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Clopidogrel and aspirin after ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized clinical trials

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Abstract

Recurrent stroke is common immediately following a transient ischemic attack (TIA) or ischemic stroke. Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin may provide greater protection against subsequent stroke than monotherapy. Electronic databases were searched for randomized clinical trials (RCTs) comparing DAPT with monotherapy in ischemic stroke/TIA. Sixteen RCTs with a total of 29,032 patients were included. Compared with monotherapy, DAPT was associated with significantly lower rates of any stroke (risk ratio [RR] 0.80; 95% confidence interval [CI] 0.72–0.89) and ischemic stroke (RR 0.75; 95% CI 0.66–0.85) during any follow-up period. Although significant increases in intracranial bleeding (RR 1.55; 95% CI 1.20–2.01) and major bleeding (RR 1.90; 95% CI 1.33–2.72) were associated with DAPT, especially with long-term follow-up, the number needed to harm was 258 and 113, respectively. Nevertheless, short-duration DAPT ($\leq$ 1 month) started during the early acute ischemic phase was associated with less bleeding than longer DAPT and greater reduction of recurrent strokes compared with monotherapy. In contrast, long DAPT and DAPT started later after the index event ($\geq$ 1 month) were associated with similar rates of any stroke and increased risks of bleeding compared with monotherapy. Other clinical outcomes were essentially similar between the two groups and included recurrent TIA (RR 0.88; 95% CI 0.72–1.07), myocardial infarction (RR 1.04; 95% CI 0.84–1.29), vascular death (RR 0.99; 95% CI 0.82–1.19), and any death (RR 1.12; 95% CI 0.88–1.42). Similar findings were observed in patients who presented with minor stroke/TIA. Conclusions: Among patients who presented with ischemic stroke/TIA, short-course clopidogrel plus aspirin immediately following the index event appears to be more effective than and as safe as monotherapy for secondary stroke prevention.

Keywords Clopidogrel · Aspirin · DAPT · Ischemic stroke · Acute stroke · TIA · Meta-analysis

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Highlights

- Dual antiplatelet therapy is associated with a significant reduction in recurrent strokes, with no increased risk of vascular events or mortality in comparison with monotherapy
- Dual antiplatelet therapy is associated with higher rates of bleeding than monotherapy
- The risk of bleeding is minimized by administering the combination drugs shortly following the ischemic event (≤ 1 week) and for a short period of time (≤ 1 month)

Introduction

The highest risk of recurrent stroke after ischemic stroke and transient ischemic attack (TIA) is immediately following the index event and the risk declines over the ensuing weeks [1]. Multiple randomized clinical trials (RCTs) have confirmed the beneficial effect of aspirin in reducing the risk of recurrent stroke by ~ 20% [2–6]. Compared with aspirin, clopidogrel monotherapy has shown a relative risk reduction of recurrent stroke of 7.3% [7].

Nevertheless, dual antiplatelet therapy (DAPT) may provide more potent synergistic inhibition of different platelet activator pathways. Therefore, DAPT is the cornerstone of management in patients with acute coronary syndrome (ACS) [8]. Nevertheless, the combination of aspirin plus extended-release dipyridamole and/or clopidogrel in the secondary prevention of stroke have shown conflicting efficacy results and increased bleeding risks [9–17]. Current American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend a short duration of DAPT (21 days) with aspirin and clopidogrel only following minor stroke (Class IIa) [18]. However, the generalizability of such intervention in non-Asian populations remains unknown. Therefore, we conducted our meta-analysis to evaluate the efficacy and safety of clopidogrel plus aspirin compared with monotherapy in all patients who presented with ischemic stroke and TIA and to a subset of patients with minor stroke. In addition, we aimed to identify the best duration and timing of DAPT following the index event in this population.

Methods

Data sources

We conducted our meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 and the PRISMA checklist was followed [19]. We registered our prespecified study protocol with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42018098979). Two authors (BK, AA) independently performed a literature search of PubMed, Embase, and the Cochrane Collaboration Central Register of Controlled Trials from inception to May 2018. Any discrepancies were resolved via a third author (MO). We used Boolean operators for connections of the following headings: "stroke," "transient ischemic stroke," "TIA", "cerebral infarction," "cerebrovascular infarction," AND "clopidogrel."

Selection criteria and data extraction

The pre-specified inclusion criteria of the meta-analysis were as follows: (1) The study design was an RCT, (2) The RCT used clopidogrel-aspirin arm vs single antiplatelet (monotherapy), and (3) The RCT evaluated clinical outcomes. Exclusion criteria were as follows: (1) The RCT included patients undergoing interventions such as stent placement, angioplasty, or thrombectomy, (2) The RCT included DAPT other than clopidogrel or studied triple antiplatelets, (3) The stroke subtype was hemorrhagic or mainly due to cardioembolic phenomenon, and (4) No clinical outcomes were reported. Two authors (TH, SA) extracted the data (baseline trial characteristics, study-level patient demographics, and clinical outcomes) and any discrepancies were resolved via consultation with a third author (BK).

Outcomes and definitions

The pre-specified primary efficacy outcome was any recurrent stroke (ischemic or hemorrhagic). Other efficacy outcomes were recurrent ischemic stroke, TIA, and myocardial infarction (MI). The primary safety outcome was intracranial bleeding, defined as any intracerebral, subdural, epidural, or subarachnoid bleeding. Other safety outcomes were major bleeding (defined per each included RCT as serious or life-threatening bleeding causing hemodynamic compromise that required blood or fluid replacement, inotropic support, hospitalization, or surgical intervention, or resulting in functional sequelae or death), vascular death, and any death. All outcomes were reported at the longest follow-up duration.

Quality assessment

The quality of the included RCTs were assessed independently by two authors (BK and MO) based on the study design and number of sites, blinding to outcomes, treatment assignment generation, and the proportion of follow-up completion.

Statistical analysis

We calculated summary risk ratios (RRs) and 95% confidence intervals (CIs) using the Mantel–Haenszel method for dichotomous data, and we used a random-effects model to account for the between-study heterogeneity. We measured the heterogeneity of the included RCTs using the Cochrane's Q statistics and I^2 test.

We assessed potential publication bias by visual inspection of the funnel plot. Furthermore, we explained any heterogeneity (≥ 20%) by performing sensitivity analyses and meta-regression analyses. Sensitivity analysis was performed by removing trials that compared clopidogrel-aspirin vs clopidogrel monotherapy. Meta-regression analyses were performed for the primary outcome based on the clopidogrel initial dose (loading or maintenance dose).

We conducted a subset analysis for patients with minor stroke, defined as a score of ≤ 3 on the National Institutes of Health Stroke Scale (NIHSS) (scores range from 0 to 42, with higher scores indicating greater severity). Furthermore, subgroup analyses were conducted for the following study-level variables: follow-up duration (≤ 3 months vs ≥ 6 months), DAPT duration (short duration ≤ 1-month, intermediate duration up to 3 months, and long duration ≥ 1 year), timing of treatment following the index stroke/TIA (acute within 48 h, subacute within 1 week, or chronic after 1 month), and the studied population (East Asian vs Western). All data were analyzed using RevMan v5.3 Windows and Comprehensive Meta-Analysis software v3.

Results

Study selection and trial characteristics

Throughout our electronic databases search, we identified 16 eligible RCTs [20–37]. We included the clinical outcomes of the studies that reported both short and long follow-up duration separately, and we also included subgroup studies that reported clinical outcomes for minor stroke/TIA such as CLAIR and CLAIR subset trials [20, 38–41]. The study selection process is shown in Fig. 1.

The total number of patients was 29,032. Most of the RCTs compared clopidogrel-aspirin vs aspirin. However, 2 RCTs compared DAPT against clopidogrel 75 mg/day [22, 25], and in the sensitivity analysis we removed these studies from the pooled estimates to explain any heterogeneity. Although most of the included trials administered clopidogrel at a dose of 75 mg/day, some trials initiated the drug with a loading dose (300 or 600 mg) [20, 22, 26, 27, 29, 31, 36, 39]. However, most of these trials used the maintenance dose for a short duration (≤ 21 days) and only two trials which used loading doses extended the treatment to 3 months [29, 36]. There were 7 RCTs conducted exclusively in Asia [23, 24, 26, 27, 31, 32, 35], 7 trials based solely in Western countries [21, 22, 25, 29, 33, 34, 36], and 2 trials conducted in both Asian and Western countries [28, 30]. The reported NIHSS score ranged between 0 and 22 and the duration of follow-up ranged from 7 days to 5 years. The characteristics of the included RCTs are detailed in Table 1. The study-level baseline demographics were similar between

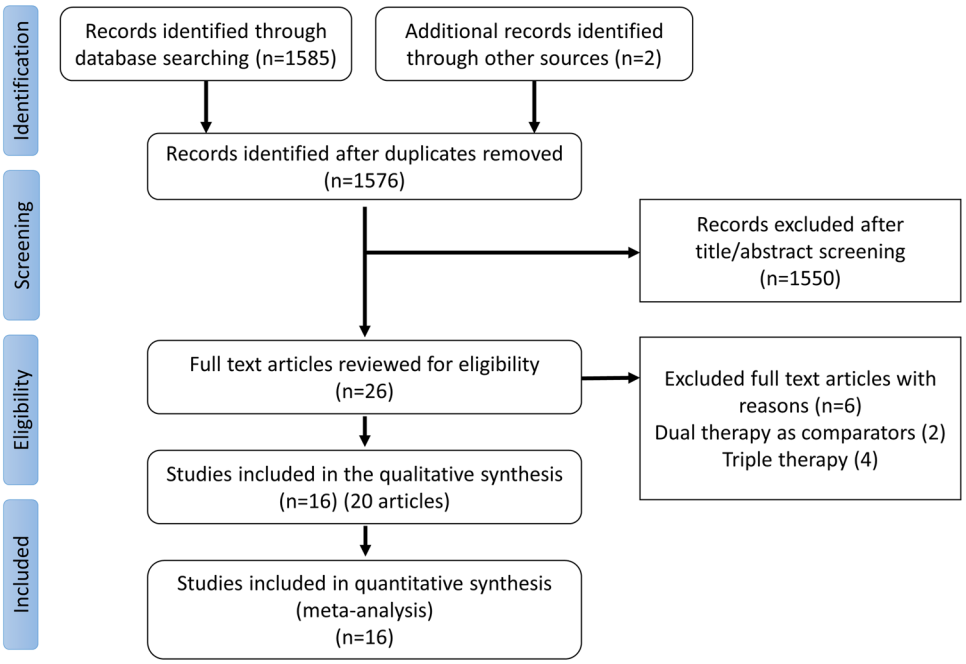


Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Table 1 The characteristics of the included randomized clinical trials

First author, year, and study name	Design and locations (countries)	Study period	Follow-up duration	NIHSS score	Stroke/TIA cause	Medications	Total no.	Primary outcome	Dual therapy	Mono-therapy	p-value
Diener 2004 MATCH	Double blinded International (28)	2000–2002	18 months	–	All types	Clop + Asp vs Clop	7599	Ischemic stroke, MI, vascular death, or rehospitalization	15.7%	16.7%	0.244
Serebruany 2005 PLUTO-Stroke	Single center United States	–	1 month	–	All types	Clop + Asp vs Asp	70	–	–	–	–
Markus 2005 CARESS	Double blinded Europe (4)	–	7 days	0–22	≥ 50% carotid stenosis	Clop + Asp vs Asp	107	Proportion of patients with microembolic signals	43.8%	72.7%	0.0046
Kennedy 2007 FASTER	Double blinded North America (2)	2003–2006	3 months	0–3	All types	Clop + Asp vs Asp	392	Recurrent stroke	7.1%	10.8%	0.19
Serebruany 2008	Single blinded United States	–	1 month	–	All types	Clop + Asp vs ER-DP + ASA vs Clop	60	–	–	–	–
Bal dit Sollier 2009	Double blinded France	2000–2001	10 days	–	All types	Clop + Asp vs Ter-utroban + Asp vs Terutroban vs Asp	48	The of mean cross-sectional surface of dense thrombus	4.6 ± 86.8	0.8 ± 84.1	0.005
Hankey 2011 CHARISMA substudy	Double blinded International (32)	2002–2003	25 months	–	All types	Clop + Asp vs Asp	4320	Recurrent stroke	4.9%	6.1%	0.09
Benavente 2012 SPS3	Double blind International (7)	2003–2011	3.4 years	–	All types	Clop + Asp vs Asp	3020	Recurrent stroke	2.5% per year	2.7% per year	0.48
Wong 2010 CLAIR	Blinded end-points Asia (5)	2003–2008	7 days	0–8	Large-artery disease	Clop + Asp vs Asp	100	Proportion of patients with microembolic signals	31.1%	54%	0.025
Lau 2013 CLAIR sub-group	Same as above	–	7 days	0–3	Large-artery disease	Clop + Asp vs Asp	65	Proportion of patients with microembolic signals	37.9%	54.5%	0.213
Wang 2015 CHANCE	Double blinded China	2009–2012	1 year	0–3	All types	Clop + Asp vs Asp	5170	Recurrent stroke	10.6%	14.0%	0.006
He 2015	Open label China	2010–2012	14 days	0–7	All types	Clop + Asp vs Asp	690	Stroke deterioration or new stroke from TIA	3.1%	6.7%	–

Table 1 (continued)

First author, year, and study name	Design and locations (countries)	Study period	Follow-up duration	NIHSS score	Stroke/TIA cause	Medications	Total no.	Primary outcome	Dual therapy	Mono-therapy	p-value
Yi 2015	Open label China	2010–2013	14 days and 6 months	0–15	Large-/small-artery disease	Clop + Asp vs Asp vs LMWH	1467	Early neurological deterioration	4.12%	14.81%	< 0.001
Hong 2016 COMPRESS	Double blinded Korea	2009–2012	1 month	0–19	Large-artery disease	Clop + Asp vs Asp	334	Recurrent stroke	36.5%	35.9%	0.91
Zuo 2017	China	2013–2014	3 months	–	> 50% intra-/extra-cranial stenosis	Clop + Asp vs Asp	200	Recurrent stroke	9.1%	27.9%	< 0.05
Johnston 2018 POINT	Double blinded International (10)	2010–2017	3 months	0–3	All types	Clop + Asp vs Asp	4881	Ischemic stroke, MI, or vascular death	5.0%	6.5%	0.02
Yi 2018	Blinded endpoints China	2009–2011	1 month	0–12	Large-artery disease	Clop + Asp vs Asp	574	Ischemic stroke, TIA, MI, and death	16.5%	20.3%	0.26

Asp aspirin, *CARESS* clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis, *CHANCE* clopidogrel in high-risk patients with acute nondisabling cerebrovascular events, *CHARISMA* clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, *CLAIR* clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals, *Clop* clopidogrel, *COMPRESS* combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study, *ER-DP* extended-release dipyridamole, *FASTER* fast assessment of stroke and TIA to prevent early recurrence, *LMWH* low molecular weight heparin, *MI* myocardial infarction, *MATCH* management of atherothrombosis with clopidogrel in high-risk patients, *NIHSS* National Institutes of Health Stroke Scale, *PLUTO-Stroke* primary hypothesis of the plavix use for treatment of stroke, *POINT* platelet-oriented inhibition in new TIA and minor ischemic stroke, *SPS3* secondary prevention of small subcortical strokes, *TIA* transient ischemic attack

Table 2 Patients' demographics

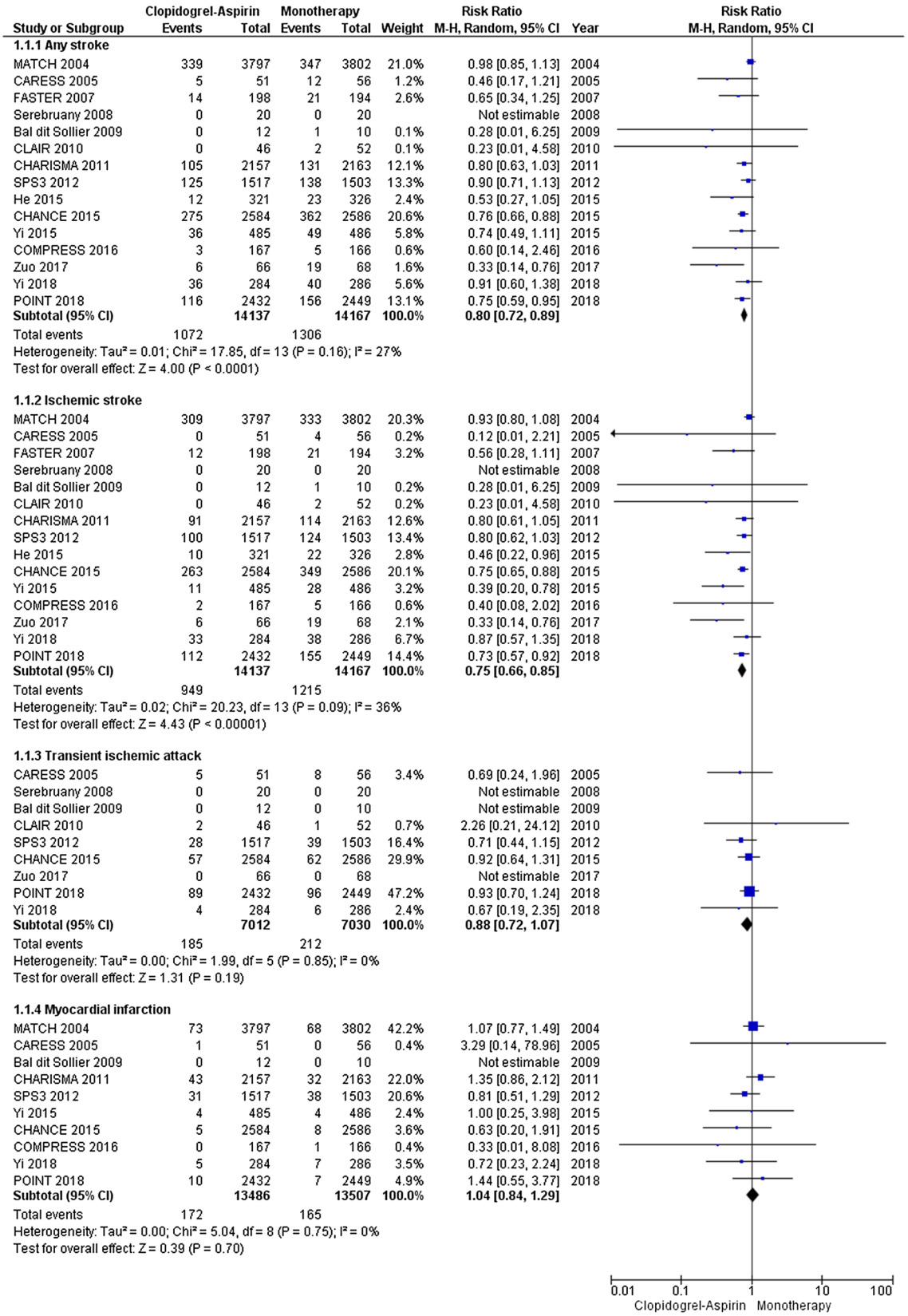
First author, year, and study name	Total number	Age	Male	HTN	DM	PVD	CHF	IHD	Dyslipidemia	Smoker	Systolic BP, mmHg	Diastolic BP, mmHg
Diener 2004 MATCH	Dual therapy N = 3797	66.5 ± 9.9	2382 (63)	2972 (78)	2598 (68)	388 (10)	–	656 (17)	2126 (56)	1825 (48)	–	–
	Monotherapy N = 3802	66.1 ± 9.9	2396 (63)	2973 (78)	2599 (68)	388 (10)	–	646 (17)	2154 (57)	1772 (47)	–	–
Serebruany 2005 PLUTO-Stroke	Dual therapy N = 35	67.7 ± 7.3	14 (40)	17 (48)	15 (42)	–	–	18 (51)	20 (57)	8 (22)	–	–
	Monotherapy N = 35	68.3 ± 6.3	21 (60)	18 (51)	12 (34)	–	–	12 (34)	17 (48)	14 (40)	–	–
Markus 2005 CARESS	Dual therapy N = 51	66.4 ± 8.1	35 (68.6)	38 (74.5)	16 (31.4)	11 (21.6)	–	17 (33)	28 (54.9)	–	–	–
	Monotherapy N = 56	62.8 ± 10.7	39 (69.6)	31 (55.4)	18 (32.1)	6 (10.7)	–	23 (41)	32 (57.1)	–	–	–
Kennedy 2007 FASTER	Dual therapy N = 100	67.1 ± 12.9	61 (61)	46 (46)	15 (15)	3 (3)	1 (1)	10 (10)	8 (8)	28 (28)	147.8 ± 20.1	27.2 ± 4.5
	Monotherapy N = 95	66.6 ± 14.2	48 (50.5)	51 (51.5)	12 (12.1)	1 (1.0)	0	5 (5.1)	9 (9.1)	25 (25.3)	149.3 ± 20.8	80 ± 12.2
Serebruany 2008	Dual therapy N = 20	60.1 ± 12.3	12 (60)	13 (65)	–	–	5 (25)	7 (35)	16 (80)	8 (40)	–	–
	Monotherapy N = 20	60.7 ± 8.4	12 (60)	15 (7S)	–	–	4 (20)	9 (45)	14 (70)	10 (50)	–	–
Bal dit Sollier 2009	Dual therapy N = 12	67.8 ± 9.2	10 (83.3)	–	–	–	–	–	–	–	–	–
	Monotherapy N = 12	70.5 ± 11.1	8 (66.7)	–	–	–	–	–	–	–	–	–
Hankey 2011 CHARISMA	Dual therapy N = 2157	64.8 ± 9.8	1350 (62.6)	1644 (76.2)	610 (28.3)	125 (5.8)	47 (2.2)	–	–	401 (18.6)	140.3 ± 19.1	80.3 ± 10.6
	Monotherapy N = 2163	64.9 ± 9.8	1380 (63.8)	1653 (76.4)	642 (29.7)	134 (6.2)	50 (2.3)	–	–	20.1%	140.2 ± 19.2	80.1 ± 10.9
Benavente 2012 SPS3	Dual therapy N = 1517	63	941 (62)	1153 (76)	531 (35)	–	–	152 (10)	–	303 (20)	143	78
	Monotherapy N = 1503	63	962 (64)	1112 (74)	571(38)	–	–	165 (11)	–	316 (21)	143	78
Wong 2010 CLAIR	Dual therapy N = 46	59.2 ± 12.5	36 (78)	27 (60)	21 (46)	4 (9)	–	8 (17.4)	23 (50)	21 (56.7)	139.4 ± 22.2	80.1 ± 11.6
	Monotherapy N = 52	56.4 ± 12.8	40 (77)	35 (69)	16 (31)	2 (4)	–	7 (13.5)	16 (33)	30 (57.7)	148.6 ± 23.1	83.9 ± 11.6
Lau 2013 CLAIR sub-group	Dual therapy N = 30	57.6 ± 13.7	22 (73.3)	18 (60)	14 (47)	3 (10)	–	–	–	–	137.1 ± 22.7	78.1 ± 10.5
	Monotherapy N = 35	56.4 ± 12.2	27 (77.1)	22 (63)	10 (29)	1 (3)	–	–	–	–	147.2 ± 23.4	84.4 ± 12.7

Table 2 (continued)

First author, year, and study name	Total number	Age	Male	HTN	DM	PVD	CHF	IHD	Dyslipidemia	Smoker	Systolic BP, mmHg	Diastolic BP, mmHg
Wang 2015 CHANCE	Dual therapy N = 2584	63 [55–72]	1732 (67)	1716 (66.4)	550 (21.3)	–	42 (1.6)	140 (5.4)	290 (11.2)	1116 (43.2)	150 [136–161]	90 [80–98]
	Mono therapy N = 2586	62 [54–71]	1688 (65.3)	1683 (65.1)	543 (21.0)	–	38 (1.5)	140 (5.4)	283 (10.9)	1105 (42.7)	150 [136–161]	90 [80–100]
He 2015	Dual therapy N = 321	62.9 2 ± 8.96	183 (57)	213 (66.36)	138 (42.99)	–	–	88 (27.4)	–	161 (50.16)	–	–
	Monotherapy N = 326	61.52 ± 10.21	185 (56.7)	224 (68.71)	128 (39.26)	–	–	92 (28.2)	–	165 (50.61)	–	–
Yi 2015	Dual therapy N = 485	69.5 ± 10.14	265 (54.6)	348 (71.75)	160 (32.99)	–	–	18 (3.7)	–	201 (41.44)	135.3 ± 2 0.32	84.1 ± 11.2
	Monotherapy N = 486	70.1 ± 11.12	268 (55.1)	345 (70.99)	165 (33.95)	–	–	17 (3.5)	–	199 (40.95)	134.9 ± 21.26	83.5 ± 10.91
Johnston 2018 POINT	Dual therapy N = 2432	65.0 [55.0–74.0]	1335 (54.9)	1693 (69.9)	678 (28.0)	–	–	257 (10.6)	–	–	–	–
	Monotherapy N = 2449	65.0 [56.0–74.0]	1351 (55.2)	1680 (68.9)	662 (27.1)	–	–	240 (9.8)	–	–	–	–
Hong 2016 COMPRESS	Dual therapy N = 174	68 (37–96)	114 (65.52)	112 (64.37)	58 (33.33)	–	–	8 (4.60)	59 (33.91)	71 (40.80)	140 (93–208)	80 (52–113)
	Monotherapy N = 175	67 (36–89)	108 (61.71)	119 (68.00)	55 (31.43)	–	–	8 (4.57)	50 (28.57)	63 (36.00)	135 (94–195)	80 (53–119)
Zuo 2017	Dual therapy N = 66	61.55 (45–80)	24 (36.4)	40 (60.6)	25 (37.8)	–	–	11 (16.7)	41 (62.1)	36 (54.5)	–	–
	Monotherapy N = 68	62.29 (45–80)	27 (39.7)	43 (65.2)	18 (27.8)	–	–	6 (8.8)	40 (58.8)	33 (48.5)	–	–
Yi 2018	Dual therapy N = 284	69.2 ± 10.1	156 (54.9)	204 (71.8)	105 (37.0)	–	–	10 (3.5)	–	112 (39.4)	137.6 ± 21.2	80.5 ± 12.4
	Monotherapy N = 286	70.1 ± 10.4	157 (54.9)	210 (73.4)	110 (38.5)	–	–	10 (3.5)	–	116 (40.6)	135.9 ± 23.2	81.6 ± 11.8

All values in mean ± SD, median [interquartile range], median (range), or number (%)

BP blood pressure, *CARESS* clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis, *CHANCE* clopidogrel in high-risk patients with acute nondisabling cerebrovascular events, *CHARISMA* clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, *CHF* congestive heart failure, *CLAIR* clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals, *COMPRESS* combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study, *DM* diabetes mellites, *FASTER* fast assessment of stroke and TIA to prevent early recurrence, *HTN* hypertension, *IHD* ischemic heart disease, *MATCH* management of atherothrombosis with clopidogrel in high-risk patients, *PLUTO-Stroke* primary hypothesis of the plavix use for treatment of stroke, *POINT* platelet-oriented inhibition in new TIA and minor ischemic stroke, *PVD* peripheral vascular disease, *SPS3* secondary prevention of small subcortical strokes


Clopidogrel-Aspirin Monotherapy Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI
1.1.1 Any stroke
MATCH 2004 339 3797 347 3802 21.0% 0.98 [0.85, 1.13] 2004
CARESS 2005 5 51 12 56 1.2% 0.46 [0.17, 1.21] 2005
FASTER 2007 14 198 21 194 2.6% 0.65 [0.34, 1.25] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 1 10 0.1% 0.28 [0.01, 6.25] 2009
CLAIR 2010 0 46 2 52 0.1% 0.23 [0.01, 4.58] 2010
CHARISMA 2011 105 2157 131 2163 12.1% 0.80 [0.63, 1.03] 2011
SPS3 2012 125 1517 138 1503 13.3% 0.90 [0.71, 1.13] 2012
He 2015 12 321 23 326 2.4% 0.53 [0.27, 1.05] 2015
CHANCE 2015 275 2584 362 2586 20.6% 0.76 [0.66, 0.88] 2015
Yi 2015 36 485 49 486 5.8% 0.74 [0.49, 1.11] 2015
COMPRESS 2016 3 167 5 166 0.6% 0.60 [0.14, 2.46] 2016
Zuo 2017 6 66 19 68 1.6% 0.33 [0.14, 0.76] 2017
Yi 2018 36 284 40 286 5.6% 0.91 [0.60, 1.38] 2018
POINT 2018 116 2432 156 2449 13.1% 0.75 [0.59, 0.95] 2018
Subtotal (95% CI) 14137 14167 100.0% 0.80 [0.72, 0.89]
Total events 1072 1306
Heterogeneity: Tau² = 0.01; Chi² = 17.85, df = 13 (P = 0.16); I² = 27%
Test for overall effect: Z = 4.00 (P < 0.0001)
1.1.2 Ischemic stroke
MATCH 2004 309 3797 333 3802 20.3% 0.93 [0.80, 1.08] 2004
CARESS 2005 0 51 4 56 0.2% 0.12 [0.01, 2.21] 2005
FASTER 2007 12 198 21 194 3.2% 0.56 [0.28, 1.11] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 1 10 0.2% 0.28 [0.01, 6.25] 2009
CLAIR 2010 0 46 2 52 0.2% 0.23 [0.01, 4.58] 2010
CHARISMA 2011 91 2157 114 2163 12.6% 0.80 [0.61, 1.05] 2011
SPS3 2012 100 1517 124 1503 13.4% 0.80 [0.62, 1.03] 2012
He 2015 10 321 22 326 2.8% 0.46 [0.22, 0.96] 2015
CHANCE 2015 263 2584 349 2586 20.1% 0.75 [0.65, 0.88] 2015
Yi 2015 11 485 28 486 3.2% 0.39 [0.20, 0.78] 2015
COMPRESS 2016 2 167 5 166 0.6% 0.40 [0.08, 2.02] 2016
Zuo 2017 6 66 19 68 2.1% 0.33 [0.14, 0.76] 2017
Yi 2018 33 284 38 286 6.7% 0.87 [0.57, 1.35] 2018
POINT 2018 112 2432 155 2449 14.4% 0.73 [0.57, 0.92] 2018
Subtotal (95% CI) 14137 14167 100.0% 0.75 [0.66, 0.85]
Total events 949 1215
Heterogeneity: Tau² = 0.02; Chi² = 20.23, df = 13 (P = 0.09); I² = 36%
Test for overall effect: Z = 4.43 (P < 0.00001)
1.1.3 Transient ischemic attack
CARESS 2005 5 51 8 56 3.4% 0.69 [0.24, 1.96] 2005
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CLAIR 2010 2 46 1 52 0.7% 2.26 [0.21, 24.12] 2010
SPS3 2012 28 1517 39 1503 16.4% 0.71 [0.44, 1.15] 2012
CHANCE 2015 57 2584 62 2586 29.9% 0.92 [0.64, 1.31] 2015
Zuo 2017 0 66 0 68 Not estimable 2017
POINT 2018 89 2432 96 2449 47.2% 0.93 [0.70, 1.24] 2018
Yi 2018 4 284 6 286 2.4% 0.67 [0.19, 2.35] 2018
Subtotal (95% CI) 7012 7030 100.0% 0.88 [0.72, 1.07]
Total events 185 212
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
1.1.4 Myocardial infarction
MATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004
CARESS 2005 1 51 0 56 0.4% 3.29 [0.14, 78.96] 2005
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CHARISMA 2011 43 2157 32 2163 22.0% 1.35 [0.86, 2.12] 2011
SPS3 2012 31 1517 38 1503 20.6% 0.81 [0.51, 1.29] 2012
Yi 2015 4 485 4 486 2.4% 1.00 [0.25, 3.98] 2015
CHANCE 2015 5 2584 8 2586 3.6% 0.63 [0.20, 1.91] 2015
COMPRESS 2016 0 167 1 166 0.4% 0.33 [0.01, 8.08] 2016
Yi 2018 5 284 7 286 3.5% 0.72 [0.23, 2.24] 2018
POINT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018
Subtotal (95% CI) 13486 13507 100.0% 1.04 [0.84, 1.29]
Total events 172 165
Heterogeneity: Tau² = 0.00; Chi² = 5.04, df = 8 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)
0.01 0.1 1 10 100
Clopidogrel-Aspirin Monotherapy

◂**Fig. 2** Forest plot of the efficacy outcomes in patients who presented with ischemic stroke and transient ischemic attack. *CARESS* clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis, *CHANCE* clopidogrel in high-risk patients with acute non-disabling cerebrovascular events, *CHARISMA* clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, *CLAIR* clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals, *COMPRESS* combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study, *FASTER* fast assessment of stroke and TIA to prevent early recurrence, *MATCH* management of atherothrombosis with clopidogrel in high-risk patients, *POINT* platelet-oriented inhibition in new TIA and minor ischemic stroke, *SPS3* secondary prevention of small subcortical strokes

the two groups. The most common risk factors for stroke/TIA were hypertension, diabetes mellitus, and dyslipidemia. Table 2 shows the patients' demographics.

Efficacy outcomes

Clopidogrel plus aspirin was associated with a significant reduction of any stroke compared with monotherapy (7.6% vs 9.2%; RR 0.80; 95% CI 0.72–0.89; P < 0.001; $I^2 = 27\%$). In addition, there was a significant reduction in recurrent ischemic strokes favoring the clopidogrel-aspirin group (6.7% vs 8.6%; RR 0.75; 95% CI 0.66–0.85; P < 0.001; $I^2 = 36\%$). Sensitivity analysis by removing the trials that compared DAPT with clopidogrel monotherapy showed persistent significant reductions of the total and ischemic strokes with considerable improvements in between-study heterogeneity ($I^2 = 0\%$ and 10%, respectively). There were no significant differences between the groups for TIA (RR 0.88; 95% CI 0.72–1.07; P = 0.19) and MI (RR 1.04; 95% CI 0.84–1.29; P = 0.70) (Fig. 2).

Meta-regression analysis of the primary outcome based on the initial clopidogrel loading dose did not suggest any significant effect modifier (Supplementary Fig. 1).

Safety outcomes

There was a significant increase in the rate of intracranial bleeding with DAPT compared with monotherapy (1.1% vs 0.7%; RR 1.55; 95% CI 1.20–2.01; P < 0.001; $I^2 = 0\%$). Sensitivity analysis by comparing DAPT with aspirin monotherapy showed a higher rate of intracranial bleeding (1.8% vs 1.0%; RR 1.42; 95% CI 1.00–2.01; P = 0.05; $I^2 = 0\%$). In addition, there was a significant increased rate of major bleeding in the clopidogrel-aspirin group (2.2% vs 1.1%; RR 1.90; 95% CI 1.33–2.72; P < 0.001; $I^2 = 47\%$). Sensitivity analysis showed persistent increased intracranial bleeding but with low heterogeneity (1.8% vs 1.1%; RR 1.63; $I^2 = 1\%$). There were no significant differences between the two groups with regard to vascular death (RR 0.99; 95% CI 0.82–1.19; P = 0.91) or any death (RR 1.12; 95% CI 0.88–1.42; P = 0.36) (Fig. 3).

Minor stroke/TIA

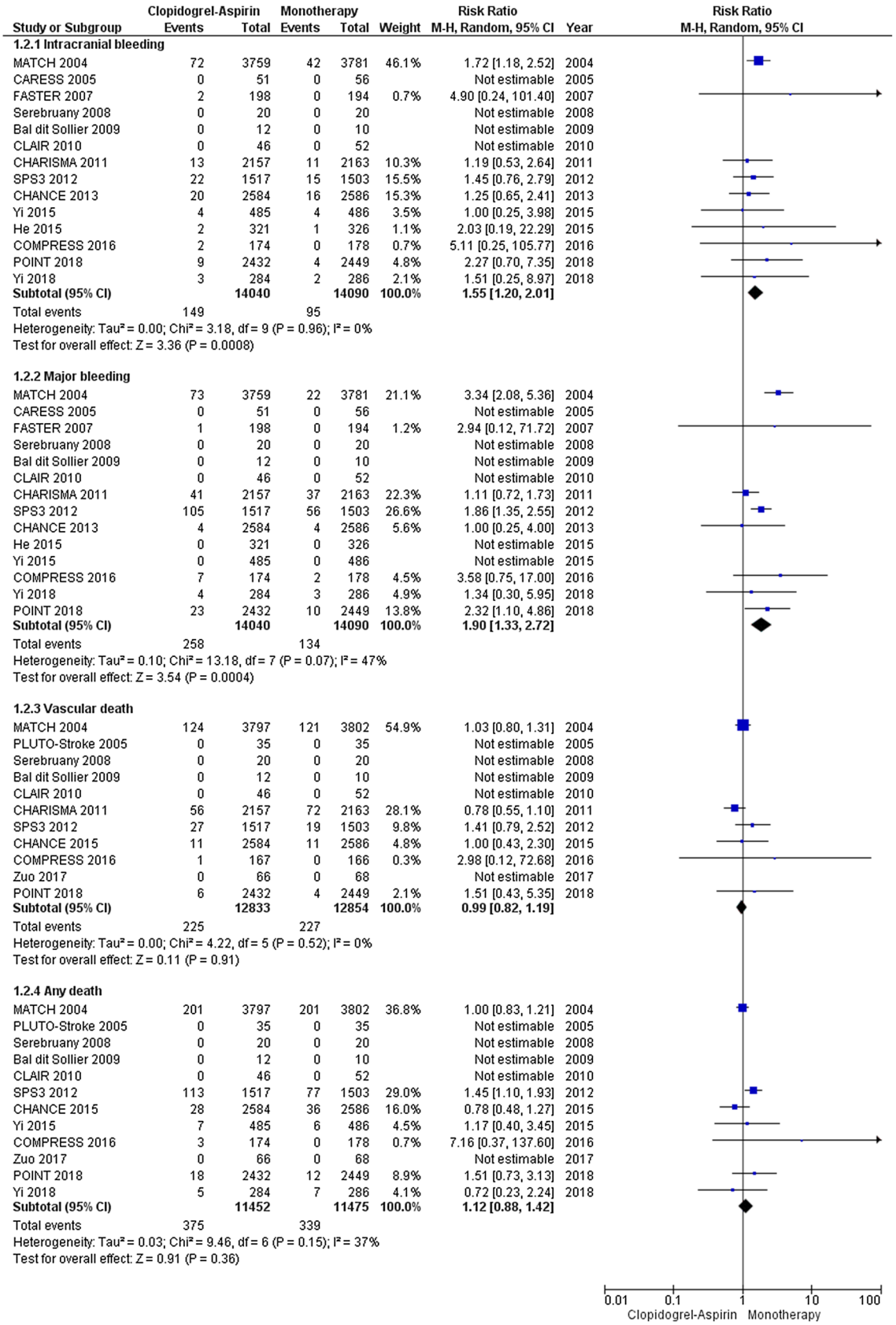
Among patients who presented with minor stroke and TIA (NIHSS score 0–3; 5 RCTs), DAPT was associated with significant reductions of any stroke and ischemic stroke compared with monotherapy [(RR 0.75; 95% CI 0.67–0.85; P < 0.001) and (RR 0.74; 95% CI 0.65–0.84; P < 0.001), respectively]. In addition, there were no differences between the two groups in TIA (RR 0.94; 95% CI 0.75–1.17; P = 0.57), MI (RR 1.00; 95% CI 0.44–2.24; P = 0.99), intracranial bleeding (RR 1.50; 95% CI 0.86–2.64; P = 0.16), vascular death (RR 1.13; 95% CI 0.57–2.27; P = 0.72), or any death (RR 1.02; 95% CI 0.54–1.94; P = 0.94). However, the rate of major bleeding was increased with DAPT (0.5% vs 0.3%; RR 1.96; 95% CI 1.03–3.71; P = 0.04) (Fig. 4).

Subgroup analyses

According to follow-up duration, there were significant reductions of any stroke and recurrent ischemic stroke with DAPT in both short- (≤ 3 months) and long-term (> 3 months) follow-up compared with monotherapy (both P < 0.01). Although the risk of intracranial bleeding increased with long-term follow-up in the DAPT group, there were no significant differences between the two groups with short-term follow-up. Both short- and long-term follow-up showed increased rates of major bleeding (Supplementary Fig. 2).

There were differences in the clinical outcomes between the two groups based on the duration of DAPT. Patients treated with short (≤ 3 months) DAPT showed greater reductions of the total/ischemic strokes without increased risk of intracranial bleeding compared with monotherapy. Shorter DAPT (≤ 1 month) was even safer in terms of major bleeding risk than intermediate or long duration therapy. Interestingly, patients treated with long duration DAPT showed similar rates of any stroke incidence compared with monotherapy. These patients also exhibited increased rates of intracranial and major bleeding (Supplementary Fig. 3).

Among patients who presented shortly after the index stroke/TIA (acute [48 h] or subacute [7 days]), DAPT was associated with lower rates of any/ischemic stroke without significant increased intracranial bleeding compared with monotherapy. In contrast, patients who presented later (chronic [≥ 1 month]) and were treated with DAPT experienced no significant reduction of any stroke but an increase in both intracranial and major bleeding compared with


Clopidogrel-Aspirin
Monotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.2.1 Intracranial bleeding
MATCH 2004 72 3759 42 3781 46.1% 1.72 [1.18, 2.52] 2004
CARESS 2005 0 51 0 56 Not estimable 2005
FASTER 2007 2 198 0 194 0.7% 4.90 [0.24, 101.40] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CLAIR 2010 0 46 0 52 Not estimable 2010
CHARISMA 2011 13 2157 11 2163 10.3% 1.19 [0.53, 2.64] 2011
SPS3 2012 22 1517 15 1503 15.5% 1.45 [0.76, 2.79] 2012
CHANCE 2013 20 2584 16 2586 15.3% 1.25 [0.65, 2.41] 2013
Yi 2015 4 485 4 486 3.5% 1.00 [0.25, 3.98] 2015
He 2015 2 321 1 326 1.1% 2.03 [0.19, 22.29] 2015
COMPRESS 2016 2 174 0 178 0.7% 5.11 [0.25, 105.77] 2016
POINT 2018 9 2432 4 2449 4.8% 2.27 [0.70, 7.35] 2018
Yi 2018 3 284 2 286 2.1% 1.51 [0.25, 8.97] 2018
Subtotal (95% CI) 14040 14090 100.0% 1.55 [1.20, 2.01]
Total events 149 95
Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 9 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)
1.2.2 Major bleeding
MATCH 2004 73 3759 22 3781 21.1% 3.34 [2.08, 5.36] 2004
CARESS 2005 0 51 0 56 Not estimable 2005
FASTER 2007 1 198 0 194 1.2% 2.94 [0.12, 71.72] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CLAIR 2010 0 46 0 52 Not estimable 2010
CHARISMA 2011 41 2157 37 2163 22.3% 1.11 [0.72, 1.73] 2011
SPS3 2012 105 1517 56 1503 26.6% 1.86 [1.35, 2.55] 2012
CHANCE 2013 4 2584 4 2586 5.6% 1.00 [0.25, 4.00] 2013
He 2015 0 321 0 326 Not estimable 2015
Yi 2015 0 485 0 486 Not estimable 2015
COMPRESS 2016 7 174 2 178 4.5% 3.58 [0.75, 17.00] 2016
Yi 2018 4 284 3 286 4.9% 1.34 [0.30, 5.95] 2018
POINT 2018 23 2432 10 2449 13.8% 2.32 [1.10, 4.86] 2018
Subtotal (95% CI) 14040 14090 100.0% 1.90 [1.33, 2.72]
Total events 258 134
Heterogeneity: Tau² = 0.10; Chi² = 13.18, df = 7 (P = 0.07); I² = 47%
Test for overall effect: Z = 3.54 (P = 0.0004)
1.2.3 Vascular death
MATCH 2004 124 3797 121 3802 54.9% 1.03 [0.80, 1.31] 2004
PLUTO-Stroke 2005 0 35 0 35 Not estimable 2005
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CLAIR 2010 0 46 0 52 Not estimable 2010
CHARISMA 2011 56 2157 72 2163 28.1% 0.78 [0.55, 1.10] 2011
SPS3 2012 27 1517 19 1503 9.8% 1.41 [0.79, 2.52] 2012
CHANCE 2015 11 2584 11 2586 4.8% 1.00 [0.43, 2.30] 2015
COMPRESS 2016 1 167 0 166 0.3% 2.98 [0.12, 72.68] 2016
Zuo 2017 0 66 0 68 Not estimable 2017
POINT 2018 6 2432 4 2449 2.1% 1.51 [0.43, 5.35] 2018
Subtotal (95% CI) 12833 12854 100.0% 0.99 [0.82, 1.19]
Total events 225 227
Heterogeneity: Tau² = 0.00; Chi² = 4.22, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
1.2.4 Any death
MATCH 2004 201 3797 201 3802 36.8% 1.00 [0.83, 1.21] 2004
PLUTO-Stroke 2005 0 35 0 35 Not estimable 2005
Serebruany 2008 0 20 0 20 Not estimable 2008
Bal dit Sollier 2009 0 12 0 10 Not estimable 2009
CLAIR 2010 0 46 0 52 Not estimable 2010
SPS3 2012 113 1517 77 1503 29.0% 1.45 [1.10, 1.93] 2012
CHANCE 2015 28 2584 36 2586 16.0% 0.78 [0.48, 1.27] 2015
Yi 2015 7 485 6 486 4.5% 1.17 [0.40, 3.45] 2015
COMPRESS 2016 3 174 0 178 0.7% 7.16 [0.37, 137.60] 2016
Zuo 2017 0 66 0 68 Not estimable 2017
POINT 2018 18 2432 12 2449 8.9% 1.51 [0.73, 3.13] 2018
Yi 2018 5 284 7 286 4.1% 0.72 [0.23, 2.24] 2018
Subtotal (95% CI) 11452 11475 100.0% 1.12 [0.88, 1.42]
Total events 375 339
Heterogeneity: Tau² = 0.03; Chi² = 9.46, df = 6 (P = 0.15); I² = 37%
Test for overall effect: Z = 0.91 (P = 0.36)
0.01 0.1 1 10 100
Clopidogrel-Aspirin Monotherapy

◂**Fig. 3** Forest plots of the safety outcomes in patients who presented with ischemic stroke and transient ischemic attack. *CARESS* clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis, *CHANCE* clopidogrel in high-risk patients with acute nondisabling cerebrovascular events, *CHARISMA* clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, *CLAIR* clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals, *COMPRESS* combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study, *FASTER* fast assessment of stroke and TIA to prevent early recurrence, *MATCH* management of atherothrombosis with clopidogrel in high-risk patients, *PLUTO-Stroke* primary hypothesis of the plavix use for treatment of stroke, *POINT* platelet-oriented inhibition in new TIA and minor ischemic stroke, *SPS3* secondary prevention of small subcortical strokes

monotherapy (Supplementary Fig. 4). In a subset of patients with minor stroke and TIA, compared with monotherapy, early DAPT in the acute ischemic phase (within 48 h) was associated with a lower rate of any/ischemic stroke without increased risk of intracranial bleeding than in those who presented later (Supplementary Fig. 5).

Based on the population studied, there were no differences between Asian and Western studies on multiple outcomes (any/ischemic strokes, TIA, MI, vascular death, or intracranial bleeding). However, Western studies showed greater increased risk of major bleeding and death than Asian studies with DAPT compared with monotherapy (Supplementary Fig. 6).

Discussion

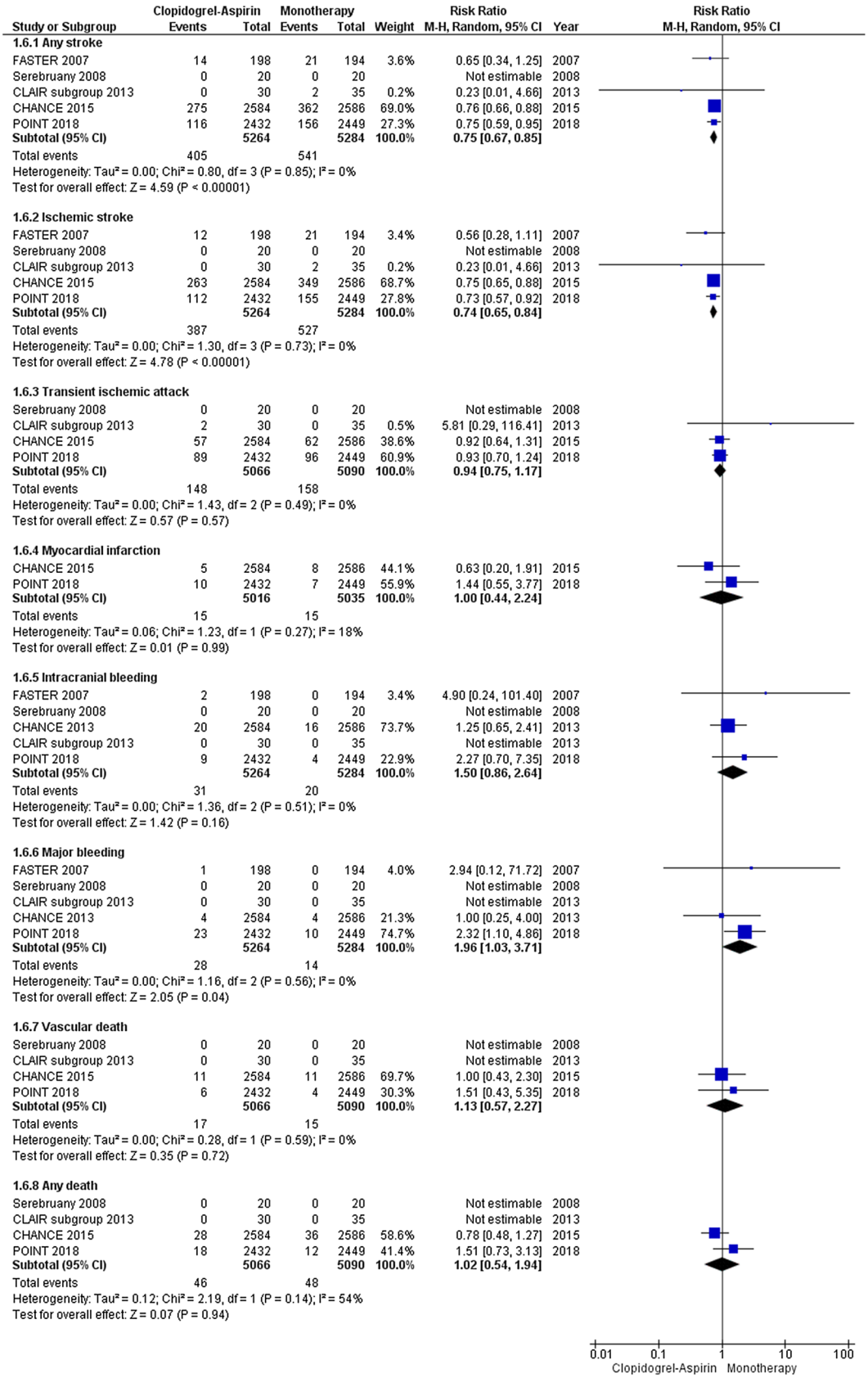
In the present meta-analysis of 16 RCTs (n = 29,032) comparing DAPT with monotherapy, we made several potentially useful observations. First, in patients who presented with ischemic stroke and TIA, DAPT significantly reduced the risk of any/ischemic stroke with no increased risk of TIA, MI, any death, or vascular death. Second, the risk of intracranial and major bleeding was increased with DAPT compared with monotherapy. However, the increased risk of intracranial bleeding was nonsignificant with DAPT compared with aspirin monotherapy. Third, the reduction of strokes with DAPT was observed during all follow-up durations (short- and long-term). However, the increased risk of intracranial bleeding was observed only with longer follow-up (> 3 months). Fourth, unlike prolonged DAPT (≥ 1 year), shorter duration dual therapy (up to 3 months) resulted in a reduction of any/ischemic strokes without increased risk of intracranial bleeding. Furthermore, the 1-month DAPT regimen did not significantly increase the risk of either intracranial or major bleeding. Fifth, DAPT was more effective in reducing any/ischemic strokes without increased risk of intracranial bleeding in patients who presented early during the acute ischemic phase (within 7 days) than those presenting late (≥ 1 month). Sixth, in a subset of patients with minor stroke/TIA and treated with DAPT, the risk of any/ischemic stroke was significantly reduced without increased risk of TIA, MI, intracranial bleeding, or mortality. However, an increased risk of major bleeding was observed with DAPT.

Previous studies of DAPT with aspirin and clopidogrel in patients with ischemic stroke and TIA have shown conflicting results [20–36]. Nevertheless, studies of microembolic signals, as an independent marker of future stroke risk, have shown a greater reduction of recurrent stroke with the clopidogrel-aspirin combination [20, 22, 27]. In our study, we found a greater benefit with clopidogrel plus aspirin in the secondary prevention of stroke. DAPT was associated with reductions of both any stroke (relative risk reduction [RRR] 18%; absolute risk reduction [ARR] 1.6%) and ischemic stroke (RRR 22%; ARR 1.9%). In addition, we found a greater benefit of DAPT immediately following the index event (within 7 days), including in patients treated within 48 h after minor stroke/TIA. Interestingly, longer durations (≥ 1 year) of DAPT showed no benefit in reducing the total stroke rate compared with monotherapy (7.6% vs 8.2%; P = 0.16) and were associated with increased bleeding events. This observation was based on pooling the estimates from 3 RCTs [22, 28, 34].

Despite the increased risk of intracranial bleeding and major bleeding with DAPT, the frequency of such events was relatively low (number needed to harm (NNH) = 258 and 113, respectively). Compared with aspirin monotherapy, DAPT was associated with a higher rate of intracranial bleeding. Nevertheless, our results showed that the initiation of DAPT in the acute ischemic phase was not associated with a significantly increased risk of intracranial bleeding (vs DAPT initiation in post-ischemic stroke phase > 1 month).

As with ACS patients, DAPT with clopidogrel plus aspirin could provide an attractive option in high thrombotic risk patients immediately following acute stroke/TIA and with short therapy duration. Our results showed no significant increase in intracranial/major bleeding events as well as persistent reduction of ischemic events, even with a shorter DAPT duration (i.e., 1 month). In patients at higher bleeding risk, the tradeoff between ischemic and bleeding risks should be weighed individually.

Some RCTs (n = 6) used a loading dose of clopidogrel (300 and 600 mg) [22, 26, 27, 29, 31, 36]; these trials either used DAPT for a short period (≤ 21 days) or assessed short-term outcomes (3 months), and the optimal loading dose in this setting remains uncertain. In a previous RCT, a loading dose of clopidogrel was not effective in reducing the risk of recurrent stroke compared with a maintenance dose only [42]. Furthermore, our meta-regression analysis for the effect of initial clopidogrel dose on recurrent stroke did not suggest any significant effect modification.


Clopidogrel-Aspirin
Monotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.6.1 Any stroke
FASTER 2007 14 198 21 194 3.6% 0.65 [0.34, 1.25] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 0 30 2 35 0.2% 0.23 [0.01, 4.66] 2013
CHANCE 2015 275 2584 362 2586 69.0% 0.76 [0.66, 0.88] 2015
POINT 2018 116 2432 156 2449 27.3% 0.75 [0.59, 0.95] 2018
Subtotal (95% CI) 5264 5284 100.0% 0.75 [0.67, 0.85]
Total events 405 541
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)
1.6.2 Ischemic stroke
FASTER 2007 12 198 21 194 3.4% 0.56 [0.28, 1.11] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 0 30 2 35 0.2% 0.23 [0.01, 4.66] 2013
CHANCE 2015 263 2584 349 2586 68.7% 0.75 [0.65, 0.88] 2015
POINT 2018 112 2432 155 2449 27.8% 0.73 [0.57, 0.92] 2018
Subtotal (95% CI) 5264 5284 100.0% 0.74 [0.65, 0.84]
Total events 387 527
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 3 (P = 0.73); I² = 0%
Test for overall effect: Z = 4.78 (P < 0.00001)
1.6.3 Transient ischemic attack
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 2 30 0 35 0.5% 5.81 [0.29, 116.41] 2013
CHANCE 2015 57 2584 62 2586 38.6% 0.92 [0.64, 1.31] 2015
POINT 2018 89 2432 96 2449 60.9% 0.93 [0.70, 1.24] 2018
Subtotal (95% CI) 5066 5090 100.0% 0.94 [0.75, 1.17]
Total events 148 158
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)
1.6.4 Myocardial infarction
CHANCE 2015 5 2584 8 2586 44.1% 0.63 [0.20, 1.91] 2015
POINT 2018 10 2432 7 2449 55.9% 1.44 [0.55, 3.77] 2018
Subtotal (95% CI) 5016 5035 100.0% 1.00 [0.44, 2.24]
Total events 15 15
Heterogeneity: Tau² = 0.06; Chi² = 1.23, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.01 (P = 0.99)
1.6.5 Intracranial bleeding
FASTER 2007 2 198 0 194 3.4% 4.90 [0.24, 101.40] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
CHANCE 2013 20 2584 16 2586 73.7% 1.25 [0.65, 2.41] 2013
CLAIR subgroup 2013 0 30 0 35 Not estimable 2013
POINT 2018 9 2432 4 2449 22.9% 2.27 [0.70, 7.35] 2018
Subtotal (95% CI) 5264 5284 100.0% 1.50 [0.86, 2.64]
Total events 31 20
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
1.6.6 Major bleeding
FASTER 2007 1 198 0 194 4.0% 2.94 [0.12, 71.72] 2007
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 0 30 0 35 Not estimable 2013
CHANCE 2013 4 2584 4 2586 21.3% 1.00 [0.25, 4.00] 2013
POINT 2018 23 2432 10 2449 74.7% 2.32 [1.10, 4.86] 2018
Subtotal (95% CI) 5264 5284 100.0% 1.96 [1.03, 3.71]
Total events 28 14
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
1.6.7 Vascular death
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 0 30 0 35 Not estimable 2013
CHANCE 2015 11 2584 11 2586 69.7% 1.00 [0.43, 2.30] 2015
POINT 2018 6 2432 4 2449 30.3% 1.51 [0.43, 5.35] 2018
Subtotal (95% CI) 5066 5090 100.0% 1.13 [0.57, 2.27]
Total events 17 15
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
1.6.8 Any death
Serebruany 2008 0 20 0 20 Not estimable 2008
CLAIR subgroup 2013 0 30 0 35 Not estimable 2013
CHANCE 2015 28 2584 36 2586 58.6% 0.78 [0.48, 1.27] 2015
POINT 2018 18 2432 12 2449 41.4% 1.51 [0.73, 3.13] 2018
Subtotal (95% CI) 5066 5090 100.0% 1.02 [0.54, 1.94]
Total events 46 48
Heterogeneity: Tau² = 0.12; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.07 (P = 0.94)
0.01 0.1 1 10 100
Clopidogrel-Aspirin Monotherapy

◂**Fig. 4** Forest plots of the clinical outcomes in patients who presented with minor ischemic stroke and transient ischemic attack. *CHANCE* clopidogrel in high-risk patients with acute nondisabling cerebrovascular events, *CLAIR* clopidogrel plus aspirin for infarction reduction in acute stroke or transient ischaemic attack patients with large artery stenosis and microembolic signals, *FASTER* fast assessment of stroke and TIA to prevent early recurrence, *POINT* platelet-oriented inhibition in new TIA and minor ischemic stroke

Current AHA/ASA guidelines recommend 21 days of clopidogrel plus aspirin only in patients presenting with minor stroke (Class IIa; level of evidence: moderate) [18]. The recommendation is mainly based on the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which recruited 5170 Chinese patients and found a greater benefit of DAPT in preventing early recurrent stroke without a higher rate of bleeding [26, 39]. Nevertheless, in a subset analysis of both Asian and non-Asian populations from 5 RCTs with NIHSS scores of 3 or less or TIA, we found significantly lower rates of any stroke (RRR 25% and ARR 2.5%) and ischemic stroke (RRR 26% and ARR 2.6%) without a significantly increased rate of intracranial bleeding in the DAPT group compared with monotherapy. Although the rates of major bleeding were significantly increased with DAPT, the NNH was high (rates 0.5% vs 0.3%; NNH 375).

In patients with stroke or TIA, antiplatelet "resistance" might represent a factor for the occurrence of stroke due to several pharmacogenetic and pharmacodynamic properties [43, 44]. Genetic polymorphisms, notably CYP2C19, are associated with increased clopidogrel response variability [45]. Among patients with stroke and TIA, carriers of CYP2C19 loss-of-function (LOF) alleles had an associated increased risk of stroke compared with noncarriers [46]. However, the frequency of CYP2C19 LOF varies substantially between white and East Asian populations (up to 30% and 60%, respectively) [45]. In our subgroup analysis of Asian vs Western studies, the rates of recurrent any or ischemic strokes in the DAPT group were almost a third more in Asians vs Westerners (9.3% and 8.2% vs 6.1% and 5.3%, respectively), possibly reflecting the higher prevalence of poor/intermediate clopidogrel metabolizers among Asian populations. Nevertheless, compared with monotherapy, we found that the combination of clopidogrel plus aspirin was associated with significant reductions of any/ischemic stroke in East Asians. In Western studies, there was an increased risk of any death, potentially driven by significantly increased rates of major bleeding. However, the average duration of DAPT in the Western studies was 211 days (vs 29 days in Asian studies), which inherently carries a higher bleeding risk and thus potentially mortality. This also supports the use of DAPT for short durations in these patients.

There are limitations to the present study. First, there were differences between the included studies with regard to the baseline stroke severity (NIHSS score), follow-up duration, drug dosage, and duration of treatment, as well as differences in the timing of randomization after stroke and TIA. However, we have tried to provide consistent results through sensitivity, subgroup, and meta-regression analyses. Second, we could not investigate the clinical outcomes based on the stroke subtypes as we lacked individual patient-level data. Third, we were not able to perform subgroup analysis based on the index stroke severity, as most trials did not provide an initial stroke assessment score, such as the NIHSS score. Fourth, we were not able to assess any functional outcomes, such as the modified Rankin score, as most trials did not provide such outcomes.

Conclusions

Among patients who presented with ischemic stroke and TIA, the combination of clopidogrel plus aspirin compared with antiplatelet monotherapy was associated with a significant reduction of recurrent stroke with no increased risk of vascular events (TIA, MI, or vascular death) or mortality. Although there was increased risk of bleeding events, mainly with long therapy duration and late stroke/TIA presentation, short course clopidogrel and aspirin was associated with less recurrent stroke and equivalent bleeding complications compared with monotherapy. Similar findings were also observed in patients who presented with minor stroke and TIA.

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Compliance with ethical standards

Conflict of interest Dr. Mustafa Hassan has received a research grant from Abbott. Dr. Mohammed Al Qasmi is on speaker bureau for Genentech. Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Jour-

nal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. The remaining authors report no relationships that could be construed as a conflict of interest.

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