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The association between advanced therapies and major adverse cerebrovascular and cardiovascular events in patients with ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Advanced therapies, including biologics and small molecules, have improved remission rates in ulcerative colitis (UC), although there are concerns over their cardiovascular safety. This systematic review and meta-analysis evaluated the risk of major adverse cerebrovascular and cardiovascular events (MACCEs) in adult UC patients receiving advanced therapies in randomized controlled trials (RCTs).

Methods This study followed the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE, EMBASE and Cochrane were searched to identify phase 3 RCTs that assessed the risk of MACCEs in UC induction and maintenance trials. Data were pooled and analysed using random effects modeling with 95% confidence intervals (CIs).

Results In a total of 31 studies retrieved from inception to February 2025, 54 RCTs were described, including 29 induction and 25 maintenance trials. These involved 11,721 patients, of whom 7307 (62.3%) were receiving advanced therapies. The risk of MACCEs was not higher in induction (odds ratio [OR] 0.62, 95%CI 0.32-1.18; P=0.14) or maintenance trials (OR 0.57, 95%CI 0.28-1.18; P=0.13) compared to placebo or active comparators. No drug agent, drug class or trial duration incurred a higher risk of MACCEs. Overall, those treated with advanced therapies did not show a greater risk of MACCE (OR 0.63, 95%CI 0.32-1.21; P=0.18). Heterogeneity for all outcomes and subgroups was low (I^2=0.00%, P>0.99).

Conclusions Advanced therapies did not increase MACCE risk in UC induction and maintenance trials. Longer follow-up studies with real-world data are required to confirm these findings outside the RCT setting.

Keywords Ulcerative colitis, biologic medicine, meta-analysis, cardiovascular disease, complications

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Conflict of Interest: None

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Introduction

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD), characterized by mucosal inflammation confined to the colon [1]. Hallmark symptoms of UC include diarrhea that can be bloody, rectal urgency and tenesmus, typically presenting in early adulthood [2]. UC follows a relapsing and remitting course, with intermittent flares of disease [1]. Mild-to-moderate UC is usually managed with 5-aminosalicylic acid (5-ASA) compounds and intermittent steroids, with surgery reserved for refractory cases [3,4]. In the modern era, advanced therapies (encompassing biologic and small molecule therapies) have become cornerstones of UC

treatment, demonstrating efficacy in inducing and maintaining remission in moderate-to-severe UC [5,6].

Patients with IBD have an increased baseline risk of cardiovascular disease (CVD) and associated complications [7-9]. Elevated inflammatory markers are thought to contribute to the onset and progression of atherosclerosis [10]. A recent meta-analysis reported a positive association between IBD and higher CVD incidence, reinforcing the evidence of increased cardiovascular morbidity and mortality in IBD patients [11].

Randomized controlled trials (RCTs) suggest that advanced therapies may confer an increased risk of major adverse cerebrovascular and cardiovascular events (MACCEs) [12]. A meta-analysis in psoriasis patients demonstrated no increased risk with anti-tumor necrosis factor (TNF)-α inhibitors and anti-interleukin (IL)-17A agents [13]. In contrast, a *post hoc* RCT in rheumatoid arthritis (RA) patients treated with tofacitinib reported a higher rate of cardiovascular events [14]. In view of these safety concerns, recent studies now use adjudication committees to review and verify MACCE reports [15].

Whilst the adverse effects of advanced therapies are well documented, evidence on their cardiovascular safety in UC is limited [16,17]. Given the increased cardiovascular risk in UC and growing concerns around advanced therapies, we aimed to systematically evaluate RCT evidence related to the MACCE risk in UC patients treated with advanced therapies. Secondary objectives included assessing whether trial design or duration influenced this risk.

Materials and methods

Search strategy and study selection

This review was registered with the International Prospective Register for Systematic Reviews (PROSPERO) with registration number CRD42024610532, and follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance (Supplementary Table 1) [18]. Medline (EBSCO), Cochrane and EMBASE were searched from inception to February 2025. The search strategy used terminology relating to "Ulcerative Colitis", "Biologic therapy", "Adverse cardiovascular event" and "randomized controlled trial" (Supplementary Table 2). No ethical approval was required, given that this was a meta-analysis of previously published data.

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Inclusion and exclusion criteria

RCTs that investigated the safety of advanced therapies in induction or maintenance trials in adult UC patient were included. Eligible studies investigated anti-TNFs (golimumab, infliximab, adalimumab), anti-integrins (vedolizumab, etrolizumab), anti-ILs, including anti-IL-12/23 (ustekinumab) and anti-IL-23 agents (mirikizumab, risankizumab, guselkumab), Jason kinase (JAK) inhibitors (filgotinib, upadacitinib, tofacitinib), and sphingosine-1-phosphate (S1P) inhibitors (ozanimod, etrasimod), using either placebo or active comparators via any route of administration. Non-randomized controlled trials, case reports, review articles, editorials, research letters, case series, case-control studies, observational studies, systematic reviews and meta-analyses were excluded. Induction studies lasting fewer than 14 days, maintenance studies shorter than 22 weeks, and phase 2 RCTs were excluded. Long-term open-label studies were excluded because of the lack of an active comparator.

Screening and data extraction

All references were imported into reference management software, where 1 reviewer (IP) removed duplicates. Two reviewers (IP and DB) independently screened the titles and abstracts against the inclusion criteria. The same reviewers extracted the data into pre-formatted tables, capturing demographics (number of participants, age, sex) and study outcomes (MACCEs). MACCEs were defined as myocardial infarction, cerebrovascular accident (ischemic and hemorrhagic stroke), cardiovascular death and all-cause mortality. Information regarding the use of independent adjudication committees was not systematically extracted, due to inconsistent reporting. If RCTs did not separately report cardiovascular or cerebrovascular events, these were recorded as zero. Trial-level event data for the included analyses are presented in Supplementary Tables 3-5. Any disagreements between reviewers were resolved by discussion; if consensus was not reached a third reviewer (BSS) made the final decision.

Risk of bias assessment

The quality of each study was assessed by 2 reviewers (IP and DB) using Cochrane's tool for RCTs (RoB2) [19]. This tool evaluates the risk of performance, reporting, detection, attrition and other potential sources of bias. Any unresolved disagreements between the 2 reviewers were settled by involving a third reviewer. A formal certainty-of-evidence assessment was not performed, as the primary objective was to evaluate a rare safety outcome with low event rates, rather than compare treatment efficacy. Publication bias was assessed visually using funnel plots, with pseudo-95% confidence intervals (CIs).

Statistical analysis

Statistical analyses were performed using Stata SE 18.5 [20]. Data were entered into Stata and confirmed accurate by an independent reviewer. Dichotomous outcomes were presented as odds ratios (ORs), while continuous outcomes were expressed as mean differences. When only median and interquartile ranges were provided, they were converted to mean and standard deviation using the equation of Hozo *et al* [21]. A continuity correction of 0.5 was applied to studies with all zero event cells, including studies with zero events in both treatment arms. Primary analyses were conducted using a random-effects model. Sensitivity analyses calculated Peto ORs for the overall, induction and maintenance analyses, which excluded studies with zero events in both arms. Results were displayed as forest plots with 95%CIs, and the unit of analysis was individual patients. In trials reporting both induction and maintenance phases, we included in our overall analysis only the outcome data associated with the longest randomized follow-up (including by drug class/agent, follow-up duration), to avoid biasing pooled estimates. Induction and maintenance datasets were analysed separately. Additional analyses were performed according to individual drug classes and agents, while further sensitivity analyses included applying a fixed-effect model across all analyses and performing a leave-one-out sensitivity analysis of the overall pooled estimate. Heterogeneity was assessed using the Cochran Q test and quantified with the I^2 statistic. An I^2 value between 0% and 50% was considered low heterogeneity; 50% to 75% represented moderate heterogeneity; and 75% to 100% indicated substantial heterogeneity [22]. Publication bias was assessed through visual inspection of funnel plot asymmetry.

Results

A total of 982 citations were retrieved, and 481 articles were screened against the inclusion criteria after the removal of duplicates (Fig. 1). Thirty-one studies reporting 54

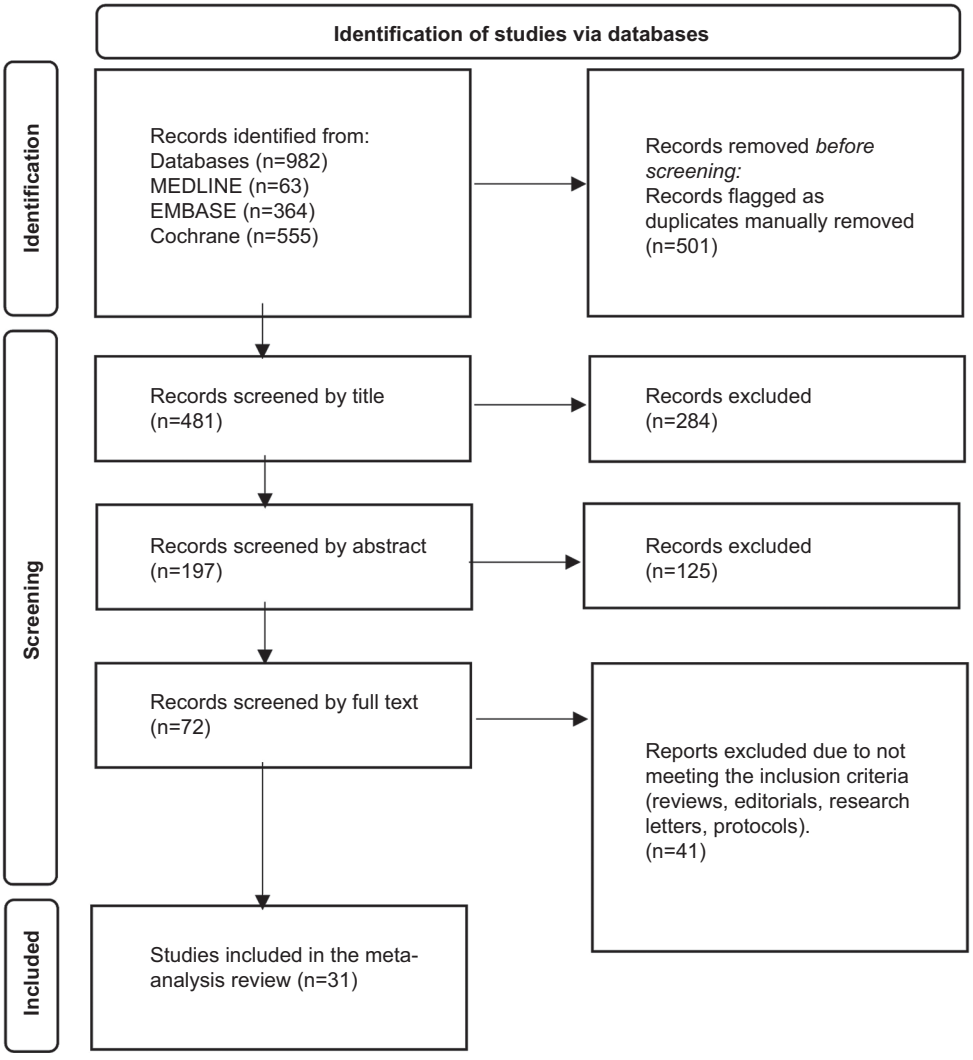

Figure 1 PRISMA flowchart

RCTs met the inclusion criteria. Several studies contained separate induction and maintenance RCTs, accounting for the discrepancy between the number of included studies and RCTs. Trials were published in English between 2005 and 2025 (Table 1). Of the 54 RCTs, 29 were induction trials, and 25 were maintenance trials. The intervention agents, their corresponding comparators and baseline characteristics of the participants in the trials are listed in Table 2.

A total of 11,721 patients with UC were included, of whom 7307 (62.3%) received biologics or small molecule therapies. Participants had a mean age of 40.6±13.3 years, and 59.1% were male. The median follow up was 52 weeks (interquartile range: 41-54 weeks).

Outcome synthesis

Overall MACCEs

The pooled OR found no greater risk of MACCEs when comparing advanced therapies to their controls (OR 0.63, 95%CI 0.32-1.21; P=0.18). Patients in 18 RCTs did not

Table 1 Study-related information

Author [ref.]	Date of publication	Journal	Design	Drug explored
Sands *et al* (UNIFI) [32]	2019	The New England Journal of Medicine	RCT	Ustekinumab
Sands *et al* (VARSITY) [33]	2019	The New England Journal of Medicine	RCT	Vedolizumab
Motoya *et al* [34]	2019	PLOS One	RCT	Vedolizumab
Feagan *et al* (GEMINI) [35]	2013	The New England 3Journal of medicine	RCT	Vedolizumab
Sandborn *et al* (PURSUIT-SC) [36]	2014	Gastroenterology	RCT	Golimumab
Rutgeers *et al* (PURSUIT-IV) [37]	2015	Alimentary Pharmacology and Therapeutics	RCT	Golimumab
Sanborn *et al* (PURSUIT-M) [38]	2014	Gastroenterology	RCT	Golimumab
Hibi *et al* (PURSUIT-J) [39]	2017	Journal of Gastroenterology	RCT	Golimumab
Rutgeers *et al* (ACT) [40]	2005	The New England Journal of Medicine	RCT	Infliximab
Jiang *et al* [41]	2015	Journal of Clinical Gastroenterology	RCT	Infliximab
Kobayashi *et al* [42]	2016	Journal of Gastroenterology	RCT	Infliximab
Xi'an Janssen [43]	2014	NA	RCT	Infliximab
Laharie *et al* [44]	2012	Lancet Gastroenterology	RCT	Infliximab
Haunauer *et al* (LIBERTY-UC) [45]	2024	Journal of Gastroenterology	RCT	Infliximab
Reinisch *et al* (ULTRA 1) [46]	2011	BMJ GUT	RCT	Adalimumab
Sandborn *et al* (ULTRA 2) [47]	2012	Gastroenterology	RCT	Adalimumab
Suzuki *et al* [48]	2013	Journal of Gastroenterology	RCT	Adalimumab
Rubin *et al* (HIBISCUS) [49]	2022	The Lancet Gastroenterology	RCT	Etrolizumab
Danese *et al* (GARDENIA) [50]	2022	The Lancet Gastroenterology	RCT	Etrolizumab
Peyrin-Biroulet *et al* (HICKORY) [51]	2022	The Lancet Gastroenterology	RCT	Etrolizumab
Vermeire *et al* (LAUREL) [52]	2022	The Lancet Gastroenterology	RCT	Etrolizumab
Sandborn *et al* (TRUE NORTH) [53]	2021	The New England journal of medicine	RCT	Ozanimod
Feagan *et al* (SELECTION) [54]	2021	The Lancet	RCT	Filgotinib
Vermiere *et al* (U-ACCOMPLISH) [55]	2021	Journal of Crohn's and Colitis	RCT	Upadacitinib
Danese *et al* (U-ACHIEVE) [56]	2021	Journal of Crohn's and Colitis	RCT	Upadacitinib
Danese *et al* (U-ACCOMPLISH) [57]	2022	The Lancet	RCT	Upadacitinib
Sandborn *et al* (OCTAVE) [58]	2017	The New England Journal of Medicine	RCT	Tofacitinib
D'Haens *et al* (LUCENT) [59]	2023	The New England Journal of Medicine	RCT	Mirikizumab
Sandborn *et al* (ELEVATE UC) [60]	2023	The Lancet	RCT	Etrasimod
Louis *et al* [61]	2024	JAMA	RCT	Risankizumab
Rubin *et al* (QUASAR) [62]	2025	The Lancet	RCT	Guselkumab

RCT, randomized controlled trial

Table 2 Baseline characteristics and trial information

Study [ref.]	Trial design	Control agent	Participants (n)			Mean age (SD)			Male sex (n)			Follow-up (weeks)
			All	Int	Con	All	Int	Con	All	Int	Con	
Ustekinumab												
Sands *et al* (UNIFI I) [32]	Induction	Placebo	961	642	319	41.7 (13.7)	41.9 (13.8)	41.2 (13.5)	582	385	197	8
Sands *et al* (UNIFI 2) [32]	Maintenance	Placebo	523	348	175	40.7 (13.6)	40.1 (13.3)	42 (13.8)	297	190	107	52
Vedolizumab												
Sands *et al* (VARSITY) [33]	Induction & maintenance	Adalimumab	769	383	386	40.6 (13.5)	40.8 (13.7)	40.5 (13.4)	450	234	216	68
Motoya *et al* [34]	Induction	Placebo	292	210	82	42.9 (14.9)	42.3 (14.4)	44 (16.0)	154	99	55	10
Motoya *et al* [34]	Maintenance	Placebo	83	41	42	42.8 (14.3)	43 (14.3)	42.6 (14.4)	54	21	23	60
Feagan *et al* (GEMINI I) [35]	Induction	Placebo	895	746	149	40.3 (13.1)	40.1 (13.2)	41.2 (12.5)	525	433	92	6
Feagan *et al* (GEMINI 2) [35]	Maintenance	Placebo	373	227	126	40 (13.7)	39.8 (13.5)	40.3 (14.0)	207	138	69	52
Golimumab												
Sandborn *et al* (PURSUIT-SC) [36]	Induction	Placebo	1065	734	331	40 (13.4)	40.4 (13.5)	39.0 (13.0)	596	421	175	6
Rutgeers *et al* (PURSUIT-IV) [37]	Induction	Placebo	291	214	77	41.0 (13.7)	41.0 (14.6)	40.9 (12.6)	174	127	47	6
Sanborn *et al* (PURSUIT-M) [38]	Maintenance	Placebo	1228	943	285	40.3 (13.4)	40.7 (13.3)	39.2 (13.7)	700	564	136	54
Hibi *et al* (PURSUIT-J) [39]	Maintenance	Placebo	123	92	31	41.6 (14.9)	41.1 (15.1)	42.9 (14.4)	80	61	19	52
Infliximab												
Rutgeers *et al* (ACT1) [40]	Induction	Placebo	364	243	121	41.9 (14.3)	42.1 (14.6)	41.4 (13.7)	222	150	72	8
Rutgeers *et al* (ACT2) [40]	Induction	Placebo	364	241	123	40.0 (13.3)	40.4 (13.2)	39.3 (13.5)	215	144	71	8
Rutgeers *et al* (ACT1) [40]	Maintenance	Placebo	364	241	121	41.9 (14.3)	42.1 (14.6)	41.4 (13.7)	222	150	72	54
Rutgeers *et al* (ACT2) [40]	Maintenance	Placebo	364	82	123	40.0 (13.3)	40.4 (13.2)	39.3 (13.5)	215	144	71	30
Jiang *et al* [41]	Induction	Placebo	123	82	41	34.3 (14.2)	34.2 (14.0)	34.5 (14.9)	75	50	25	8
Jiang *et al* [41]	Maintenance	Placebo	123	104	41	34.3 (14.2)	34.2 (14.0)	34.5 (14.9)	75	50	25	30
Kobayashi *et al* [42]	Induction	Placebo	208	73	104	38.9 (12.8)	40 (12.7)	37.8 (12.9)	123	66	67	8
Kobayashi *et al* [42]	Maintenance	Placebo	145	50	72	NP	NP	NP	NP	NP	NP	30
Xi'an Janssen [43]	Induction	Placebo	99	50	49	37	NP	NP	NP	NP	NP	8
Xi'an Janssen [43]	Maintenance	Placebo	99	57	49	37	NP	NP	NP	NP	NP	26
Laharie *et al* [44]	Induction	Ciclosporin	115	295	58	37.5 (18.5)	36 (19.3)	39 (17.8)	60	30	30	14
Hanauer *et al* (LIBERTY-UC) [45]	Maintenance	Placebo	438		144	37.7 (3.2)	37.0 (3.0)	39 (3.3)	246	163	83	54
Adalimumab												
Reinisch *et al* (ULTRA 1) [46]	Induction	Placebo	390	260	130	37.8 (9.44)	38.2 (9.6)	37.0 (9.0)	238	156	82	8
Sandborn *et al* (ULTRA 2) [47]	Induction	Placebo	494	248	246	40.4 (12.9)	39.6 (12.5)	41.3 (13.2)	294	142	152	8
Sandborn *et al* (ULTRA 2) [47]	Maintenance	Placebo	494	248	246	40.4 (12.8)	39.6 (12.5)	41.3 (13.2)	NP	NP	NP	52
Suzuki *et al* [48]	Induction	Placebo	273	243	96	42.7 (14.4)	43.4 (14.8)	41.3 (13.6)	181	111	70	8
Suzuki *et al* [48]	Maintenance	Placebo	263	171	92	42.7 (14.4)	NP	NP	NP	NP	NP	52

(*Contd...*)

Table 2 (*Continued*)

Study [ref.]	Trial design	Control agent	Participants (n)			Mean age (SD)			Male sex (n)			Follow-up (weeks)
			All	Int	Con	All	Int	Con	All	Int	Con	
Etrolizumab												
Rubin *et al* (HIBISCUS I) [49]	Induction	Adalimumab	358	144	214	38.2 (9.3)	38.7 (10.0)	36 (9.8)	195	156	39	10
Rubin *et al* (HIBISCUS II) [49]	Induction	Adalimumab	358	143	215	38.1 (9.2)	38.5 (9.3)	36.5 (8.3)	203	165	38	10
Danese *et al* (GARDENIA)[50]	Induction	Infliximab	397	199	198	37 (9.2)	37 (9.7)	37 (8.7)	250	118	132	10
Danese *et al* (GARDENIA)[50]	Maintenance	Infliximab	198	95	103	38 (9.2)	NP	NP	NP	NP	NP	52
Peyrin-Biroulet *et al* (HICKORY) [51]	Induction	Placebo	479	384	95	38.4 (10.1)	39 (10.2)	36 (9.7)	278	224	54	14
Peyrin-Biroulet *et al* (HICKORY) [51]	Maintenance	Placebo	232	115	117	40.0 (9.6)	38 (9.5)	42 (9.3)	132	60	72	66
Vermeire *et al* (LAUREL) [52]	Maintenance	Placebo	214	108	106	37.0 (9.2)	38.0 (8.5)	36.0 (9.8)	112	60	52	62
Ozanimod												
Sandborn *et al* (TRUE NORTH) [53]	Induction	Placebo	1012	796	216	41.8 (13.6)	41.7 (13.6)	41.9 (13.6)	602	459	143	10
Sandborn *et al* (TRUE NORTH) [53]	Maintenance	Placebo	457	230	227	41.8 (13.6)	NP	NP	NP	NP	NP	52
Filgotinib												
Feagan *et al* (SELECTION) [54]	Induction	Placebo	659	522	137	41.7 (13.1)	41.0 (12.9)	42.0 (13.2)	367	280	87	10
Feagan *et al* (SELECTION A) [54]	Induction	Placebo	689	547	142	43.3 (14.5)	44.0 (14.9)	43,0 (14.2)	420	334	86	10
Feagan *et al* (SELECTION B) [54]	Maintenance	Placebo	664	381	283	42.6 (13.5)	NP	NP	342	NP	NP	58
Upadacitinib												
Vermeire *et al* (U-ACCOMPLISH) [55]	Induction	Placebo	515	341	174	40.7 (9.6)	40.0 (9.5)	42.0 (9.6)	321	214	107	8
Danese *et al* (U-achieve) [56]	Induction	Placebo	473	319	154	43.5 (9.9)	43.0 (10)	44.5 (9.7)	295	198	97	8
Danese *et al* (U-ACCOMPLISH) [57]	Maintenance	Placebo	451	302	149	40.3 (17.9)	40.5 (16.2)	40.0 (21.0)	272	187	85	52
Tofacitinib												
Sandborn *et al* (OCTAVE 1) [58]	Induction	Placebo	598	476	122	41.4 (14.3)	41.3 (14.1)	41.8 (15.3)	354	277	77	8
Sandborn *et al* (OCTAVE 2) [58]	Induction	Placebo	541	429	112	40.9 (13.4)	41.1 (13.5)	40.4 (13.2)	314	259	55	8
Sandborn *et al* (OCTAVE sustain) [58]	Maintenance	Placebo	593	395	198	42.7 (14.0)	42.4 (14.0)	43.4 (14.0)	329	213	116	52
Mirikizumab												
D'Haens *et al* (LUCENT 1) [59]	Induction	Placebo	1162	868	294	42.5 (13.9)	42.9 (13.9)	41.3 (13.8)	695	530	165	12
D'Haens *et al* (LUCENT 2) [59]	Maintenance	Placebo	1162	868	294	42.5 (13.9)	42.9 (13.9)	41.3 (13.8)	695	530	165	52
Etrazimod												
Sandborn *et al* (ELEVATE UC 12) [60]	Induction	Placebo	354	238	116	40.3 (13.4)	40.3 13.5	40.4 13.3	208	135	73	12
Sandborn *et al* (ELEVATE UC 52) [60]	Maintenance	Placebo	433	289	144	40.4 (14.0)	41.2 (14.0)	38.9 (14.0)	240	152	88	52
Risankizumab										385		
Louis *et al* (INSPIRE) [61]	Induction	Placebo	975	650	325	42.1 (13.8)	41.8 (13.5)	42.8 (14.3)	586	212	201	12
Louis *et al* (COMMAND)[61]	Maintenance	Placebo	548	365	183	40.9 (14.0)	41.7 (13.8)	39.2 (14.2)	525		313	52
Guselkumab										283		
Rubin *et al* (QUASAR) [62]	Induction	Placebo	701	421	280	40.5 (13.7)	41.0 (13.9)	39.8 (13.4)	444	202	161	24
Rubin *et al* (QUASAR) [62]	Maintenance	Placebo	568	378	190	40.7 (13.7)	40.5 (13.8)	41.2 (13.6)	311		109	44

Int, intervention; Con, control; NP, not provided

experience MACCEs while receiving an intervention, but 15 MACCEs were observed during the randomized controlled phase of 10 trials. The heterogeneity was low among the included trials (I^2=0.00%, P>0.99) (Fig. 2).

Association between MACCEs and drug class

Anti-TNFs, anti-integrins, anti-ILs, JAK inhibitors and S1P inhibitors were not associated with a greater risk of MACCEs. The corresponding pooled ORs were: 0.57, 95%CI 0.19-1.74; P=0.32 for anti-TNFs; 0.76, 95%CI 0.18-3.11; P=0.70 for anti-integrins; 0.38, 95%CI 0.06-2.17; P=0.27 for anti-ILs; 0.86, 95%CI 0.15-4.74; P=0.86 for JAK inhibitors; and 0.70, 95%CI 0.08-7.59; P=0.83 for S1P inhibitors (Fig. 3).

Association of MACCEs with trial design and duration

Considered separately, by RCT design, intervention agents were not associated with a greater risk of MACCEs in either induction (OR 0.62, 95%CI 0.32-1.18; P=0.14) or maintenance trials (OR 0.57, 95%CI 0.28-1.18; P=0.13) (Fig. 4). Similarly, trials grouped by treatment duration (up to 26, 52 and 78 weeks) did not demonstrate a greater risk of MACCEs (Supplementary Fig. 1).

Additional analyses

In subgroup analysis, individual drug agents were not associated with a greater risk of MACCEs. When the RCTs were further stratified by induction or maintenance design, no drug agent or class was associated with a greater risk of MACCEs. Finally, when fixed-effect modeling was applied for all included outcomes, the MACCE risk remained unaffected, while the Peto ORs for the overall, induction and maintenance trials remained consistent with the primary results (Supplementary Figs. 2-14). The leave-one-out analysis revealed no significant discrepancies compared to the original analysis (Supplementary Fig. 15).

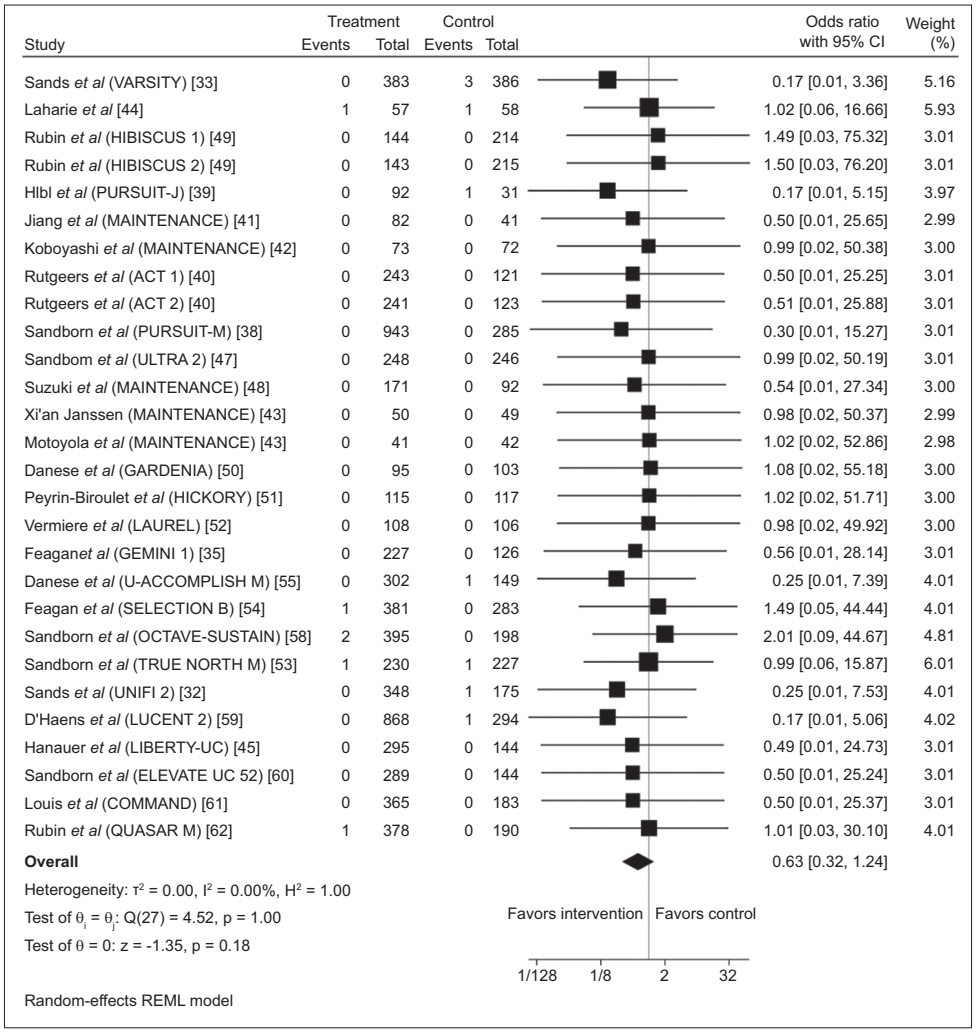

Figure 2 Forest plots of comparison of major adverse cerebrovascular and cardiovascular events overall. The solid squares denote the odds ratios (ORs). The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size

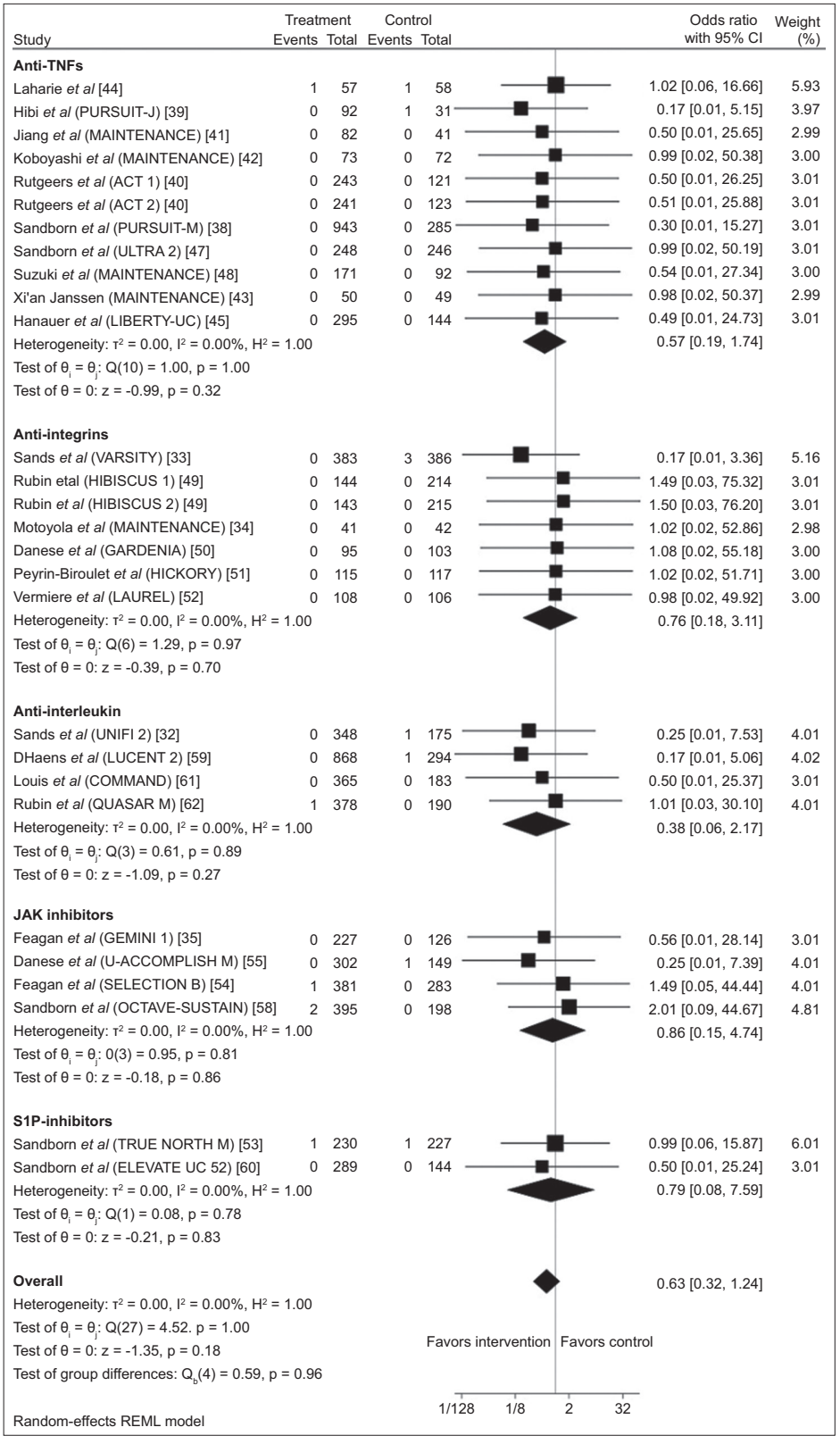

Figure 3 Forest plots of comparison of major adverse cerebrovascular and cardiovascular events overall per drug group. The solid squares denote the odds ratios (ORs). The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size

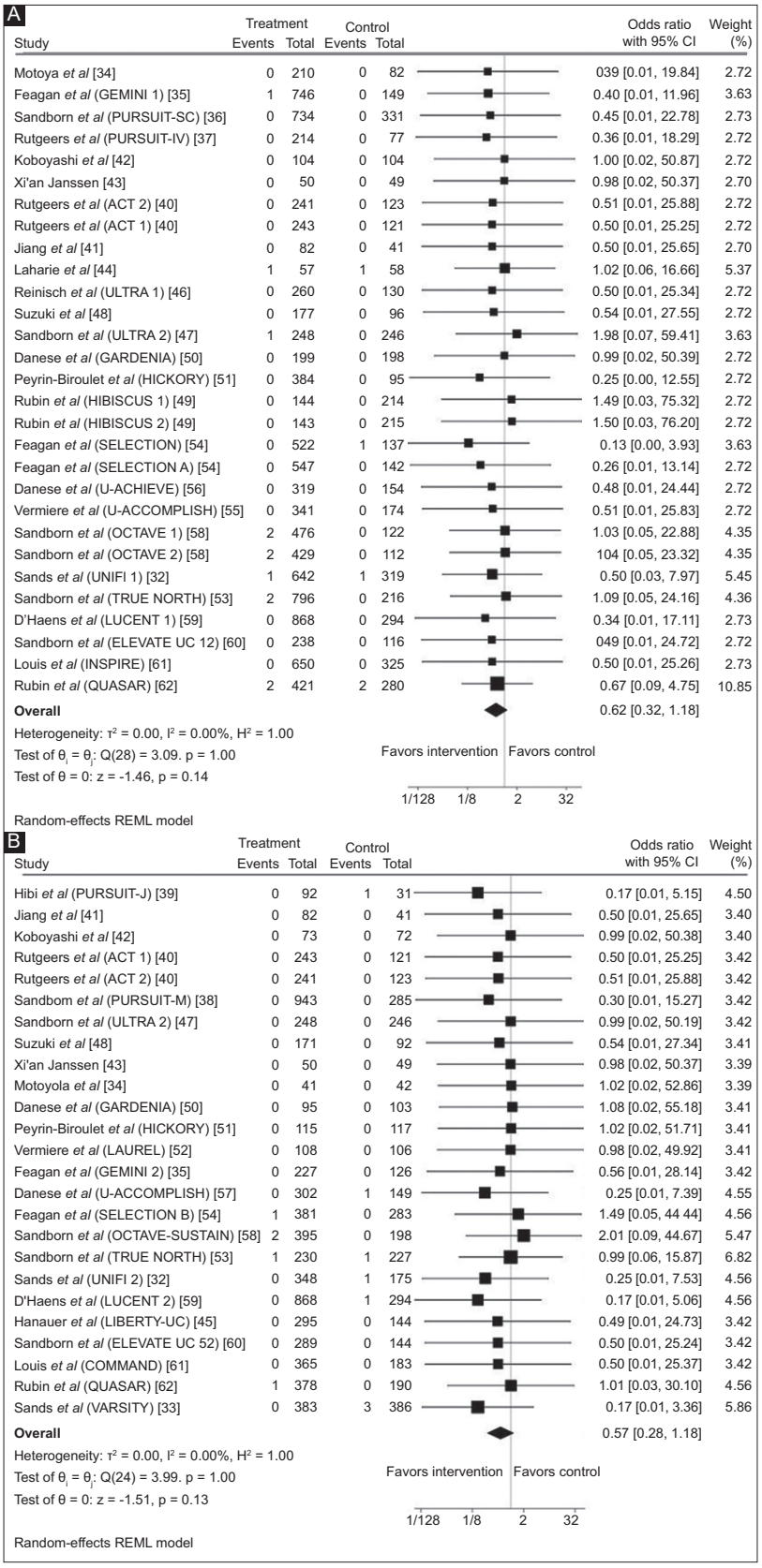

Figure 4 Forest plots of comparison of major adverse cerebrovascular and cardiovascular events in Induction (A) and maintenance (B) trials. The solid squares denote the odds ratios (ORs). The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size

Risk of bias assessment

The overall quality of the studies was high, with most studies rated as having a low or uncertain risk of bias. Two studies were rated uncertain regarding their selection bias, whilst 6 were rated uncertain about blinding of participants (Supplementary Figs. 16 and 17).

Visual inspection of the funnel plot suggested a low risk of publication bias, although the interpretability is limited given the sparse events in our overall analysis (Supplementary Fig. 18).

Discussion

This meta-analysis of RCTs found no greater risk of MACCEs in UC patients receiving advanced therapies, compared to placebo and active comparators. This remained true for comparisons of anti-TNFs, anti-integrins, anti-IL12/23 and anti-IL23 agents, JAK-inhibitors and S1P inhibitors. Additionally, we did not find a greater MACCE risk with induction therapy, despite the higher therapeutic dosing and inflammatory burden in these patients, while maintenance therapy and trial duration did not influence this risk. The pooled OR did not demonstrate a significant difference in MACCE risk with biologics and small molecules. The low heterogeneity for all outcomes, and low risk of bias in the included studies, strengthen the confidence in our results.

The cardiovascular safety of biologic agents is under debate. A recent meta-analysis of immune-mediated inflammatory disorders (IMIDs), including IBD, RA, psoriasis/psoriatic arthritis and ankylosing spondylitis, reported an elevated MACCE risk in those treated with IL-12/23, JAK-inhibitors and anti-TNF-α agents. However, direct comparisons between these therapies showed no significant differences [16]. Conversely, a meta-analysis of IBD patients treated with biologics found no greater risk of cardiovascular adverse events (AEs) [15]. Our findings align with the latter study, and further demonstrate no greater MACCE risk with newer biologic therapies (mirikizumab and guselkumab) or classes (anti-IL-23 agents and S1P-inhibitors), none of which have been assessed in prior UC meta-analyses. This discrepancy between broader IMID and UC-specific findings may reflect differences in the baseline cardiovascular risk, inflammatory burden and patient populations included in these analyses [15,16].

Recent evidence supports the elevated risk of cardiovascular AEs in people with IBD. A large meta-analysis found a significant association of cardiovascular risk in IBD patients after adjusting for baseline cardiovascular risk factors [23]. Similarly, a nationwide cohort study of 28,833 Danish patients reported an increased risk of ischemic heart disease within the first year of IBD diagnosis. Notably, anti-TNF-α therapy reduced this risk, suggesting that anti-inflammatory treatments may help mitigate cardiovascular burden [24]. Furthermore, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), demonstrated a significantly lower rate of recurrent cardiovascular events with canakinumab (anti-IL-1β) in a high CVD-risk cohort [25]. These findings, along with the lack of increased risk observed in our analysis, suggest that anti-inflammatory interventions could potentially minimize future cardiovascular risk by managing systemic inflammation.

The risk of MACCEs with small molecule therapies varies across studies. A meta-analysis of multiple sclerosis patients treated with S1P-inhibitors (e.g., ozanimod and etrasimod), reported a 1.21-fold higher risk of cardiovascular AEs [26]. However, a *post hoc* analysis from the True North trial, which evaluated UC patients over a 94-week follow up, found no greater MACCE risk in ozanimod-treated patients [27]. Similarly, a meta-analysis of JAK inhibitors in IBD patients showed no significant difference in events, though tofacitinib exhibited a dose-dependent trend towards higher risk [28]. The Oral Rheumatoid Arthritis (ORAL) surveillance trial further reported a higher MACCE incidence in older RA patients treated with tofacitinib compared to those receiving anti-TNFs [29]. Our study did not observe a greater MACCE risk with small molecule therapies, whilst further demonstrating the lack of associated risk with newer agents (etrasimod). However, this observed effect in UC studies may be attributed to the lower prevalence of cardiovascular risk factors in this population compared to other IMIDs [30,31].

There are several limitations that should be considered when interpreting our findings. Few studies explicitly reported MACCEs or used adjudication committees for adjudicating suspected cases. Most trials had short durations (median 52 weeks) and relatively small sample sizes. These factors could influence the power of the studies to observe a change in MACCE risk, and may not capture the long-term risk of MACCEs in UC patients on advanced therapies. The low event rate, despite the large number of participants included in our analysis, highlights the need for cautious interpretation and may have contributed to the low heterogeneity observed across our analyses. Additionally, we included only phase 3 RCTs, which often exclude patients with a pre-existing or elevated risk of CVD. Therefore, the background risk for both the treatment and control groups was probably reduced, limiting the generalisability of our findings. Rare cardiovascular events may be more reliably captured in large registries, administrative datasets, post-marketing surveillance studies and dedicated prospective cohorts with a longer follow-up, and more detailed assessment of cardiovascular risk factors and inflammatory burden.

There are clinical implications to our study. The safety results of our meta-analysis can help guide gastroenterologists starting patients on advanced therapies. The absence of a greater MACCE risk in our analysis suggests that therapy selection for UC patients should be guided by disease activity, rather than concerns about the cardiovascular risk associated with any medication. Moreover, given the higher prevalence of CVD in this population, our findings suggest that anti-inflammatory intervention could help reduce cardiovascular risk and potentially improve the cardiovascular burden of UC patients.

In conclusion, we found no significant greater risk of MACCEs with the use of advanced therapies in patients with UC. Future large prospective and real-world studies are

required to investigate the long-term cardiovascular impact of these agents.

Summary Box

What is already known:

- Patients with ulcerative colitis (UC) have a higher baseline risk of cardiovascular disease, probably driven by systemic inflammation
- Advanced therapies (including biologic and small molecule therapies) are highly effective treatments for the induction and maintenance of remission in UC
- Concerns regarding major adverse cerebrovascular and cardiovascular events (MACCEs) have prompted the use of adjudication committees to confirm and verify MACCEs for certain biologics

What the new findings are:

- Advanced therapies were not associated with a greater risk of MACCEs in randomized controlled trials involving patients with UC
- No individual drug or drug class was associated with a higher MACCE risk
- Treatment phase (induction and maintenance) and trial duration did not influence MACCE risk

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Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 1-2
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 2-3
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	Page 3
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 3-4
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 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary table 2
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
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
	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.	Pages 4-5
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 5
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 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)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 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 model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	Page 5
	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).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location reported
		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.	Page 5 and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1,2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6 and supplementary Figures 16,17
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.	Figures 2-4 and Supplementary Figures 1-15
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 6-7 and Figures 2-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 6-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7 and Supplementary Figures 7-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7 and Supplementary Figure 18
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 7-8
	23b	Discuss any limitations of the evidence included in the review.	Page 8
	23c	Discuss any limitations of the review processes used.	Page 8
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 8,9
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
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 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
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.	Supplementary material

Supplementary Table 2 Example Search strategy

Search	Query	Items found
#6	(#1 AND #2 AND #4 AND #5)	364
#5	("randomized controlled trial" OR "randomized control trial" OR RCT OR Random* Control* Trial*).af.	147,544
#4	("cardiovascular event" OR "cardiovascular events" OR "adverse events" OR "cardiovascular outcomes" OR "coronary event" OR "coronary events" or "acute coronary syndrome") OR (Myocard*infarct* OR heart failure* OR cardiac failure* OR "congestive heart failure" OR Stroke* OR bleed* OR embol* OR ischem* OR thrombos* OR ACS*).ab.	2,317,688
#3	("monoclonal antibodies" OR biologic* OR "biological drug" OR "biologic medicine" OR "biologic pharmaceutical" OR "Biologic therapy" OR Adalimumab OR Certolizumab OR Infliximab OR Ustekinumab OR Vedolizumab OR Risankizumab OR "Janus kinase inhibitors" OR tofacitinib OR upadacitinib OR filgotinib OR ozanimod).ti.	283,085
#2	("monoclonal antibodies" OR biologic* OR "biological drug" OR "biologic medicine" OR "biologic pharmaceutical" OR "Biologic therapy" OR Adalimumab OR Certolizumab OR Infliximab OR Ustekinumab OR Vedolizumab OR Risankizumab OR "Janus kinase inhibitors" OR tofacitinib OR upadacitinib OR filgotinib OR ozanimod).ab.	1,479,164
#1	(Ulcer* colit* OR "Ulcerative colitis" OR UC OR Pancolitis* OR Colitis* OR "Left-sided colitis" OR "Distal colitis" OR proctit*).ti.	65,916

Supplementary Table 3 Event by trial dataset for the overall analysis

Trial [ref.]	Intervention MACCEs	Intervention N	Control MACCEs	Control N
Sands *et al* (VARSITY) [33]	0	383	3	386
Laharie *et al* [44]	1	57	1	58
Rubin *et al* (HIBISCUS 1) [49]	0	144	0	214
Rubin *et al* (HIBISCUS 2) [49]	0	143	0	215
Hibi *et al* (PURSUIT-J) [39]	0	92	1	31
Jiang *et al* (MAINTENANCE) [41]	0	82	0	41
Kobayashi *et al* (MAINTENANCE) [42]	0	73	0	72
Rutgeers *et al* (ACT 1) [40]	0	243	0	121
Rutgeers *et al* (ACT 2) [40]	0	241	0	123
Sandborn *et al* (PURSUIT-M) [38]	0	943	0	285
Sandborn *et al* (ULTRA 2) [47]	0	248	0	246
Suzuki *et al* (MAINTENANCE) [48]	0	171	0	92
Xi'an Janssen (MAINTENANCE) [43]	0	50	0	49
Motoyola *et al* (MAINTENANCE) [34]	0	41	0	42
Danese *et al* (GARDENIA) [50]	0	95	0	103
Peyrin-Biroulet *et al* (HICKORY) [51]	0	115	0	117
Vermeire *et al* (LAUREL) [52]	0	108	0	106
Feagan *et al* (GEMINI 1) [35]	0	227	0	126
Danese *et al* (U-ACCOMPLISH M) [55]	0	302	1	149
Feagan *et al* (SELECTION B) [54]	1	381	0	283
Sandborn *et al* (OCTAVE-SUSTAIN) [58]	2	395	0	198
Sandborn *et al* (TRUE NORTH M) [53]	1	230	1	227
Sands *et al* (UNIFI 2) [32]	0	348	1	175
D'Haens *et al* (LUCENT 2) [59]	0	868	1	294
Hanauer *et al* (LIBERTY-UC) [45]	0	295	0	144
Sandborn *et al* (ELEVATE UC 52) [60]	0	289	0	144
Louis *et al* (COMMAND) [61]	0	365	0	183

MACCEs, major adverse cerebrovascular and cardiovascular events

Supplementary Table 4 Event by trial dataset for induction trials

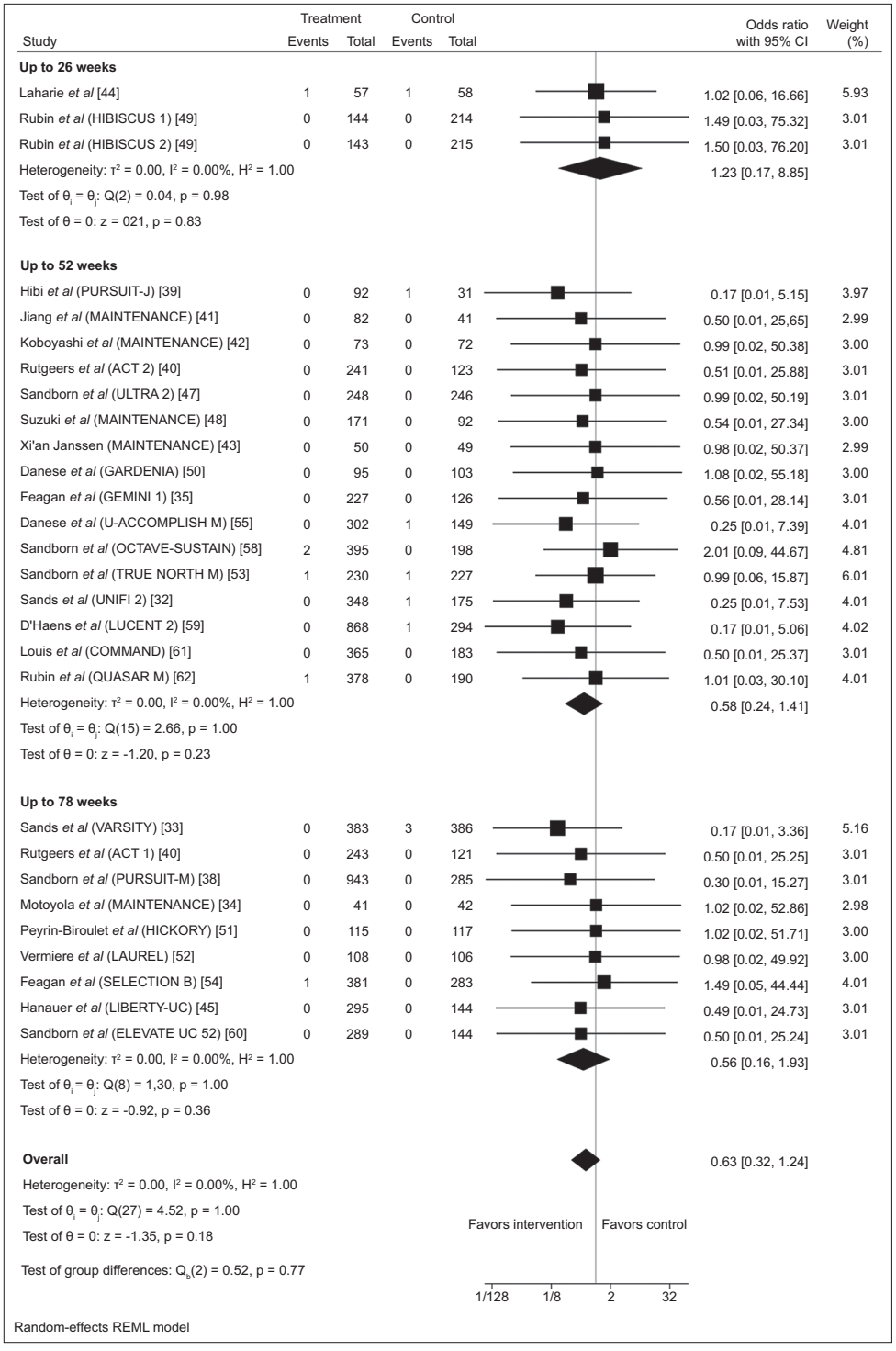
Trial [ref.]	Intervention MACCEs	Intervention N	Control MACCEs	Control N
Motoya *et al* [34]	0	210	0	82
Feagan *et al* (GEMINI 1) [35]	1	746	0	149
Sandborn *et al* (PURSUIT-SC) [36]	0	734	0	331
Rutgeers *et al* (PURSUIT-IV) [37]	0	214	0	77
Kobayashi *et al* [42]	0	104	0	104
Xi'an Janssen [43]	0	50	0	49
Rutgeers *et al* (ACT 2) [40]	0	241	0	123
Rutgeers *et al* (ACT 1) [40]	0	243	0	121
Jiang *et al* [41]	0	82	0	41
Laharie *et al* [44]	1	57	1	58
Reinisch *et al* (ULTRA 1) [46]	0	260	0	130
Suzuki *et al [48]*	0	177	0	96
Sandborn *et al* (ULTRA 2) [47]	1	248	0	246
Danese *et al* (GARDENIA) [50]	0	199	0	198
Peyrin-Biroulet *et al* (HICKORY) [51]	0	384	0	95
Rubin *et al* (HIBISCUS 1) [49]	0	144	0	214
Rubin *et al* (HIBISCUS 2) [49]	0	143	0	215
Feagan *et al* (SELECTION) [54]	0	522	1	137
Feagan *et al* (SELECTION A) [54]	0	547	0	142
Danese *et al* (U-ACHIEVE) [56]	0	319	0	154
Vermeire *et al* (U-ACCOMPLISH) [55]	0	341	0	174
Sandborn *et al* (OCTAVE 1) [58]	2	476	0	122
Sandborn *et al* (OCTAVE 2) [58]	2	429	0	112
Sands *et al* (UNIFI 1) [32]	1	642	1	319
Sandborn *et al* (TRUE NORTH) [53]	2	796	0	216
D'Haens *et al* (LUCENT 1) [59]	0	868	0	294
Sandborn *et al* (ELEVATE UC 12) [60]	0	238	0	116
Louis *et al* (INSPIRE) [61]	0	650	0	325
Rubin *et al* (QUASAR) [62]	2	421	2	280

MACCEs, major adverse cerebrovascular and cardiovascular events

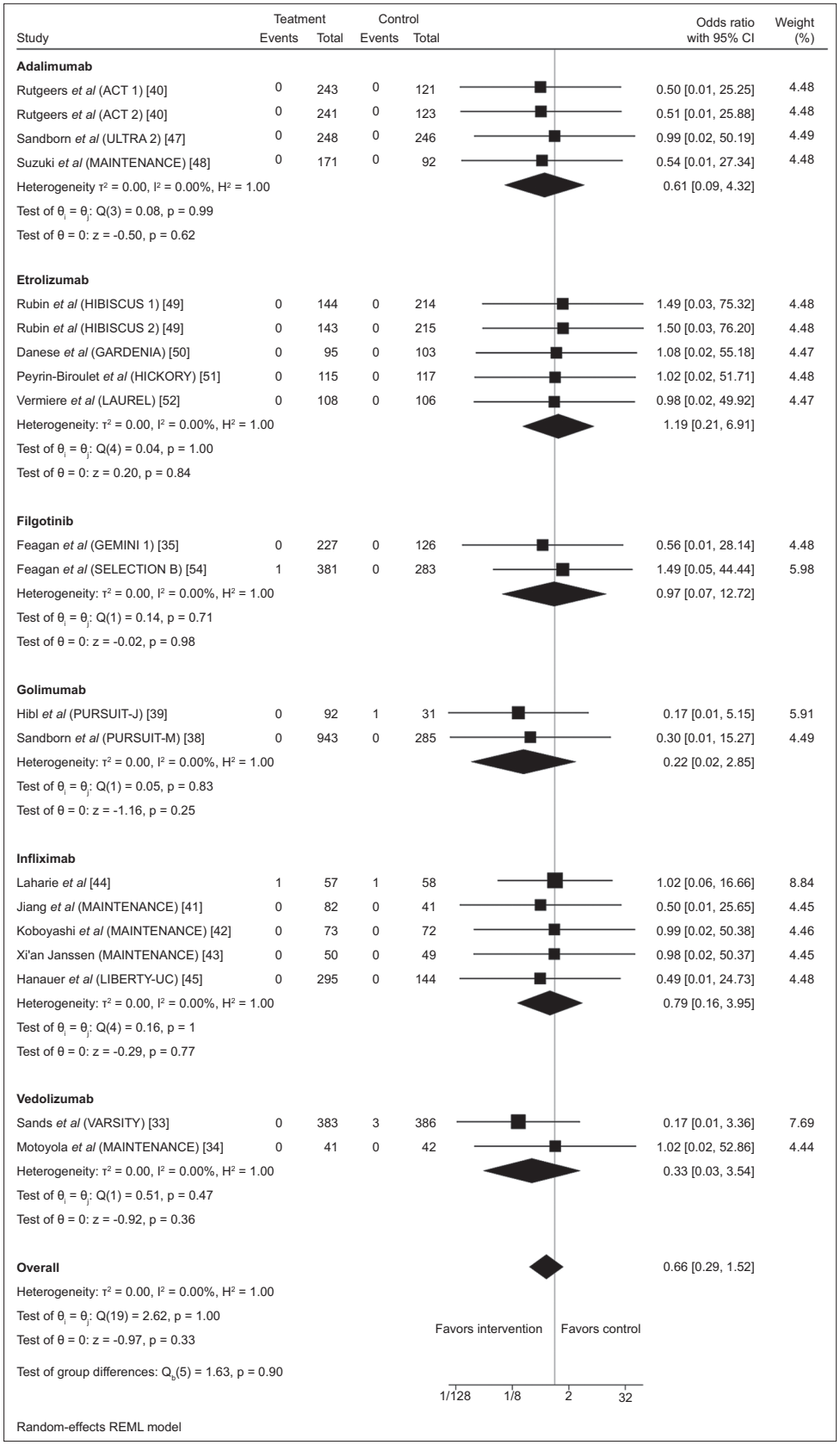
Supplementary Table 5 Event by trial dataset for maintenance trials

Trial [ref.]	Intervention MACCEs	Intervention N	Control MACCEs	Control N
Hibi *et al* (PURSUIT-J) [39]	0	92	1	31
Jiang *et al* [41]	0	82	0	41
Kobayashi *et al* [42]	0	73	0	72
Rutgeers *et al* (ACT 1) [40]	0	243	0	121
Rutgeers *et al* (ACT 2) [40]	0	241	0	123
Sandborn *et al* (PURSUIT-M) [38]	0	943	0	285
Sandborn *et al* (ULTRA 2) [47]	0	248	0	246
Suzuki *et al* [48]	0	171	0	92
Xi'an Janssen [43]	0	50	0	49
Motoya *et al* [34]	m	41	0	42
Danese *et al* (GARDENIA) [50]	0	95	0	103
Peyrin-Biroulet *et al* (HICKORY) [51]	0	115	0	117
Vermeire *et al* (LAUREL) [52]	0	108	0	106
Feagan *et al* (GEMINI 2) [35]	0	227	0	126
Danese *et al* (U-ACCOMPLISH) [57]	0	302	1	149
Feagan *et al* (SELECTION B) [54]	1	381	0	283
Sandborn *et al* (OCTAVE-SUSTAIN) [58]	2	395	0	198
Sandborn *et al* (TRUE NORTH) [53]	1	230	1	227
Sands *et al* (UNIFI 2) [32]	0	348	1	175
D'Haens *et al* (LUCENT 2) [59]	0	868	1	294
Hanauer *et al* (LIBERTY-UC) [45]	0	295	0	144
Sandborn *et al* (ELEVATE UC 52) [60]	0	289	0	144
Louis *et al* (COMMAND) [61]	0	365	0	183
Rubin *et al* (QUASAR) [62]	1	378	0	190
Sands *et al* (VARSITY) [33]	0	383	3	386

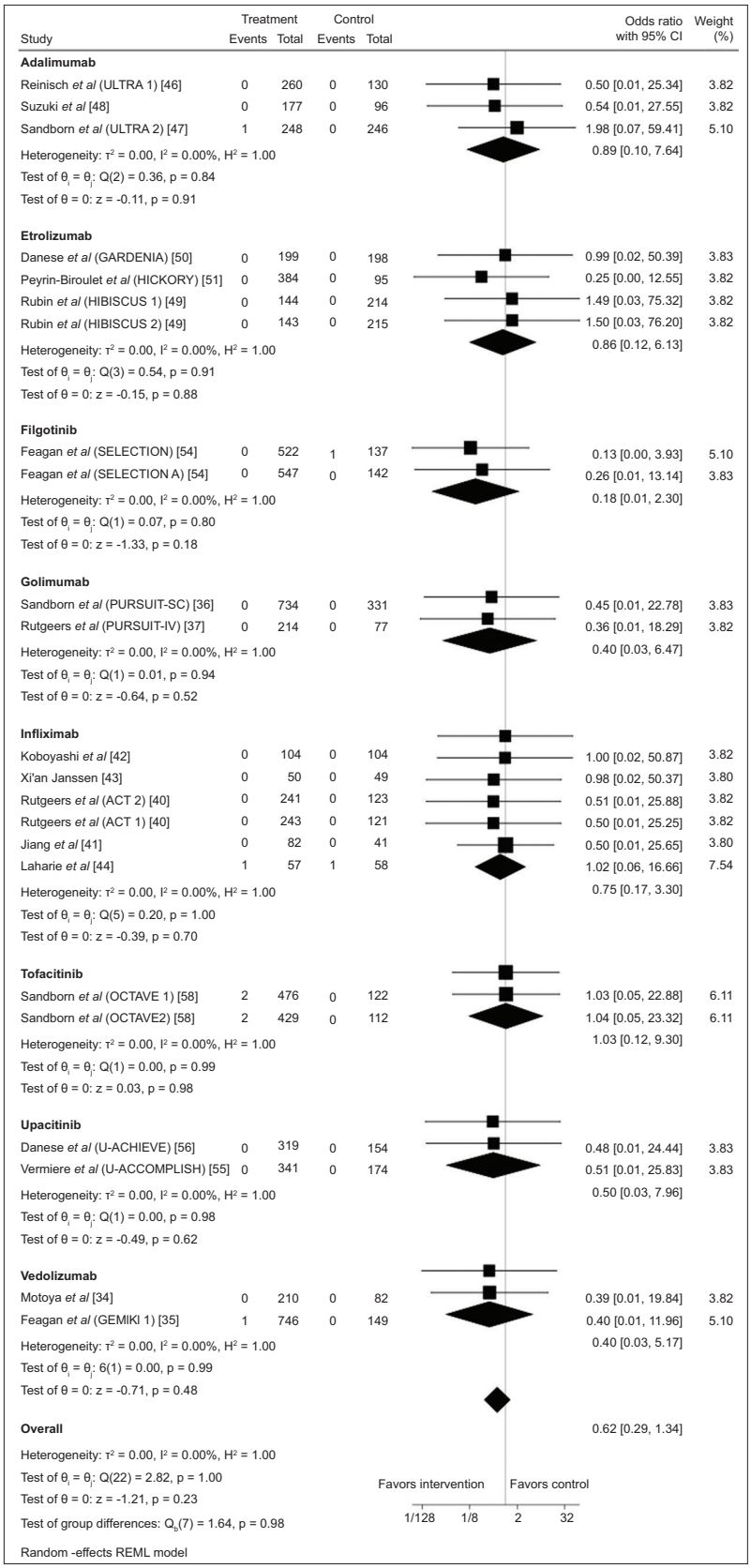
MACCEs, major adverse cerebrovascular and cardiovascular events



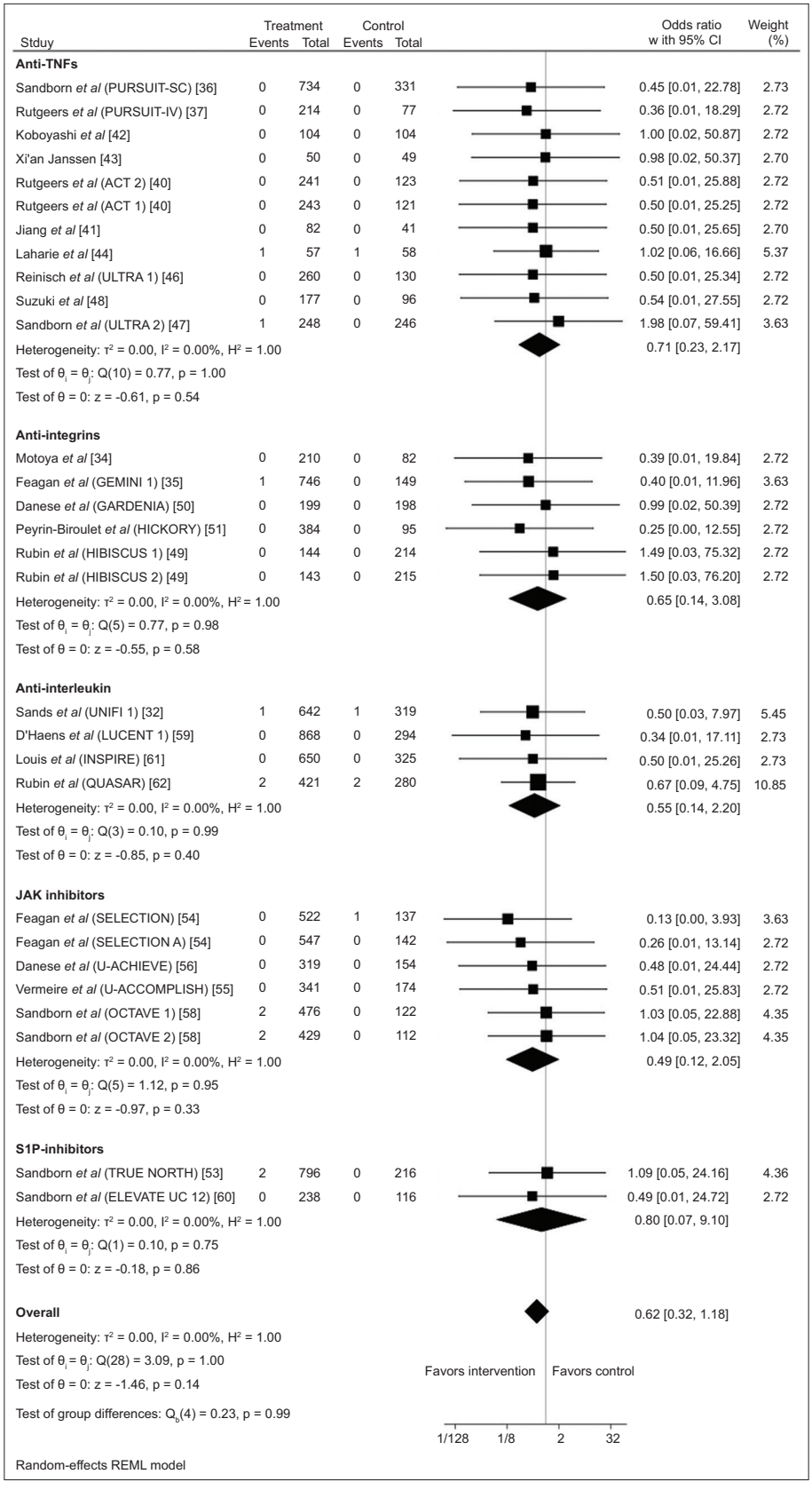
Supplementary Figure 1 Risk of major adverse cerebrovascular and cardiovascular events per trial duration



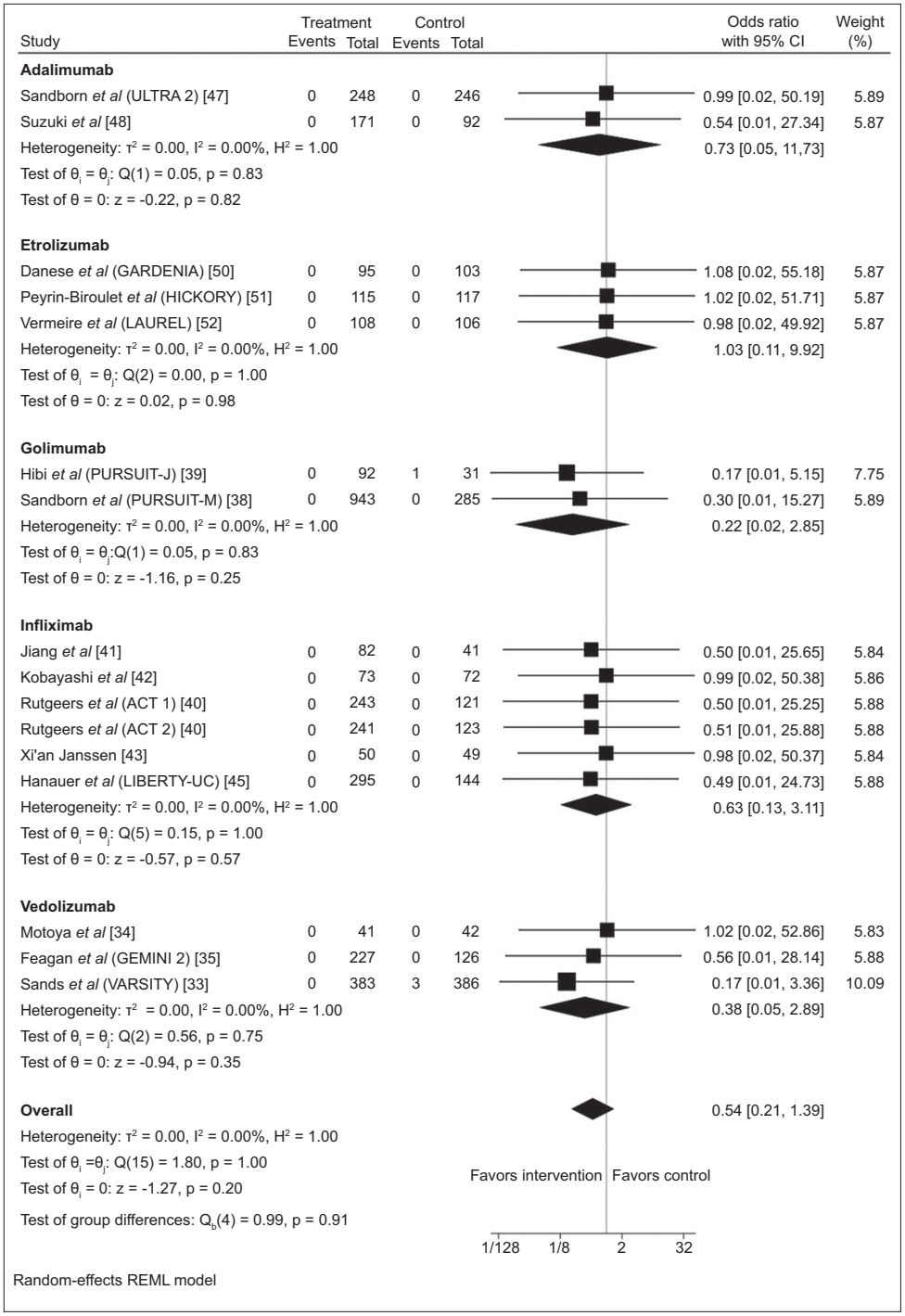
Supplementary Figure 2 Risk of major adverse cerebrovascular and cardiovascular events overall per drug agent



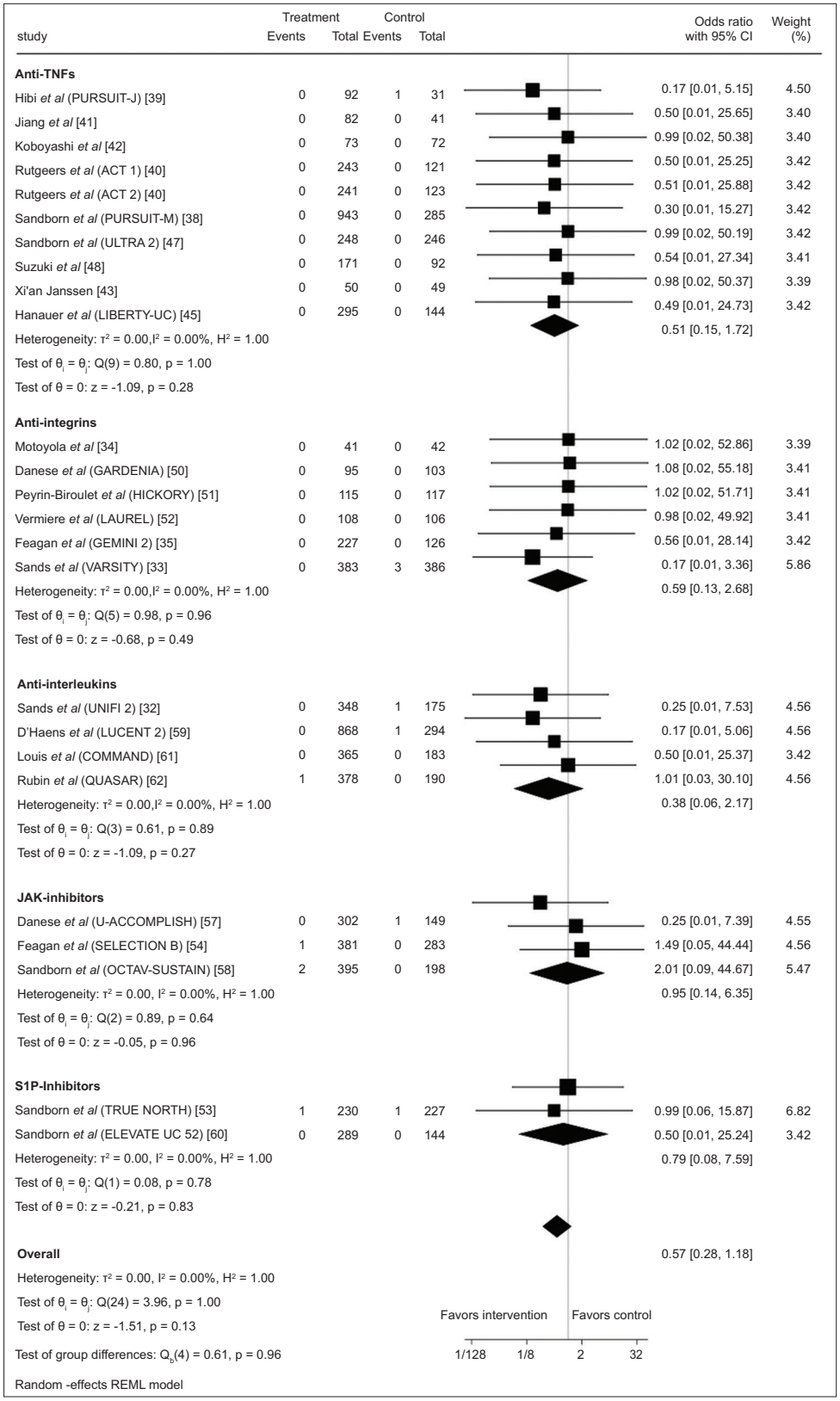
Supplementary Figure 3 Risk of major adverse cerebrovascular and cardiovascular events in induction trials per drug agent



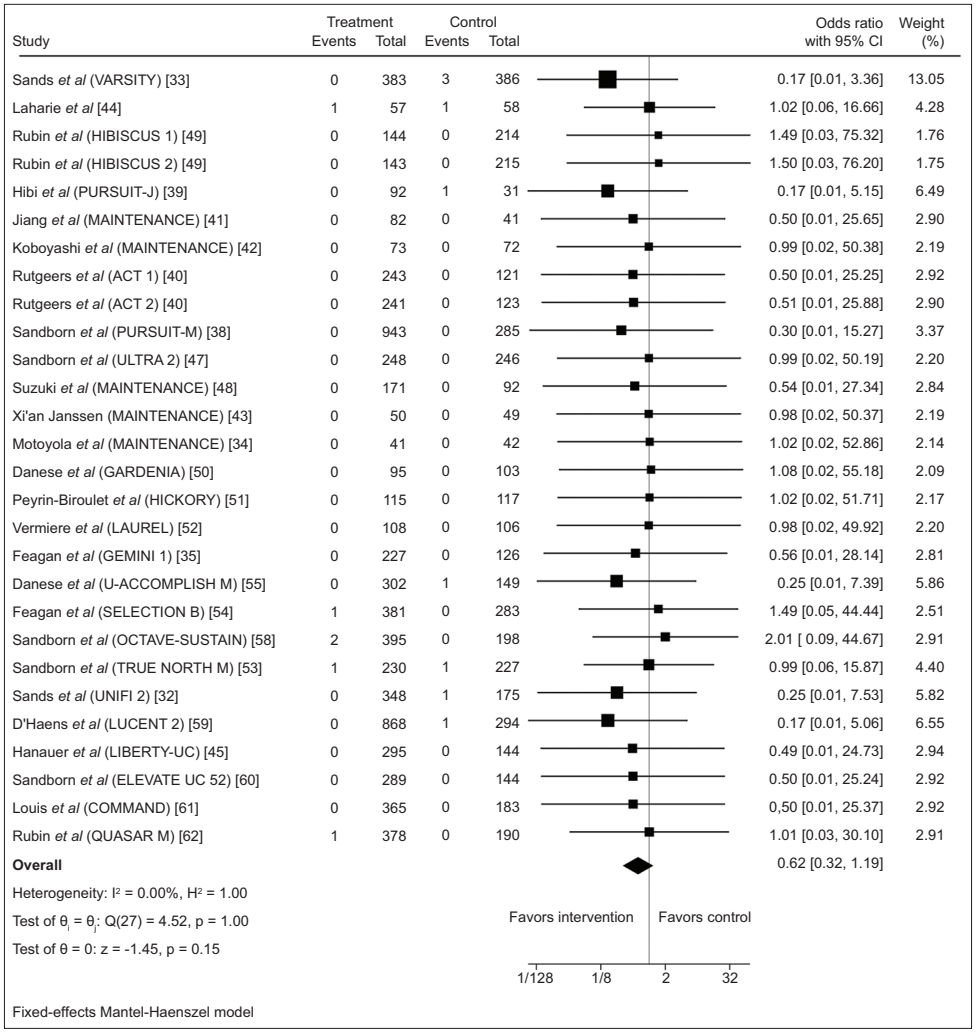
Supplementary Figure 4 Risk of major adverse cerebrovascular and cardiovascular events in induction trials per drug group



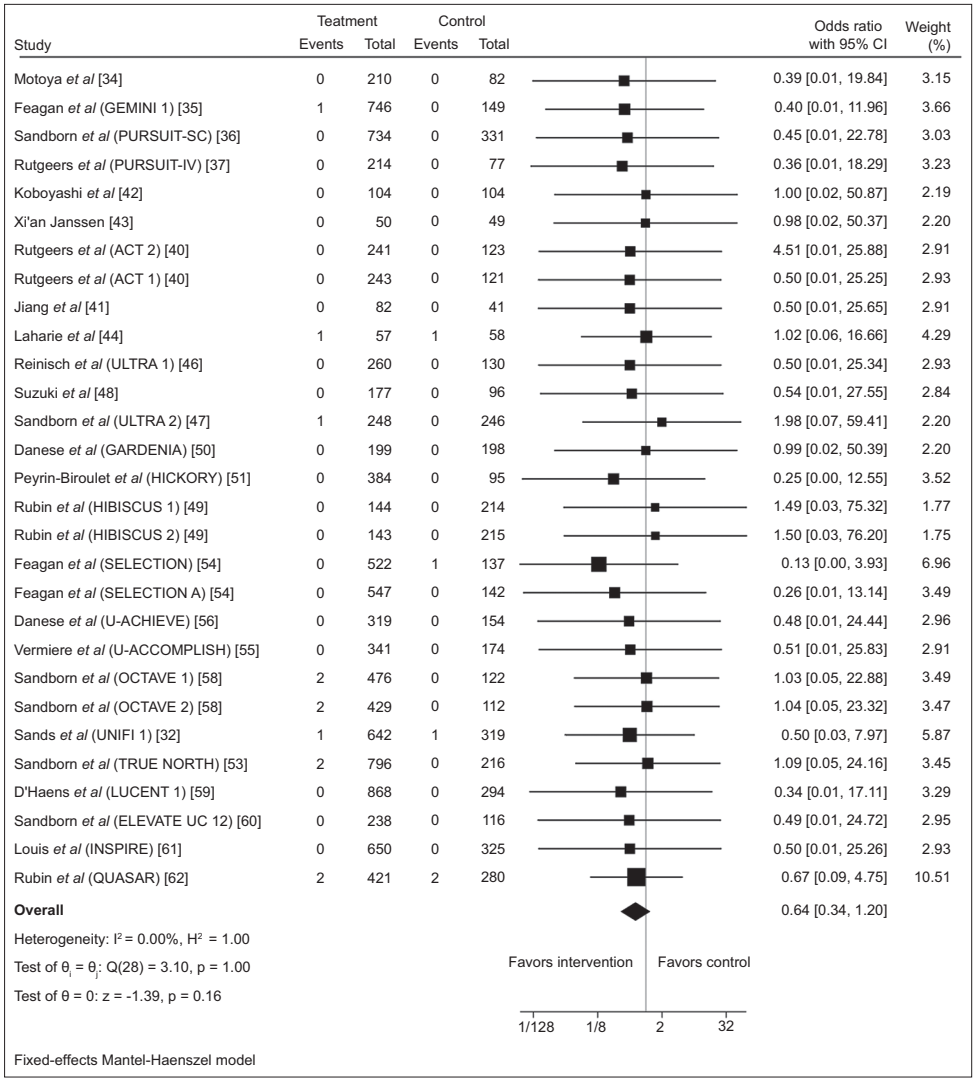
Supplementary Figure 5 Risk of major adverse cerebrovascular and cardiovascular events in maintenance trials per drug agent



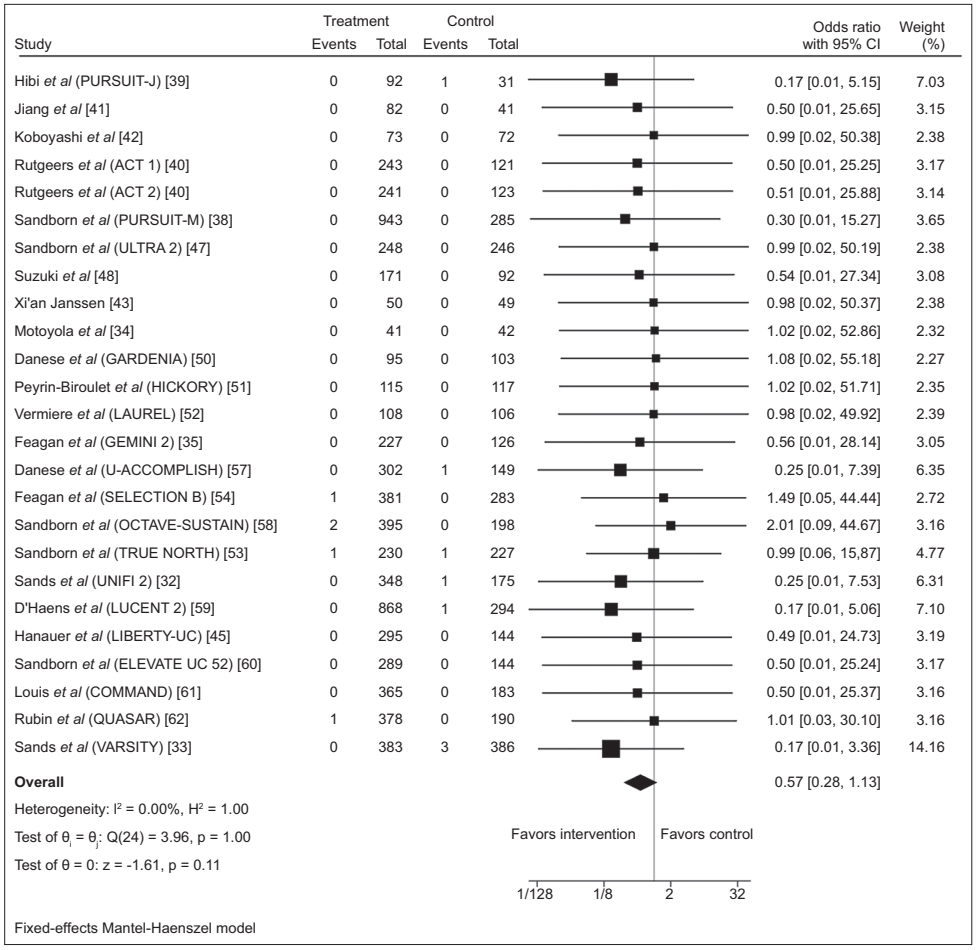
Supplementary Figure 6 Risk of major adverse cerebrovascular and cardiovascular events in maintenance trials per drug group



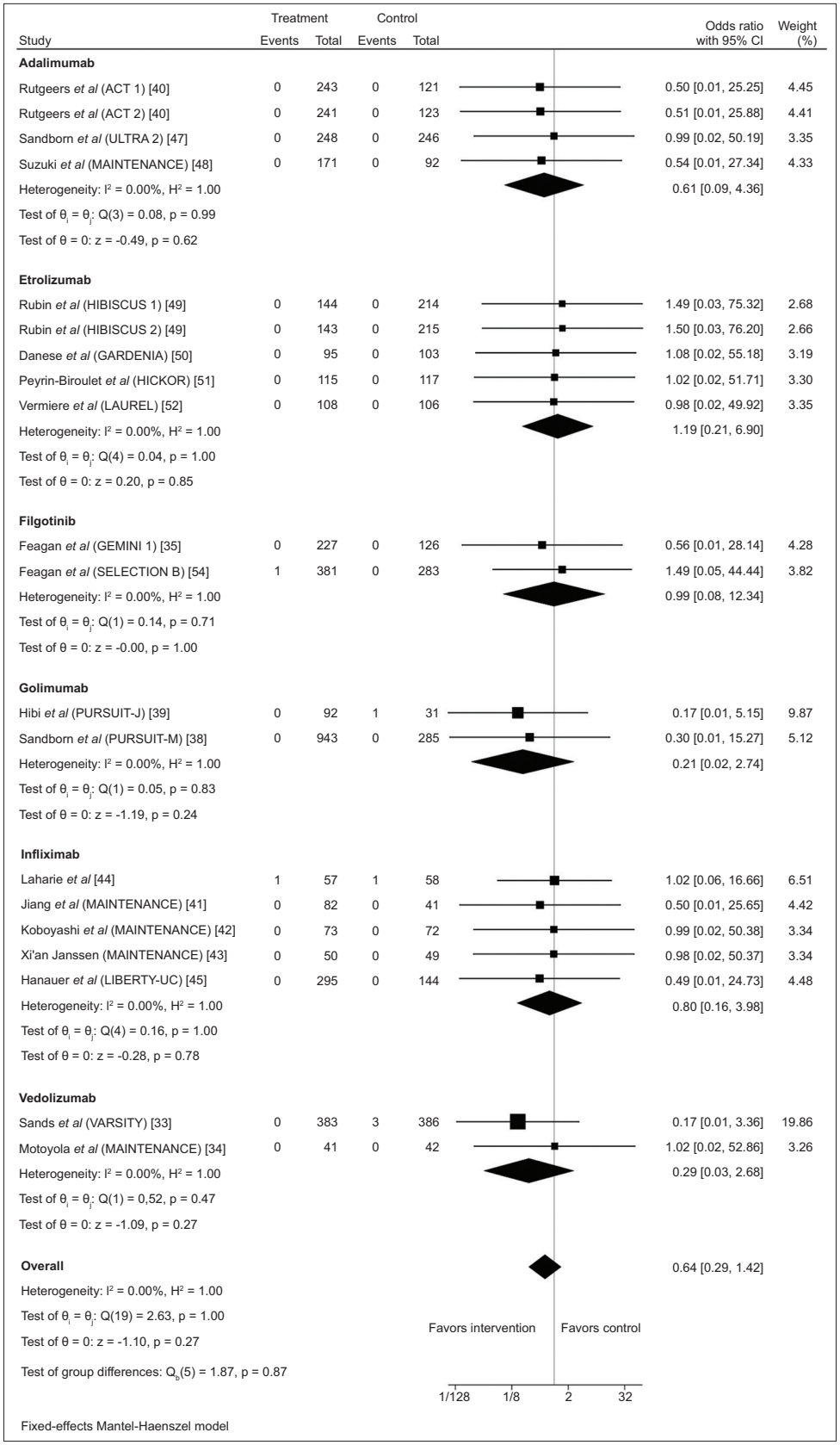
Supplementary Figure 7 Risk of major adverse cerebrovascular and cardiovascular events overall, using a fixed-effects model



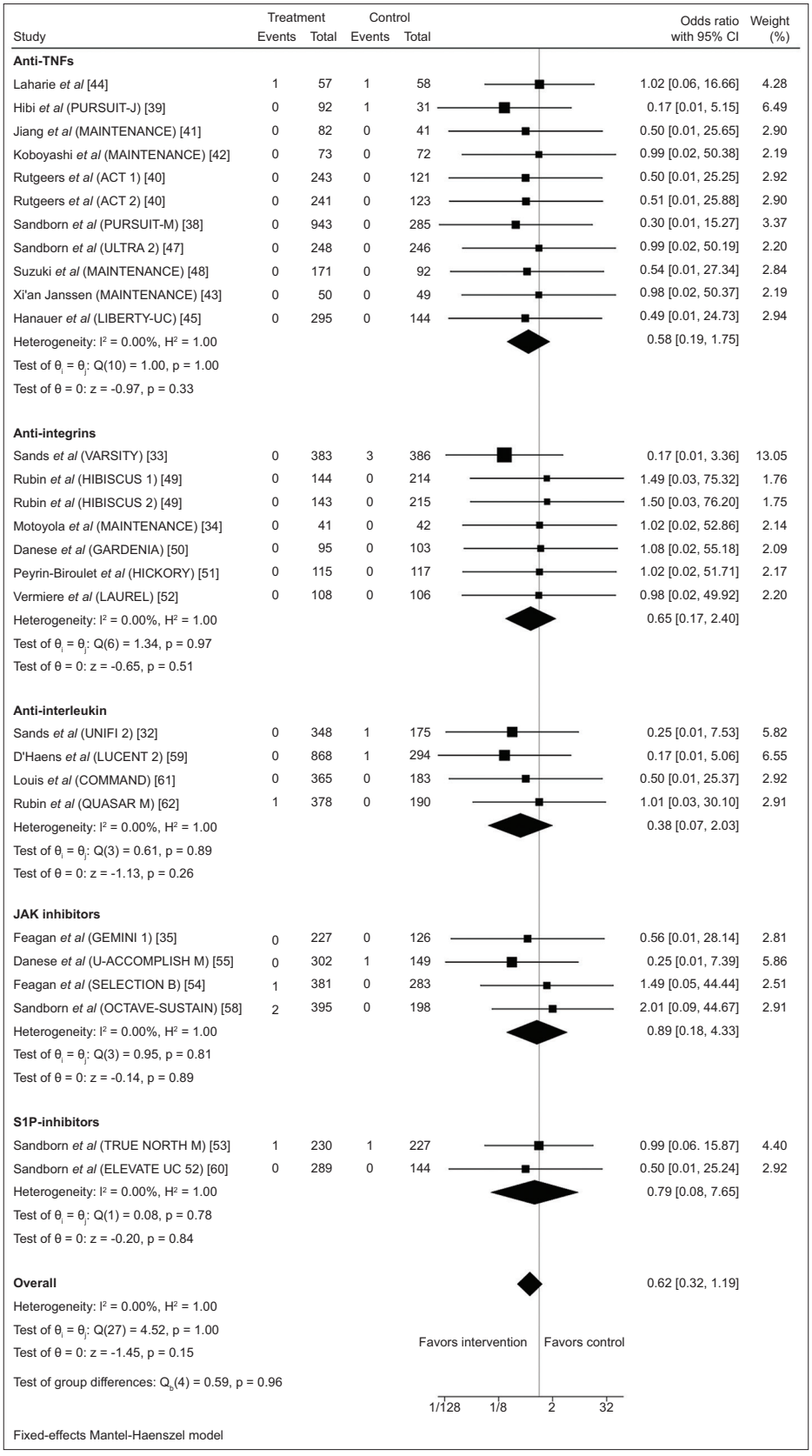
Supplementary Figure 8 Risk of major adverse cerebrovascular and cardiovascular events with induction therapy, using a fixed-effects model



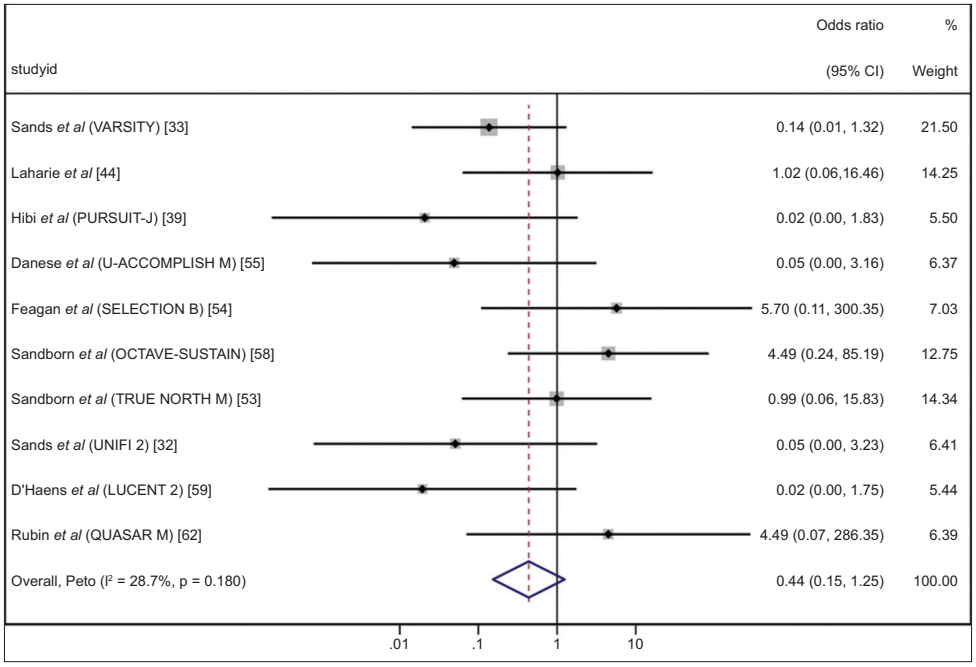
Supplementary Figure 9 Risk of major adverse cerebrovascular and cardiovascular events with maintenance therapy, using a fixed-effects model



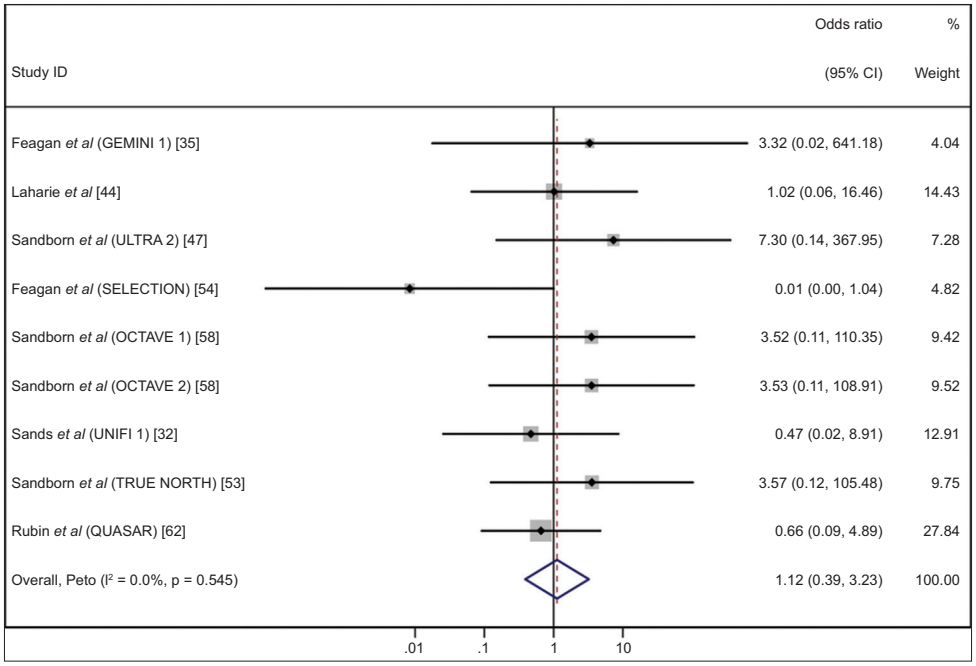
Supplementary Figure 10 Risk of major adverse cerebrovascular and cardiovascular events with individual agents, using a fixed-effects model



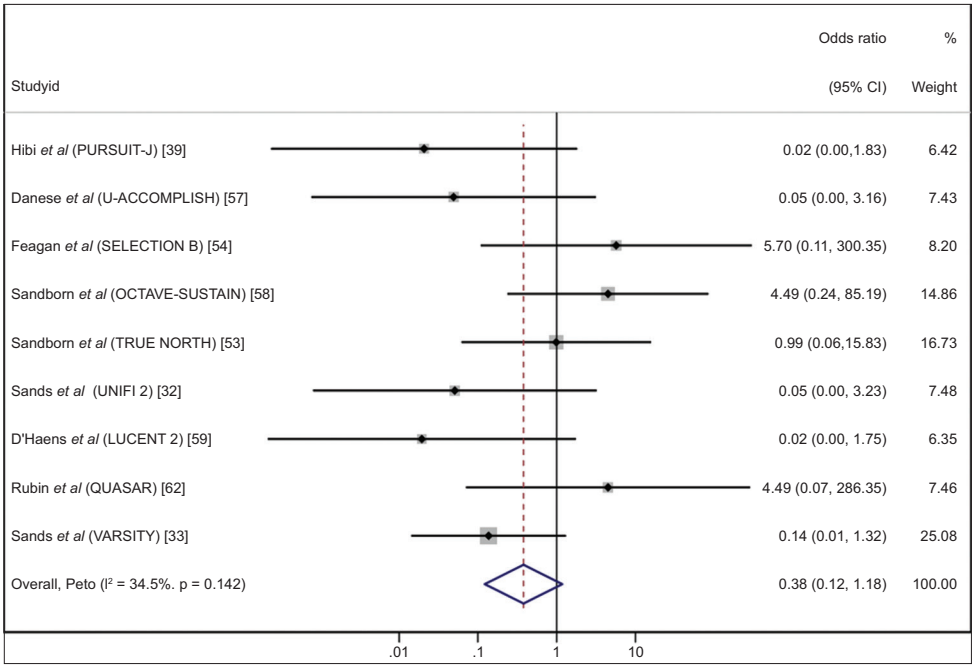
Supplementary Figure 11 Risk of major adverse cerebrovascular and cardiovascular events with drug groups, using a fixed-effects model



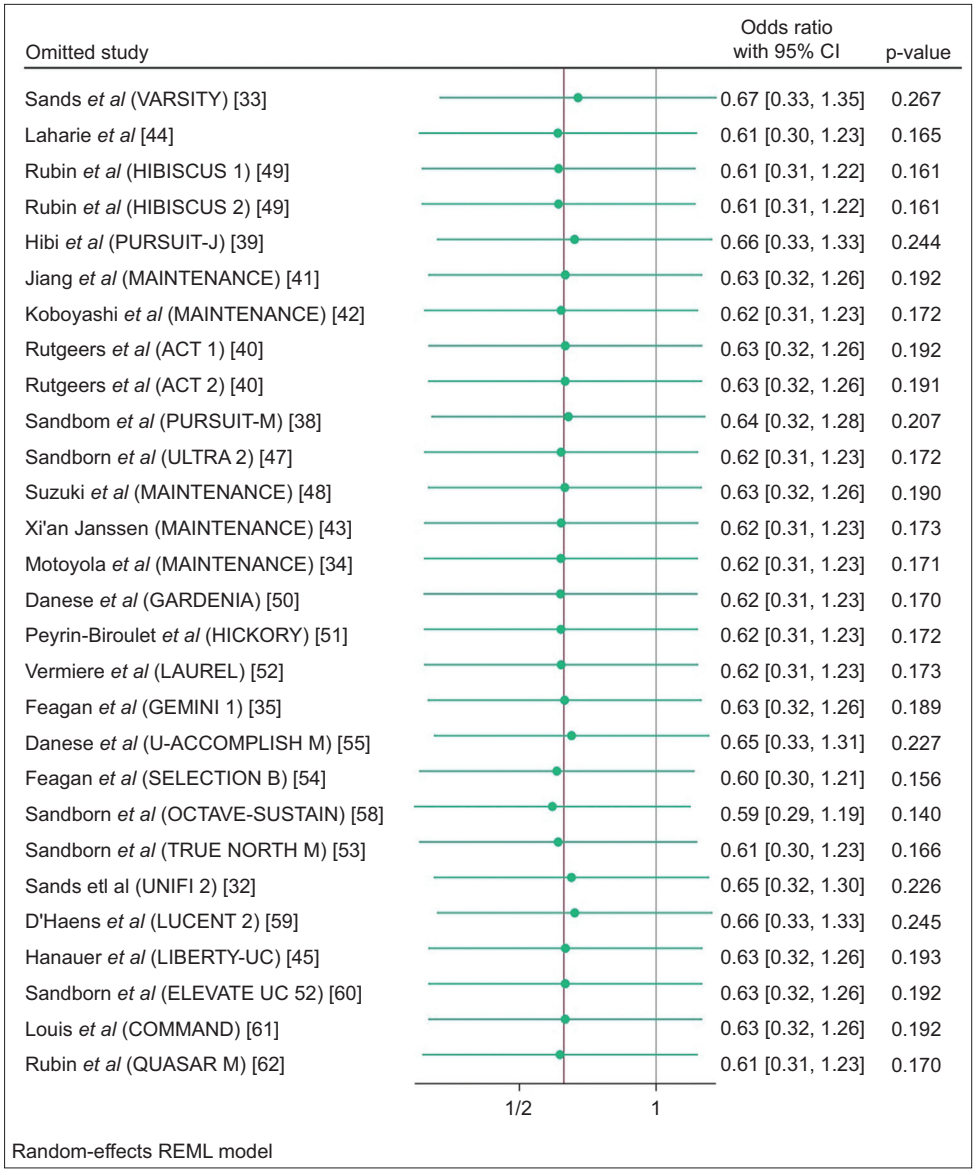
Supplementary Figure 12 Peto odds ratio for the overall risk of major adverse cerebrovascular and cardiovascular events
CI, confidence interval



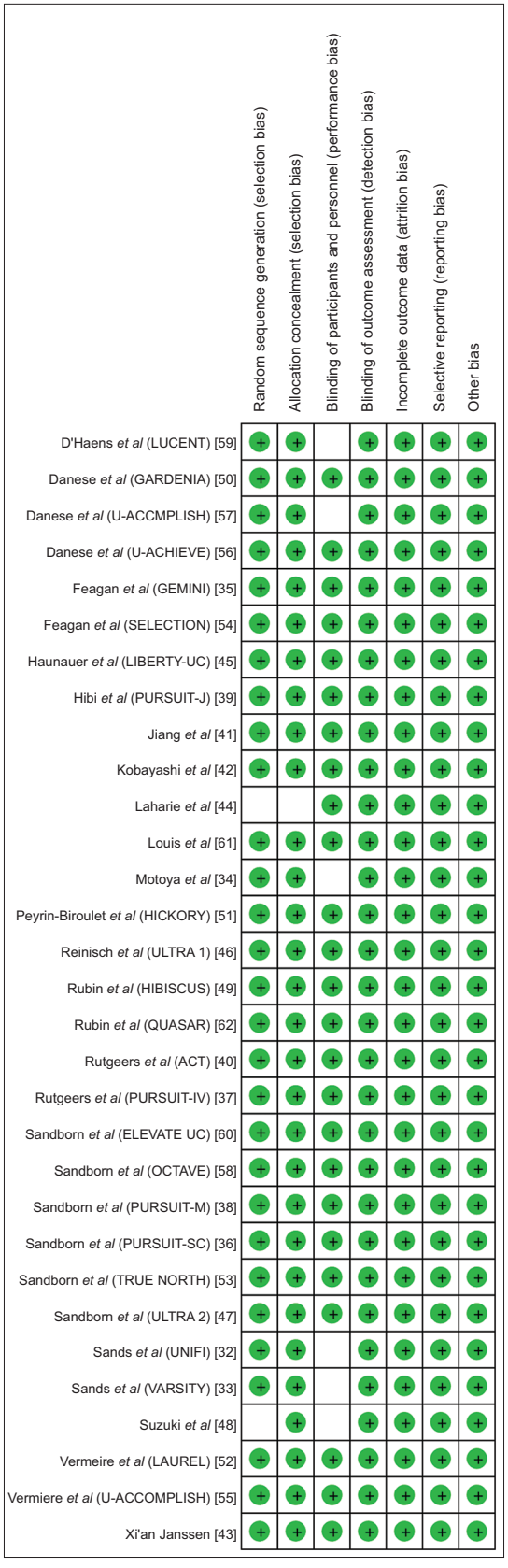
Supplementary Figure 13 Peto odds ratio for the risk of major adverse cerebrovascular and cardiovascular events in induction trials
CI, confidence interval



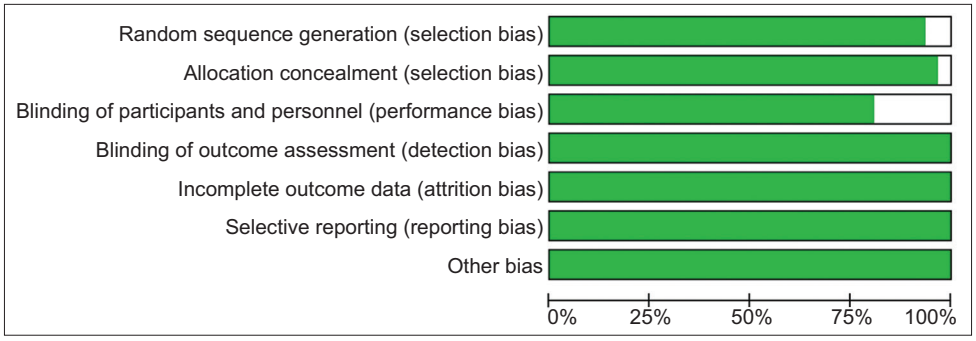
Supplementary Figure 14 Peto odds ratio for the risk of major adverse cerebrovascular and cardiovascular events in maintenance trials
CI, confidence interval



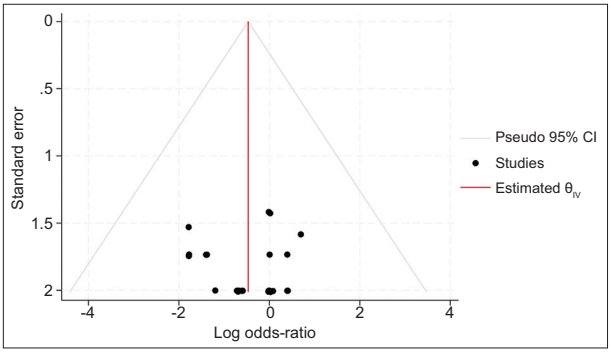
Supplementary Figure 15 Leave-one-out sensitivity analysis using a random effects model. The green dot illustrates the pooled effect estimate, the green horizontal line represents the 95% confidence intervals (CIs), and the grey line represents the line of no effect



Supplementary Figure 16 Risk of bias summary graph showing the authors' judgments about each risk of bias item for each included study. Greene circles indicate low risk of bias, white cells indicate unclear risk of bias, and red circles indicate high risk of bias.



Supplementary Figure 17 Supplementary figure 17 Risk of bias summary graph showing the authors' judgments about each risk of bias item, presented as percentages across all included study. Greene areas indicate low risk of bias, white areas indicate unclear risk of bias, and red areas indicate high risk of bias.



Supplementary Figure 18 Funnel plot using data from 54 trials. The black dots represent the included studies. The horizontal axis displays the log odds ratio. The solid vertical line represents the summary estimate of treatment effect using a random effects model, whilst the diagonal lines represent the pseudo 95% confidence intervals (CIs)
CI, confidence interval