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.

Running Head: A critical review of meta-analyses of DAPT trials.

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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.

KEY WORDS: meta-analysis; meta-analyses; dual antiplatelet therapy; statistics; percutaneous coronary intervention; methods

INTRODUCTION

The need to provide convincing evidence to support clinical strategies and the recommendations made in the clinical guidelines has fed 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[2,3,7-9]. The problem is that the precise duration is variable and the clinical indications are sometimes subjective (3 months vs. more than 1 year[9]). 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.

METHODS

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.

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.

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).

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.

RESULTS

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. 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 (Figure 1).

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 figure 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, 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.

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.

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.

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.

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.

Quality of the Meta-analysis reporting and study bias.

Three of the meta-analyses did not adhere to any quality guideline (Quorom, Prisma, etc..), table 1. One reported it fulfilled Quorom criteria and 13 claimed adherence to Prisma. One meta-analisys[11] 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 (ie. 2 of them were published as letter to the editor[15,,21], 3 with non-structured abstracts[19,22,24] or several lacking of explicit funding reporting[15,17,22,24,27], 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 randomised trials being the most frequently used tool in 8 cases, Table 1.

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[3,5,9]. 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 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 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[11,16].

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 (Quorom, Prisma among others) 46[-48]. Statements are voluntary and usually provide a checklist including important items that should be included in the manuscript. Although sometimes the check list[47] item interpretation can be debatable (ie. 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 metanalysis quality/protocol guidance and clearly did not comply with the Prisma statement[46,47]. Only one of the papers reviewed here (Udell et al[27)] 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 metanalysis 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[9,10]. 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[12, 19] included the study by Hu and Wang[38], 2012). Also, three of the studies included in the analyses were prematurely ended (ITALIC[32], ISAR-SAFE[36] and SECURITY[31]), 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.

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[37] 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[50].

Furthermore, it was noticed that some meta-analyses[22] 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 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.

For example, focusing on one "good" RCT, ISAR SAFE[36] (high fidelity, table 5). Regarding this RCT, one meta-analysis[14] 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[36]. The authors of the meta-analysis did not discuss this point in their manuscript[14]. 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 figure 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[6,49].

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.

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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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FIGURE LEGENDS

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

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

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

TABLES LEGENDS

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[46] 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)[47]. Of note, not all the papers stating Prisma compliance would have all the Prisma checklist[47] completed in their main manuscript (editorial formats with space limitations such letters[15,21], unstructured abstracts[19,22,24] or lack of explicit funding reporting[15,17,22,24,27] among others). Not all the papers adhering the PRISMA Statement reach 27/27 item in the checklist. **Cites Quorom, a former guidance statement (1999) on meta-analyses reporting[48]. ***Ad hoc[49]: The authors use their own criteria to evaluate the risk of bias/quality of the trials included in their analyses.

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.

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.

Table 4. Mortality outcomes. p≥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.

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 [9] and Bittl et al [10]. Fidelity assessment of study quality as determined by the ACC/AHA task force based (2016) on assessment of monitoring, protocol adherence, and data validity[10].

TABLES

Table 1.

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	EHJ	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]	Zlada 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	31666	32194	29631	32372	9979	37427	28343	32135	31550	15874	33435	32136
PRODIGY[28]	■	■	■	■	■	■	■	■	■	■			■	■	■	■	■
OPTIMIZE[29]	■	■	■	■	■	■	■	■	■	■		■	■	■	■		■
EXCELLENT[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.

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	9961	9359	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.

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 vs12		↓	-	↑	↑	↑	↑	↓
					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	↓	↓	-	↑	=	↑	-	↓

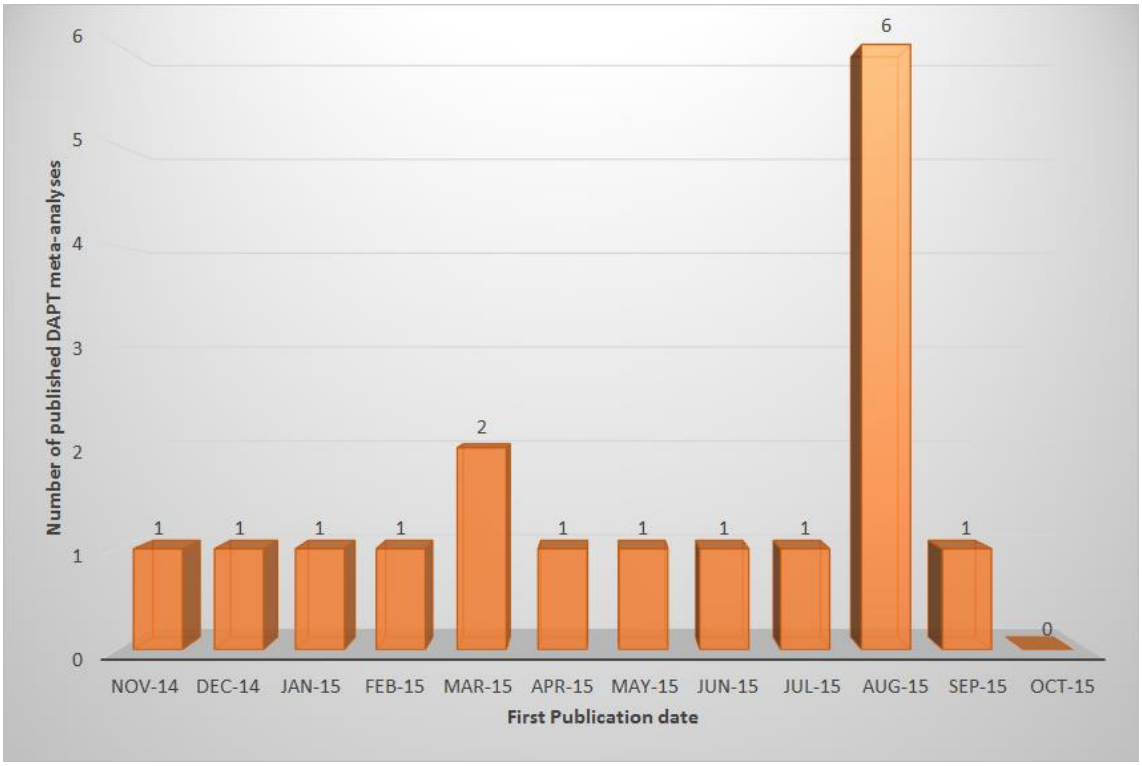
Table 4..

Meta-analysis	Comparation	CVD	ACD	NCVD	Conclusions
Elmariah et al[11]	<6m vs ≥6 m	NS	NS	NS	No more CVD, ACD, NCVD with extended vs apirin 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 <12-12 thienop <12-12 total	NS NS NS	NS ↑ 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.
Palla et al[22]	≤6 -12 >12-12	NS NS	NS ↑	N/A 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.
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 efficacy or
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.

Table 5.

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**

Online Figure 1. Publications. Number of published meta-analyses (about the same topic) per month.



Online Table 1. **Citations.** Meta-analyses that mention prior works (Meta-analyses) published on the very same topic they assess. Sometimes, these did not reference previous manuscripts including the same studies.

Meta-analysis	Number of citations	First publication
Elmariah et al[11]		**16/11/2014**
Bulluck et al[12]	**0**	**13/12/2014**
Giustino et al[13]	**1**	**20/01/2015**
Navarese et al[14]	**1**	**23/02/2015**
Liou et al[15]	**0**	**05/03/2015**
Palmerini et al[16]	**1**	**14/03/2015**
Cassese et al[17]	**2**	**23/04/2015**
Spencer et al[18]	**1**	**26/05/2015**
Verdoia et al[19]	**1**	**11/06/2015**
Yang et al[20]	**0**	**22/07/2015**
Costa et al[21]	**1**	**06/08/2015**
Palla et al[22]	**1**	**11/08/2015**
Zhang et al[23]	**1**	**12/08/2015**
Tsoi et al[24]	**3**	**17/08/2015**
Ziada et al[25]	**1**	**26/08/2015**
Udell et al[26]	**4**	**31/08/2015**
Abo-Salem et al[27]	**0**	**11/09/2015**

Online Table 2. Periods of time. Definitions of short and long term periods.

Meta-analysis	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]
Short term defined as	3m - 12m	<12m	<12m	6m - 12m	3m- 6m	>12m	3 - 12m / 6 - 12m / 6 - 24m
Long term definded as	12m - 48m	>12m	≥12m	12m - 24m	18m-30m	<12m	3 - 12m / 6 - 12m / 6 - 24m
Standard term defined as		12m			12m		12m
Comparison of durations	3 - 12m vs 12 - 48m	<12m vs 12m >12m vs 12m	≤6m vs 1 year 1 year vs >1 year 6 m vs >1 year	≥12m vs ≤12m	≥12m vs 3 - 6m 18 - 30m vs 12m	>12m vs 12m ≥12m vs <12m	3 - 12m / 6 - 12m / 6 - 24m