

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

Babikir Kheiri¹ · Mohammed Osman² · Ahmed Abdalla³ · Tarek Haykal¹ · Bakr Swaid¹ · Sahar Ahmed⁴ · Adam Chahine¹ · Mustafa Hassan⁵ · Ghassan Bachuwa¹ · Mohammed Al Qasmi⁶ · Deepak L. Bhatt⁷

Published online: 3 December 2018 © Springer Science+Business Media, LLC, part of Springer Nature 2018

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 $(\leq 1 \text{ month})$ 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 (≥ 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

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11239-018-1786-z) contains supplementary material, which is available to authorized users.

Deepak L. Bhatt dlbhattmd@post.harvard.edu

- ¹ Department of Internal Medicine, Hurley Medical Center/ Michigan State University, Flint, MI 48503, USA
- ² Division of Cardiology, West Virginia University School of Medicine, Morgantown, WV 26506, USA
- ³ Division of Hematology & Oncology, Ascension St. John Hospital, Grosse Pointe Woods, MI 48236, USA

- ⁴ Research Assistance, Flint, MI 48503, USA
- ⁵ Division of Cardiology, Hurley Medical Center/Michigan State University, Flint, MI 48503, USA
- ⁶ Division of Neurology, Hurley Medical Center/Michigan State University, Flint, MI 48503, USA
- ⁷ Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

- 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, studylevel 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 lifethreatening 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 followup 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 I² test.

We assessed potential publication bias by visual inspection of the funnel plot. Furthermore, we explained any heterogeneity ($\geq 20\%$) 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 chara	acteristics of the in	icluded random	ized clinical trials								
First author, year, and study name	Design and loca- tions (countries)	Study period	Follow-up dura- tion	NIHSS score	Stroke/TIA cause	Medications	Total no.	Primary out- come	Dual therapy	Mono-therapy	p-value
Diener 2004 MATCH	Double blinded International (28)	2000–2002	18 months	1	All types	Clop + Asp vs Clop	7599	Ischemic stroke, MI, vascular death, or rehospitaliza- tion	15.7%	16.7%	0.244
Serebruany 2005 PLUTO-Stroke	Single center United States	I	1 month	I	All types	Clop+Asp vs Asp	70	I	I	I	I
Markus 2005 CARESS	Double blinded Europe (4)	I	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	I	1 month	I	All types	Clop+Asp vs ER-DP+ASA vs Clop	09	I	1	1	I
Bal dit Sollier 2009	Double blinded France	2000–2001	10 days	1	All types	Clop + Asp vs Ter- utroban + Asp vs Terutroban vs Asp	48	The of mean cross-sectional surface of dense throm- bus	4.6±86.8	0.8±84.1	0.005
Hankey 2011 CHARISMA substudy	Double blinded International (32)	2002–2003	25 months	I	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	I	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	I	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 deteriora- tion or new stroke from TIA	3.1%	6.7%	1

Table 1 (continu	led)										
First author, year, and study name	Design and loca- tions (countries)	Study period	Follow-up dura- tion	NIHSS score	Stroke/TIA cause	Medications	Total no.	Primary out- come	Dual therapy	Mono-therapy I	o-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 neurologi- cal deteriora- tion	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% (16.(
Zuo 2017	China	2013–2014	3 months	I	> 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 vascu- lar death	5.0%	6.5% (0.02
Yi 2018	Blinded end- points 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%).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 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 events, CHARISMA clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, CLAIR clopidogrel plus aspirin for infarction reduction in acute stroke the plavix use for treatment of stroke, POINT platelet-oriented inhibition in new TIA and minor ischemic stroke, SP33 secondary prevention of small subcortical strokes, TIA transient ischemic attack

Table 2 Patients'	' demographics											
First author, year, and study name	Total number	Age	Male	NTH	DM	PVD	CHF	CIHI	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)	I	656 (17)	2126 (56)	1825 (48)	1	. 1
	Monotherapy $N = 3802$	66.1 ± 9.9	2396 (63)	2973 (78)	2599 (68)	388 (10)	I	646 (17)	2154 (57)	1772 (47)	I	I
Serebruany 2005 PLUTO-	Dual therapy $N = 35$	67.7±7.3	14 (40)	17 (48)	15 (42)	I	I	18 (51)	20 (57)	8 (22)	I	I
Stroke	Monotherapy $N = 35$	68.3 ± 6.3	21 (60)	18 (51)	12 (34)	I	I	12 (34)	17 (48)	14 (40)	I	I
Markus 2005 CARESS	Dual therapy $N = 51$	66.4 ±8.1	35 (68.6)	38 (74.5)	16 (31.4)	11 (21.6)	I	17 (33)	28 (54.9)	I	I	I
	Monotherapy $N = 56$	62.8 ± 10.7	39 (69.6)	31 (55.4)	18 (32.1)	6 (10.7)	I	23 (41)	32 (57.1)	I	I	I
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)	I	I	5 (25)	7 (35)	16 (80)	8 (40)	I	I
	Monotherapy $N = 20$	60.7 ± 8.4	12 (60)	15 (7S)	I	I	4 (20)	9 (45)	14 (70)	10 (50)	I	I
Bal dit Sollier 2009	Dual therapy $N = 12$	67.8±9.2	10 (83.3)	I	I	I	I	I	I	I	I	I
	Monotherapy $N = 12$	70.5 ± 11.1	8 (66.7)	I	I	I	I	I	I	I	I	I
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)	I	I	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)	I	I	20.1%	140.2 ± 19.2	80.1 ± 10.9
Benavente 2012 SPS3	Dual therapy $N = 1517$	63	941 (62)	1153 (76)	531 (35)	I	I	152 (10)	I	303 (20)	143	78
	Monotherapy $N = 1503$	63	962 (64)	1112 (74)	571(38)	I	I	165 (11)	I	316 (21)	143	78
Wong 2010 CLAIR	Dual therapy N=46	59.2±12.5	36 (78)	27 (60)	21 (46)	4 (9)	I	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)	I	7 (13.5)	16 (33)	30 (57.7)	148.6 ± 23.1	83.9±11.6
Lau 2013 CLAIR sub-	Dual therapy $N = 30$	<i>5</i> 7.6 ± 13.7	22 (73.3)	18 (60)	14 (47)	3 (10)	I	I	I	I	137.1 ± 22.7	78.1±10.5
group	Monotherapy $N = 35$	56.4 ± 12.2	27 (77.1)	22 (63)	10 (29)	1 (3)	I	Ι	I	I	147.2 ± 23.4	84.4±12.7

Table 2 (continu	ed)										
First author, year, and study name	Total number	Age	Male	NTH	DM	PVD	CHF	OHI	Dyslipidemia	Smoker	Systolic BP, mmHg
Wang 2015 CHANCE	Dual therapy N=2584	63 [55–72]	1732 (67)	1716 (66.4)	550 (21.3)	. 1	42 (1.6)	140 (5.4)	290 (11.2)	1116 (43.2)	150 [136–161]
	Mono therapy $N = 2586$	62 [54–71]	1688 (65.3)	1683 (65.1)	543 (21.0)	I	38 (1.5)	140 (5.4)	283 (10.9)	1105 (42.7)	150 [136–161]
He 2015	Dual therapy $N = 321$	$62.9\ 2\pm 8.96$	183 (57)	213 (66.36)	138 (42.99)	I	I	88 (27.4)	I	161 (50.16)	1
	Monotherapy $N = 326$	61.52 ± 10.21	185 (56.7)	224 (68.71)	128 (39.26)	I	I	92 (28.2)	I	165 (50.61)	1
Yi 2015	Dual therapy $N = 485$	69.5 ± 10.14	265 (54.6)	348 (71.75)	160 (32.99)	I	I	18 (3.7)	I	201 (41.44)	$135.3 \pm 2\ 0.32$
	Monotherapy $N = 486$	70.1±11.12	268 (55.1)	345 (70.99)	165 (33.95)	I	I	17 (3.5)	I	199 (40.95)	134.9 ± 21.26
Johnston 2018 POINT	Dual therapy $N = 2432$	65.0 [55.0– 74.0]	1335 (54.9)	1693 (69.9)	678 (28.0)	I	I	257 (10.6)	1	Ι	I
	Monotherapy $N = 2449$	65.0 [56.0– 74.0]	1351 (55.2)	1680 (68.9)	662 (27.1)	I	I	240 (9.8)	I	I	1
Hong 2016 COMPRESS	Dual therapy $N = 174$	68 (37–96)	114 (65.52)	112 (64.37)	58 (33.33)	I	I	8 (4.60)	59 (33.91)	71 (40.80)	140 (93–208)
	Monotherapy $N = 175$	67 (36–89)	108 (61.71)	119 (68.00)	55 (31.43)	I	I	8 (4.57)	50 (28.57)	63 (36.00)	135 (94–195)
Zuo 2017	Dual therapy N=66	61.55 (45–80)	24 (36.4)	40 (60.6)	25 (37.8)	I	I	11 (16.7)	41 (62.1)	36 (54.5)	I
	Monotherapy $N = 68$	62.29 (45–80)	27 (39.7)	43 (65.2)	18 (27.8)	I	I	6 (8.8)	40 (58.8)	33 (48.5)	I
Yi 2018	Dual therapy $N = 284$	69.2 ± 10.1	156 (54.9)	204 (71.8)	105 (37.0)	I	I	10 (3.5)	I	112 (39.4)	137.6 ± 21.2

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ion 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 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, CHARSMA clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management and avoidance, CHF congestive heart failure, CLAIR clopidogrel plus aspirin for infarcin new TIA and minor ischemic stroke, PVD peripheral vascular disease, SPS3 secondary prevention of small subcortical strokes

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1.1.4 Any stroke MATCH 2004 339 3757 347 3002 21.0% 0.46 [0.37, 1.13] 2004 CAREES 2005 5 5 11 26 1.2% 0.46 [0.34, 1.23] 2007 Serebruary 2008 0 20 0 0.44 [0.30, 1.20] 2008 Net estimable 2008 Serebruary 2008 0 20 0 1.4 2.65 [0.34, 1.22] 2007 Serebruary 2008 0 20 1.5 1.2 2.05 [0.1, 2.2] 2.001 2.29 [0.001, 2.2] 2.001 CHARMAD 2011 105 2.167 138 10.33 [0.00 [0.01, 1.14] 2.016 - - FR3 2012 122 517 138 12.44 0.58 [0.02, 0.101, 2.24] 2.016 - - FN2 2016 3 84.5 44 48.6 8.6 % 0.74 [0.46, 1.38] 2016 - - Y12016 38 2.244 40 2.86 0.58 [0.02, 0.01, 1.24] 2017 - - - - - - - - - -	Study or Subgroup	Ciopidogrel-/ Events	Aspirin Total	Monoth Events	erapy Total	Weight	Risk Ratio M-H, Random, 95% Cl	Year	Risk Ratio M-H, Random, 95% Cl
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FASTER 2007 14 198 21 194 2.98 0.65 [0.34, 1.25] 2007 Serethuary 2008 0 12 1 10 0.15 0.28 [0.01, 6.52] 2009 Baid Boliner 2009 0 12 1 10 0.15 0.28 [0.01, 6.52] 2009 CHAREMA 2011 106 2.157 13 12.03 13.38 0.40 [0.05, 10.03 0.01 He 2016 12 2.17 13 15.03 13.38 0.40 [0.05, 10.03 0.01 He 2016 12 2.21 13 3.38 2.44 0.59 [0.27, 1.05] 0.15 + ViD16 136 157 5 156 0.56 0.51 [0.42, 1.05] 2.017 + ViD16 136 124 153 4.00 2.65 0.05 [0.24, 1.11] 2.017 + ViD16 136 124 153 0.04 [0.72, 0.89] 2.017 + + + + + + + + + + + + + + + + + <t< td=""><td>CARESS 2005</td><td>5</td><td>51</td><td>12</td><td>56</td><td>1.2%</td><td>0.46 [0.17, 1.21]</td><td>2005</td><td></td></t<>	CARESS 2005	5	51	12	56	1.2%	0.46 [0.17, 1.21]	2005	
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CHAPGSMA 2011 105 2157 138 1283 1215 009 071 131 2012 1 He 2015 12 321 32 338 2.4% 0.59 0071 131 2012 1 He 2015 12 321 32 338 2.4% 0.59 0071 131 2012 1 He 2015 12 524 382 2268 2.8% 0.59 0.77 10.48 1015 1 CANNOE 2015 35 448 40 486 5.8% 0.74 10.49, 111 2015 1 COMPRESS 2016 3 167 5 168 0.8% 0.39 10.40, 138 2016 1 COMPRESS 2016 3 167 5 168 0.8% 0.39 10.40, 138 2016 1 COMPRESS 2016 116 2422 156 2.449 131% 0.79 10.59, 0.85 2018 1 COMPRESS 2016 107 21 755, df = 13 (P = 0.16), P = 27% 1 Test consult effect 2 = 4.00 (P < 0.0001) 1 112 2147 1306 1 Test consult effect 2 = 4.00 (P < 0.0001) 1 112 215 114 215 21 10 0.2% 0.58 (0.80, 1.08) 2014 1 CARESS 2005 0 12 1 198 32 1 194 32% 0.56 (0.28, 1.11) 2007 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.11, 221) 2005 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.11, 221) 2005 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2018 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2019 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2010 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.21) 2017 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2017 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2017 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2017 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2017 1 CARESS 2005 0 12 1 10 0.2% 0.28 (0.01, 0.28) 2017 1 CARESS 2005 0 12 10 10 Not estimable 2009 1 CARESS 2015 21 3 348 20 226 2.2% 0.48 (0.80 (0.21, 1.18) 2011 1 CARESS 2015 21 3 348 20 226 2.2% 0.49 (0.20, 0.20) 2015 1 CARESS 2015 21 3 348 20 226 6 2.4% 0.49 (0.82, 0.29) 2015 1 CARESS 2015 2 1 167 2 158 6 0.2% 0.40 (0.80 (0.21, 1.38) 2017 1 CARESS 2015 2 1 167 2 150 10 Not estimable 2009 1 CARESS 2015 2 1 167 2 150 10 Not estimable 2009 1 CARESS 2015 2 1 167 2 150 10 Not estimable 2009 1 CARESS 2015 2 1 167 2 150 168 0.4% 0.32 (0.14, 1.38) 2015 1 CARESS 2015 1 12 2017 1 CARESS 2015 1 15	CLAIR 2010	ů N	46	2	52	0.1%	0.23 (0.01, 4.58)	2000	
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μa 2015 12 121 123 224 6 0510271 105 2015 CHANCE 2015 275 224 480 658 0.75 05106 000 COMPRESS 2015 3 167 5 168 0.68 0.75 0.610 142.448 111 2015 ComPRESS 2015 3 167 5 168 0.68 0.39 10.41.0.76 2017 Subord (155, 01) 116 2423 168 168 0.39 0.39 10.80 12.01 You 30 3 3 440 0.28 0.78 0.78 0.69 0.78 0.78 0.78 0.78 0.78 0.78 0.78 0.72 0.78	SPS3 2012	125	1517	130	1503	12.1%	0.00 [0.03, 1.03]	2011	_
CHANCE 2015 275 254 362 208% 076 06.01 2.401 COMPRESS 2016 3 167 5 166 0.5% 0.601 1.2.401 2016 CAU2017 6 6.66 19 6.6 0.5% 0.601 1.60 1.38 2016 W 2015 36 244 0.224 1.20 0.761 0.60, 0.238 2017 W 2015 1.20 1.20 1.20 0.761 0.60, 0.238 2018 - W 2015 1.4157 1.4167 100.0% 0.30 0.01, 0.72, 0.891 2016 Heterogenethy: Tau"= 0.01; Ch"= 17.26, d"= 13 (P = 0.16); P= 27%. Testfor overall effect Z = 4.00 (P = 4.00001) - 0.22 0.31 0.80 0.52 2.001 AIRCH 2004 308 378 3.23 3.20 2.0.3% 0.31 0.80 0.61, 0.65 2.010 - 0.25 0.016 0.52 2.001 - 0.25 0.016 0.05 0.011 2.017	Un 2015	125	221	130	226	2 100	0.50 [0.71, 1.15]	2012	
Universe 2013 2.98 2.286 302 2.98 0.05% 0.05% 2.018 2.018 2.018 2.019 2.016 2.0.5% 2.018 2.018 2.019 2.016 2.0.5% 2.011 2.010 2.016 2.0.5% 2.011 2.010 2.016 2.0.5% 2.011 2.010 2.016 2.0.5% 2.011 2.010 2.016 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.018 2.019 2.0100 2.010 2.0100 2.0100 2.010 2.010	CUANCE 2015	275	321	20	320	2.4 %	0.00 [0.27, 1.00]	2013	-
$ \begin{array}{c} 1.013 \\ 1.013 \\ 0.00 \\ 0.00 \\ 0.00 \\ 0.00 \\ 1.013 \\ 0.00 $		275	2004	302	2000	20.0%	0.70 [0.00, 0.00]	2015	
Converses 2016 3 167 3 168 0.48% 0.48% 0.491 (0.14, 2.48 2016 12.017 36 264 40 286 5.6% 0.31 (0.14, 0.78 2017 12.018 36 244 40 286 5.6% 0.31 (0.14, 0.78 2017 12.018 40 286 5.6% 0.31 (0.14, 0.78 2017 12.018 4157 156 2017 13.06 14137 156 2449 13.1% 0.33 (0.14, 0.78 0.58 2018 4460 29 0.01 201 167 4137 156 2017 14.157 156 2016 2010 14.12 behavior scale affect 2 = 0.0001 14.12 behavior scale affect 2 = 0.0001 14.13 behavior scale affect 2 = 0.0001 14.13 behavior scale affect 2 = 0.0001 14.13 behavior scale affect 2 = 0.00001 14.13 behavior scale affect 2 = 0.00001 14.14 behavior scale affect 2 = 0.00001 14.14 behavior scale affect 2 = 0.00001 14.14 behavior scale affect 2 = 0.00001 14.15 behavior scale affect 2 = 0.00001 14.15 behavior scale affect 2 = 0.00001 14.15 behavior scale affect 2 = 0.00001 14.14 behavior scale affect 2 = 0.000001 14.14 behavior scale affect 2 = 0.000001 14.14 beha	11 2015	30	485	49	480	5.8%	0.74 [0.49, 1.11]	2015	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CUMPRESS 2016	3	167	5	100	0.0%	0.00 [0.14, 2.46]	2016	
n 2018 3 36 244 40 206 5.0% UP [0.60, 1.48] 2018 4137 100.0% 0.80 [0.72, 0.89] 2018 4137 100.0% 0.80 [0.72, 0.89] 2018 4137 14477 100.0% 0.80 [0.72, 0.89] 4100 2019 4100 4100 2019 4100 4100 4100 4100 4100 4100 4100 4	200 2017	8	00	19	88	1.6%	0.33 [0.14, 0.76]	2017	
CONT 2018 118 2232 126 22449 131% 0.75 (0.59, 0.59, 0.93) Total events 1072 1306 41477 14167 1000, 0.072, 0.039) Total events 1072 1306 0.03 (0.72, 0.039) 0.03 (0.07, 0.039) Marcharon 300 3797 333 3802 20.3% 0.93 (0.80, 1.08) 2004 ArtCH 2004 309 3797 333 3802 20.3% 0.93 (0.80, 1.08) 2004 ArtCH 2004 309 3797 333 3802 20.3% 0.93 (0.80, 1.08) 2004 Setebruary 2008 0 20 0 20 Not estimable 2008 Setebruary 2009 12 10 0.28 (0.07, 6.29) 2009	Yi 2018	36	284	40	286	5.6%	0.91 [0.60, 1.38]	2018	
Subtrain (9%): (1) 14137 14167 100.0% 0.00 [0.72, 0.89] (0.80, 1.08] 2004 Heterogeneity: Tau ² = 0.01; Ch ² = 17.85, df = 13 (P = 0.16); P = 27% Fest 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 ACRESS 2005 0 51 4 66 0.2% 0.12 [0.01, 2.21] 2005 ACRESS 2005 0 12 198 21 194 3.2% 0.56 [0.28, 1.11] 2007 Serbehuary 2008 0 20 0 20 Not estimable 2008 Bi di Soliter 2009 0 12 1 10 0.2% 0.28 [0.01, 6.25] 2019 CHARISMA 2011 91 2157 114 2163 13.4% 0.80 [0.61, 1.05] 2011 CHARISMA 2011 91 2157 114 2163 13.4% 0.80 [0.61, 1.05] 2011 CHARISMA 2011 91 2157 114 2163 13.4% 0.80 [0.61, 1.05] 2015 CHARISMA 2011 91 2157 114 2163 13.4% 0.80 [0.61, 1.05] 2015 CHARISMA 2011 91 2157 114 425 284 286 228 0.45 [0.02, 0.78] 2015 CHARISMA 2011 91 2157 166 0.6% 0.44 [0.02, 0.98] 2015 CHARISMA 2011 91 2127 21 235 248 348 0.3% 0.33 [0.12, 0.73] 2015 CHARISMA 2012 1 20 237 CH 256 2438 14.4% 0.73 [0.57, 0.82] 2017 T 2015 11 2432 155 2448 14.4% 0.73 [0.57, 0.92] 2017 T 2018 312 242 315 244 14.4% 0.73 [0.57, 0.92] 2017 T 2018 112 2432 155 2448 14.4% 0.73 [0.67, 0.92] 2017 T 2018 112 2432 155 2448 14.4% 0.73 [0.67, 0.92] 2017 T 41467 100.0% 0.59 [0.24, 1.96] 2005 Not estimable 2009 E 2017 6 66 19 68 21% 0.33 [0.14, 0.78] 2047 T 2018 312 22 32.3 (df = 12) (P = 0.09); P = 36% Test for overall effect Z = 4.43 (P < 0.00001) 1.13 Transient ischemic attack CARESS 2005 5 51 8 56 3.4% 0.69 [0.24, 1.96] 2005 S Febturany 2008 0 20 0 20 Not estimable 2009 C 2017 0 66 06 8Not estimable 2009 C 2017 7 0 66 3602 42.2% 107 [0.77, 1.49] 2004 T 2018 4 232 96 2449 47 2% 0.93 [0.70, 1.24] 2016 T 2018 1 4217 32 079 (0.00% 0.38 [0.72, 1.07] T 2018 4 232 96 2449 47 2% 0.93 [0.70, 1.24] 2016 T 2018 4 232 96 2449 47 2% 0.03 [0.01, 1.29] 2015 T 414070904 173 31 1517 38 1503 20.6% 0.31 [0.71, 1.49] 2004 C 2017 7 0 66 068 Not estimable 2009 C 2015 57 2844 62 2868 29.9% 0.93 [0.71, 1.44] 2015 	POINT 2018	116	2432	156	2449	13.1%	0.75 [0.59, 0.95]	2018	•
Total events 1072 1306 Heirogeneity: Tary = 0.01, Ch ² = 178, df = 13 (f = 0.16); l ² = 27% Fest for overall effect Z = 4.00 (P < 0.0001) 1.12 Iostemic stroke MATCH 2004 309 3797 333 3602 20.3% 0.93 (0.80, 1.08] 2004 ARESS 2005 0 51 4 56 0.2% 0.12 (0.10, 2.21) 2005 ARESS 2005 0 51 4 56 0.2% 0.12 (0.10, 2.21) 2005 Brebunay 2008 0 20 0 20 Not estimable 2008 Bail di Solier 2009 0 12 1 10 0.2% 0.28 (0.16, 25) 2009 	Subtotal (95% CI)		14137		14167	100.0%	0.80 [0.72, 0.89]		•
Heterogeneity: Tau ² = 0.1; Ch ^m = 13 (P = 0.16); P = 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, 1.09] 2004 CARESS 2005 0 51 4 65 0.2% 0.12 (0.01, 2.21) 2005 Ver ASTER 2007 12 198 21 194 3.2% 0.56 (0.28, 1.11) 2007 Seebehuary 2008 0 12 1 10 0.2% 0.28 (0.01, 2.52) 2019 Unit set to a stroke 2009 Descent and 2009 0 12 1 10 0.2% 0.28 (0.01, 2.52) 2009 CHARISMA 2011 91 2157 114 2163 13.4% 0.80 (0.61, 1.05) 2011 H 2015 10 321 22 326 2.8% 0.46 (0.22, 0.98) 2015 CHARISMA 2011 91 2157 114 1053 13.4% 0.80 (0.61, 1.05) 2015 CHARISMA 2011 91 2157 114 2163 72, 8% 0.45 (0.20, 0.78) 2015 CHARISMA 2011 91 2157 114 4153 12.6% 0.40 (0.02, 0.07) 2015 CHARISMA 2011 91 2157 114 4153 284 486 3.2% 0.33 (0.20, 0.78) 2015 CHARISMA 2011 21 22 322 155 2449 14.4% 0.73 (0.57, 0.92) 2015 CHARISMA 2012 12 2432 155 2449 14.4% 0.73 (0.57, 0.92) 2016 CHARISMA 2013 112 2432 1155 2449 14.4% 0.73 (0.57, 0.92) 2017 M 2018 112 2432 1155 2449 14.4% 0.73 (0.57, 0.92) 2018 CHARISMA 2014 949 1215 Heterogeneity: Tau ² = 0.02, ch ² = 20.23, df = 13 (P = 0.09); P = 36% Test for overall effect Z = 4.3 (P < 0.00001) L1.3 Transient ischemic attack CARESS 2005 5 51 8 56 3.4% 0.69 (0.24, 1.96] 2005 Not estimable 2009 CLAR 2010 2 46 1 52 207% 2.26 [0.21, 24.12] 2010 Serebuary 2008 0 20 0 20 Not estimable 2008 CLAR 2010 2 46 1 52 27 POINT 2018 89 2432 96 2449 47 2% 0.93 (0.70, 1.24) 2016 M Cell and Soliter 2002, Ch ² = 1.99, df = 6 (P = 0.35); P = 0% Test for overall effect Z = 1.31 (P = 0.19) L1.4 Wood and infortion M CCH 2004 73 3797 68 3022 42.2% 1.07 (0.77, 1.49] 2004 M 2015 4 465 4 2868 248 98 0.058 (0.12, 2011 M 2015 4 24.52 172 Heterogeneity: Tau² = 0.00; Ch² = 5 (0.4) df = 30 (P = 0.76); P = 0% Test for overall effect Z = 1.31 (P = 0.19) H 2015 4 24.84 6 286 3.24% 1.00 (0.23, 23.91) 2015 H 416 0056 Ch² 5 284 8 286 3.6% 0.63 (0.21, 911) 2015 D 2014 7016 5 284 6 P = 0.76); 	Total events	1072		1306					
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$\begin{array}{c} \text{Contracted} & Contr$	12010 OMDDECC 2016	11	400	20	400	0.2%	0.39 [0.20, 0.70]	2010	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	OMPRESS 2016	2	167	5	100	0.6%	0.40 [0.08, 2.02]	2016	
12/018 33 284 33 284 6.7% 0.87 [0.57, 0.52] 2018 010117 2018 112 2432 155 2449 14.4% 0.73 [0.57, 0.52] 2018 iotal events 949 1215 1215 1216 1216 1217 1216 ieterogeneily: Tau"= 0.02; Chi"= 20.23, df= 13 (P = 0.09); P = 36% 0.59 [0.24, 1.96] 2005 1215 iest for overall effect: Z = 4.43 (P < 0.00001)	200 2017	6	66	19	68	2.1%	0.33 [0.14, 0.76]	2017	
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Total events 949 1215 Heterogeneity: Tau ² = 0.02; Chi ² = 20.23, df = 13 ($P = 0.09$); $P = 36\%$ Test for overall effect: Z = 4.43 ($P < 0.00001$) L1.43 Transient ischemic attack ARESS 2005 5 51 8 56 3.4% 0.69 [0.24, 1.96] 2005 Serebruary 2008 0 20 0 20 Not estimable 2009 Sal di tisollier 2009 0 12 0 10 Not estimable 2009 SUAR 2010 2 46 1 52 0.7% 2.26 [0.21, 24.12] 2010 JPS3 2012 28 1517 39 1503 16.4% 0.71 [0.44, 1.15] 2012 SHANCE 2015 57 2584 62 2586 29.9% 0.92 [0.64, 1.31] 2015 Subtotal (95% CI) 7012 7030 100.0% 0.88 [0.72, 1.07] Total events 185 212 Heterogeneity: Tau ² = 0.00; Chi ² = 1.99, df = 5 ($P = 0.85$); $P = 0\%$ Test for overall effect: Z = 1.31 ($P = 0.19$) H.1.4 Myocardial infarction AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.07 [0.77, 1.49] 2004 AATCH 2004 73 3797 68 3802 42.2% 1.00 [0.72, 3.98] 2015 DATAT 2018 155 2584 8 2586 3.6% 0.63 [0.20, 1.91] 2015 DATAT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018 ADTAT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018 ADTAT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018 ADTAT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018 ADTAT 2018 10 2432 7 2449 4.9% 1.44 [0.55, 3.77] 2018 ADTAT 2018 10 2432	°OINT 2018 Subtotal (95% CI)	112	2432 14137	155	2449 14167	14.4% 100.0%	0.73 [0.57, 0.92] 0.75 [0.66, 0.85]	2018	•
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0.01 0.1 1 10 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; I²=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; I²=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; I²=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 [\geq 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

Study or Subgroup	Clopidogrel- Events	Aspirin Total	Monoth Events	erapy Total	Weight	Risk Ratio M-H, Random, 95% Cl	Year	Risk Ratio M-H, Random, 95% Cl
1.2.1 Intracranial bleed	ing							
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 Heterogeneity: Tau² = 0 Test for overall effect: Z	149 .00; Chi² = 3.1 = 3.36 (P = 0.	18, df = 9 (.0008)	95 (P = 0.96)	; I² = 0%				
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					
Test for overall effect: Z 1.2.3 Vascular death	= 3.54 (P = 0	.0004)						
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 Heterogeneity: Tau² = 0 Test for overall effect: Z	225 .00; Chi² = 4.: = 0.11 (P = 0	22, df = 5 (.91)	227 (P = 0.52)	; I² = 0%				
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					Ĩ
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.03; Chi ² = 9.4 = 0.91 (P = 0.	46, df = 6 (.36)	(P = 0.15)	; I² = 379	6			
								0.01 0.1 1 10 100

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√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 plateletoriented 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 followup (>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) = 258and 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 (\leq 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	Monothe	erapy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.6.1 Any stroke								
FASTER 2007 Serebruary 2009	14	198	21	194	3.6%	0.65 [0.34, 1.25] Not estimable	2007	
CLAIR subaroup 2013	ů	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	T
Subtotal (95% CI)	405	5264	541	5284	100.0%	0.75 [0.67, 0.85]		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	405 0; Chi² = 0.80, 4.59 (P < 0.00	df= 3 (P 001)	= 0.85); I ²	= 0%				
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	-
Subtotal (95% CI)	112	5264	155	5284	100.0%	0.74 [0.65, 0.84]	2010	•
Total events	387		527					
Heterogeneity: Tau² = 0.0 Test for overall effect: Z =	0; Chi² = 1.30, 4.78 (P < 0.00	df = 3 (P 001)	= 0.73); I ²	= 0%				
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 POINT 2018	57 90	2584	62 06	2586	38.6% 60.0%	0.92 [0.64, 1.31]	2015	—
Subtotal (95% CI)	03	5066	90	5090	100.0%	0.94 [0.75, 1.17]	2010	₹
Total events	148		158					
Heterogeneity: Tau² = 0.0 Test for overall effect: Z =	0; Chi² = 1.43, 0.57 (P = 0.57	df = 2 (P)	= 0.49); I ²	= 0%				
1.6.4 Myocardial infarction	on							
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	
Total events	15	5010	15	5055	100.0%	1.00 [0.44, 2.24]		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	6; Chi ² = 1.23, 0.01 (P = 0.99	df=1 (P)	= 0.27); I ²	= 18%				
1.6.5 Intracranial bleedin	a							
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	
POINT 2018	U Q	2432	4	35 2449	22.9%	2 27 IO 70 7 351	2013	
Subtotal (95% CI)	Ŭ	5264	4	5284	100.0%	1.50 [0.86, 2.64]	2010	◆
Total events	31		20					
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	0; Chi² = 1.36, 1.42 (P = 0.16	df = 2 (P)	= 0.51); I ²	= 0%				
1.6.6 Major bleeding								
FASTER 2007	1	198	0	194	4.0%	2.94 [0.12, 71.72]	2007	
CLAIR subgroup 2013	U	20	0	20		Not estimable	2008	
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 Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	28 0; Chi² = 1.16, 2.05 (P = 0.04	df= 2 (P)	14 = 0.56); I ²	= 0%				
1.6.7 Vascular death								
Serebruany 2008	0	20	0	20		Not estimable	2008	
CLAIR subgroup 2013	õ	30	Ő	35		Not estimable	2013	\perp
CHANCE 2015	11	2584	11	2586	69.7%	1.00 [0.43, 2.30]	2015	
POINT 2018 Subtotal (95% CI)	6	2432	4	2449	30.3%	1.51 [0.43, 5.35]	2018	
Total events	17	5000	15	5050	100.070	1.10[0.01, 2.21]		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	0; Chi² = 0.28, 0.35 (P = 0.72	df=1 (P)	= 0.59); I ²	= 0%				
1.6.8 Any death								
Serebruany 2008	0	20	0	20		Not estimable	2008	
CLAIR subgroup 2013	0	30	Ő	35		Not estimable	2013	
CHANCE 2015	28	2584	36	2586	58.6%	0.78 [0.48, 1.27]	2015	- - +_
POINT 2018 Subtotal (95% CI)	18	2432	12	2449	41.4%	1.51 [0.73, 3.13]	2018	
Total events	46	5000	48	2090	100.0%	1.02 [0.34, 1.94]		
Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	2; Chi ² = 2.19, 0.07 (P = 0.94	df=1 (P)	= 0.14); I ²	= 54%				
	-							
								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.

Acknowledgements We would like to thank Katherine Negele, editorial assistant, research department, Hurley Medical Center, for assistance with manuscript editing.

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), Journal 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.

References

- Rothwell PM, Giles MF, Chandratheva A et al (2007) Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 370:1432–1442
- 2. Kernan WN, Ovbiagele B, Black HR et al (2014) Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association
- 3. International Stroke Trial Collaborative Group (1997) The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 349:1569–1581
- CAST (Chinese Acute Stroke Trial) Collaborative Group (1997) CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 349:1641–1649
- Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324:71–86
- Rothwell PM, Algra A, Chen Z et al (2016) Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet 388:365–375
- CAPRIE Steering committee (1996) A randomized blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 348:1329–1339
- Levine GN, Bates ER, Bittl JA et al (2016) 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
- 9. Diener HC, Cunha L, Forbes C et al (1996) European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 143:1–13
- The ESPRIT Study Group (2006) Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 367:1665–1673
- 11. Geeganage CM, Diener H-C, Algra A et al (2012) Dual or mono antiplatelet therapy for patients with acute ischemic stroke or

transient ischemic attack: systematic review and meta-analysis of randomized controlled trials. Stroke 43:1058–1066

- Li X, Zhou G, Zhou X, Zhou S (2013) The efficacy and safety of aspirin plus dipyridamole versus aspirin in secondary prevention following TIA or stroke: a meta-analysis of randomized controlled trials. J Neurol Sci 332:92–96
- Ge F, Lin H, Liu Y et al (2016) Dual antiplatelet therapy after stroke or transient ischaemic attack - how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischaemic attack: a systematic review and meta-analysis. Eur J Neurol 23:1051–1057
- 14. Niu PP, Guo ZN, Jin H et al (2016) Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: an updated network meta-analysis. BMJ Open 6:e009013
- Sacco RL, Diener H-C, Yusuf S et al (2008) Aspirin and extendedrelease dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 359:1238–1251
- 16. Bath PM, Woodhouse LJ, Appleton JP et al (2018) Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet 391:850–859
- 17. Sprigg N, Gray LJ, England T et al (2008) A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: safety, tolerability and feasibility. PLoS ONE 3:e2852
- Powers WJ, Rabinstein AA, Ackerson T et al (2018) 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association
- Moher D, Shamseer L, Clarke M et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1–9
- Lau AY, Zhao Y, Chen C et al (2014) Dual antiplatelets reduce microembolic signals in patients with transient ischemic attack and minor stroke: subgroup analysis of CLAIR study. Int J Stroke 9:127–132
- 21. Bal Dit Sollier C, Crassard I, Simoneau G et al (2009) Effect of the thromboxane prostaglandin receptor antagonist terutroban on arterial thrombogenesis after repeated administration in patients treated for the prevention of ischemic stroke. Cerebrovasc Dis 28:505–513
- 22. Markus HS, Droste DW, Kaps M et al (2005) Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. Circulation 111:2233–2240
- 23. Zuo F-T, Liu H, Wu H-J et al (2017) The effectiveness and safety of dual antiplatelet therapy in ischemic cerebrovascular disease with intracranial and extracranial arteriostenosis in Chinese patients: a randomized and controlled trail. Med 96:e5497
- Yi X, Lin J, Zhou J et al (2018) The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. Oncotarget 9:17725–17734
- 25. Serebruany VL, Malinin AI, Pokov AN, Hanley DF (2008) Antiplatelet profiles of the fixed-dose combination of extended-release dipyridamole and low-dose aspirin compared with clopidogrel with or without aspirin in patients with type 2 diabetes and a history of transient ischemic attack: a randomized, single-b. Clin Ther 30:249–259
- 26. Wang Y, Pan Y, Zhao X et al (2015) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. Circulation 132:40–46

- 27. Wong KSL, Chen C, Fu J et al (2010) Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 9:489–497
- Hankey GJ, Johnston SC, Easton JD et al (2011) Effect of clopidogrel plus ASA vs. ASA early after TIA and ischaemic stroke: a substudy of the CHARISMA trial. Int J Stroke 6:3–9
- Kennedy J, Hill MD, Ryckborst KJ et al (2007) Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 6:961–969
- Diener H-C, Bogousslavsky J, Brass LM et al (2004) Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 364:331–337
- He F, Xia C, Zhang JH et al (2015) Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. J Clin Neurosci 22:83–86
- 32. Hong KS, Lee SH, Kim EG et al (2016) recurrent ischemic lesions after acute atherothrombotic stroke: clopidogrel plus aspirin versus aspirin alone. Stroke 47:2323–2330
- 33. Serebruany VL, Malinin AI, Ziai W et al (2005) Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in patients after recent ischemic stroke: For the Plavix Use for Treatment of Stroke (PLUTO-Stroke) trial. Stroke 36:2289–2292
- Benavente O, Hart R, McClure L et al (2012) Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med 367:817–825
- 35. Yi X, Chi W, Wang C et al (2015) Low-molecular-weight heparin or dual antiplatelet therapy is more effective than aspirin alone in preventing early neurological deterioration and improving the 6-month outcome in ischemic stroke patients. J Clin Neurol 11:57–65

- Johnston SC, Easton JD, Farrant M et al (2018) Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med. https://doi.org/10.1056/NEJMoa1800410
- Bhatt DL, Fox KA, Hacke W et al (2006) Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 354:1706–1717
- 38. Wang D, Gui L, Dong Y et al (2016) Dual antiplatelet therapy may increase the risk of non-intracranial haemorrhage in patients with minor strokes: a subgroup analysis of the CHANCE trial. Stroke Vasc Neurol 1:29–36
- Wang Y, Wang Y, Zhao X et al (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369:11–19
- 40. Yi X, Lin J, Wang C et al (2014) A comparative study of dual versus monoantiplatelet therapy in patients with acute large-artery atherosclerosis stroke. J Stroke Cerebrovasc Dis 23:1975–1981
- 41. Wang C, Yi X, Zhang B et al (2015) Clopidogrel plus aspirin prevents early neurologic deterioration and improves 6-month outcome in patients with acute large artery atherosclerosis stroke. Clin Appl Thromb Hemost 21:453–461
- 42. Zhao Y, Yang W, Tan Z et al (2017) Clopidogrel loading dose versus maintenance dose to treat patients with acute ischaemic stroke in China (CLASS-China): results from a prospective double-blind randomised clinical trial. Stroke Vasc Neurol 2:118–123
- 43. Anstey E, Li S, Thomas L et al (2016) Race and sex differences in management and outcomes of patients after ST-elevation and non-ST-elevation myocardial infarct: results from the NCDR. Clin Cardiol 39:585–595
- 44. Schmaier AA, Bhatt DL (2018) Are patients getting their aspirin's worth in ischemic stroke? J Am Hear Assoc 7:e009564
- Simon T, Danchin N (2017) Clinical impact of pharmacogenomics of clopidogrel in stroke. Circulation 135:34–37
- 46. Pan Y, Chen W, Xu Y et al (2017) genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation 135:21–33