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Reviews

Meta-Analysis Design and Results in Real Life: Problem Solvers or Detour to Maze. A Critical Review of Meta-Analysis of DAPT Randomized Controlled Trials



Ivan J. Núñez Gil ^{a,*}, Ainhoa Elizondo ^b, Simona Gradari ^c, Pedro A. Villablanca ^d, Hector Bueno ^{e,f,g}, Gisela Feltes ^h, Alicia Quirós ⁱ, Harish Ramakrishna ^j, Louka Boshra ^j, Antonio Fernandez Ortiz ^{a,f,g}

- ^a Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain
- ^b Medical Department Astrazeneca, Spain
- ^c Biochemistry Department, Faculty of Medicine, Universidad Autónoma, Madrid, Spain
- ^d Department of Medicine, Division of Cardiology, Montefiore Medical Center, New York, USA
- ^e i + 12 Research Institute and Cardiology Department, Hospital 12 de Octubre, Madrid, Spain
- ^f Spanish National Centre for Cardiovascular Research (CNIC), Madrid, Spain
- ^g Faculty of Medicine, Universidad Complutense de Madrid, Spain
- ^h Cardiology Department, Hospital Virgen del Mar, Madrid, Spain
- ⁱ Biostatistics, Leon University, León, Spain
- ^j Department of Anesthesiology and Cardiology, Mayo Clinic, Phoenix, USA

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ABSTRACT

Background: Therapeutic strategies - such as duration of dual antiplatelet therapy after coronary artery stenting - usually generate a large quantity of meta-analyses. The meta-analyses that include the same randomized clinical trials should produce similar results. Our aim in the study is to analyze the quality and to compare the results of meta-analyses focused on a controversial topic such as dual antiplatelet therapy after percutaneous coronary intervention.

Methods: We searched all published meta-analyses published up to November 2015 (near DAPT trial publication) selecting those that included the same randomized clinical trials comparing patterns of briefer versus longer-term double antiplatelet therapy.

Results: Seventeen meta-analyses achieved our selection criteria. Of the seventeen analyzed, we identified seven (41.1%) based on the same ten randomized clinical trials (RCTs), yet their results varied widely. Many of the meta-analyses differed in only some minor aspect of the design (i.e. eligible studies, length of comparators and statistical methods used). Some authors differed in the number of patients participating in RCTs and even, despite reviewing the same underlying trials, only 2 of the 7 meta-analyses included the same number of patients.

Conclusion: Meta-analyses around cardiovascular, all-cause or non-cardiovascular death differ frequently. In the DAPT duration setting, several meta-analyses have been recently published based on the same data, presenting several issues making it difficult to determine clear recommendations on certain points.

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* Corresponding author at: Cardiology, Cardiovascular Institute, Hospital Clínico San Carlos, Street: Prof Martín Lagos SN, 28040 Madrid, Spain.
 E-mail address: ibnsky@yahoo.es (I.J. Núñez Gil).

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1. Introduction

The need to provide convincing evidence to support clinical strategies and the recommendations made in the clinical guidelines has led the production of systematic reviews and meta-analyses [1]. The European Society of Cardiology defines three levels of evidence to support guideline recommendations according to the type of available data, A, B and C. The highest level of evidence, A can be derived both from multiple randomized clinical trials and from meta-analyses [2]. In a step forward, ACCF/AHA Guidelines recently described a new classification: level A, meta-analyses derived from high-quality randomized controlled trials (RCTs), level B-R meta-analyses derived from moderate-quality RCTs and, finally, Level B-NR in which meta-analyses derive from moderate-quality non-randomized studies, observational studies or registry studies [3].

Although the general usefulness of the meta-analyses is clear, misuse can result in severely misleading results [4,5]. A known and obvious weakness of meta-analyses is that these are subject to the quality of the aggregated studies, furthermore, many trials are sufficiently different so that when carrying out a meta-analysis, the results can be flawed [4]. On the other hand, the production of systematic reviews and meta-analyses has grown widespread. Potentially, a large proportion of these systematic reviews and meta-analyses may be unnecessary, misleading, and/or conflicted [6].

In the cardiology field, current oral antiplatelet therapy after stent implantation includes aspirin in combination with a P2Y12 receptor antagonist. This dual antiplatelet therapy (DAPT) duration depends on the evaluation of several factors considering thrombotic and bleeding risk [2,3,8]. The problem is that the precise duration is variable and the clinical indications are sometimes subjective (3 months vs. >1 year [7]). Thus, we aimed to analyze the quality of meta-analyses and, for academic purposes, we chose a clinical hot topic such as duration of dual antiplatelet therapy after percutaneous coronary intervention.

2. Methods

2.1. Data sources and search strategy

We conducted an electronic systematic review across the databases EMBASE, KNOWLEDGE DISCOVERY PLATFORM and MEDLINE searching for meta-analyses published before November 2015. We searched with the Medical Subject Headings (MESH) terms: “antithrombotic agent”, “treatment duration”, “Cochrane review”, “systematic review”, “metaanalysis”, “meta-analysis”, “metanalysis”, “dual”, “double” and “DAPT”. Results were then limited to meta-analyses including RCTs and duplication was removed. The main objective of the analysis was to search for confirmations or inconsistencies among the studies providing a general view on the value of these studies around the clinical question of interest.

2.2. Eligibility criteria

We reviewed all meta-analyses that incorporated studies that compared longer versus shorter duration DAPT (aspirin plus a P2Y12 inhibitor) after coronary artery disease diagnosis, published until November 2015 (month of the search).

Meta-analyses to be included had to meet three criteria. First, to be a meta-analysis of published RCTs carried out in human patients. Second, treatment of patients should include aspirin and a P2Y12 inhibitor. Finally, at least one of the following outcomes was reported: cardiovascular death, all cause death, myocardial infarction, stroke, definite/probable stent thrombosis and major bleeding.

Meta-analyses involving patients with cardiac structural procedures or coronary artery bypass grafting, concomitant therapy with an oral anticoagulant (triple therapy) were excluded. To promote the availability of DAPT contemporary RCTs we finally selected those meta-analyses published in 2015. No language restrictions were enforced.

2.3. Study selection

Two investigators (I.N. and A.E.) independently reviewed each title and abstract based on inclusion and exclusion criteria. If any of the reviewers identified a potentially relevant title the full article was obtained and reviewed to determine eligibility. Reviewers resolved disagreements by consensus (I.N., A.E. and S.G.).

2.4. Data extraction

Two investigators (S.G. and A.E.) independently abstracted the following information from each eligible study: authors, publication date, funding, participant demographic and clinical data, definitions and planned duration of DAPT in each group, indication for stent placement, if any, type of stent, outcome event rates, quality and bias assessment, conclusions, practical recommendations, comments, limitations and studies included. The criterion used to divide the experimental groups was based on treatment duration: “short” and “long” duration as concrete periods of time were recorded. Finally, using the same strategy, clinical endpoints, such as cardiovascular death, all cause death, myocardial infarction, stroke, stent thrombosis and major bleeding, were registered to fully understand which results were consistent through the meta-analyses included in this systematic review. Several meta-analyses included the very same RCTs.

3. Results

3.1. Eligible meta-analyses

We identified 71 potentially suitable manuscripts, all in English, of which 25 were duplicated. 46 abstracts were screened and 29 excluded

for the following reasons: year of publication (16), patients with TAVI (1) or CABG (1), anticoagulation (4) or not published yet in a peer reviewed journal during the period mentioned (6). One was rejected because it included registries.

Finally, 17 meta-analyses met the inclusion criteria and were eligible for full-text review [9–27]. Additionally, we searched for meta-analyses including the same studies to compare the primary endpoint results and seven results were met. The selection process of the studies is shown in the flow diagram (Fig. 1).

3.2. Meta-analyses and studies characteristics

We identified 17 meta-analyses addressing DAPT following percutaneous coronary intervention published before November 2015. Table 1 describes the journal where the study was published, the impact factor of the journal, the first publication date, the first author and the trials that each study included to carry out the meta-analysis.

The first meta-analysis evaluated was published on 16th November 2014 and the last one on 11th September 2015. During this period, covering practically a year, one meta-analysis on the same topic had been published every month, with the month of August 2015 being especially noteworthy with 6 publications (online Fig. 1). Furthermore, 12 of the manuscripts mention the prior meta-analyses published on the same topic in their references (online Table 1). Many of meta-analyses are very similar to previous ones, differing slightly in some aspects of the design (for instance, the choice of eligible studies [26–43], treatment length of comparators and statistical methods used).

As shown in Table 1, seven out of 17 meta-analyses (41.1%) included an identical set of 10 RCTs.

3.3. Number of patients in each study

Most authors differ in the number of patients participating in some studies. Moreover, even in meta-analyses reviewing the same trials, the global sum does not coincide frequently either, as depicted in Table 2 (only 2 of 7 meta-analyses including the same RCTs considered the same number of patients). Usually, these differences are not justified or explained in the manuscripts.

3.4. Length assessment

Each of the seven meta-analyses (online Table 2) mentioned employed different time period definitions for short and long-term periods. However, neither in the title of the meta-analyses nor in the conclusions, is the exact period considered mentioned, thereby complicating the correct interpretation of the results.

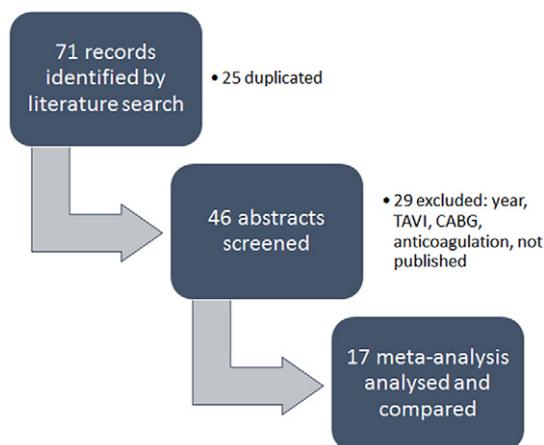


Fig. 1. Flow diagram. Flow diagram of scientific literature search and study selection. CABG: coronary artery bypass grafting. TAVI: transcatheter aortic valve implantation.

3.5. Outcome assessment

Outcome results differ among meta-analyses (Table 3). These inconsistencies could be explained by the application of different statistical methods and/or may be due to the different time lengths considered in long and short-term DAPT, as previously mentioned. Table 3 displays the results by outcome and study.

3.6. Mortality as a final end point

In some cases, when assessed, the final conclusions of the meta-analyses regarding cardiovascular, all-cause or non-cardiovascular death differ, as shown in Table 4. All three end points are included only in 3 of the 17 papers.

3.7. Quality of the meta-analysis reporting and study bias

Three of the meta-analyses did not adhere to any quality guideline (Quorum, Prisma, etc.), Table 1. One reported it fulfilled Quorum criteria and 13 claimed adherence to Prisma. One meta-analysis [9] did not mention any guideline adherence but complied with Prisma requirements. Assessing the meta-analyses with the Prisma 2009 checklist, even some of the papers stating fulfillment to the statement, failed to comply with all the items but sometimes this was due to editorial requirements (i.e. 2 of them were published as letter to the editor [13,19], 3 with non-structured abstracts [17,20,22] or several lacking of explicit funding reporting [13,15,20,22,25], among others).

Regarding the quality of the RCTs (risk of bias) included in the meta-analyses, 12 of them reported explicitly their quality assessment, The Cochrane Collaboration's tool for assessing risk of bias in randomized trials being the most frequently used tool in 8 cases, Table 1.

4. Discussion

Meta-analysis is a useful tool in evidence-based medicine. Today, scientific societies and regulatory agencies consider it one of the most reliable and a higher source of knowledge despite some well-known, serious limitations [2,5,6]. This relevance has triggered a disproportionate production of meta-analyses.

The main objectives of a meta-analysis are to: summarize and integrate results from a number of individual studies, analyze differences in the results among studies, overcome small sample sizes of individual studies to detect effects of interest, analyze end points that require larger sample sizes, increase precision in estimating effects, evaluate effects in subsets of patients, determine if new studies are needed to further investigate an issue, generate new hypotheses for future studies and, if possible, provide useful recommendations.

Consequently, we aimed to review the current state of the art in this field. Thus, we choose a controversial topic (DAPT duration) as the basis of our study where several RCTs with many thousands of patients recruited and a high number of meta-analyses have been published [3,5,7]. We reviewed only meta-analyses including exclusively RCTs. This way, it was possible, in theory, to analyze only the best type of meta-analyses (ESC level of evidence A; ACCF/AHA level of evidence A or BR) with “high quality trial data”, representing the best-case scenario [5].

When the word “meta-analysis” is introduced in PubMed, with a filter between 2004 and 2005, 3573 manuscripts are found. Searching the same words with a filter between 2014 and 2015, 8694 papers are obtained. Not surprisingly, we found 17 meta-analyses published in a short period dealing with the very same question and patients.

Several of them ignored other similar manuscripts (probably explained in part by publication schedules). In theory, it is not recommended to consider performing a meta-analysis if there is one already published including simply the same RCTs. Additionally, in our opinion, the basis for carrying out meta-analyses should not be an issue in and of

Table 1
 Reviewed meta-analyses. Meta-analyses included in the current review, together with their journal, impact factor and date of publication. In grey, trials included in each meta-analysis are depicted. The row about Prisma [44] guidance on good meta-analyses compliance states those manuscripts explicitly citing adherence to this statement or without that (*) but with good compliance (27/27 items in the 2009 checklist) [45]. Of note, not all the papers stating Prisma compliance would have all the Prisma checklist [45] completed in their main manuscript (editorial formats with space limitations such letters [13,19], unstructured abstracts [17,20,22] or lack of explicit funding reporting [13,15,20,22,25] among others). Not all the papers adhering the PRISMA Statement reach 27/27 item in the checklist. **Cites Quorum, a former guidance statement (1999) on meta-analyses reporting [46]. ***Ad hoc [47]: The authors use their own criteria to evaluate the risk of bias/quality of the trials included in their analyses.

Journal	Lancet	IJC	JACC	BMJ	IJC	Lancet	Clin Res Cardiol	Annals of Internal Medicine	Angiology	Iran Red Crescent Med J	IJC	American Journal of Therapeutics	Clinical Trials and Regulatory Science in Cardiology	Nature	Catheterization and Cardiovascular Interventions	EHI	Cardiovascular Therapeutics
Impact Factor	39.207	4.638	17.759	19.967	4.638	39207	4.324	16.440	2931	0.676	4.638	1.132	n/a	11.57	2.181	15.064	2.243
First Published	16/11/2014	13/12/2014	20/01/2015	23/02/2015	05/03/2015	14/03/2015	23/04/2015	26/05/2015	11/06/2015	22/07/2015	06/08/2015	11/08/2015	12/08/2015	17/08/2015	26/08/2015	31/08/2015	11/09/2015
Meta-analysis	Elmariah et al ¹¹	Bulluck et al ¹²	Giustino et al ¹³	Navarese et al ¹⁴	Liou et al ¹⁵	Palmerini et al ¹⁶	Cassese et al ¹⁷	Spencer et al ¹⁸	Verdoia et al ¹⁹	Yang et al ²⁰	Costa et al ²¹	Palla et al ²²	Zhang et al ²³	Tsoi et al ²⁴	Ziada et al ²⁵	Udell et al ²⁶	Abo-Salem et al ²⁷
PRISMA compliance	YES*	YES*	YES**	YES	NO	YES	YES	YES*	YES	NO	YES	YES	YES	YES	YES	YES	NO
Studies included \ Patients N	69644	16534	32135	32287	15870	31866	32194	29531	32372	9979	37427	28343	32135	31550	15874	33435	32136
PRODIGY ²⁸																	
OPTIMIZE ²⁹																	
EXCELLEN ³⁰																	
SECURITY ³¹																	
ITALIC ³²																	
DES LATE ³³																	
ARCTIC-int ³⁴																	
DAPT ³⁵																	
ISAR-SAFE ³⁶																	
RESET ³⁷																	
Hu 2012 ³⁸																	
PEGASUS ³⁹																	
CASPAR ⁴⁰																	
SPS3 ⁴¹																	
CHARISMA ⁴²																	
ACTIVE ⁴³																	
CREDO ⁴⁴																	
CURE ⁴⁵																	
Studies quality assesment	Cochrane	Cochrane	NO	Cochrane	NO	NO	Cochrane	Cochrane/GRADE	AD HOC***	JADAD Score	NO	Cochrane	Cochrane	AD HOC***	JUNI Criteria	Cochrane	NO

Table 2

Number of patients. Total counts for the meta-analyses including the same ten randomized studies. In grey, variations over the total number of patients included in each randomized study. In blue, the number stated by the authors for their analysis.

Study	N	Giustino et al ¹³	Navarese et al ¹⁴	Palmerini et al ¹⁶	Cassese et al ¹⁷	Zhang et al ²³	Tsoi et al ²⁴	Abo-Salem et al ²⁷
ISAR-SAFE ³⁶	4000	4000	4005	4000	4000	4000	4000	4000
ITALIC ³²	1850	1822	1850	1894	1850	1822	1822	1822
SECURITY ³¹	1399	1399	1399	1399	1399	1399	1399	1399
OPTIMIZE ²⁹	3119	3119	3211	3119	3119	3119	3119	3119
PRODIGY ²⁸	1970	1970	1970	1970	1970	1970	1970	1970
EXCELLENT ³⁰	1443	1443	1443	1443	1443	1443	1443	1443
RESET ³⁷	2117	2117	2117	2117	2148	2117	2117	2117
DAPT ³⁵	9961	9961	9961	9961	9961	9359	9961	9961
DES LATE ³³	5045	5045	5045	5045	5045	5045	5045	5045
ARCTIC-int ³⁴	1259	1259	1286	1259	1259	1259	1276	1259
TOTAL	32163	32135	32287	32207	32194	32135	31550	32135
In paper				31666				32136

Table 3

Effect estimates. Estimations for each meta-analysis and variable are shown. $p \geq 0.05$ (red color); $p < 0.05$ (green color). Up-arrow (risk factor); down-arrow (protective factor). The “=” sign means an effect estimator = 1.00. S-DAPT = short term DAPT. L-DAPT = long term DAPT. End points: MB = major bleeding, ST = stent thrombosis, MI = myocardial infarction, ACD = All cause death, CVD = cardiovascular death, SK: Stroke. Highlighted the 7 meta-analyses including the same 10 trials.

Meta-analysis	Patients N	ACS (%) media	Long (months)	Short (months)	Results	CVD	ACD	NCVD	MI	SK	ST	RR	MB
Elmariah et al ¹¹	69644	35,1	≥ 6	<6	≥ 6 vs <6	↑	↑	↑	-	-	-	-	-
Bulluck et al ¹²	16534	49.3	3-6-12	12-24->24	3 vs 12		↓	-	↑	=	=	↑	↓
					6 vs 12		↓	-	↑	↑	↑	↑	↓
					6 vs 24		=	-	↑	↓	↑	-	↓
					12 vs >24		↓	-	↑	↓	↑	↓	↓
Giustino et al ¹³	32135	41,9	12	3-6	3-6 vs 12	↓	↓	-	↑	↓	-	↓	
Navarese et al ¹⁴	32287	55	<12	<12	<12 vs 12	↓	↓	-	↑	↓	=	↑	↓
					>12 vs 12	↑	↑	-	↓	↓	↓	↑	↑
Liou et al ¹⁵	15870	50,7	12-24	<12	<12 vs 12-24	↓	↓	-	↑	-	↑	-	↓
Palmerini et al ¹⁶	31666	44,6	≥ 12	6-<12	3-12 vs ≥ 12	↓	↓	↓	↑	↑	↑	-	↓
Cassese et al ¹⁷	32194	42,6	12-24	6-12	12-24 vs 6-12	↑	↑	-	↓	↓	↓	-	↑
Spencer et al ¹⁸	29531	42,5	12-24/12-42	3-6 / 6-18	3-6 vs 12-24 6-18 vs 12-42	↑	↑	-	↓	↓		↑	↑
Verdoia et al ¹⁹	32372	48	>12-18-36	3-6-12	3-6-12 vs >12-18-36	↓	↓	-	↑	-	↑	-	↓
Yang et al ²⁰	9979	49	≥ 12	≤ 6	≤ 6 vs ≥ 12	↑	↑	-	↓	↓	↑	-	↓
Costa et al ²¹	37427	-	12	<12	12 vs >12 ticagrelor	↓	↓	↑	-	-	-	-	-
					12 vs >12 thienopyridine	↑	↑	↑	-	-	-	-	-
					12 vs >12 total	↓	↑	↑	-	-	-	-	-
Palla et al ²²	28343	-	> 12	≤ 6	≤ 6 vs 12	↓	↓	-	↑	↑	↑	-	↓
					>12 vs 12	↑	↑	-	↓	↓	↓	-	↑
Zhang et al ²³	32135	29,3	≥ 12 and 18-30	3-6	3-6 vs ≥ 12 and 18-30	↑	↑	-	↓	↑	↓	-	↑
Tsoi et al ²⁴	31550	-	≥ 12	<12	12 vs >12	↑	↑	-	↓	↓	↓	-	↑
					<12 vs >12 12 vs <12	↓	↑	-	↓	↑	↓	-	↑
Ziada et al ²⁵	15874	53	12-24	3-6	3-6 vs 12-24	↓	↓	-	↑	↓	↑	-	↓
Udell et al ²⁶	33435	95	>12	aspirin alone	<12 vs aspirin	↓	↓	↑	↓	↓	↓	-	↑
Abo-Salem et al ²⁷	32136	41,1	3-12/6-12/6-24	3-12/6-12/6-24	3 vs 12 / 6 vs 12-24 / 12 vs 17-36	↓	↓	-	↑	=	↑	-	↓

Table 4

Mortality outcomes. $p \geq 0.05$ (red color); $p < 0.05$ (green color). Up arrow (risk factor); Down-arrow (protective factor). NA: not assessed. ACD = All cause death. CVD = cardiovascular death. NCVD = no cardiovascular death. Highlighted the 7 meta-analyses including the same 10 trials.

Meta-analysis	Comparison	CVD	ACD	NCVD	Conclusions
Elmariah et al ¹¹	<6m vs ≥6 m	NS	NS	NS	No more CVD, ACD, NCVD with extended vs aspirin alone or short DAPT.
Bulluck et al ¹²	3m vs 12m 6m vs 12 m 6m vs 24m 12m vs >24m	N/A N/A N/A N/A	NS NS NS NS	N/A N/A N/A N/A	3-6 months of DAPT is safe with no increased risk of ACD.
Giustino et al ¹³	3-12m vs 12-48m	NS	NS	N/A	ACD was numerically higher with L-DAPT without reaching statistical significance.
Navarese et al ¹⁴	>12m vs 12m	NS	↑	N/A	The increase in ACD but not CVD with extended DAPT requires further investigation.
Liou et al ¹⁵	< 12 m vs 12-24 m	NS	NS	N/A	No significant differences were found in the risk of all-cause or cardiac mortality.
Palmerini et al ¹⁶	≤6 m vs 1 year /1 year vs>1 year/ 6 m vs>1 year	NS	↑	↑	DAPT beyond 1 year is associated with increased ACD because of an increased risk of NCVD not off set by a reduction in CVD.
Cassese et al ¹⁷	≥12m vs ≤12m	NS	↑	N/A	Prolonging the duration of DAPT does result in an increased risk of ACD.
Spencer et al ¹⁸	3-6m vs 12-24m and 6-18m vs 12-42m	NS	↑	N/A	No significant difference in rates of cardiovascular mortality between the longer- and shorter-duration groups.
Verdoia et al ¹⁹	≥12m vs ≤12m	NS	↓	N/A	A shorter DAPT is associated with reduction in ACD.
Yang et al ²⁰	≤ 6 m vs ≥ 12 m	NS	NS	N/A	Longer duration of therapy did not reduce the risk of mortality, including, all causes of death and cardiac death.
Costa et al ²¹	<12-12 ticagrelor	NS	NS	NS	Prolonged treatment with thienopyridines increased ACD. Ticagrelor provided a more favorable impact on ACD driven by a trend towards CVM reduction and a null-effect on NCVD.
	<12-12 thienop	NS	↑	↑	
	<12-12 total	NS	NS	NS	
Palla et al ²²	≤6 -12	NS	NS	N/A	Short term DAPT has similar incidence of ACD compared to standard duration DAPT. Long-term DAPT significantly increased ACD compared to standard duration DAPT.
	>12-12	NS	↑	N/A	
Zhang et al ²³	18-30 vs 12	N/A	↑	N/A	A more extended DAPT (18 to 30 months) increases risks of ACD than standard 12-month therapy.
Tsoi et al ²⁴	12->12 <12->12/ 12-<12	NS NS	↓ NS	N/A N/A	DAPT beyond 12 months no significant decrease in cardiac mortality, but there is an increase in major bleeds and all-cause mortality. DAPT for 12 months or for a shorter duration do not differ with respect to effectiveness.
Ziada et al ²⁵	3-6m vs 12-24m	NS	NS	N/A	Abbreviated-duration DAPT (≥6 months) was associated with no evidence of a significant increase in risk of ACD.
Udell et al ²⁶	>12 m vs aspirin	↓	NS	NS	Compared with aspirin alone, DAPT beyond 1 year significant reductions in CVD. Dual antiplatelet therapy beyond 1 year does not increase NCVD.
Abo-Salem et al ²⁷	3-12m / 6-12m / 6-24m	NS	↑	N/A	DAPT continued beyond 6 months increases ACD compared to shorter DAPT (aspirin alone). There was no difference in CVD.

itself, but rather to provide new data or answers regarding the underlying clinical question.

Despite treating the same topic and using similar titles, definitions and inclusion of studies, the meta-analyses reviewed here presented some variations. In some cases, the authors included trials with data

heterogeneity, making an appropriate interpretation of results difficult and depicting divergent results in many variables, even in hard end-point events, such as mortality, compared with other meta-analyses on the same topic. However, the problem here was not only the statistical heterogeneity assessed, which can be explored either with I2 or Q

Table 5

Studies and fidelity. Main features of published randomized studies investigating various durations of dual antiplatelet therapy following percutaneous coronary intervention (PCI). Adapted from Marco Roffi et al. [7] and Bittl et al. [8]. Fidelity assessment of study quality as determined by the ACC/AHA task force based (2016) on assessment of monitoring, protocol adherence, and data validity [8].

Study (year)	N	ACS %	DAPT duration	Timing of randomization	Stent type	Primary endpoint	Bleeding events	Premature Stop	Fidelity
PRODIGY (2012)²⁸	1970	75%	6 vs. 24	1 month after PCI	1:1:1:1 randomisation BMS (25%) vs. E-ZES (25%) vs. PES (25%) vs. EES (25%)	Death, MI, stroke: 10% in aspirin vs. 10.1% in DAPT group (HR 0.98, 95% CI 0.74–1.29, P = 0.91) (2 years after stenting)	BARC type 5, 3 or 2:3.5% in aspirin vs. 7.4% in DAPT (HR 0.46, 95% CI 0.31–0.69, P < 0.001)		High
RESET (2012)³⁷	2117	55%	3 vs. 12	PCI	ZES in the 3 months DAPT arm vs. SES in the 12 months DAPT arm	CV death, MI, ST, TVR, major or minor bleeds: 4.7% in aspirin vs. 4.7% in DAPT (difference 0.0%, 95% CI –2.5% to 2.5%, P = 0.84, Pnon-inferiority < 0.001) (1 year after stenting)	TIMI major: 0.2% in aspirin vs. 0.6% in DAPT, difference –0.4% (95% CI –0.9 to 0.2, P = 0.18)		Unclear
EXCELLENT (2012)³⁰	1443	52%	6 vs. 12	PCI	1:1 randomisation EES (75%) vs. SES (25%)	Target vessel failure 4.8% aspirin and 4.3% in DAPT group (HR 1.14, 95% CI 0.70–1.86, P = 0.60; absolute risk difference 0.5% points; upper limit of 1-sided 95% CI 2.4%; P < 0.001 for non-inferiority) (1 year after stenting)	TIMI major: 0.3% in aspirin vs. 0.6% in DAPT group (HR 0.50, 95% CI 0.09–2.73, P = 0.42)		Intermediate
OPTIMIZE (2013)²⁹	3119	32%	3 vs. 12	PCI	E-ZES (100%)	Death, MI, stroke, major bleeds: 6% in aspirin vs. 5.8% in DAPT (HR 1.03, 95% CI 0.77–1.38, Log-rank P = 0.84, Pnon-inferiority = 0.002) (1 year after stenting)	TIMI major: 0.6% in aspirin vs. 0.9% in DAPT (HR 0.71, 95% CI 0.32–1.60, P = 0.41)		High
SECURITY (2014)³¹	1399	38%	6 vs. 12	no reported	E-ZES (41%); EES (20%); others (33%)	Cardiac death, MI, stroke, definite or probable ST or BARC type 3 or 5 bleeds at 12 months: 4.5% vs. 3.7% in aspirin vs. DAPT (risk difference 0.8%, 95% CI –2.4% to 1.7%, P = 0.469, Pnon-inferiority < 0.05) (1 year after stenting)	BARC type 3 or 5: 0.6% in aspirin vs. 1.1% in the DAPT group (risk difference –0.5%, 95% CI –1.4% to 0.4%, P = 0.283)	Yes	Intermediate
ISAR-SAFE (2015)³⁶	4000	40%	6 vs. 12	6 months after PCI	PES (2%), SES (8%), EES (48%), ZES (15%), BES (8%), BMS (0.3%)	Death, MI, ST, stroke and TIMI major bleeds at 9 months after randomization: 1.5% in aspirin vs. 1.6% in DAPT (HR 0.91, 95% CI 0.55–1.50, P = 0.70, Pnon-inferiority < 0.001) (2 years after stenting)	TIMI major bleeds: 0.2% in aspirin vs. 0.3% in DAPT (HR 0.80, 95% CI 0.21–2.98, P = 0.74)	Yes	High
ITALIC/ITALIC + (2015)³²	1850	23%	6 vs. 24	PCI	EES (100%)	Death, MI, urgent TVR, stroke and major bleeds: 1.6% in aspirin vs. 1.5% in DAPT (risk difference 0.11, 95% CI –1.04 to 1.26, P = 0.85, Pnon-inferiority = 0.0002) (2 years after stenting)	Minor bleeds: 0.4% in DAPT vs. 0.5% in aspirin (HR 1.247, 95% CI 0.335–4.643, P = 0.74)	Yes	Intermediate
DES LATE (2014)³³	5045	61%	12 vs. 24	12 months after PCI	SES (44%); PES (20%); ZES (19%); EES (11%); others (6%)	CV death, MI or stroke 2.4% in the aspirin vs. 2.6% in DAPT (HR 0.94, 95% CI 0.66–1.35, P = 0.75) (2 years after stenting)	TIMI major bleeds: 1.1% in aspirin vs. 1.4% in DAPT group (HR 0.71, 95% CI 0.42–1.20, P = 0.20)		Intermediate
ARTIC-INTERRUPTION (2014)³⁴	1259	30%	12 vs. 24	12 months after PCI	First generation DES 4.3%	Death, MI, ST, stroke, or urgent revascularization: 4% in DAPT group compared with 4% with aspirin alone (HR 1.17, 95% CI 0.68–2.03, P = 0.58) (2 years after stenting)	STEEPLE major bleeds: 1% in DAPT versus < 0.5% in aspirin group (HR 0.15, 95% CI 0.02–1.20, P = 0.07)		Intermediate
DAPT (2014)³⁵	9961	43%	12 vs. 30	12 months after PCI	PES 26%, SES 11%, EES 47%, ZES 12%	Death, MI or stroke 4.3% in DAPT vs. 5.9% in aspirin (HR 0.71, 95% CI 0.59–0.85, P < 0.001) (33 months after stenting)	GUSTO moderate or severe bleeds 2.5% in DAPT vs. 1.6% in aspirin (HR 1.61, 95% CI 1.21–2.16, P = 0.001)		High

tests. There was also clinical and methodological heterogeneity that should be considered when deciding the model to be used for the analysis (random vs. fixed or not performing that meta-analysis at all).

These relevant issues are found even in manuscripts published in very high impact journals, in our view. Interestingly, sometimes the same journal published various meta-analyses about the same topic with different studies and different results [9,14].

After reviewing the selected meta-analyses, some of the aspects that impeded or created uncertainty in terms of the usefulness of the direct comparison and the evaluation of the manuscripts were depicted (unexplained variance in number of patients included, different key definitions, variable endpoints...).

In order to improve the quality of meta-analyses reporting, some international initiatives arose years ago (Quorum, Prisma among others) [44–46]. Statements are voluntary and usually provide a checklist including important items that should be included in the manuscript. Although sometimes the check list [45] item interpretation can be debatable (i.e. Funding: Frequently the authors only state their disclosures avoiding the explicit mention of the funding of the paper. In theory, if you have no disclosures, there is no funding to disclose but it should be explicitly reported anyway). Leaving these small issues aside, 3 over our 17 meta-analyses, Table 1, did not mention adherence to any type of meta-analysis quality/protocol guidance and clearly did not comply with the Prisma statement [44,45]. Only one of the papers reviewed here [25] provided a registration number (PROSPERO registration information, an international prospective register of systematic reviews, in a similar way to the widespread reported clinicaltrials.gov for other types of studies) of their meta-analysis protocol.

Recently, the ACC/AHA Task Force on Clinical Practice Guidelines convened a writing committee to evaluate the usefulness of long-term DAPT to prevent thrombotic complications in patients who underwent stent implantation and in post-MI patients. Each trial underwent evaluation for fidelity by assessment of monitoring, protocol adherence and data validity. The authors classified their fidelity as unclear, intermediate or high.

Only 4 of the 10 RCTs (mentioned in Table 2) were rated as high fidelity and 3 were stopped prematurely [7,8]. This point is depicted in Table 5, and could be relevant regarding the validity or real “level of evidence” provided by a meta-analysis including “lower quality” trials.

We highlighted some key points that are noteworthy in terms of making it difficult to conduct valid comparison and the evaluation of the studies. First, some meta-analyses included articles published only as abstracts, possibly without all data (e.g., two of them [10,17] included the study by Hu and Wang [36]). Also, three of the studies included in the analyses were prematurely ended (ITALIC [30], ISAR-SAFE [34] and SECURITY [29]), which is an issue to consider with caution. However, although when studies are prematurely ended it does not mean that the study is a bad quality study, nonetheless it is very important to consider why it was ended. Hence, the meta-analysis process probably cannot differentiate/ponder itself between high and low quality RCTs (Fig. 3).

For these reasons, not all the studies included in Table 5 have a high-fidelity assessment. Some of them were deemed to have an intermediate level of fidelity and the RESET [35] study had an unclear fidelity evaluation. The evaluation for fidelity is done by assessment of monitoring, protocol adherence and data validity.

Taking all the previous reasons into consideration, it would be warranted that the authors of a meta-analysis performed a thorough quality assessment of the studies they include in their meta-analyses. Over the 17 meta-analyses assessed in this study only 12 of them reported some type of explicit standardized quality assessment in this regard, Table 1. Interestingly, Moher et al. found that trial quality was analyzed in only 48% of a sample of 240 meta-analyses they reviewed in 1999 [47].

Furthermore, it was noticed that some meta-analyses [20] published tables including studies with patients that were not included in the analysis. This does not allow one to easily understand the real pool of patients included in the analysis. Hence, there are frequent

Meta-analysis Minimum Requirements
- There exists a standardized approach to the reporting of meta-analyses. The PRISMA Statement is a good start point. Cochrane recommendations too.
-Well-defined objectives, including precise definitions of clinical variables and outcomes. Is our meta-analysis going to answer a relevant question?
-An appropriate and well-documented study identification and selection strategy literature searches are a critical component of the methodology for meta-analysis. The method of conducting the search should be carefully described.
-Searching abstracts over the preceding 5 years should be conducted, as well as providing surveillance of the ClinicalTrials.gov or similar websites for any trials that may not have yet been published but are in existence. Cochrane website is an asset. Sensitivity analysis should be conducted on all meta-analyses. Values at the extreme for risk estimates may contribute to uncertainty, and one might want to include or exclude trials at the fringes of the inclusion and exclusion criteria and range of effect size.
-Are there similar/recent meta-analysis in the literature? Is ours needed?
-Justification of data analytic techniques.
-Description and evaluation of heterogeneity with meta-regression analysis.
-Evaluation of bias in the identification and selection of studies.
-A meta-analysis should be as carefully planned as any other research project, with a detailed written protocol being prepared in advance. i.e. PROSPERO.

Fig. 2. Requirements. Minimum requirements when thinking of performing a meta-analysis.

inconsistencies/variations in the number of patients originally included in the study and the number of patients incorporated in the meta-analysis for that study. One of the most common errors is the inaccurate transcription of data. The authors sometimes include intention to treat (ITT) patients or modified ITT patients and for this reason the numbers differ.

Key Points Results
Majority of MA are identical to previous ones differing intentionally in some aspects of the design
Few of the authors mention the prior meta-analyses published on the same topic in their references
MA's include articles published only as abstract, without sufficient data
Some studies included in the analyses are prematurely ended
Not all the studies included in the MA have a high fidelity assessment
Publication of tables including studies which patients are not then included in the analysis
Incongruences in the number of patients originally included in the study and the number of patients incorporated in the MA
Lack of coincidence in the p-values reported in the forest plots and the text
Odd Ratio values are not always reported in the same way in the text and in the forest plot in the same MA
Each MA showed their results in different way (OR, HR or RR)
Each MA applied different statistical methods.
Lack of homogeneity in the definition of “short” and “long” treatment duration
Bibliography is not always correctly numbered
Often found mistakes in the text

Fig. 3. Key points. Key points with some of the meta-analysis (MA) limitations or issues found after reviewing MA on the DAPT duration topic.

For example, focusing on one “good” RCT, ISAR SAFE [34] (high fidelity, Table 5). Regarding this RCT, one meta-analysis [12] used 4005 patients from the trial. The other similar 6 meta-analyses, Table 2, including the very same trials considered only 4000. ISAR SAFE trial was stopped prematurely after enrolment of 4005 of 6000 planned patients. However, only 4000 patients were included in the final analysis. The five patients excluded (1 assigned to 6 months of clopidogrel and 4 assigned to 12 months of clopidogrel) withdrew their consent immediately or were excluded by the treating physician before taking any study medication and were not included in the final analysis [34]. The authors of the meta-analysis did not discuss this point in their manuscript [12]. Most likely, this should have been properly defined in the Methods section and statistically addressed for the avoidance of doubt.

For what concerns the statistical results, we identified a lack of concordance in the *p*-values reported in the forest plots and the text. The odds ratio values are not always reported uniformly in the text and/or in the forest plot in the meta-analysis. In the same publication, the odds ratios (or other parameters as measures of treatment effect) are expressed both comparing shorter versus longer or longer versus shorter.

Some other practical relevant limitations that were found are summarized in Fig. 2.

At this point, the solution is complex. Probably, cooperation that mandate patient-level data sharing would produce more reliable results with less duplication of groups relying on study-level data; following the principles set forth regarding the reporting/quality of included trials; standardized reporting of trial fidelity; risk of bias; etc. In addition meta-analyses should be very clear regarding their population of interest because this point could modify the response to the clinical question. Also, perhaps journal editors should be more demanding and critical of meta-analyses as these papers can only be published if editors are willing to accept.

With all of this in mind, we still consider that the key role of RCTs remains undisputed in modern clinical research. A RCT, if the design and size are appropriate, could probably provide more definitive data than any other type of clinical research information [1,5]. However, a well-carried out meta-analysis can provide complementary (and cheaper) information that is valuable to a researcher, clinician, or policy-maker.

While RCTs remain the highest level of clinical evidence, meta-analysis can provide more generalized information that is often lacking in such protocols. However, their reliability is highly variable, depending on several circumstances that need to be thoroughly appraised when reading each one. This concept is of paramount importance when available trials are sub-optimal, a frequent issue (Table 5) making the performance of meta-analysis even more questionable [6,47].

5. Conclusion

The current massive production of meta-analysis needs to be carefully reconsidered. In the DAPT duration setting, several meta-analyses have been recently published based on the same data, presenting several issues making it difficult to determine clear recommendations on certain points.

Thus, in order to properly consider a meta-analysis result for clinical practice guideline recommendations or regulatory purposes, a careful review or method audit should be performed first and perhaps, re-evaluate its level of evidence.

List of abbreviations

CABG	coronary artery bypass grafting
DAPT	dual antiplatelet therapy
ITT	intention to treat
RCTs	randomized controlled trials
TAVI	transcatheter aortic valve implantation

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Appendix A. Supplementary data

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