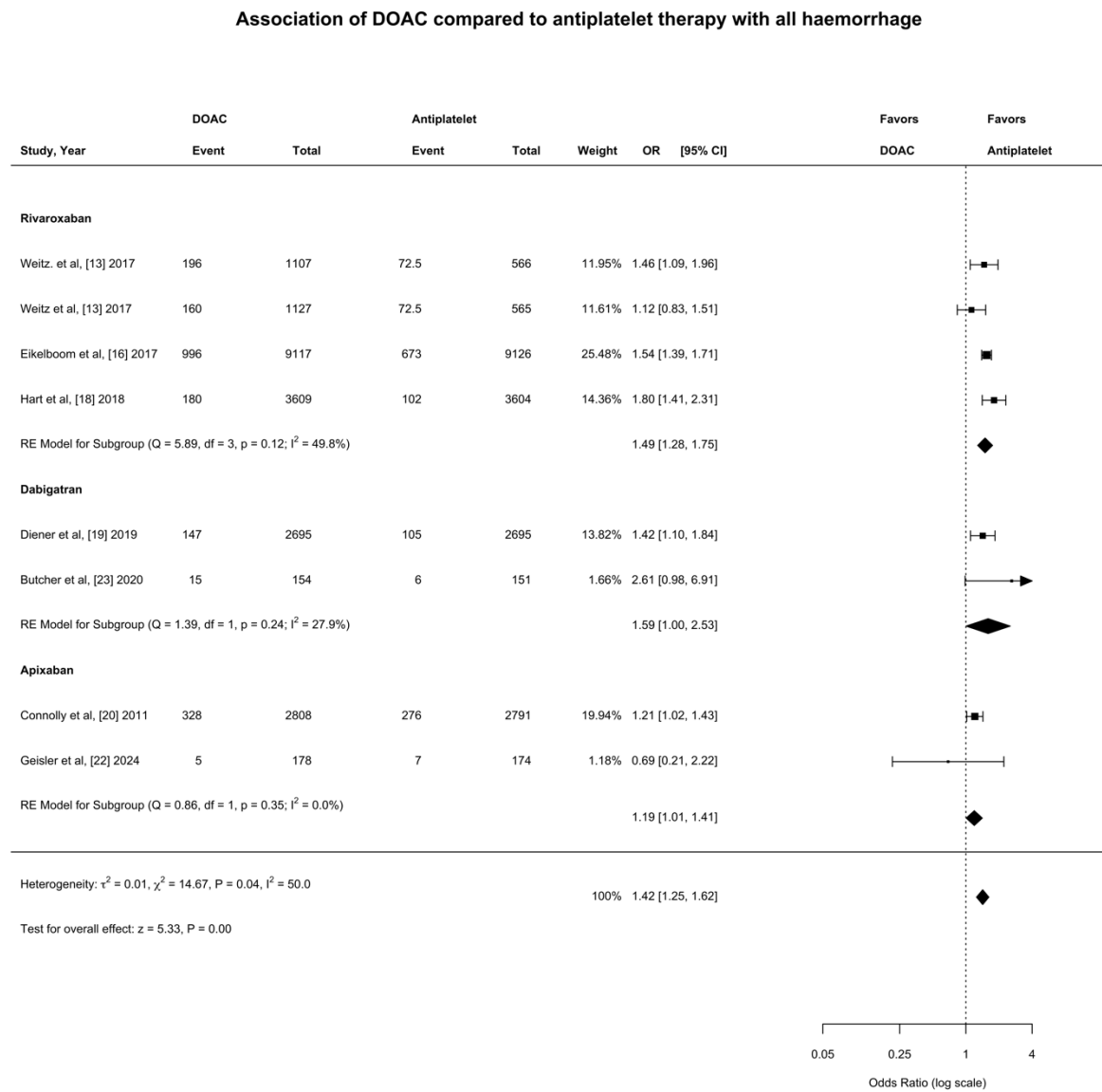
eFigure 5. Association of DOAC compared to antiplatelet therapy with GI haemorrhage



eFigure 5 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with GI haemorrhage events. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

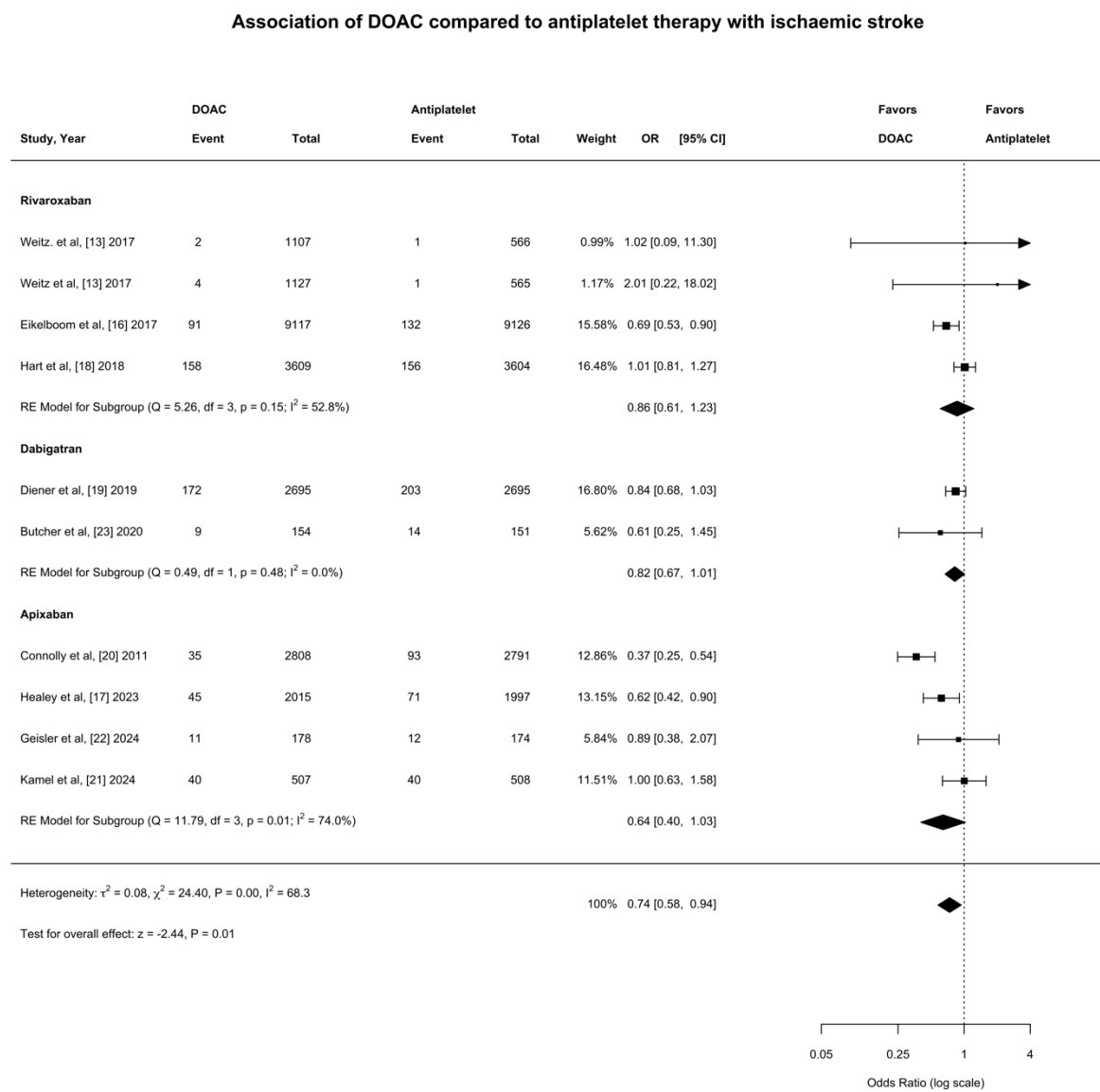
DOAC- Direct oral anticoagulation, CI-Confidence Interval, GI-gastrointestinal.

eFigure 6. Association of DOAC compared to antiplatelet therapy with all haemorrhage



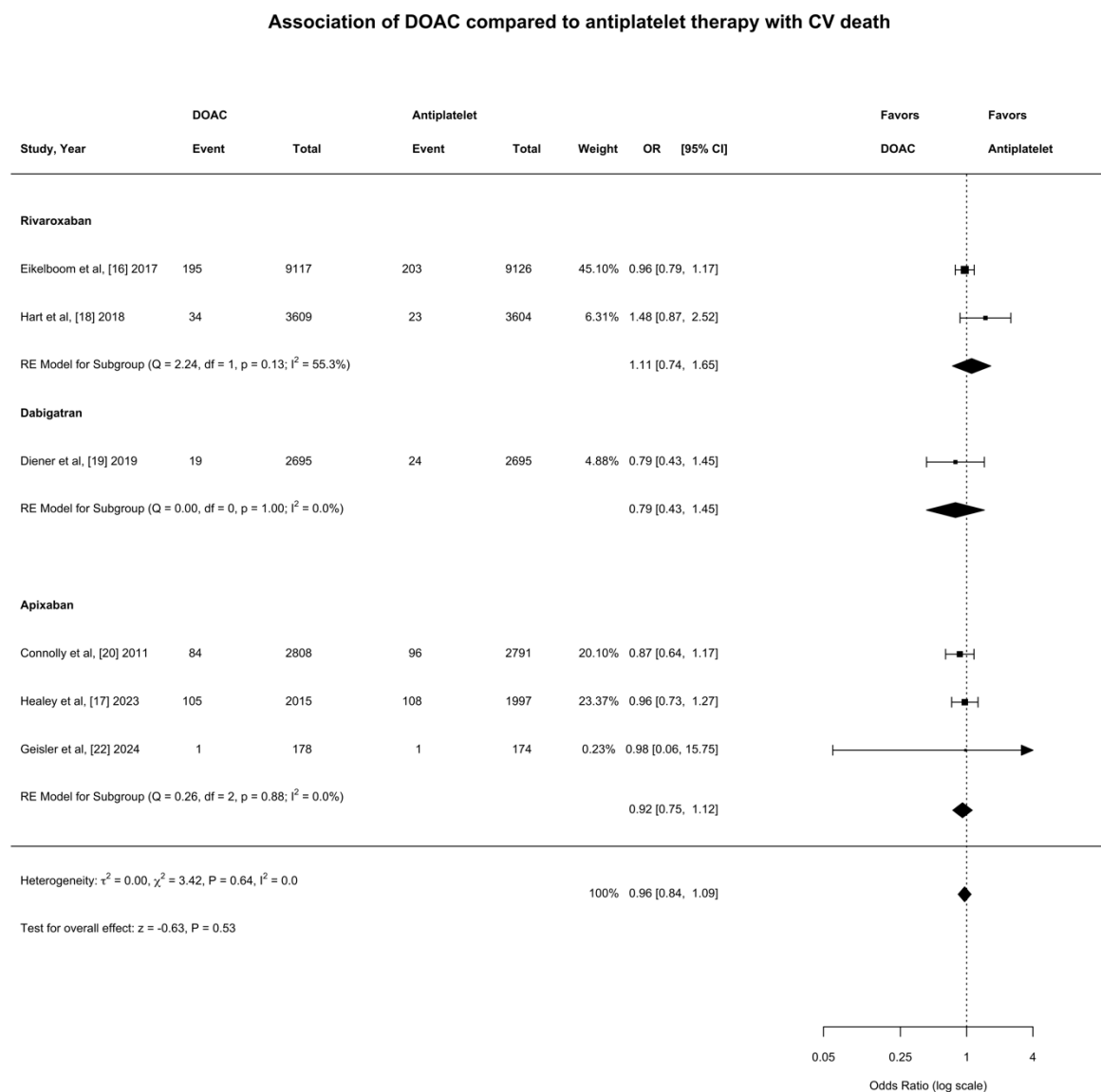
eFigure 6 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with all haemorrhage. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. DOAC-Direct oral anticoagulation, CI-Confidence Interval.

eFigure 7. Association of DOAC compared to antiplatelet therapy with ischaemic stroke



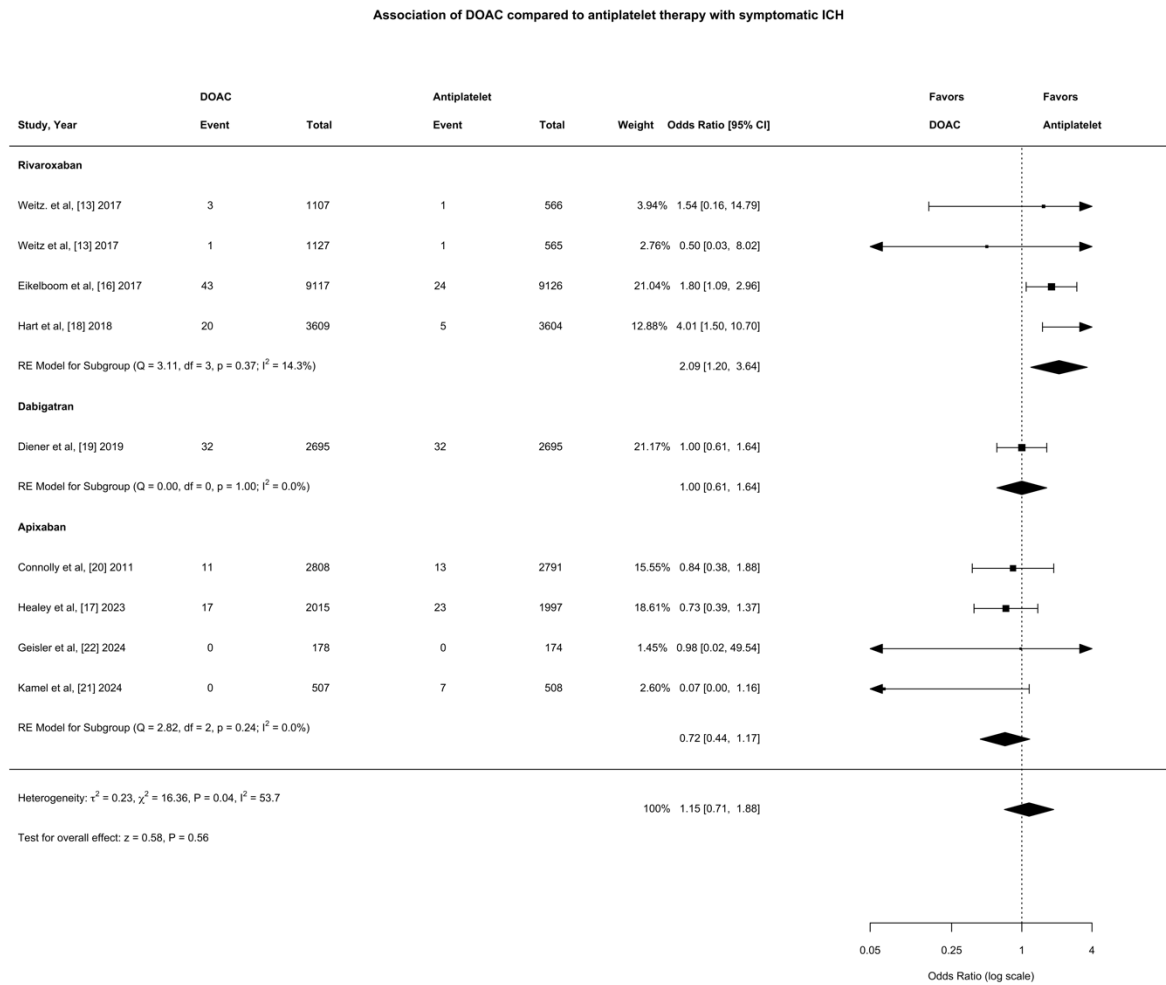
eFigure 7 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with ischaemic stroke. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. DOAC-Direct oral anticoagulation, CI-Confidence Interval.

eFigure 8. Association of DOAC compared to antiplatelet therapy with CV death



eFigure 8 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with cardiovascular death. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect. DOAC-Direct oral anticoagulation, CI-Confidence Interval, CV-Cardiovascular death.

eFigure 9. Association of DOAC compared to antiplatelet therapy with intracranial haemorrhage, sensitivity analysis excluding trials with zero events



eFigure 9 – Forest plot demonstrating the association of direct oral anticoagulant therapy compared to antiplatelet therapy with symptomatic intracranial haemorrhage. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.

DOAC- Direct oral anticoagulation, CI-Confidence Interval.