Extended Dual Antiplatelet for Diabetic Elderly Patients After Drug-eluting Stent Implantation: an Evidence-based Clinical Review

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ABSTRAK

Terapi antiplatelet sangat penting untuk pasien dengan penyakit jantung koroner yang menjalani prosedur drug-eluting stent (DES). Panduan klinis saat ini merekomendasikan dual antiplatelet (DAPT) dengan aspirin dan inhibitor P2Y12 selama minimal 12 bulan. Perpanjangan DAPT lebih dari 12 bulan dapat dipertimbangkan untuk mencegah very late stent trombosis. Beberapa faktor telah diketahui berkontribusi terhadap trombosis stent, termasuk diabetes dan usia lanjut, namun durasi optimal DAPT untuk pasien tersebut masih kontroversial. Kajian klinis ini membandingkan efektivitas terapi dual antiplatelet yang diperpanjang (>12 bulan) dibandingkan dengan durasi standar (12 bulan) dalam mengurangi kejadian infark miokard dan trombosis stent, terutama pada pasien diabetes berusia lanjut.

Pencarian literatur dilakukan dalam database PubMed dan Cochrane dengan menggunakan kata kunci "dual antiplatelet", "durasi", "diabetes melitus onset dewasa", "usia lanjut", dan "drug-eluting stent". Jenis artikel berupa meta-analisis, uji klinis, atau uji klinis terandomisasi yang membandingkan dual antiplatelet diperpanjang dengan durasi standar. Keluaran klinis adalah infark miokard dan trombosis stent. Pencarian awal dilakukan secara spesifik untuk mencari penelitian pada populasi diabetes dan usia lanjut, namun lingkup pencarian diperluas menjadi pasien dewasa dengan/tanpa diabetes. Didapatkan 5 uji klinis dan 1 meta-analisis, yang menunjukkan penurunan risiko dalam kejadian trombosis stent dan infark miokard. Kajian klinis ini memiliki beberapa keterbatasan, antara lain potensi bias seleksi dan proporsi pasien diabetes serta usia lanjut yang terbatas dalam uji klinis. Kajian klinis ini menunjukkan bahwa lebih baik memberikan perpanjangan DAPT hanya untuk pasien dengan risiko iskemik tinggi dan risiko perdarahan rendah (tailored therapy).

Kata kunci: *diabetes melitus, drug-eluting stent, dual antiplatelet diperpanjang, infark miokard, lanjut usia, trombosis stent.*

ABSTRACT

Antiplatelet is an important drug for patients with coronary heart disease undergoing drug-eluting stent implantation. Current guidelines recommend dual antiplatelet with aspirin and a P2Y12 inhibitor for at least 12 months. Continuation of DAPT beyond 12 months may be considered for preventing very late stent thrombosis. Several patient-related factors that contribute to stent thrombosis have been recognized, including diabetes and advanced age, but the optimal DAPT duration for these patients is still controversial. This article reviews the efficacy of extended (>12 months) compared to standard (12 months) DAPT for reducing myocardial infarction and stent thrombosis rates, especially in diabetic elderly patients.

Literature screening was conducted at PubMed and Cochrane database using "dual antiplatelet", "duration", "adult-onset diabetes mellitus", "elderly" and, "drug-eluting stent" as keywords. Article types were limited to meta-analysis, systematic review, randomized clinical trial, or clinical trial that compared the efficacy of extended to standard duration of DAPT. Clinical outcomes used were myocardial infarction and stent thrombosis. The initial search was done to find relevant studies specifically assessing diabetic and elderly patients, then widened to diabetic and non-diabetic patients of any age above eighteen years. A total of 5 clinical trials and 1 meta-analysis were reviewed, showing an overall risk reduction of stent thrombosis and myocardial infarction. This review has several limitations, such as its potential selection bias and under-represented proportion of diabetic and elderly patients. High-risk subgroups like diabetes mellitus has a tendency of increased ischemic risk, while advanced age could have both increased ischemic risk and bleeding risk. This review suggests that it is better to reserve extended dual antiplatelet therapy for patients with high ischemic risk and low bleeding risk (tailored therapy).

Key words: *adult-onset diabetes mellitus, drug-eluting stent, extended dual antiplatelet, elderly, myocardial infarction, stent thrombosis.*

INTRODUCTION

Coronary heart disease is caused by atherosclerosis of coronary arteries. Revascularization of occluded coronary artery by percutaneous coronary intervention (PCI) could be indicated both in the setting of acute coronary syndrome (ACS) and non-ACS, such as refractory angina despite optimal medical treatment. A coronary stent, as foreign body in blood vessel, will induce platelet adhesion and aggregation, resulting in thrombus.[1,2] Antiplatelet is an important therapy for inhibiting platelet aggregation and preventing stent thrombosis, especially in high-risk patients. The risk of stent thrombosis is increased dramatically in patients who prematurely discontinue antiplatelet therapy, and stent thrombosis is associated with a mortality rate of 20-45%.[3] Currently, the American Heart Association recommends dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitor for at least 12 months, continued with aspirin monotherapy indefinitely for patients receiving drug-eluting stent (DES), both in ACS and non-ACS setting. Lately, it has been shown that DES has a higher incidence of very late stent thrombosis, which occurs more than 12 months after stent implantation. Therefore, continuation of DAPT beyond 12 months may be considered in patients undergoing DES implantation. However, if the risk of morbidity from bleeding outweighs the anticipated benefit afforded by DAPT, earlier discontinuation of P2Y12 inhibitor therapy is reasonable.[3]

Several patient-related factors that contribute to stent thrombosis have been recognized, including diabetes and advanced age.[3,4] Diabetic patients are characterized by increased atherothrombotic risk, associated with their pro-inflammatory and prothrombotic status. Platelet function is regulated by insulin, and the adhesion or aggregation of platelets is enhanced in insulin-resistant patients. The up-regulation of the P2Y12 receptor signaling pathway has also been shown in type 2 diabetes. Platelet in diabetic patients appear to be in activated state even in the absence of vascular injury, and respond more frequently even to subthreshold stimuli. Insulin resistance also increases fibrinolysis suppression, and associated with the increased production of different coagulation factors promoting platelet adhesion to the vascular sub-endothelium.[5] The complexity of platelet activation and subsequent higher risk of thrombosis in diabetic patients may become a reasonable consideration for prolonging DAPT beyond the recommended duration.

Coronary stent implantion is one of the most frequent hospital procedure done in elderly population, and the proportion of patients undergoing PCI who were 75 to 84 years of age has doubled, while those who were 85 years of age increased five fold.[1,6] Elderly undergo physiological changes, such as increased arterial stiffness and endothelial dysfunction. In addition,

they usually present with multiple pathologies, such as hypertension, diabetes mellitus, and renal failure. Such conditions may lead to increased atherothrombotic risk, and it may be reasonable to prolong DAPT beyond the recommended duration. However, older patients are at higher risk of complications from antiplatelet therapies; it could make prolonging DAPT contraindicated despite the potential clinical benefit.[7,8] In addition, elderly patients often have multipharmacological treatment with many potential drug-drug interactions.[9] Therefore, any medication, including antiplatelet, should be scrutinized in order to determine whether it should be continued or not.

Several studies proved that dual antiplatelet therapy with aspirin and P2Y12 can decrease cardiovascular mortality in patients after coronary DES implantation. Even so, the optimal duration is still controversial. Therefore, clinicians need to know whether extended (>12 months) DAPT after DES implantation is: (1) indicated in all patients because the cardiovascular benefit outweighs the risk of bleeding; (2) considered in certain individual (tailored-therapy) with high-risk profile (such as diabetic or elderly patient) based on patient's cardiovascular risk factor and bleeding risk; (3) contraindicated in all patients because of significantly increased morbidity or mortality associated with bleeding risk.

CLINICAL QUESTION

In diabetic elderly patients, does extended dual antiplatelet (>12 months) after drug-eluting stent implantation reduce myocardial infarction and/or stent thrombosis rates better than standard (12 months) dual antiplatelet therapy?

METHODS

The search strategy and study selection criteria were based on problem-intervention-comparison-outcome (PICO) model to answer the clinical question, as described in **Table 1**. Since the cilinical question type is intervention, searching would be focused to find meta-analysis, systematic review, or clinical trial to answer the clinical question.

Table 1. PICO components

Problem	Intervention	Comparison	Outcome
Diabetic elderly patients who underwent coronary drug-eluting stent implantation	Extended dual antiplatelet therapy (more than twelve months) and continued with aspirin monotherapy	Standard dual antiplatelet therapy (twelve months) and continued with aspirin monotherapy	Myocardial infarction and/ or stent thrombosis

Data Sources and Search Strategy

We screened Pubmed and Cochrane database on April 10–17, 2015 for data comparing extended duration and standard duration of dual antiplatelet therapy. Dual antiplatelet therapy was defined as aspirin plus a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor). We used "dual antiplatelet", "duration", "adult-onset diabetes mellitus", "elderly" and, "drug-eluting stent" as keywords. Filters were used to limit article types, which is "meta-analysis", "systematic review", "randomized clinical trial", or "clinical trial". No filter for date of publication was used, and the articles found were publicated between 2006 and 2015. The keywords and number of articles found in each search were listed in **Table 2**.

Selection Criteria

Articles included in this review were systematic review, meta-analysis, randomized clinical trial, or clinical trial comparing twelve and over twelve months dual antiplatelet therapy after drug-eluting stent implantation. Exclusion criteria for this review were: articles with observational design, dual antiplatelet duration of less than twelve months (clinical trial/meta-analysis/ systematic review) or duration timeframes not reported (meta-analysis or systematic review), animal studies, studies assessing endpoint other than stent thrombosis/ myocardial infarction, and studies assessing the effects of drug other than the combination of aspirin and a thienopyridine. Articles written in languages other than English or Indonesian were also excluded.

The initial search was done to find relevant studies specifically assessing diabetic and elderly patients. However, due to the scarcity of

Table 2. Searching strategy in several database

Engines	Search Terms	Hits
Pubmed	(((((((dual antiplatelet) AND duration) AND drug eluting stent[MeSH Terms] AND aspirin[MeSH Terms]) AND thienopyridines[MeSH Terms])) AND elderly)) AND diabetes mellitus, adult onset[MeSH Terms]	0
Pubmed	(((((((dual antiplatelet) AND duration) AND drug eluting stent[MeSH Terms] AND aspirin[MeSH Terms]) AND thienopyridines[MeSH Terms])) AND diabetes mellitus, adult onset[MeSH Terms]	0
Pubmed	(((((dual antiplatelet) AND duration) AND drug eluting stent[MeSH Terms] AND aspirin[MeSH Terms]) AND thienopyridines[MeSH Terms])) AND elderly	29
Pubmed	(((dual antiplatelet) AND duration) AND drug eluting stent[MeSH Terms] AND aspirin[MeSH Terms]) AND thienopyridines[MeSH Terms]	49
Cochrane	'dual antiplatelet AND "duration" AND "drug eluting stent" AND diabetes mellitus AND elderly	0
Cochrane	'dual antiplatelet AND "duration" AND "drug eluting stent" AND diabetes mellitus	0
Cochrane	'dual antiplatelet AND "duration" AND "drug eluting stent" AND elderly	0
Cochrane	'dual antiplatelet AND "duration" AND "drug eluting stent"	46

such studies, the scope of search was widened gradually from diabetic and elderly patients, to diabetic and non-diabetic patients of any age above eighteen years old. Such steps were necessary to collect as many high-quality studies as possible. The literature screening, study selection, and reasons for exclusion were described in the PRISMA flowchart (**Figure 1**).

Selection Bias and Publication Bias

All relevant studies were included in this review, even studies with negative results. However, selection bias could happen because not all relevant studies have full-text availability. Several studies with no full-text availability were included in the meta-analysis we found, therefore they are indirectly included in this review. Ultimately, only one relevant clinical trial were not included due to no full-text availability.

Eligible studies, which conformed to the inclusion and exclusion criteria, were assessed for their risk of bias. Publication bias was graded using the components of evidence-based medicine recommended by the British Medical Journal (BMJ), which consist of randomization, allocation concealment, blinding of participants, and other sources of bias. The characteristics of included studies, along with potential sources of bias were summarised in **Table 3** and **Table 4**.

RESULTS

Studies and Patients

From the 95 initial studies, 86 studies did not meet the prespecified inclusion criteria. A total of 5 clinical trials and 1 meta-analysis were finally included in the review (**Figure 1**). Clopidogrel and aspirin was the most frequent drug combination in dual antiplatelet therapy. Follow-up period varied from 18 to 48 months after stent implantation. Sample size varied between studies, from several hundreds to almost ten thousands. Each study had varying proportion of diabetic and elderly subjects. All studies had less than 50% diabetic subjects, and all studies had subjects with mean age over 60 years old. Only two studies analysed these high-risk subgroups separately (**Table 3** and **Table 4**).[10-15]

Stent Thrombosis

In three randomized clinical trials, extended dual antiplatelet therapy have similar clinical benefit to twelve-month therapy. Extended dual antiplatelet therapy showed a reduction of roughly 50% in the rates of stent thrombosis for diabetic patients, and roughly 80% for elderly (>75 years old) patients. One clinical trial had no data for stent thrombosis, and another one reported a significantly different rates of stent thrombosis between the two groups, with a relatively small number needed to treat (**Table 3**). A meta-analysis showed a reduction of roughly 70% in the odds of myocardial infarction and demonstrated statistically significant difference, but its number needed to treat (NNT) was relatively high (**Table 4**).

Myocardial Infarction

In two clinical trials, myocardial infarction rates were similar in twelve-month and extended

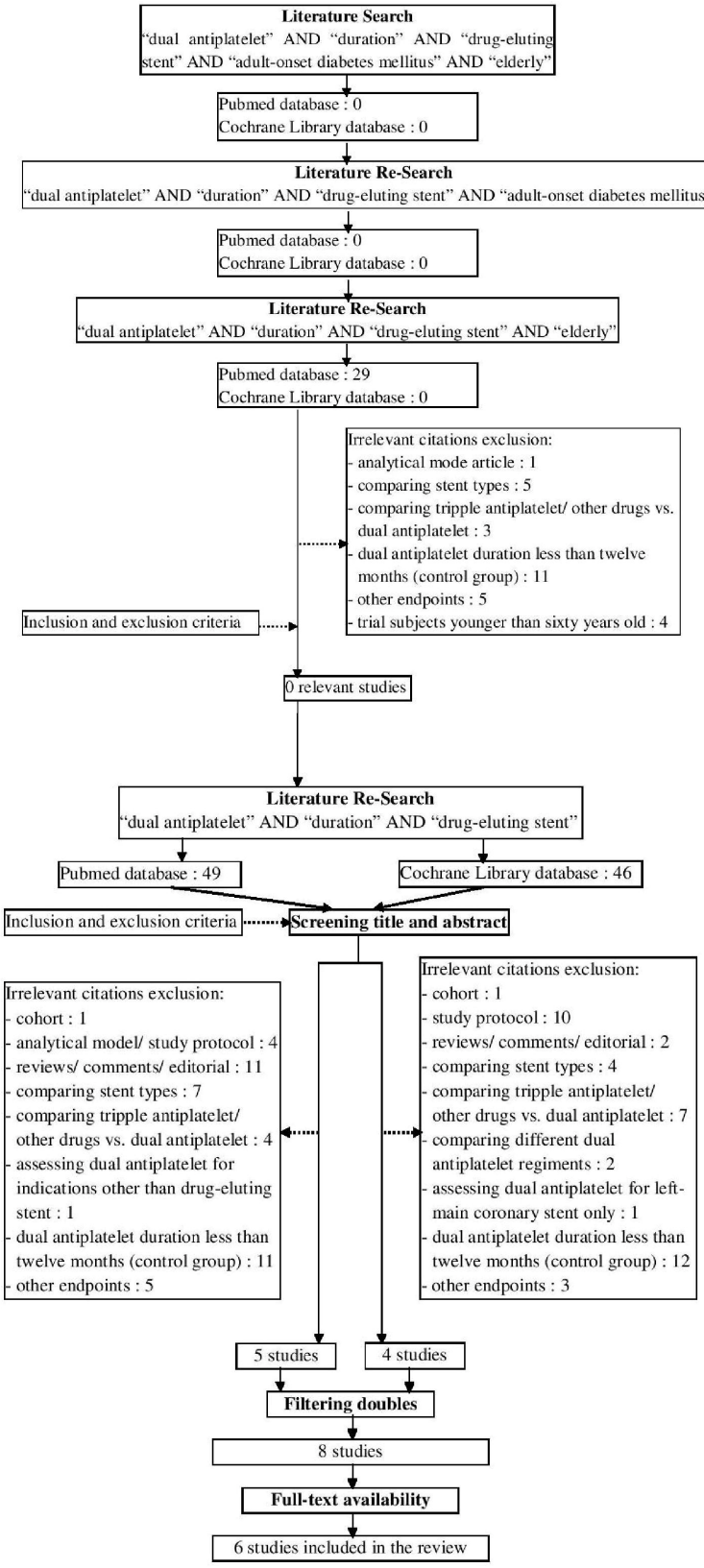

Figure 1. PRISMA flowchart

Table 3. Characteristics of included clinical trials comparing 12 months versus extended (>12 months) dual antiplatelet therapy

Criteria	Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents (DAPT Trial)[10]	Prolonged Clopidogrel Use After Bare Metal and Drug-Eluting Stent Placement: The Veterans Administration Drug-Eluting Stent Study[11]	Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents[12]	Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Randomized. Controlled Trial (DES-LATE Trial)[13]	Prolonged Dual Anti-platelet Therapy Improves Clinical Outcomes in High-risk Patients Implanted with Sirolimus-eluting Stents[14]
Was the assignment of patients to treatments randomized?	Yes	No (secondary data from hospital registry)	Yes	Yes	No (consecutive sampling)
-- And was the randomization list concealed?	Yes		No	No	
Were all the patients who entered the trial accounted for at its conclusion? And were they analysed in the groups to which they were randomized?	Yes (intention-to-treat-analysis)	Yes (intention-to-treat anaysis)	Yes (intention-to-treat anaysis)	Yes (intention-to-treat anaysis)	Yes (intention-to-treat anaysis)
Were patients and clinicians kept “blind” to which treatment was being received?	Yes (double-blind)	No	No (open-label)	No (open-label)	Not mentioned
Aside from the experimental treatment. were the groups treated equally?	Yes (standard treatment according to international guidelines)	Yes (standard treatment according to international guidelines)	Yes (standard treatment according to international guidelines)	Yes (standard treatment according to international guidelines)	Not mentioned
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes	No (higher systolic dysfunction in dual therapy)
Control Event Rate (CER)	Stent thrombosis: 1.4%	Stent thrombosis: no data	Stent thrombosis: 0.4%	Stent thrombosis: 0.5%	Stent thrombosis: 5.6%
	Myocardial infarction : 4.1%	Myocardial infarction: 7.4%	Myocardial infarction: 0.7%	Myocardial infarction: 1.2%	Myocardial infarction: 5.6%
Experimental Event Rate (EER)	Stent thrombosis: 0.4%	Stent thrombosis: no data	Stent thrombosis: 0.4%	Stent thrombosis: 0.3%	Stent thrombosis: 1.1%
	Myocardial infarction: 2.1%	Myocardial infarction: 5.4%	Myocardial infarction: 0.7%	Myocardial infarction: 0.8%	Myocardial infarction: 1.1%
Relative Risk Reduction (RRR)	Stent thrombosis: 71.4%	Stent thrombosis: no data	Stent thrombosis: 0%	Stent thrombosis: 40%	Stent thrombosis: 80.4%
	Myocardial infarction : 48.8%	Myocardial infarction: 27.0%	Myocardial infarction: -14.3%	Myocardial infarction: 33.3%	Myocardial infarction: 80.4%

Absolute Risk Reduction (ARR)	Stent thrombosis: 1% (0.63 - 1.37%)	Stent thrombosis: no data	Stent thrombosis: 0% (-0.48-0.48%)	Stent thrombosis: 0.2% (-0.15-0.55%)	Stent thrombosis: 4.5% (0.62-8.38%)
	Myocardial infarction : 2% (1.32-2.68%)	Myocardial infarction: 2% (1.22-2.78%)	Myocardial infarction: -0.1% (-0.75-0.55)	Myocardial infarction: 0.4% (-0.15-0.95%)	Myocardial infarction: 4.5% (0.62-8.38%)
Confidence Interval (CI) 95%	Stent thrombosis: +/-0.37%	Stent thrombosis: no data	Stent thrombosis: +/-0.48%	Stent thrombosis: +/-0.35%	Stent thrombosis: +/- 3.88%
	Myocardial infarction : +/-0.68%	Myocardial infarction: +/-0.78%	Myocardial infarction: +/-0.65%	Myocardial infarction: +/-0.55%	Myocardial infarction: +/-3.88%
Number Needed to Treat (NNT)	Stent thrombosis: 100 (58 – 159) pts	Stent thrombosis: no data	Stent thrombosis: indefinite	Stent thrombosis: 500 pts	Stent thrombosis: 23 (11-162) pts
	Myocardial infarction : 50 (38 – 76) pts	Myocardial infarction: 50 (35-82) pts	Myocardial infarction: indefinite	Myocardial infarction: 250 pts	Myocardial infarction: 23 (11-162) pts
Additional information:					
Dual antiplatelet duration	12 mo vs. 30 mo	<12 mo vs >12mo	12 mo vs. 36 mo	12 mo vs. 36 mo	12 mo vs. 18 mo
Dual antiplatelet regimen	aspirin 75 – 162 mg + clopidogrel 75 mg or prasugrel 10 mg daily	aspirin 100 mg + clopidogrel 75 mg daily	aspirin 100-200 mg + clopidogrel 75 mg daily	aspirin 100-200 mg + clopidogrel 75 mg daily	aspirin 100 mg + clopidogrel 75 mg daily
Time from stenting to group allocation	12 months	None (secondary data)	12 – 24 months	12 – 18 months	12 months
Non-adherence rates at the end of study	4.6% (monotherapy)	None	1.6% (monotherapy)	4.6% (monotherapy)	None
	4.7% (dual therapy)		17.1% (dual therapy)	5.4% (dual therapy)	
Follow-up period (after stent)	30 months	48 months	36 months	36 months	18 months
Subjects (total)	9 961	14 925	2 701	5 045	336
Diabetic (%)	30.1 (monotherapy)	42.8 (monotherapy)	27.1 (monotherapy)	28.2 (monotherapy)	46.9 (monotherapy)
	31.1 (dual therapy)	44.3 (dual therapy)	25.1 (dual therapy)	28.0 (dual therapy)	40.3 (dual therapy)
Mean age (years old)	61.6 $\pm$ 10.1 (monotherapy)	63.8$\pm$10.1 (monotherapy)	61.9 $\pm$ 9.9 (monotherapy)	62.3 $\pm$ 10.1 (monotherapy)	64.7 $\pm$ 7.5 (monotherapy)
	61.8 $\pm$ 10.2 (dual therapy)	63.7$\pm$ 9.5 (dual therapy)	62.0 $\pm$ 9.8 (dual therapy)	62.5 $\pm$ 10.0 (dual therapy)	65.8 $\pm$ 8.4 (dual therapy)
Subgroup analysis					
Diabetic: Stent thrombosis	HR 0.53 (0.23 - 1.20)	None	None	None	None
Myocardial infarction	HR 0.73 (0.51 – 1.05)	None	None	HR 0.63 (0.35 – 1.12)	None
Elderly :	(defined as >75 years old)			(defined as >65 years old)	
Stent thrombosis	HR 0.23 (0.03 - 2.06)	None	None	None	None
Myocardial infaction	HR 0.76 (0.38 - 1.54)	None	None	HR 0.81 (0.51 – 1.30)	None
Evidence quality	Good	Poor	Fair	Fair	Poor

Table 4. Characteristics of included meta-analysis comparing 12 months versus extended (>12 months) dual antiplatelet therapy

Criteria	Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials[15]
Is it a systematic review of high-quality studies which are relevant to your question?	Yes. All studies are randomized clinical trial comparing extended (>12 mo) vs 12 mo dual therapy. Dual antiplatelet used are P2Y12 inhibitor and aspirin
Does it include a methods section that describes:	
Finding and including all the relevant trials?	Yes. Literature search were done in all major database, congress proceedings and unpublished research. All relevant randomized clinical trials were included
Assessing their individual validity?	Yes
Were the results consistent from study to study?	Yes. No significant heterogeneity for both outcomes (stent thrombosis and myocardial infarction), as indicated by p value > 0.1 and I2 < 40%
Are they clinically significant?	Stent thrombosis (very late) CER = 0,98% EER = 0,32% RRR = 67,5% ARR = 0,66% (0,41-0,91%) CI 95% = +/-0,25% NNT = 152 (109 – 244) pts Odds Ratio 0,33 (0,21 – 0,51) Myocardial infarction CER = 2,89% EER = 1,55% RRR = 46,37% ARR = 1,34% (0,88 – 1,80%) CI 95% = +/-0,46% NNT = 75 (55 – 114) pts Odds Ratio 0,53 (0,42 – 0,66)
How precise are the results?	The results can be interpreted with confidence. The confidence limits around the odds ratio demonstrated a statistical significance, favoring extended dual antiplatelet.
Evidence quality	Good

*CER = Control Event Rate, EER = Experimental Event Rate, RRR = Relative Risk Reduction, ARR = Absolute Risk Reduction, CI = Confidence Interval, NNT = Number Needed to Treat

dual antiplatelet therapy. In a randomized clinical trial, myocardial infarction rate differs significantly and the clinical benefit outweighs the bleeding risk, as shown by a number needed to treat of fifty patients or less. In DAPT trial, extended dual antiplatelet therapy showed a reduction of roughly 30% in the rates of myocardial infarction for diabetic patients, and roughly 30% for elderly (>75 years old) patients. In DES-LATE trial, extended dual antiplatelet therapy showed a reduction of roughly 40% in the rates of myocardial infarction for diabetic patients, and roughly 20% for elderly (>65 years old) patients. In another two trials, the clinical benefit is more pronounced, as shown by an even smaller number needed to treat; however, these trials have more potential bias than the other studies. A meta-analysis showed a reduction of roughly 50% in the odds of myocardial infarction with extended dual antiplatelet therapy and demonstrated statistically significant difference, but its number needed to treat was relatively high.

DISCUSSION

There were variable results across the clinical trials, with some trials reporting clinical benefits in preventing stent thrombosis or myocardial infarction despite increased bleeding risk, while others reported no benefit. Three trials reported clinical benefit, one is an nonrandomized clinical trial with a relatively small sample size, and another one is also nonrandomized, with different dual antiplatelet duration within the trial. Accordingly, the good results might happen due to pure coincidence. Nonetheless, the clinical benefit might arise because a large proportion of patients in those trials had high ischemic risk, as indicated in the DAPT trial. The extended group also showed a greater risk reduction in myocardial infarction than stent thrombosis, which might demonstrate a protective effect of dual antiplatelet on preventing thrombosis in coronary vessels, beyond the stented area.[10,11]

Two RCTs reported no clinical benefits from extended dual antiplatelet. However, these trials had inadequate statistical power and higher non-adherence rates in dual therapy group, especially in Park, et al.[12] In addition, the randomization occurred at a varying time-frame after stenting, mostly 18 months after stenting, so most subjects had stopped taking dual antiplatelet for six months.[12,13] In those periods, the atherosclerotic process may had progressed; this could make dual antiplatelet, which primary function was for atherothrombotic prevention, less useful. Coupled with the high non-adherence rate, this could make the adverse events in dual therapy group slightly higher than monotherapy in Park, et al.[12] Therefore, the results from these trials must be interpreted carefully. One meta-analysis reported significant clinical benefit from extended dual antiplatelet. Different types of P2Y12 inhibitor and drug-eluting stents were used across and within trials. This situation reflected real-world clinical practice, where patients were treated with different antiplatelet and stent types, based on clinical settings and drug availability. Another problem was different extended antiplatelet duration and follow up period between trials, which might affect the clinical outcomes.[14] Nonetheless, the meta-analysis showed little or no heterogeneity in the trials -suggesting that overall benefits of extended dual antiplatelet were robust and justified.[15]

Overall, the diabetic population is under-represented in all clinical trials, moreover the elderly population. Elderly with multiple non-cardiovascular comorbidities, like many elderly patients in real-world clinical practice, were often excluded from trials, which further under-representing elderly population. The most representing clinical trial for these high-risk subgroups was Jia et al.[14] However, it had many potential bias and inadequate statistical power. Therefore, none of the trials' results could be extrapolated for diabetic or elderly subgroups.

The varying results from clinical trials might indicate that the certainty of whether extended therapy is better than twelve-month therapy, could not be generalized to all patients. This might be caused by a spectrum of risk factors, which played important roles in ischemic events, and resulted in a tendency of increasing clinical benefit (lower number needed to treat), in accordance with increasing proportion of high-risk patients. With evidence showing the tendency of greater clinical benefit from extended dual antiplatelet, the question was not whether to extend the dual therapy, but for whom the clinicians need to reserve the extended dual antiplatelet.

Diabetes

Coronary artery revascularization of diabetics continues to be a challenge: these patients suffer from a worse outcomes after PCI, compared with non-diabetics.[16] This fact was also demonstrated in DAPT trial's subgroup analysis, with a smaller risk reduction for both stent thrombosis and myocardial infarction in diabetic patients than their non-diabetic counterparts.[10] Diabetic patients have been shown to have a poor response to clopidogrel in both the acute and chronic phases of therapy. Moreover, insulin-requiring diabetics have the strongest platelet reactivity despite dual antiplatelet therapy.[5]

While it has been known that diabetes mellitus is associated with prothrombotic state, the question of what is the most effective way to use antiplatelet therapy for this matter, remains un-answered. Currently, there is no

evidence that increasing aspirin dose would be useful. Increasing the loading or maintenance doses of clopidogrel may be an option. Several studies showed that increasing loading dose or maintenance dose would improve drug responsiveness and antiplatelet effects.[5] The current low-dose aspirin/clopidogrel regimen has a slightly increased bleeding risk if used for an extended duration, as demonstrated consistently across all studies in this review. The bleeding was mainly mild or moderate, and rarely fatal. However, if the dose was increased, the bleeding risk could increase greatly. Further trials were needed to evaluate the safety profile of the high-dose aspirin/clopidogrel regimen, as well as its clinical benefits, since most already existed trials measured laboratory outcomes, such as platelet activity, rather than clinical events.

Since most studies included in this review were performed under clopidogrel, further trials are needed to explore the effect of novel P2Y12 inhibitor on diabetic patients. Several studies indicated that prasugrel, as well as ticagrelor, was more superior than clopidogrel in preventing recurrent ischemic events for post-ACS diabetic patients. Since dual antiplatelet with clopidogrel was indicated to have deleterious effect on advanced diabetic nephropathy, using a novel P2Y12 inhibitor or other antiplatelet, such as cilostazol, to replace clopidogrel might be an option for such patients.[16,17] Another option was adding a third antiplatelet, such as cilostazol; preliminary studies showed a more pronounced clinical benefit of triple antiplatelet compared to dual antiplatelet in diabetic patients.[18] Finally, the drug-eluting stent itself might also play a role in stent thrombosis, both in diabetic and general population, but no studies to date has evaluated the effects of extended dual antiplatelet therapy on different drug-eluting stent types.[19-22] Additionally, in real clinical practice, a diabetic patient often has several comorbidities or complications, which might increase the ischemic risk. Therefore, further risk stratification are needed to evaluate each diabetic subgroups, such as diabetics receiving DES for ACS indications, insulin-requiring diabetics, diabetics without complications, with left ventricle systolic dysfunction, or with renal failure.

Elderly

In the subgroup analysis, the incidence of major/moderate bleeding in elderly patients was surprisingly lower than non-elderly.[9] This might be caused by pure coincidence, as a result of much smaller proportion of elderly patients compared to non-elderly. Moreover, the elderly included in the trial, by design, most likely had a relatively low risk of bleeding, who experienced no major bleeding during twelve-month dual antiplatelet and tolerated the therapy well. Meanwhile, in real-world clinical practice, elderly patients could present with comorbidities which can increase the bleeding risk, such as peptic ulcer or esophageal varices. Results from DAPT trial also showed increasing cancer-related bleeding in extended dual-therapy group, most likely caused by undiagnosed cancer before enrollment.[9] Several comorbidities could require drugs that increase bleeding risk, such as anticoagulants, glucocorticosteroid, or NSAID.[23] Certain drugs has also been shown to have impact on antiplatelet drugs, such as proton-pump inhibitor (PPI), especially omeprazole and esomeprazole.[4] Therefore, it is necessary to do a comprehensive and holistic assessment for elderly patients, especially to screen for comorbidities which can increase ischemic or bleeding risk. It is also important to use rational prescribing to avoid potential drug interactions.

Several studies indicated an increasing clinical benefit of extended dual antiplatelet for patients with high ischemic risk. However, there is no good evidence that could show the optimal duration of dual antiplatelet for elderly patients, who often had risk factors for both ischemic and bleeding events. Therefore, further trials are needed to evaluate the efficacy of extended dual antiplatelet therapy on elderly populations, especially in elderly with multiple pathologies.

Implications for Clinical Practice

Studies included in this review showed a tendency of greater clinical benefit from extended dual antiplatelet. However, as the incidence of very late stent thrombosis in general population is very small, the number needed to treat becomes very large, far over fifty patients. It indicates that

the use of extended dual antiplatelet therapy for every post-DES patients is ineffective, exposing patients to unnecessary bleeding risk, and clearly not cost-effective. This is especially important in Asian population, which has a relatively low incidence of very late stent thrombosis.[24]

Overall, this review suggests that the standard twelve-month dual antiplatelet therapy is not necessarily the optimal care. Longer duration should be carefully considered, weighing the patient's bleeding and ischemic risk profile. Due to the uncertainty on increased bleeding risk, an extended dual antiplatelet regimen may better reserved to patients at high ischemic risk and low bleeding risk. Further trials with adequate power are needed to test the clinical efficacy of such tailored dual antiplatelet. This review can-not be used as a guide for tailoring dual antiplatelet therapies for a specific patient. However, it can provide a little insight on which patient is more likely need an extended dual antiplatelet therapy.

Limitations

This article has several limitations. First, its potential selection bias due to full-text unavailability. However, it is minimized by including meta-analysis, which analyzed the trials unavailable to the authors. Second, the trials have an under-represented proportion of diabetic and elderly patients, therefore results can-not be extrapolated in these high-risk subgroups. Third, this review only analyzed patient-related factors, not attending to other factors which may contribute to clinical outcomes, such as stent-related factors and different dual antiplatelet regimens. Lastly, this review did not compare the efficacy between different extended antiplatelet duration.

CONCLUSION

It is not beneficial to extend dual antiplatelet therapy for every patients receiving drug-eluting stents. Overall, the extended dual antiplatelet therapy showed a risk reduction of stent thrombosis and myocardial infarction, at the price of increased bleeding risk. High-risk subgroups like diabetes mellitus has a tendency of increased ischemic risk, while advanced age could have both increased ischemic risk and bleeding risk. This review suggests that it is better to reserve extended dual antiplatelet therapy for patients with high ischemic risk and low bleeding risk (tailored therapy).

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