Meta-Analysis of Aspirin Versus Dual Antiplatelet Therapy Following Coronary Artery Bypass Grafting

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Although aspirin monotherapy is considered the standard of care after coronary artery bypass grafting (CABG), more recent evidence has suggested a benefit with dual antiplatelet therapy (DAPT) after CABG. We performed a meta-analysis of observational studies and randomized controlled trials comparing outcomes of aspirin monotherapy with DAPT in patients after CABG. Subgroup analyses were conducted according to surgical technique (i.e., on vs off pump) and clinical presentation (acute coronary syndrome vs no acute coronary syndrome). Random effects overall risk ratios (RR) were calculated using the DerSimonian and Laird model. Eight randomized control trials and 9 observational studies with a total of 11,135 patients were included. At a mean follow-up of 23 months, major adverse cardiac events (10.3% vs 12.1%, RR 0.84, confidence interval [CI] 0.71 to 0.99), all-cause mortality (5.7% vs 7.0%, RR 0.67, CI 0.48 to 0.94), and graft occlusion (11.3% vs 14.2%, RR 0.79, CI 0.63 to 0.98) were less with DAPT than with aspirin monotherapy. There was no difference in myocardial infarction, stroke, or major bleeding between the 2 groups. In conclusion, DAPT appears to be associated with a reduction in graft occlusion, major adverse cardiac events, and all-cause mortality, without significantly increasing major bleeding compared with aspirin monotherapy in patients undergoing CABG. **(Am J Cardiol 2018;121:32–40)**

The optimal antiplatelet strategy following revascularization with coronary artery bypass grafting (CABG) remains controversial.[1,2] Aspirin had always been the drug of choice to prevent graft occlusion and adverse cardiac events after CABG.[3] A subgroup analysis, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial,[4] demonstrated that clopidogrel monotherapy was superior to aspirin monotherapy in reducing recurring ischemic events after CABG. Addition of a P2Y12 inhibitor is thought to help preserve graft patency and reduce adverse cardiac events by inhibiting platelet-mediated progression of graft disease, but the evidence regarding the utility of dual antiplatelet therapy (DAPT) for preserving graft patency and reducing adverse cardiac events is not well established.[3,5,6] Recently new data have emerged comparing DAPT with aspirin monotherapy following CABG, and thus we aimed to assess the safety and efficacy of DAPT compared with aspirin monotherapy in patients undergoing CABG in both acute coronary syndrome (ACS) and non-ACS settings.

Methods

We followed both the Preferred Reporting Items for Systematic reviews and Meta-Analyses[7] and the Meta-analysis Of Observational Studies in Epidemiology[8] protocols for reporting the present meta-analysis. Also, we registered the current meta-analysis at the International Prospective Register for Systematic Reviews (*www.crd.york.ac.uk*).

We searched the major electronic databases, including MEDLINE (PubMed), Web of Science, and the Cochrane Library database from inception until June 2017 for all Randomized control trial (RCTs) and observational studies comparing DAPT with aspirin only in patients after CABG. The search was conducted using the following keywords: "dual," "antiplatelet," "clopidogrel," "aspirin," "ticagrelor," "prasugrel," and "coronary artery bypass grafting," without any language restrictions. We also reviewed the references of previous meta-analyses and published studies for any studies not included in the main database search. Finally, we screened major cardiovascular conferences (e.g., American Heart Association, American College of Cardiology, and European Society of Cardiology) for relevant abstracts published within the past 2 years.

Two investigators (NA and NP) assessed the records for eligibility and screened the retrieved records by title and/or abstract. Differences were resolved through consensus between the authors. Included studies met the following criteria: (1)

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See page 38 for disclosure information.

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studies comparing DAPT (i.e., aspirin and P2Y12 inhibitor) with aspirin only; (2) patients after CABG; (3) clinical follow-up duration >4 weeks; and (4) studies reporting the outcomes of interest. Studies were excluded if they met any of the following criteria: (1) duplicate publication (latest report was selected in that case), (2) ongoing studies or unpublished abstracts, and (3) DAPT compared with any antiplatelet agent other than aspirin.

The same authors (NA and NP) performed data extraction independently, which was cross-checked by a third author (AM). The data extracted included information regarding the study design, patient characteristics, and various outcomes assessed. The primary outcome of interest was the mid- to long-term (>30 days) composite of myocardial infarction (MI), stroke, or death (either all-cause mortality or cardiovascular mortality, based on the trial definition of the composite outcome). Secondary outcomes included major bleeding, all-cause mortality, MI, stroke, and graft occlusion. We used the definitions adopted by the original articles to identify each outcome in our meta-analysis. The methodological quality of randomized trials was assessed by the Cochrane Collaboration's tool for assessing risk of bias.[9] We assessed the quality of observational trials by the Newcastle-Ottawa scale,[10] which consists of 3 items: patient selection, comparability of the study groups, and assessment of the outcome. A score of 0 to 9 was allocated to each observational study, with studies achieving 6 or more stars considered to be of good quality.

We calculated means and standard deviations for continuous variables and percentages and frequencies for the categorical variables. Using the sample size of each study, we calculated a weighted mean follow-up duration for each outcome of interest. We adopted the DerSimonian and Laird method for calculation of summary random effects risk ratios (RRs) for each outcome of interest.[11] We also used I^2 statistic test for assessment of in-between study heterogeneity, with values <25%, 25% to 50%, and >50% corresponding to low, moderate, and high degree of heterogeneity, respectively.[12] Publication bias was assessed by Egger test.[13] We performed a subgroup analysis for all outcomes of interest according to the study type (i.e., RCT vs observational). We also performed subgroup analyses according to the CABG technique (i.e., on- vs off-pump CABG), and clinical presentation (ACS vs non-ACS) for both the primary outcome and the graft occlusion. We used a confidence interval (CI) of 95% and p-value <0.05 as a reflection of statistically sig-

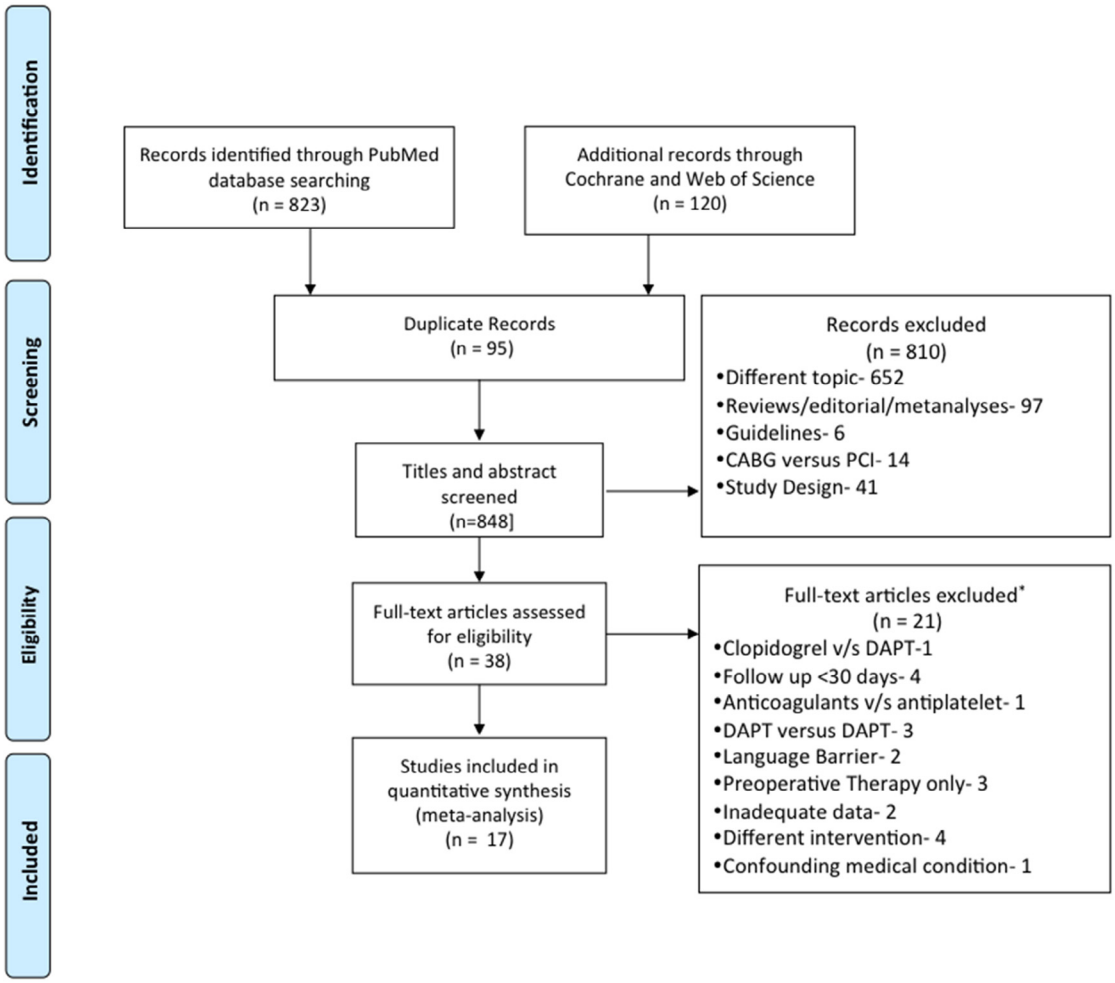

Figure 1. Search strategy and study inclusion criteria. *See online Table S1 for details. CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.

nificant results in all of our analyses, and all analyses were conducted using STATA software version 14 (StataCorp, College Station, TX).

Results

A total of 848 potentially eligible records were identified, out of which 810 were excluded by screening the title or abstract (Figure 1). Full texts of the remaining 38 studies were examined. A full list of excluded studies after examination of the full texts, together with the reason of exclusion of each study, is reported in online Table S1. Ultimately, a total of 17 studies, 8 RCT,[14–21] 5 post hoc analyses of RCT,[22–26] and 4 observational studies,[27–30] with a total of 11,135 patients with a mean follow-up of 23 months, were selected. Thirteen of 17 studies reported the duration of DAPT with a mean duration of 7.4 months. Table 1 summarizes the main characteristics of the included studies and Table 2 summarizes the patients' characteristics of the included studies. All studies were of high quality, with low incidence of bias (Table 1 and online Figure S1).

At a mean follow-up of 23 months, DAPT was associated with a lower incidence of the composite of MI, stroke, or death (10.3% vs 12.1%, RR 0.84, CI 0.71 to 0.99, p = 0.03, $I^2 = 0\%$), with no evidence of interaction by study type ($P_{Interaction} = 0.16$) (Figure 2) and no evidence of publication bias by Egger test. Subgroup analysis illustrated that both CABG technique and clinical presentation did not effect the outcome ($P_{Interaction} = 0.26$ and 0.49 respectively, online Figures S2 and S3).

At a mean follow-up of 23 months, the incidence of all-cause mortality was less with DAPT than with aspirin monotherapy, with evidence of moderate to high heterogeneity between the included studies (5.7% vs 7.0%, RR 0.67, CI 0.48 to 0.94, p = 0.02, $I^2 = 54\%$). The high heterogeneity was mainly driven by the observational studies (Figure 3). There was no evidence of publication bias by Egger test (p = 0.25). The incidences of MI (RR 0.91, CI 0.72 to 1.15, p = 0.44, $I^2 = 2\%$), stroke (RR 0.79, CI 0.55 to 1.15, p = 0.31, $I^2 = 0\%$), and major bleeding (RR 1.1, CI 0.94 to 1.29, p = 0.22, $I^2 = 0\%$) were similar between both groups without any evidence of publication bias (online Figures S4, S5 and S6).

Regarding the graft occlusion outcome, the incidence was less with DAPT than with aspirin monotherapy at a mean follow-up of 23 months (11.3% vs 14.2%, RR 0.79, CI 0.63 to 0.98, p = 0.03, $I^2 = 23\%$) (Figure 4). Subgroup analysis by CABG technique showed that patients undergoing off-pump CABG derived more benefit from DAPT (RR 0.46, CI 0.24 to 0.94, P, $I^2 = 23\%$) than did patients with on-pump CABG (RR 0.98, CI 0.59 to 1.61, p = 0.94) $P_{interaction} = 0.06$ (Figure 5, online Figure S7), but the difference was not significant. There was no evidence of publication bias by Egger test. Online Figure S8 illustrates the subgroup analysis of graft

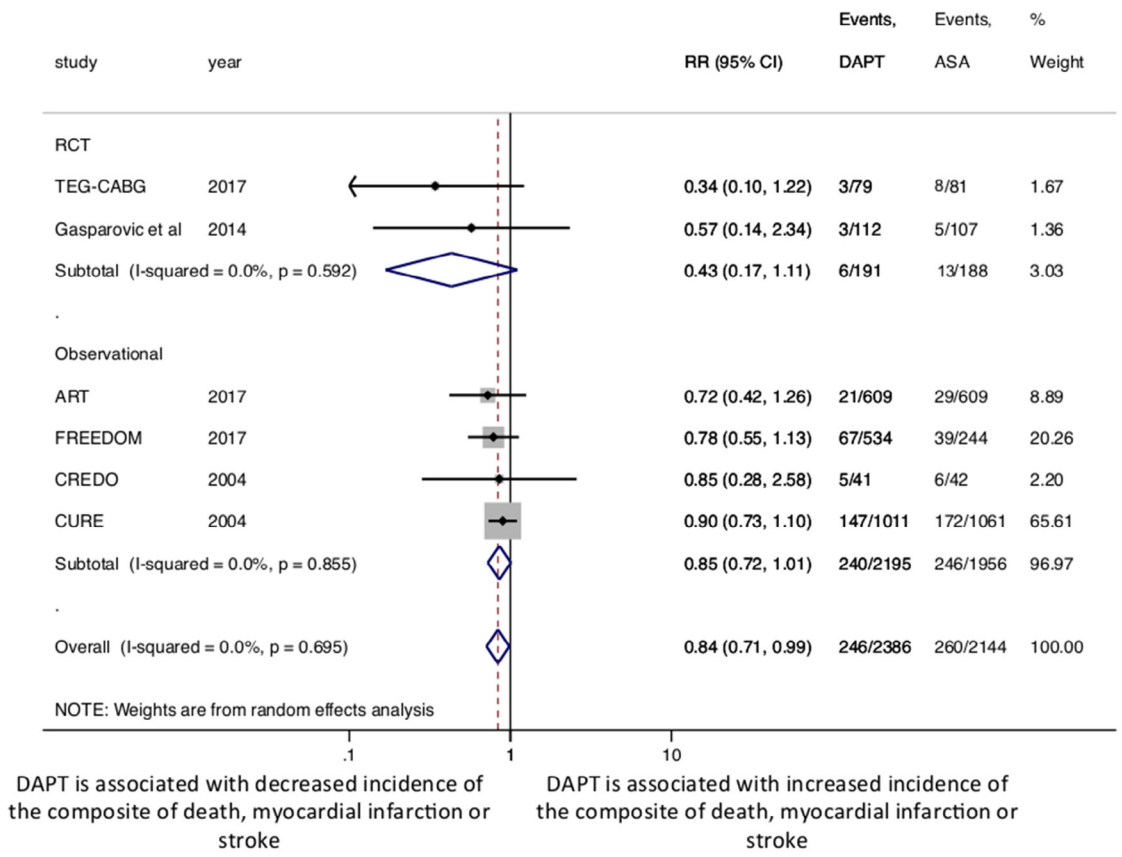

Figure 2. Summary risk ratio of the composite of death, myocardial infarction, or stroke. ASA = aspirin; CI = confidence interval; DAPT = dual antiplatelet therapy; RCT = randomized control trial; RR = relative risk.

Table 1
Baseline characteristics of the included studies

Study/1st Author	Type of Study		Follow up (months)	Major Bleeding	MACE	CABG Technique	Indication		DAPT Duration (months)	DAPT	Newcastle-Ottawa Score for Observational Studies
	RCT	Non RCT					ACS	Non-ACS			
TEG-CABG	+	0	3	NR	MI, CVA, DVT, mortality	On pump	+	+	3	a + c	NA
ART	0	+	12	NR	CV death, MI, CVA, revascularization	Off and on pump	+	+	NR	a + c	8(S4C1E3)
FREEDOM	0	+	60	NR	NR	Off and on pump	+	+	12	a + c, a + t	8(S4C1E3)
ASAP-CABG	+	0	12	TIMI	NR	Off and on pump		NR	8	a + c	NA
ROOBY	0	+	12		NR	Off and on pump	+	+	NR	a + c	8(S4C1E3)
Gasparovic	+	0	6	BARC	All cause mortality, MI, CVA, CV rehospitalisation	On pump	0	+	6	a + c	NA
CRYSSA	+	0	12	CURE definition*	CV death, MI, CVA, revascularization	Off pump	0	+	12	a + c	NA
Sorensen	0	+	16	ICD Codes	NR	NR	+	0	NR	a + c	7(S3C1E3)
CASCADE	+	0	12	CURE definition*	CV death, MI, CVA, cardiac ischemia hospitalization, revascularization	Off and on pump	+	+	12	a + c	NA
Sun	+	0	1	Trial definition†	NR	On pump		NR	1	a + c	NA
Gao G	+	0	3	NR	CV death, MI, revascularization	Off and on pump		NR	3	a + c	NA
Mujanovic	+	0	3	NR	NR	Off pump		NR	3	a + c	NA
Sanon	0	+	48	NR	NR	NR	+	+	NR	a + c	7(S3C1E3)
Halkos	0	+	6	CURE definition*	NR	Off pump	+	+	1	a + c	8(S4C1E3)
Gurbuz	0	+	38	NR	NR	Off pump	+	+	15	a + c	7(S3C1E3)
CREDO	0	+	12	TIMI		NR	+	+	12	a + c	8(S4C1E3)
CURE	0	+	12	CURE definition*	CV death, MI, CVA	NR	+	0	9	a + c	8(S4C1E3)

* Substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood.

† Intracranial hemorrhage, intraocular bleeding leading to vision loss, bleeding requiring surgical intervention at a site separate from the original operative site, bleeding causing death, or bleeding requiring transfusion of >1 unit of red blood cells.

a = aspirin; ACS = acute coronary syndrome; BARC = bleeding academic research consortium; c = clopidogrel; C = comparability; CABG = coronary artery bypass graft; CV = cardiovascular; CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; DVT = deep venous thrombosis; E = exposure; ICD = international classification of diseases; MACE = major adverse cardiac event; MI = myocardial infarction; NA = not applicable; NR = not reported; RCT = randomized control study; S = selection; t = ticagrelor; TIMI = thrombolysis in myocardial infarction.

Table 2
Demographic characteristics of all studies included in the meta-analysis

Study/1st author	TEG-CABG	ART	FREEDOM	ASAP-CABG	ROOBY	Gasparovic	CRYSSA	Sorensen	CASCADE	Sun	Gao G	Mujanovic	Sanon	Halkos	Gurbuz	CREDO	CURE
Total (n)	79 / 81	609 / 609	544 / 251	12 / 8	345 / 608	112 / 107	150 / 150	945 / 945	56 / 57	49 / 50	113 / 111	10 / 10	962 / 962	193 / 171	325 / 266	41 / 42	1101 / 1061
Age (years)	65 / 67	62 / 63	61 / 64	- / -	61 / 62	65 / 65	60 / 59	65 / 64	65 / 68	66 / 64	60 / 58	58 / 60	- / -	63 / 64	67 / 68	-/-	- / -
Male	67/68	88/87	72/68	- / -	99/99	74/77	73/75	77/78	91/88	94/86	82/83	- / -	- / -	67/65	- / -	-/-	- / -
Hypertension	77/81	- / -	84/85	100/87	83/87	96/96	47/63	- / -	48/53	69/70	63/57	- / -	84/83	83/82	- / -	-/-	- / -
Hyperlipidemia	97/95	- / -	84/85	100/87	87/86	96/96	55/57	95/95	88/87	67/84	35/40	- / -	- / -	- / -	58/71	-/-	- / -
Previous MI	70/64	24/26	27/22	- / -	25/25	- / -	38/35	- / -	- / -	47/32	49/44	- / -	44/43	- / -	49/43	-/-	- / -
Diabetes	32/32	27/26	100/100	42/62	45/41	38/38	- / -	6/5	25/33	37/34	39/40	- / -	9/9/	38/43	23/26	-/-	- / -
Smoker	42/41	14/12	18/14	0/12	31/32	34/38	- / -	- / -	16/ 10	14/4	52/60	- / -	47/47	- / -	- / -	-/-	- / -
COPD	14/18	6/8/	4/6/	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	-/-	- / -
CKD	- / -	- / -	4/7/	- / -	5/5/	- / -	- / -	0 / 0	- / -	- / -	- / -	- / -	22/20	- / -	- / -	-/-	- / -
CHF	- / -	23/23	- / -	- / -	- / -	- / -	- / -	- / -	23/18	8/6/	- / -	- / -	20/15	- / -	- / -	-/-	- / -
Aspirin (mg)	75 / 75	- / -	- / -	81 / 81	- / -	300 / 300	100 or 150/100	- / -	162 / 162	81 / 81	100 / 100	100 / 100	- / -	- / -	81 / 325	-/-	75–325 / 75–325
Venous Grafts	64/63	45/45	- / -	67/70	-/-	- / -	56/57	- / -	- / -	58/58	68/67	- / -	- / -	- / -	33/34	-/-	- / -
Arterial Grafts	36/37	55/55	-/-	34/30	- / -	- / -	43/42	- / -	-/-	42/42	32/32	- / -	- / -	- / -	66/66	-/-	- / -
Off Pump	0/0	71/71	19/17	- / -	64/44	- / 0	100/100	- / -	5/1	0 / 0	53/65	100/100	- / -	100/100	100/100	-/-	- / -
On Pump CABG	100/100	29/30	80/82	- / -	36/56	- / -	- / -	- / -	95/98	100/100	48/35	0 / 0	- / -	0 / 0	0 / 0	-/-	- / -
ACS	60/52	42/39	27/32	- / -	- / -	- / -	- / -	- / -	25/23	8/10/	- / -	- / -	45/42	26/24	36/37	-/-	- / -
Cardiomyopathy	- / -	22/95	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	-/-	- / -
Ejection fraction	- / -	- / -	60 / 60	- / -	- / -	53 / 5	55 / 54	- / -	- / -	- / -	60 / 61	51 / 53	- / -	52 / 49	- / -	-/-	- / -
BMI	28 / 27	- / -	- / -	- / -	-/-	29 / 30	26 / 26	- / -	28 / 28	29 / 33	26 / 25	- / -	- / -	- / -	- / -	-/-	- / -
Obesity	-/-	- / -	-/-	- / -	-/-	- / -	-/-	- / -	-/-	- / -	-/-	- / -	-/-	-/-	- / -	-/-	-/-

Variables are presented as dual antiplatelets/aspirin only percentages.

Values were rounded to the nearest integer.

ACS = acute coronary syndrome; BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; mg = milligrams; MI = myocardial infarction.

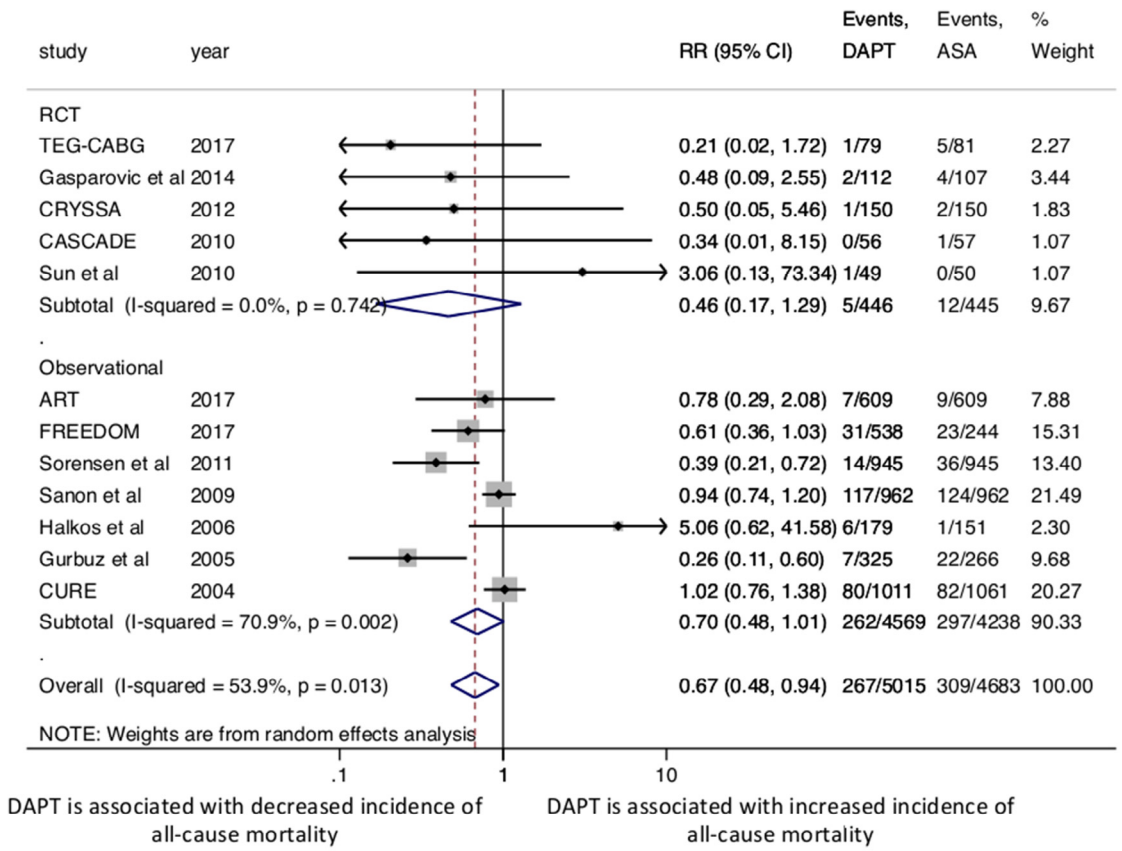

Figure 3. Summary risk ratio of all-cause mortality. ASA = aspirin; CI = confidence interval; DAPT = dual antiplatelet therapy; RCT = randomized control trial; RR = relative risk.

occlusion outcome according to the clinical presentation (ACS vs non-ACS).

Discussion

The current analysis of 17 studies suggests that the use of DAPT after CABG may be associated with decreased all-cause mortality and the composite of MI, stroke, or death, together with improved graft patency without an obvious increase in major bleeding. The association regarding the primary composite outcome was not altered by the CABG technique or clinical presentation.

The mechanism of benefit with DAPT after CABG is probably related to reduced graft occlusion. Early graft loss is related to postsurgical factors such as inflammation and conduit trauma, which can result in a prothrombotic state and thrombotic occlusion of the graft.[3] Hence, DAPT has a conceptual benefit in maintaining graft patency. Use of cardiopulmonary bypass can result in platelet dysfunction and clotting disorders, which can prevent early graft thrombosis.[3] Hence, it would be expected that off-pump CABG might act as a hypercoagulable state, because of higher level of platelet activity and relative resistance to aspirin.[3] In our analysis, CABG technique was not an effect-modifying variable on subgroup analysis. This may have been because the subgroups were underpowered to detect a difference.

Lack of a significant difference in major bleeding between the DAPT and the aspirin monotherapy cohorts is an unexpected finding in our current analysis. The trials adhered to a strict protocol regarding postsurgical initiation of antiplatelet therapy to avoid bleeding.[17,18,20] The adherence to a postsurgical DAPT protocol could have helped prevent any early postoperative bleeding. It is possible more minor degrees of bleeding were increased, although this was not evaluated. It is also possible that healthier, younger patients were selected to receive DAPT, and this may account for some of the lack of effect on major bleeding. The lower all-cause mortality and higher graft patency associated with DAPT after CABG compared with aspirin monotherapy without a significant difference in MI is another unexpected finding. The protective effect of recent revascularization with CABG on ischemic end points could explain the lack of difference in MI during mid- to long-term follow-up. Graft loss was identified by routine follow-up angiography or computerized tomography and not acute presentation in the included studies. Hence, possibly graft loss did not result in ACS. Additionally, a potential benefit in all-cause mortality was driven mostly by observational studies with significant heterogeneity, suggesting at least some proportion of the lower mortality could be caused by residual confounding.

Previous meta-analyses on this subject have yielded conflicting results. The most recent meta-analysis by Verma et al[5] demonstrated no mortality benefit with DAPT compared with single antiplatelet therapy in patients after CABG. This was contradictory to Deo et al[6] who demonstrated a mortality benefit with DAPT compared with aspirin monotherapy

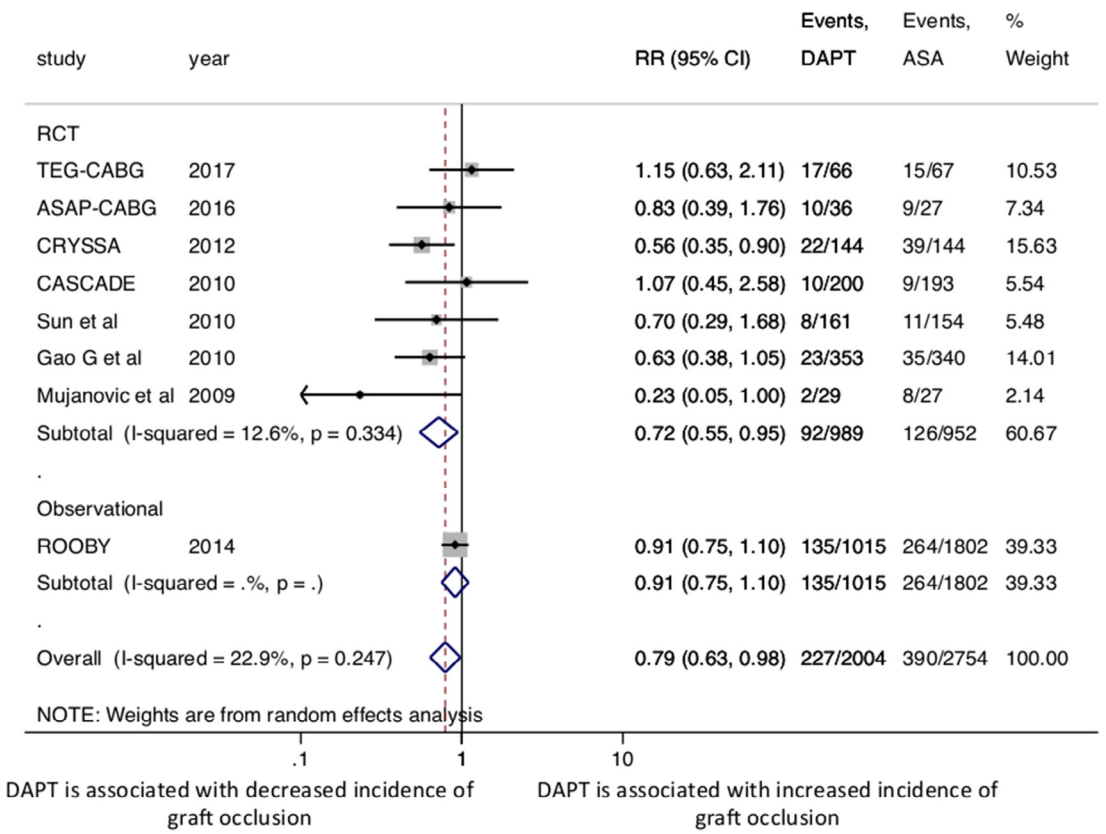

Figure 4. Summary risk ratio of graft occlusion outcome. ASA = aspirin; CI = confidence interval; DAPT = dual antiplatelet therapy; RCT = randomized control trial; RR = relative risk.

following CABG in short-term (<30 days) follow-up. Our study is the first to show potential improvement in both mid- to long-term mortality and the composite of MI, stroke, or death.

There are limitations to the current study. First, the study designs of the included studies were different. Although the studies were of high quality, inclusion of observational studies is a potential source of bias. We attempted to overcome such limitation by conducting a subgroup analysis according to the study type and showing that there was no evidence of effect modification by study type. Second, the definition of graft occlusion varied in studies, which could have confounded our results. Also we could not account for operator expertise on this outcome. Third, data were analyzed on a trial level, so we could not assess whether all baseline characteristics were balanced in groups. Fourth, there was evidence of a moderate to high degree of heterogeneity in some of the assessed outcomes such as all-cause mortality; this could be explained by the variation in the duration of follow-up and DAPT administration. And lastly, we could not evaluate the role of more potent P2Y12 inhibitors (ticagrelor and prasugrel) in the DAPT cohort because there are no current studies comparing them with aspirin monotherapy.

In conclusion, compared with aspirin monotherapy, DAPT appears to be associated with a reduction in all-cause mortality, graft occlusion, and the composite of MI, stroke, or death, without a significant association with increasing major bleeding in patients undergoing CABG. Thus, DAPT may be a useful antiplatelet regimen for patients undergoing CABG in both ACS and non-ACS settings, although further randomized trials are required to establish this approach.

Disclosures

Dr. Anderson is a consultant for Biosense Webster, a Johnson & Johnson Company. Dr. 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: Cleveland Clinic, Duke Clinical Research Institute, Harvard 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), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (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

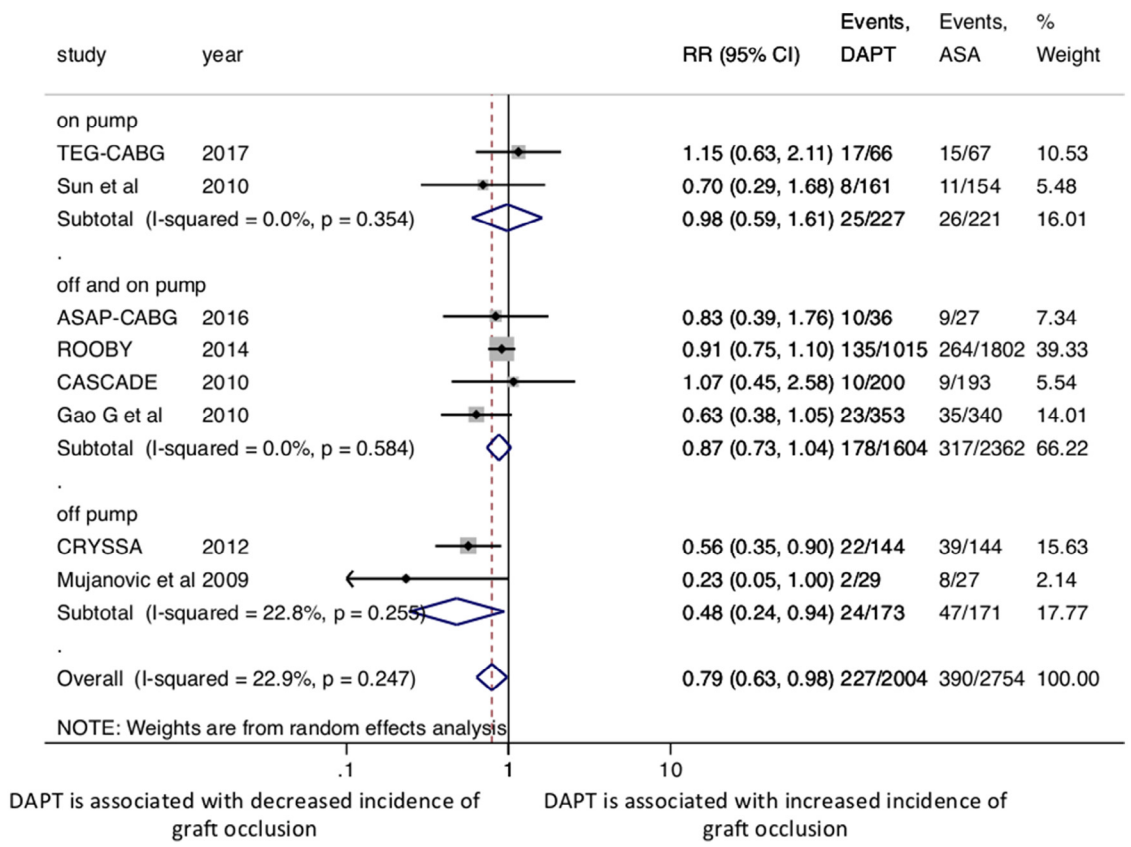

Figure 5. Summary risk ratio of graft occlusion according to CABG technique (i.e., on vs off pump). ASA = aspirin; CI = confidence interval; DAPT = dual antiplatelet therapy; RR = relative risk.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2017.09.022.

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