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Mono or dual antiplatelet therapy for treating patients with peripheral artery disease after lower extremity revascularization: a systematic review and meta-analysis

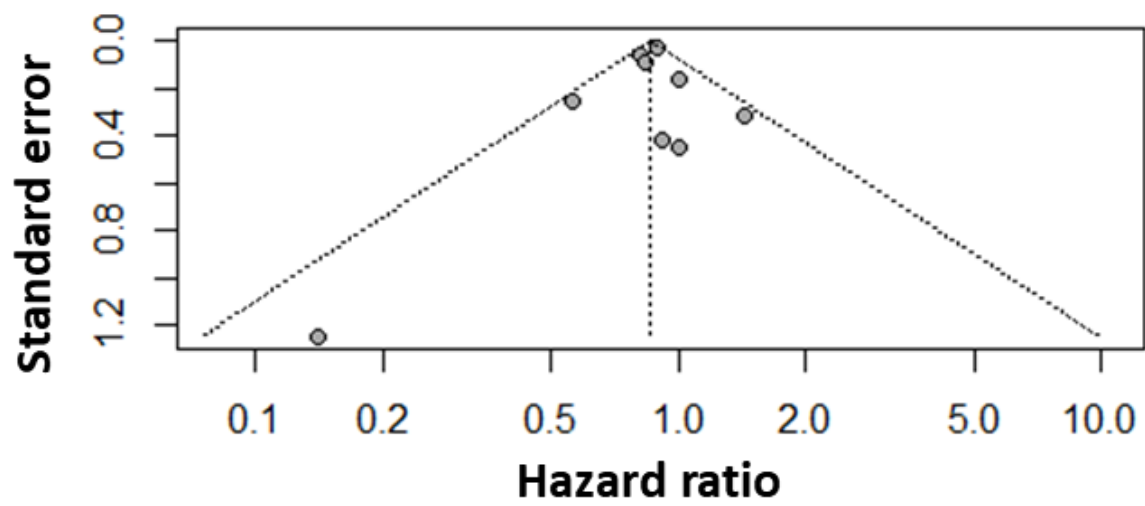
Shang-Yu Tsai^{1,2}, Ying-Sheng Li¹, Che-Hsiung Lee^{3,4}, Shion-Wei Cha⁵, Yao-Chang Wang², Ta-Wei Su¹, Sheng-Yueh Yu¹, Chi-Hsiao Yeh^{1,2,6} *

Study	RoB 2.0 Domains					Overall
	D1	D2	D3	D4	D5	
Belch et al. 2010						
ACHILLES Study 2012						
MIRROR Study 2013						

Supplementary Figure S1. Bias analysis of the RCTs using RoB 2.0. D1, bias arising from the randomization process; D2 bias due to deviations from intended interventions; D3 bias due to missing outcome data; D4 Bias in the measurement of the outcome; D5, Bias in the selection of the reported. Low risk of bias: ; some concerns of bias: . Overall risk of bias is equal to the most severe level of bias found in any domain.

Study	ROBINS-I Domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Armstrong et al. 2015								
Soden et al. 2016								
Thott et al. 2017								
Cho et al. 2019								
Chinai et al. 2020								
Ipema et al. 2020								
Belkin et al. 2021								

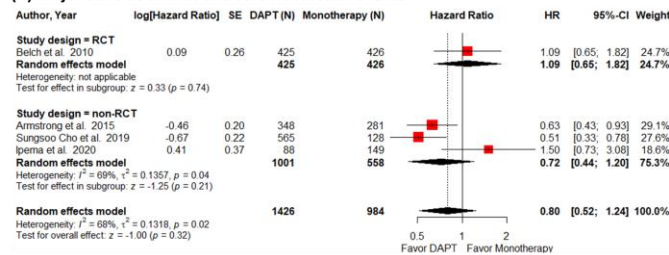
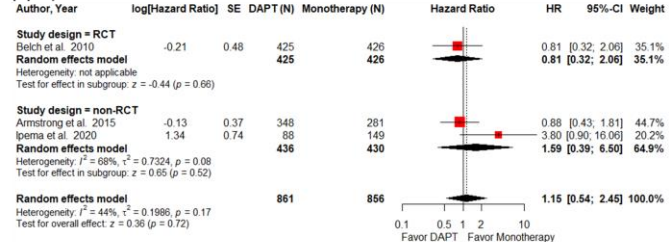
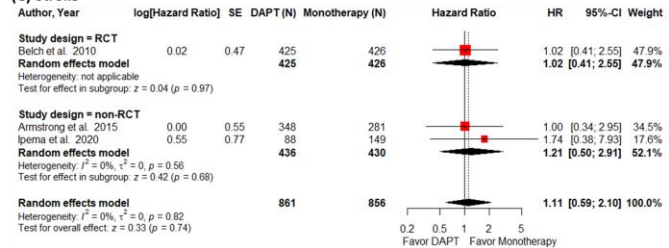
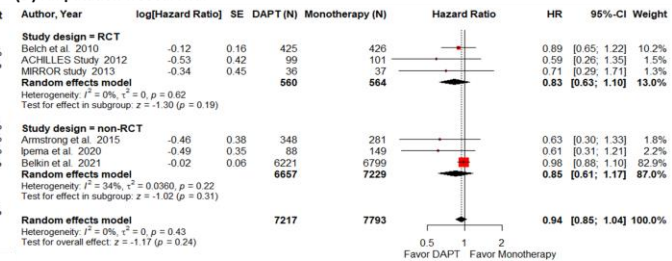
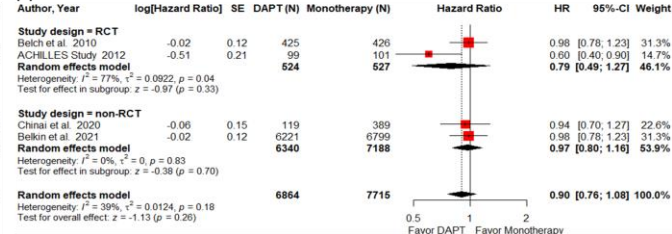
Supplementary Figure S2. Bias analysis for the NRCTs using ROBINS-I. D1, Bias due to confounding; D2 bias due in the selection of participants into the study; D3 bias due to classification of interventions; D4 Bias due to departures from intended interventions; D5, Bias due to missing data; D6 Bias in the measurement of outcomes; D7 Bias in the selection of the reported result. Low risk of bias: ; Moderate risk of bias: ; Serious risk of bias:  . Overall risk of bias is equal to the most severe level of bias found in any domain.



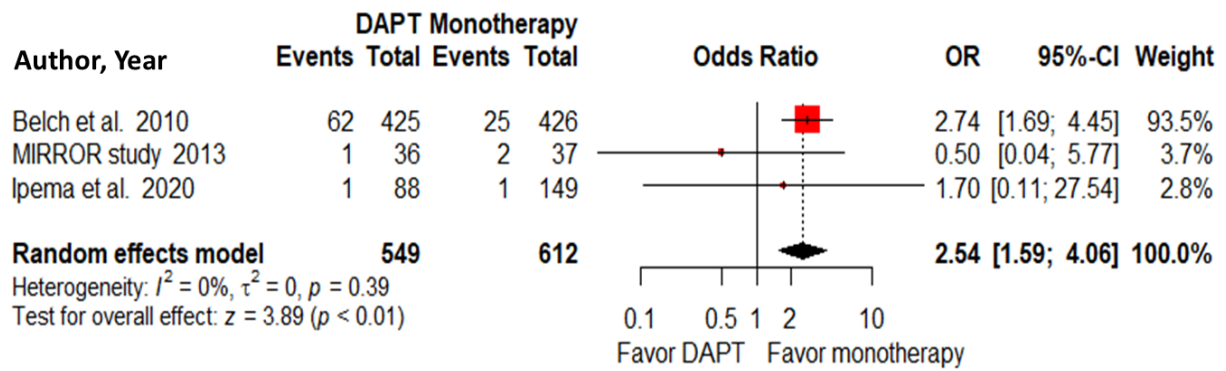
Supplementary Figure S3. Funnel plot analysis assessing publication bias. Used for the comparison between DAPT and monotherapy in diabetic patients after interventions, no obvious asymmetry was found in the included papers for all-cause mortality.



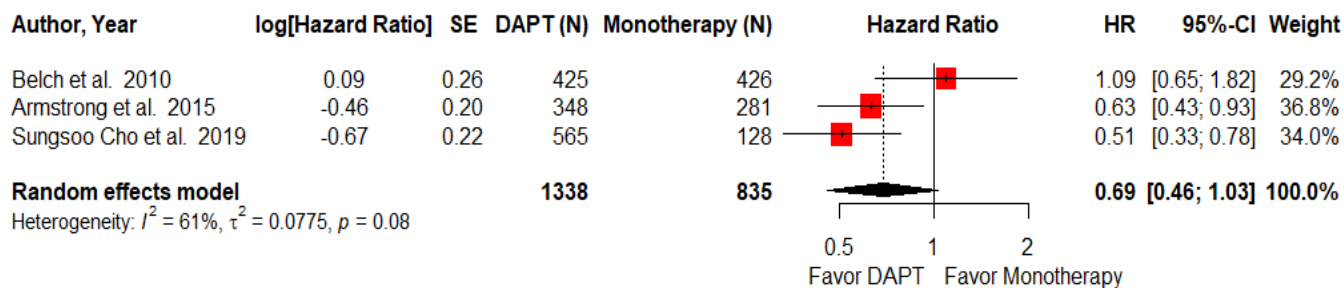
Supplementary Figure S4. Forest plots of the operation-method subgroup meta-analysis were used for comparison between DAPT and monotherapy among PAD patients after lower limb revascularization. PAD patients receiving endovascular intervention with DAPT had significantly reduced all-cause mortality rate (A), major adverse limb events (B), and re-intervention (C). However, DAPT in PAD patients after lower limb revascularization did not reduce major adverse cardiac and cerebrovascular events (D), stroke (E), myocardial infarction (F), amputation-free survival (G), and major amputation (H). HR, hazard ratio; CI, confidence interval; PAD, peripheral artery disease; DAPT, dual antiplatelet therapy; SE, standard error; RCT, randomized control trials.

(A) Major adverse cardiac and cerebrovascular events**(B) Myocardial infarction****(C) Stroke****(D) Amputation-free survival****(E) Re-intervention**

Supplementary Figure S5. Forest plots of the study-design subgroup meta-analysis were used for comparison between DAPT and monotherapy in PAD patients after lower limb revascularization. DAPT did not reduce the major adverse cardiac and cerebrovascular events (A), myocardial infarction (B), stroke (C), amputation-free survival (D), and re-intervention (E) among PAD patients after lower limb revascularization based on either the RCT or NRCT studies. HR, hazard ratio; CI, confidence interval; PAD, peripheral artery disease; DAPT, dual antiplatelet therapy; SE, standard error; RCT, randomized control trials.



Supplementary Figure S6. Forest plots of the minor bleeding meta-analysis were used for comparison between DAPT and monotherapy among PAD patients after lower limb revascularization. A higher minor bleeding rate was noted among PAD patients with DAPT. OR, odds ratio; CI, confidence interval; PAD, peripheral artery disease; DAPT, dual antiplatelet therapy; SE, standard error; RCT, randomized control trials.



Supplementary Figure S7. Forest plots of the major adverse cardiac and cerebrovascular events meta-analysis used for comparison between DAPT and monotherapy after exclusion of the article by Ipema et al. DAPT did not significantly reduce the risk of major adverse cardiac and cerebrovascular events. High heterogeneity persisted among the remaining pooled studies. OR, odds ratio; CI, confidence interval; PAD, peripheral artery disease; DAPT, dual antiplatelet therapy; SE, standard error.

Supplementary Table S1. Definitions of the outcomes.

Major adverse cardiac and cerebrovascular events	
Belch et al.	Cardiovascular death, myocardial infarction, or stroke
Armstrong et al.	Death, myocardial infarction or stroke
Sungsoo Cho et al.	Death, myocardial infarction or stroke
Ipema et al.	Death, myocardial infarction or stroke
Amputation-free survival	
Belch et al.	Death, graft occlusion/revascularization/replacement or amputation above ankle
ACHILLES study	Death, target lesion revascularization or bypass/amputation
Chinai et al.	Death or major lower or limb amputation above ankle
Belkin et al.	Death, graft occlusion or revascularization or above-knee amputation
Major adverse limb events	
Armstrong et al.	Major amputation above the level of the ankle joint, thrombolysis, or surgical bypass
Sungsoo Cho et al.	Occurrence of repeat revascularization or major amputation
Ipema et al.	Major Amputation (above the ankle), target lesion revascularization or target vessel revascularization (endovascular or surgical)
Major bleeding	
<ul style="list-style-type: none">● GUSTO classification major and fatal● Bleeding Academic Research Consortium (BARC) type 3-5● International Society on Thrombosis and Haemostasis definition, major bleeding	
Minor bleeding	
<ul style="list-style-type: none">● GUSTO classification mild and moderate● Bleeding Academic Research Consortium (BARC) type 1-2● International Society on Thrombosis and Haemostasis definition, all non-major bleeding	

Supplementary Table S2. Dosage of DAPT and complications of the included studies.

Study	Type	Patients (n)	Anti-coagulant	Regimen of DAPT	Aortoiliac interventions (%)	ALI (%)	CAD (%)	CVD (%)
Belch et al. 2010 [23]	Prospective multicenter RCT	951	No	Aspirin 75-100 mg , Clopidogrel 75 mg	No	No	34.7	N/A
ACHILLES study 2012 [24]	Prospective multicenter RCT	200	No	Aspirin (low dose) Clopidogrel 75mg /Ticlopidine 500mg	No	No	45	N/A
MIRROR study 2013 [25]	Prospective RCT	80	N/A	Aspirin 100 mg Clopidogrel 75 mg	No	No	32.5	18.8
Armstrong et al. 2015 [26]	PSM retrospective study	629	No	No dosage information	Yes (32.0)	No	51	16
Soden et al. 2016 [27]	PSM retrospective study	15,985	Yes	No dosage information	N/A	Yes (9.8)	31.6	N/A
Soden et al. 2016 [27]	PSM retrospective study	40,684	Yes	No dosage information	N/A	Yes (6.2)	30.9	N/A
Thott et al. 2017 [29]	Retrospective study	1,941	N/A	Aspirin plus clopidogrel, no dose	No	No	45.4	11.8
Cho et al. 2019 [28]	PSM retrospective study	693	No	aspirin (100 mg) and clopidogrel (75 mg)	Yes (30.7)	No	51.9	18.3
Chinai et al. 2020 [30]	Retrospective study	508	No	No dosage information	Yes (31.3)	No	44.1	15.8
Ipema et al. 2020 [31]	Retrospective study	237	No	ASA 80mg and clopidogrel 75mg	No	No	35.9	20.7
Belkin et al. 2021 [32]	Retrospective study	13,020	No	No dosage information	No	No	30.1	N/A

PSM, propensity-score-weighted matching; DAPT, dual antiplatelet therapy; ALI, acute limb ischemia; CAD, coronary artery disease; CVD, cerebrovascular disease; N/A, not application.

Supplementary Table S3. PRISMA checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 21
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 43-81
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 82-86
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 110-118
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 92-95
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 95-100
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 101-108
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 101-108
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 120-127
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 125-126
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 129-131
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 133-135
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 172-173
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 136-141
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses.	Line 136-141
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 141-149

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not Applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not Applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 129-131
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Line 133, 143-144
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 152-153
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Line 154-162
Study characteristics	17	Cite each included study and present its characteristics.	Line 165-173
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Line 179-190
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Line 192-274
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not Applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Line 276-288
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 307-319
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not Applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Line 179-190
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 276-288
	23b	Discuss any limitations of the evidence included in the review.	Line 410-418
	23c	Discuss any limitations of the review processes used.	Line 404-410
	23d	Discuss implications of the results for practice, policy, and future research.	Line 420-427
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Line 88-90
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Line 88-90

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Line 88-90
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 444-446
Competing interests	26	Declare any competing interests of review authors.	Line 453
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not Applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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