EuroIntervention 2014;9:1013-1020

Review and recommendations on the current practice of meta-analyses: a guide to appraise the evidence

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The accompanying supplementary data are published online at: http://www.pcronline.com/eurointervention/68th_issue/172

Systematic reviews and meta-analyses identify, appraise and synthesise all evidence on a specific research question. They are considered the highest level of evidence, help physicians stay up to date and enable them to make informed clinical decisions[1]. It is therefore not surprising that this study design has become increasingly popular[2,3].

Inevitably, the phenomenon of duplicate meta-analyses is also increasingly common. A recent study showed that more than half of meta-analyses have at least one overlapping meta-analysis, and some topics had up to 13 overlapping meta-analyses[2]. While some degree of duplication is warranted in research, large numbers of overlapping meta-analyses seem unnecessary and could reflect wasted efforts and inefficiency in the process of summarising evidence[2]. In addition, the interpretation of evidence becomes confusing if the conclusions of duplicate meta-analyses are discordant.

In this paper, we review the current practice of meta-analyses in cardiovascular medicine, the implications of overlapping meta-analyses, and provide recommendations on the interpretation and prioritisation of (duplicate) meta-analyses.

The increasing popularity of meta-analyses

The increasing popularity of meta-analyses is illustrated in **Figure 1**. A PubMed search showed that the number of meta-analyses in the cardiovascular field has increased almost 1800% between 1993 and 2012, whereas the number of randomised controlled trials (RCTs) increased by only 140% in the same period. In 1993, on average 28 RCTs were published for every meta-analysis, whereas this RCT:meta-analysis ratio was 2.7:1 in 2012. This trend is an indication of the relative growth of meta-analyses as compared with other published research and was seen both in the cardiovascular discipline **(Figure 1A)** as well as in other medical disciplines **(Figure 1B)**. Between 1993 and 2013, on average 18% of all meta-analyses concerned a cardiovascular topic. This proportion has remained stable over time.

This increasing popularity has led to duplicate meta-analyses on the same topic[4]. A recent study investigated overlapping meta-analyses on the same topic by assessing a randomly selected 5% of all published meta-analyses in 2010. The authors found that 67% of all meta-analyses had at least one overlapping meta-analysis that did not represent an update, and 5% of the research questions were investigated in at least eight overlapping meta-analyses[2]. Replication of research generally leads to more knowledge and confidence in the conclusions, but could also represent wasted time and effort. Some authors suggest that four or more meta-analyses on the same topic with similar eligibility criteria and outcomes is too many, but there is no specific number regarding the correct amount of duplication[4].

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DOI: 10.4244/EIJV9I9A172

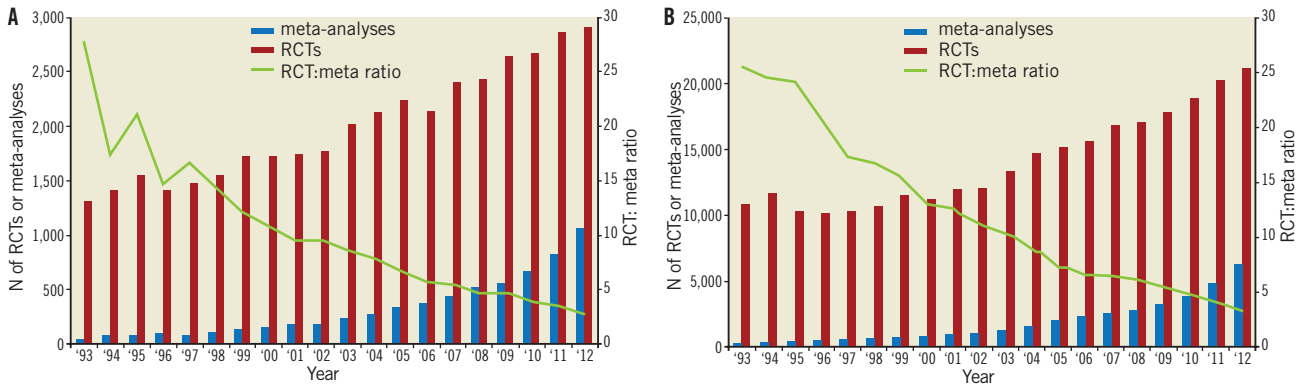

Figure 1. *Number of annually published meta-analyses and RCTs in (A) the cardiovascular field and (B) all disciplines. The red and blue bars represent the annually published RCTs and meta-analyses, respectively. The green line represents the number of published meta-analyses compared with the number of published RCTs in each year. It is an indication of the relative growth of meta-analyses as compared with the overall growth of published research in the cardiovascular field. Data are based on the following PubMed searches: A) (randomi* OR meta-analysis [ptyp]); B) (randomi* OR meta-analysis [ptyp]) ("Cardiovascular Diseases"[Mesh]). N: number; RCT: randomised controlled trial*

Examples of overlapping meta-analyses

Two case examples of overlapping meta-analyses in the cardiovascular field are illustrated in **Table 1**, **Online Table 1** and **Table 2**, **Online Table 2**, respectively. For each meta-analysis, we extracted information on the year of publication, search date, treatment effect for outcomes of interest, number of studies screened and selected, and patient population. We also noted first author, journal and year of publication of the studies included and combined in each meta-analysis.

Through a PubMed search, seven overlapping meta-analyses of intracoronary versus intravenous administration of abciximab in patients with acute coronary syndromes were identified[5-11]. An additional meta-analysis with patient-level data on the same topic is published in this issue of the Journal[12]. The meta-analyses were published between 2010 and 2013 (88% in 2012-2013), and the number of primary studies included ranged between four and ten **(Table 2)**. Seven meta-analyses included only RCTs, and one meta-analysis comprised both RCTs and observational studies (OSs). The search dates ranged from November 2009 to May 2012, which was reflected in the number of screened studies (from 37 to 6,562). The treatment effect for mortality was reported in all meta-analyses but was of inconsistent statistical significance: four (50%) meta-analyses found a statistically

Table 1. Overlapping meta-analyses on intracoronary versus intravenous administration of abciximab.

	Hansen et al[5]	Navarese et al[7]	Shimada et al[8]	De Luca et al[6]	De Rosa et al[9]	Kubica et al[10]	Wang et al[11]	Piccolo et al[12]
Publication date	2010	2012	2012	2012	2012	2012	2013	2013
Search date	November 2009	March 2011	August 2011	December 2011	March 2012	April 2012	May 2012	NA
Effect (95% CI) for MACE	0.62 (0.38-1.03)	NA	0.59 (0.27-1.28)	NA	0.47 (0.31-0.71)	NA	0.55 (0.40-0.76)	NA
Effect (95% CI) for mortality	0.57 (0.35-0.94)	0.43 (0.20-0.94)	0.44 (0.20-0.95)	0.85 (0.59-1.23)	0.42 (0.20-0.86)	0.67 (0.34–1.34)	0.69 (0.45-1.07)	0.77 (0.51-1.17)
Effect (95% CI) for myocardial infarction	NA	0.54 (0.23-1.28)	NA	0.79 (0.46-1.33)	NA	0.61 (0.40-0.92)	0.59 (0.37-0.93)	NA
Effect (95% CI) for repeat revascularisation	NA	0.53 (0.29-0.99)	NA	NA	NA	0.66 (0.40-1.09)	0.64 (0.32-1.29)	NA
Effect (95% CI) for major bleeding	NA	0.91 (0.46-1.79)	NA	1.19 (0.76-1.87)	NA	1.18 (0.76-1.83)	1.00 (0.57-1.74)	NA
Screened studies	979	2,351	37	1,865	48	6,562	660	NA
Pooled patients	2,301	1,246	1,148	3,259	4,226	3,331	3,916	3,158
Studies included	5 RCTs, 3 OSs	6 RCTs	4 RCTs	8 RCTs	10 RCTs	7 RCTs	9 RCTs	5 RCTs
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study- and patient-level

For the selection of overlapping meta-analyses of intracoronary vs. intravenous administration of abciximab in patients with acute coronary syndromes we searched PubMed for meta-analyses of randomised controlled trials and/or observational studies published any time using the search terms abciximab [Title] AND meta-analysis [Title/abstract] AND intracoronary [Title/abstract] without language restrictions. Effect estimates are reported for intracoronary vs. intravenous administration. An extension of this table, including the primary studies in each meta-analysis, is available in the online supplement (Online Table 1). CABG: coronary artery bypass grafting; CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; NA: not available; OSs: observational studies; PCI: percutaneous coronary intervention; RCTs: randomised controlled trials; STEMI: ST-segment elevation myocardial infarction

Table 2. Overlapping meta-analyses on PCI versus CABG in patients with left main coronary artery disease.

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Publication date	2008	2009	2010	2011	2011	2012	2012	2012	2013	2013	2013	2013
Search date	September 2006	December 2008	June 2009	April 2011	NA	May 2011	July 2011	October 2011	January 2011	April 2011	2011	NA
Effect (95% CI) for MACCE	0.46 (0.24-0.90)	1.16 (0.68–1.96)	NA	1.28 (0.95-1.72)	1.24 (0.93-1.67)	0.55 (0.43-0.70)*	NA	NA	1.20 (0.92-1.56)	1.26 (1.02-1.57)	1.61 (NA), p<0.001	NA
Effect (95% CI) for mortality	NA	1.11 (0.66–1.85)	1.12 (0.80-1.56)*	0.74 (0.43-1.29)	0.72 (0.42-1.24)	0.92 (0.60-1.40)*	0.68 (0.45-1.02)	0.97 (0.81-1.15)	0.81 (0.62-1.06)	0.74 (0.46-1.19)	0.69 (NA), p:0.05	1.01 (0.68-1.45)
Effect (95% CI) for MI	NA	NA	0.70 (0.45-1.09)*	0.98 (0.54-1.78)	0.97 (0.54-1.74)	0.67 (0.43-1.05)*	1.07 (0.65-1.76)	NA	1.32 (0.91-1.91)	1.19 (0.69-2.06)	NA	NA
Effect (95% CI) for stroke	NA	NA	NA	0.15 (0.03-0.67)	0.14 (0.04-0.55)	NA	0.23 (0.09-0.58)	0.29 (0.16-0.51)	0.31 (0.20-0.49)	0.26 (0.10-0.69)	NA	NA
Effect (95% CI) for repeat revascularisation	NA	4.01 (2.01–7.98)	0.44 (0.32-0.59)*	2.25 (1.54-3.29)	2.17 (1.48-3.17)	0.40 (0.30-0.55)*	3.52 (2.72-4.56)	4.44 (3.42-5.78)	3.73 (2.71-5.14)	1.94 (1.43-2.61)	3.60 (NA), p<0.001	NA
Screened studies	823	7,294	NA	254	189	106	472	76	355	1,236	9,120	12
Pooled patients	670	3,773	2,905	1,611	1,611	2,601	5,079	6,992	11,148	1,611	5,674	4,574
Studies included	3 OSs	2 RCTs, 8 OSs	2 RCTs, 8 OSs	4 RCTs	4 RCTs	3 RCTs	3 RCTs, 9 OSs	11 RCTs, 2 OSs	4 RCTs, 23 OSs	4 RCTs	3 RCTs, 13 OSs	4 RCTs, 8 OSs
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Bayesian
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level

For the selection of overlapping meta-analyses of PCI vs. CABG in patients with left main disease we searched PubMed for meta-analyses of randomised controlled trials and/or observational studies published any time using the search terms left main [Title] AND meta-analysis [Title/abstract] AND PCI [Title/abstract] without language restrictions. An extension of this table, including the primary studies in each meta-analysis, is available in Online Table 2. *Treatment effects are reported as PCI vs. CABG, except in the meta-analyses by Lee et al and Kajimoto et al, in which treatment effects were reported as CABG vs. PCI. CABG: coronary artery bypass grafting; CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction; NA: not available; OSs: observational studies; p: p-value; PCI: percutaneous coronary intervention; RCTs: randomised controlled trials; STEMI: ST-segment elevation myocardial infarction

significant benefit of intracoronary abciximab administration, whereas four studies (50%) did not. Similarly, the risk of major adverse cardiac events (MACE) was significantly reduced in only two of four (50%) meta-analyses reporting on this outcome, the risk of myocardial infarction in two of four (50%), and the risk of repeat revascularisation in one of three (33%). Of four meta-analyses that sought to assess the risk of bleeding, none (0%) found a significant difference between intracoronary and intravenous administration.

Another PubMed search identified twelve meta-analyses of PCI vs. CABG in patients with left main coronary artery disease. These meta-analyses were published between 2008 and 2013 (58% in 2012-2013) and the number of primary studies included ranged between 3 and 27 **(Table 3)**[13-24]. Four meta-analyses included only RCTs, one meta-analysis comprised only OSs and seven meta-analyses included both RCTs and OSs. The authors' search dates varied from September 2006 to April 2011, and the number of screened studies ranged between 12 and 9,120. Mortality was reported in eleven meta-analyses, all of which found no statistically significant benefits of either treatment. MACCE was reported in eight meta-analyses, of which three (38%), one (13%) and four (50%) found a higher, lower or similar risk for this composite endpoint after PCI versus CABG. All meta-analyses that reported an effect size for myocardial infarction (n=7) found no statistically significant difference between treatments. Also, all ten meta-analyses that investigated repeat revascularisation found

Table 3. Potential sources of discordance in overlapping meta-analyses.

Design	Analysis	Interpretation
Search (date, key words)	Summary measure (crude OR, HR, RR)	Interpretation of all results, including heterogeneity, publication bias and quality assessment
Information sources used (databases, abstracts from meetings)	Fixed/random effects analysis	Combining all results and linking this to the overall conclusion of the meta-analysis
Eligibility criteria	Heterogeneity assessment	
Data extraction (solitary/duplicate, retrieving unpublished data)	Publication bias assessment	
Study- or patient-level data	Quality assessment of primary studies	
Definitions, length of follow-up	Extensiveness of extra analyses (sensitivity analyses, meta-regression)	

OR: odds ratio; HR: hazard ratio; RR: relative risk

significantly higher rates after PCI than after CABG. On the other hand, stroke was significantly higher with CABG in all six meta-analyses reporting this outcome.

Taken together, these findings indicate that meta-analyses on the optimal administration route for abciximab and the optimal treatment strategy for left main revascularisation published in the last five years differed not only in the magnitude of the treatment effect for some outcomes, but also occasionally in the direction of the effect (e.g., MACCE in the left main meta-analyses). In the illustrative examples above, these differences might be attributed to varying eligibility criteria regarding inclusion of OSs, the target population analysed (e.g., acute coronary syndromes or ST-segment elevation myocardial infarction in the abciximab route meta-analyses; patients with diabetes mellitus or acute coronary syndromes in the left main revascularisation meta-analyses), and the non-consideration of studies published after the search date of each meta-analysis. In contrast, while more recent meta-analyses might have included newly published studies, their incremental value remains uncertain (e.g., similar results were noted in all meta-analyses of left main revascularisation with regard to all the components of MACCE). Interestingly, three meta-analyses of left main revascularisation included exactly the same four RCTs but derived slightly different summary effects, underscoring the potential for differences introduced at the stage of data synthesis[15,16,22].

What to do when meta-analyses overlap

Overlapping meta-analyses can result in uncertainty when they come to discordant conclusions. Discordance can occur at the level of results or interpretation, and the underlying sources are summarised in **Table 3**[25,26]. Effect sizes can differ because some meta-analyses use slightly different eligibility criteria for study selection, such as the eligibility of abstracts or language restrictions. Perhaps more subtle are discordances due to handling and interpretation of heterogeneity and publication bias.

Heterogeneity is an apparent difference between the results of the primary studies[27,28], and may be present when study populations, interventions, outcomes, or methodologies differ across the studies. Heterogeneity is generally quantified by the I^2 or Cochran's Q-statistic[29]. To evaluate heterogeneity, authors should not only examine the statistic, but also scrutinise potential sources of heterogeneity by comparing primary study characteristics, design, follow-up duration, patient characteristics and outcome definitions[30]. Meta-regression is a typical approach to relate sources of variation in heterogeneous treatment effects to specific study characteristics. However, study-level meta-analyses have some limitations in explaining heterogeneity, and using individual patient data in patient-level meta-analyses may lead to a more unbiased assessment[31]. In addition, patient-level meta-analyses allow better alignment of definitions and follow-up. This is illustrated by the above-mentioned meta-analysis by Piccolo et al, which pooled individual patient data from trials of intracoronary versus intravenous administration of abciximab, enabling investigation of detailed endpoints such as post-procedural Thrombolysis In Myocardial Infarction (TIMI) 3 flow, myocardial blush grade and complete ST-segment resolution[12].

Publication bias is the tendency by investigators, reviewers and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings[32]. Tests that assess publication bias include funnel plots, Harbord-Egger tests, and trim and fill analyses[33-35]. If these tests identify missing studies with a smaller effect or an effect in the opposite direction, investigators should be very careful with their conclusions regarding the presence and/or direction of the association under study.

Discordant meta-analyses form challenges for authors, clinicians and editorial boards. Which meta-analysis is most applicable to the clinical question, and which one is methodologically most solid? A flow chart to help with the interpretation of discordant meta-analyses is provided in **Figure 2**[26]. When meta-analyses truly study the same question, the flow chart guides the reader to methodological appraisal of the discordant meta-analyses. Quality scoring lists might be useful as well, such as the Oxman Guyatt list and the AMSTAR checklist[36,37]. These checklists can be used to map the methodological quality of meta-analyses. AMSTAR includes questions on design (e.g., "was there duplicate study selection and data extraction?"; "was a comprehensive search performed?"), analysis (e.g., "was the scientific quality of the included studies documented?"; "were the methods used to combine the findings of the studies appropriate?"), and interpretation (e.g. "was the scientific quality of the included studies used appropriately in formulating conclusions?"). The use of scoring systems for assessing quality seems easy and attractive, and AMSTAR is a validated quality measurement tool. On the other hand, calculating these summary scores involves assigning weights to different items in the scale and thus prioritising studies based on arbitrary assumptions. Using full reporting of how meta-analyses were rated based on each criterion is preferable.

How to preserve the value of meta-analyses

A list of considerations for maintaining the value of meta-analyses and for improving the quality of research in this field is provided in **Table 4**. Adherence to accepted guidelines for reporting is essential to preserve the quality and value of meta-analyses. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, formerly QUORUM) statement consists of a 27-item

Table 4. Maintaining the value of meta-analyses.

Adhere to the PRISMA/MOOSE checklists
Perform high-quality analyses and interpret appropriately (see Figure 2, Table 3 and PRISMA/MOOSE)
Reflect on timing when updating a meta-analysis
Provide the rationale for performing a meta-analysis, referring to prior work
Register the protocol in the PROSPERO registry
Evaluate the whole body of evidence on a topic, not only small fragments

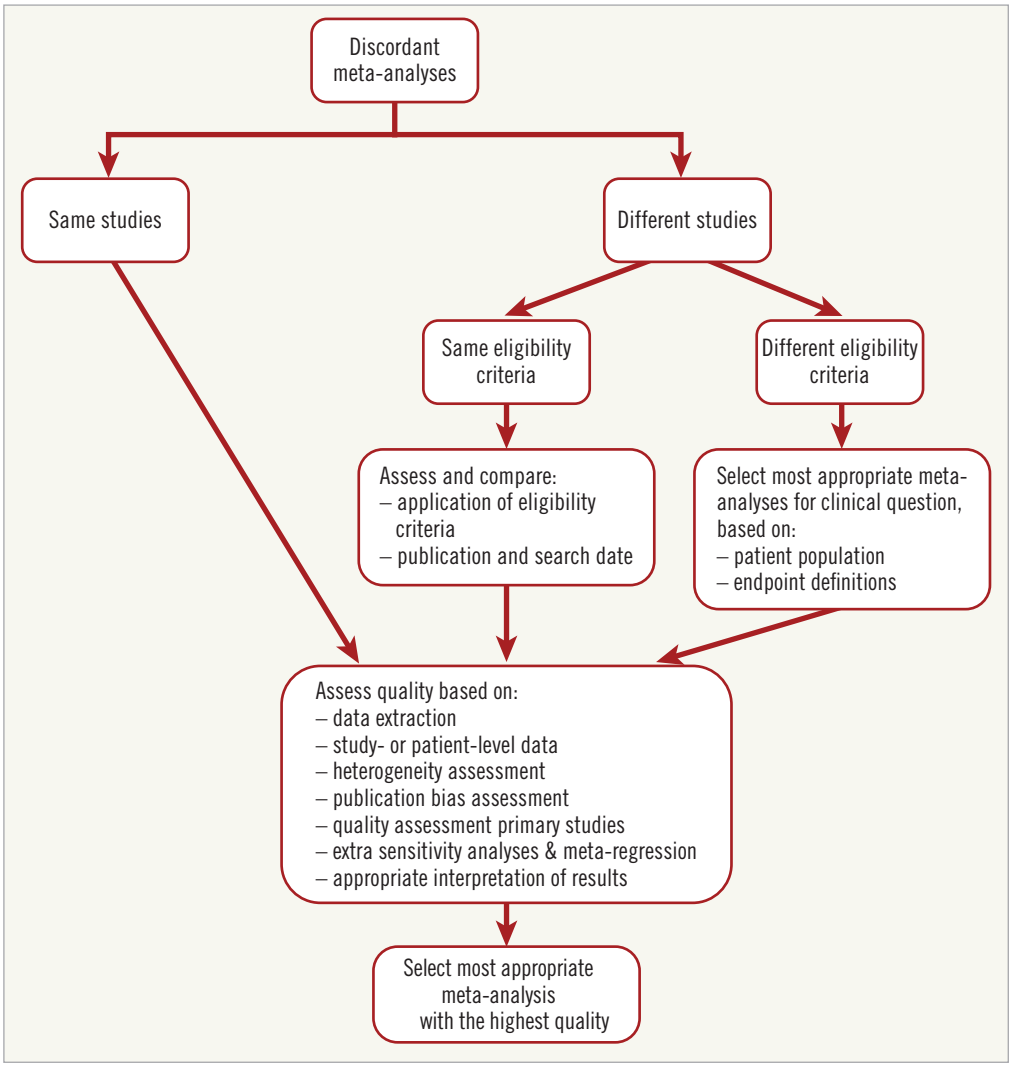

Figure 2. *Flow chart for the interpretation of discordant, overlapping meta-analyses. The flow chart helps the reader interpret overlapping, discordant meta-analyses, by guiding him/her to a methodological appraisal. Adapted from Jadad et al[26].*

checklist and a four-phase flow diagram aimed at improving the consistency and completeness of reporting of meta-analyses of RCTs[38]. An analogous document has been elaborated by the MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) group for meta-analyses of OSs[39].

Because the evidence on a topic is typically dynamic and evolves over time, incorporation of new studies into an existing meta-analysis may lead to different conclusions[40]. Additional incentives for updating a meta-analysis may include the potential availability of new tools or markers to characterise subgroups[41], the introduction of new outcome measures[42], or even advances in the methodology for conducting a systematic review/meta-analysis[24]. However, the merits of publishing a new meta-analysis on the same topic need to be evaluated, since redundant overlapping meta-analyses reflect waste of resources and potentially add confusion. Authors of possibly overlapping meta-analyses should report the rationale for performing the meta-analysis (e.g., outdated and/or low-quality previous meta-analyses). The PICO (Population, Intervention, Comparator, and Outcome) framework could be used to point out what aspect of the research question has changed. Optimal timing for a new meta-analysis depends on the speed of scientific progress in the specific field and the importance of the research question. Periodic literature surveillance, expert opinions and scanning of abstracts are helpful to identify new relevant evidence that may eventually be used for an updated meta-analysis. Once the need for updating a meta-analysis has been identified, the update should be performed properly and effectively. Technically, a previous search strategy can be useful, and specific statistical methods for updating a meta-analysis have been described, such as "cumulative meta-analysis" and "null meta-analyses ripe for updating" approaches[43,44]. Bayesian methodology for meta-analysis might provide a way to update and/or consolidate the evidence on a topic. In contrast to the frequentist approach, Bayesian statistics incorporate clinical judgement and pertinent information that would otherwise be excluded, and establish inferences based on a wide range of flexible methods based on the theory of conditional probability[24,45,46].

An important potential strategy to avoid multiplication of unnecessary meta-analyses is consultation of dedicated registries. For instance, the PROSPERO registry (http://www.crd.york.ac.uk/NIHR_PROSPERO) includes over 2,000 prospectively registered protocols of systematic reviews and meta-analyses in health and social care[47-49]. Registering meta-analyses into a central database, similar to registration of trials into www.clinicaltrials.gov, helps to avoid unplanned duplication, increases transparency in the review process, and enables assessment of the results of reported reviews versus what was initially planned by the authors in the protocol. While authors increase the reputation of their work, journal editors are provided with a safeguard against flawed methodologies.

Finally, meta-analyses should be comprehensive and not only evaluate small fragments of the evidence on a clinical question of interest[50]. To address this issue, umbrella reviews and network meta-analyses are gaining attention[24,51]. Umbrella reviews consider multiple treatment comparisons for the management of the same disease or condition, with each comparison considered separately and clustered meta-analyses performed as appropriate[52,53]. A treatment network typically uses nodes for each available treatment, and each link between the nodes reflects a comparison of treatments in at least one or more primary studies. Compared with classic meta-analyses, umbrella reviews and network meta-analyses provide the reader with a wider vision on many treatments for a given condition, although typical limitations of standard meta-analyses (e.g., inherent bias of studies included, heterogeneity and publication bias) continue to apply.

Conclusions

The explosive dissemination of meta-analyses entailed the publication of duplicate meta-analyses on the same topic. The scope of a meta-analysis is to provide the reader with the most up-to-date evidence on the effect of an intervention and increase the statistical power of treatment comparisons for a given condition beyond that of individual studies, with the ultimate goal of informing clinical practice and guiding healthcare decisions. To reflect the evolving knowledge on a topic, meta-analyses are regularly updated as new studies become available. However, redundancy of overlapping meta-analyses on the same topic is frequently obvious and reflects waste of time, energies and economic resources. Considerations regarding heterogeneity, publication bias and quality of primary studies serve as a basis to appreciate the evidence across overlapping meta-analyses. Raising the quality of research is a collective effort of authors, peer reviewers, editors and other players in the field. When preparing and submitting a meta-analysis, authors should take responsibility for advancing the field by adhering to the appropriate reporting guideline, reporting the rationale for performing the (updated) meta-analysis, registering their project in a dedicated database and evaluating the whole body of evidence. Similarly, peer reviewers and editorial boards should carefully evaluate the additional merits of the meta-analysis under review over previous work, thereby filtering out inappropriate meta-analyses, avoiding confusion and maintaining the value of meta-analyses.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Davidoff F, Haynes B, Sackett D, Smith R. Evidence based medicine. *BMJ.* 1995;310:1085-6.
2. Siontis KC, Hernandez-Boussard T, Ioannidis JP. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ.* 2013;347:f4501.
3. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med.* 2010;7:e1000326.
4. Moher D. The problem of duplicate systematic reviews. *BMJ.* 2013;347:f5040.
5. Hansen PR, Iversen A, Abdulla J. Improved clinical outcomes with intracoronary compared to intravenous abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *J Invasive Cardiol.* 2010;22:278-82.
6. De Luca G, Verdoia M, Suryapranata H. Benefits from intracoronary as compared to intravenous abciximab administration for STEMI patients undergoing primary angioplasty: a meta-analysis of 8 randomized trials. *Atherosclerosis.* 2012;222:426-33.
7. Navarese EP, Kozinski M, Obonska K, Margheri M, Gurbel PA, Kubica J, De Luca G. Clinical efficacy and safety of intracoronary vs. intravenous abciximab administration in STEMI patients undergoing primary percutaneous coronary intervention: a meta-analysis of randomized trials. *Platelets.* 2012;23:274-81.
8. Shimada YJ, Nakra NC, Fox JT, Kanei Y. Meta-analysis of prospective randomized controlled trials comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol.* 2012;109:624-8.
9. De Rosa S, Caiazzo G, Torella D, Indolfi C. Intracoronary abciximab reduces death and major adverse cardiovascular events in acute coronary syndromes: a meta-analysis of clinical trials. *Int J Cardiol.* 2013;168:1298-305.
10. Kubica J, Koziński M, Navarese EP, Tantry US, Grześk G, Fabiszak T, Kubica A, Świątkiewicz I, Bliden KP, Gurbel PA. Updated evidence on intracoronary abciximab in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. *Cardiol J.* 2012;19:230-42.
11. Wang JN, Diao S, Tang YJ, Hou AJ, Yuan HB, Zheng Y, Zhou YH. Intracoronary versus intravenous administration of abciximab in patients with acute coronary syndrome: a meta-analysis. *PloS One.* 2013;8:e58077.
12. Piccolo R, Eitel I, Iversen A, Gu Y, Dominguez-Rodriguez A, De Smet B, Mahmoud K, Abreu-Gonzales P, Thiele H, Piscione F. Intracoronary versus intravenous bolus abciximab administration in patients undergoing primary percutaneous coronary intervention with acute ST-elevation myocardial infarction: a pooled analysis of individual patient data from 5 randomized controlled trials. *EuroIntervention.* 2014;9:1111-21.

13. Biondi-Zoccai GG, Lotrionte M, Moretti C, Meliga E, Agostoni P, Valgimigli M, Migliorini A, Antoniucci D, Carrié D, Sangiorgi G, Chieffo A, Colombo A, Price MJ, Teirstein PS, Christiansen EH, Abbate A, Testa L, Gunn JP, Burzotta F, Laudito A, Trevi GP, Sheiban I. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. *Am Heart J.* 2008;155:274-83.

14. Naik H, White AJ, Chakravarty T, Forrester J, Fontana G, Kar S, Shah PK, Weiss RE, Makkar R. A meta-analysis of 3,773 patients treated with percutaneous coronary intervention or surgery for unprotected left main coronary artery stenosis. *JACC Cardiovasc Interv.* 2009;2:739-47.

15. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol.* 2011;58:1426-32.

16. Ferrante G, Presbitero P, Valgimigli M, Morice MC, Pagnotta P, Belli G, Corrada E, Onuma Y, Barlis P, Locca D, Eeckhout E, Di Mario C, Serruys PW. Percutaneous coronary intervention versus bypass surgery for left main coronary artery disease: a meta-analysis of randomised trials. *EuroIntervention.* 2011;7:738-46.

17. Kajimoto K, Miyauchi K, Yamamoto T, Daida H, Amano A. Meta-analysis of randomized controlled trials on the treatment of unprotected left main coronary artery disease: one-year outcomes with coronary artery bypass grafting versus percutaneous coronary artery intervention with drug-eluting stent. *J Card Surg.* 2012;27:152-7.

18. Lee MS, Yang T, Dhoot J, Liao H. Meta-analysis of clinical studies comparing coronary artery bypass grafting with percutaneous coronary intervention and drug-eluting stents in patients with unprotected left main coronary artery narrowings. *Am J Cardiol.* 2010;105:1070-5.

19. Alam M, Huang HD, Shahzad SA, Kar B, Virani SS, Rogers PA, Paniagua D, Bozkurt B, Palacios I, Kleiman NS, Jneid H. Percutaneous coronary intervention vs. coronary artery bypass graft surgery for unprotected left main coronary artery disease in the drug-eluting stents era - an aggregate data meta-analysis of 11,148 patients. *Circ J.* 2013;77:372-82.

20. Gao F, Zhou YJ, Shen H, Wang ZJ, Yang SW, Liu XL. Meta-analysis of percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with diabetes and left main and/or multivessel coronary artery disease. *Acta Diabetol.* 2013;50:765-73.

21. Jang JS, Choi KN, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS, Urm SH, Chun JH, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. *Am J Cardiol.* 2012;110:1411-8.

22. Desch S, Boudriot E, Rastan A, Buszman PE, Bochenek A, Mohr FW, Schuler G, Thiele H. Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease. A meta-analysis of randomized controlled trials. *Herz.* 2013;38:48-56.

23. Sá MP, Soares AM, Lustosa PC, Martins WN, Browne F, Ferraz PE, Vasconcelos FP, Lima RC. Meta-analysis of 5,674 patients treated with percutaneous coronary intervention and drug-eluting stents or coronary artery bypass graft surgery for unprotected left main coronary artery stenosis. *Eur J Cardiothorac Surg.* 2013;43:73-80.

24. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177-85.

25. Shrier I, Boivin JF, Platt RW, Steele RJ, Brophy JM, Carnevale F, Eisenberg MJ, Furlan A, Kakuma R, Macdonald ME, Pilote L, Rossignol M. The interpretation of systematic reviews with meta-analyses: an objective or subjective process? *BMC Med Inform Decis Mak.* 2008;8:19.

26. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *CMAJ.* 1997;156:1411-6.

27. Deeks JJ, Higgins JPT, Altman DG. Analysing Data and Undertaking Meta-Analyses. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, Chichester, UK; 2008. p.243-96.

28. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539-58.

30. Osnabrugge RL, Kappetein AP, Janssens AC. Carriage of reduced-function CYP2C19 allele among patients treated with clopidogrel. *JAMA.* 2011;305:467-8.

31. Teramukai S, Matsuyama Y, Mizuno S, Sakamoto J. Individual patient-level and study-level meta-analysis for investigating modifiers of treatment effect. *Jpn J Clin Oncol.* 2004;34:717-21.

32. Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA.* 1990;263:1385-9.

33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-34.

34. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med.* 2006;25:3443-57.

35. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ.* 2001;323:101-5.

36. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol.* 1991;44:1271-8.

37. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* 2009;62:1013-20.

38. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The

PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6:e1000100.

39. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283:2008-12.

40. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med.* 2007;147:224-33.

41. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Räber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *JACC Cardiovasc Interv.* 2011;4:645-53.

42. White HD, Chew DP, Dauerman HL, Mahaffey KW, Gibson CM, Stone GW, Gruberg L, Harrington RA, Bhatt DL. Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J.* 2012;163:82-90.e4.

43. Sutton AJ, Donegan S, Takwoingi Y, Garner P, Gamble C, Donald A. An encouraging assessment of methods to inform priorities for updating systematic reviews. *J Clin Epidemiol.* 2009;62:241-51.

44. Tsertsvadze A, Maglione M, Chou R, Garritty C, Coleman C, Lux L, Bass E, Balshem H, Moher D. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. *J Clin Epidemiol.* 2011;64:1208-15.

45. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10:277-303.

46. Goodman SN. Bayesian methods for evidence evaluation: are we there yet? *Circulation*. 2013;127:2367-9.

47. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. *Lancet.* 2011;377:108-9.

48. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. PROSPERO at one year: an evaluation of its utility. *Syst Rev.* 2013;2:4.

49. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev.* 2012;1:2.

50. Ioannidis JP, Karassa FB. The need to consider the wider agenda in systematic reviews and meta-analyses: breadth, timing, and depth of the evidence. *BMJ.* 2010;341:c4875.

51. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet.* 2012;379:1393-402.

52. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ.* 2009;181:488-93.

53. Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA.* 2012;308:1246-53.

Online data supplement

Online Table 1. Overlapping meta-analyses on intracoronary versus intravenous administration of abciximab.

Online Table 2. Overlapping meta-analyses on PCI versus CABG in patients with left main coronary artery disease.

Online data supplement

Online Table 1. Overlapping meta-analyses on intracoronary versus intravenous administration of abciximab.

	Hansen et al[5]	Navarese et al[7]	Shimada et al[8]	De Luca et al[6]	De Rosa et al[9]	Kubica et al[10]	Wang et al[11]	Piccolo et al[12]
Publication date	2010	2012	2012	2012	2012	2012	2013	2013
Search date	November 2009	March 2011	August 2011	December 2011	March 2012	April 2012	May 2012	NA
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study- and patient-level
Effect size (95% CI) for MACE	0.62 (0.38-1.03)	NA	0.59 (0.27-1.28)	NA	0.47 (0.31-0.71)	NA	0.55 (0.40-0.76)	NA
Effect size (95% CI) for mortality	0.57 (0.35-0.94)	0.43 (0.20-0.94)	0.44 (0.20-0.95)	0.85 (0.59-1.23)	0.42 (0.20-0.86)	0.67 (0.34–1.34)	0.69 (0.45-1.07)	0.77 (0.51-1.17)
Effect size (95% CI) for myocardial infarction	NA	0.54 (0.23-1.28)	NA	0.79 (0.46-1.33)	NA	0.61 (0.40-0.92)	0.59 (0.37-0.93)	NA
Effect size (95% CI) for repeat revascularisation	NA	0.53 (0.29-0.99)	NA	NA	NA	0.66 (0.40-1.09)	0.64 (0.32-1.29)	NA
Effect size (95% CI) for major bleeding	NA	0.91 (0.46-1.79)	NA	1.19 (0.76-1.87)	NA	1.18 (0.76-1.83)	1.00 (0.57-1.74)	NA
Screened studies	979	2,351	37	1,865	48	6,562	660	NA
Pooled patients	2,301	1,246	1,148	3,259	4,226	3,331	3,916	3,158
Studies included	5 RCTs, 3 OSs	6 RCTs	4 RCTs	8 RCTs	10 RCTs	7 RCTs	9 RCTs	5 RCTs
Wohrle et al, *Circulation* 2003	Yes	No	No	No	Yes	No	Yes	No
Kakkar et al, *Catheter Cardiovasc Interv* 2004	Yes	No	No	No	Yes	No	Yes	No
Bellandi et al, *Catheter Cardiovasc Interv* 2004	Yes	No	No	Yes	No	No	Yes	No
Galanche-Osuna et al, *Rev Esp Cardiol* 2006	Yes	No	No	No	Yes	No	Yes	No
Thiele et al, *Circulation* 2008	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bertrand et al, *Int J Cardiol* 2008	Yes	No	No	No	No	No	No	No
Dominguez-Rodriguez et al, *Atherosclerosis* 2009	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Iversen et al, (abstract) 2009	Yes	No	No	No	No	No	No	No
Gu et al, *Circulation* 2010	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bertrand et al, *Am J Cardiol* 2010	No	Yes	Yes	Yes	Yes	Yes	No	No
Dave et al, (abstract) 2010	No	Yes	No	Yes	No	Yes	No	No
Iversen et al, *J Interv Cardiol* 2011	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Iversen et al, *Cardiology* 2011*	No	No	No	No	Yes	Yes	Yes	No
Eitel et al, *Clin Res Cardiol* 2011*	No	No	No	No	Yes	Yes	No	No
Thiele et al, *Lancet* 2012	No	No	No	Yes	Yes	Yes	Yes	Yes

For the selection of overlapping meta-analyses of intracoronary vs. intravenous administration of abciximab in patients with acute coronary syndromes we searched PubMed for meta-analyses of randomised controlled trials and/or observational studies published any time using the search terms abciximab [Title] AND meta-analysis [Title/abstract] AND intracoronary [Title/abstract] without language restrictions. Effect estimates are reported for the longest follow-up available. Estimated effects are reported for intracoronary vs. intravenous administration. *Represented long-term evaluation of previously published studies. CABG: coronary artery bypass grafting; CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; NA: not available; OSs: observational studies; PCI: percutaneous coronary intervention; RCTs: randomised controlled trials; STEMI: ST-segment elevation myocardial infarction

Online Table 2. Overlapping meta-analyses on PCI versus CABG in patients with left main coronary artery disease.

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Publication date	2008	2009	2010	2011	2011	2012	2012	2012	2013	2013	2013	2013
Search date	September 2006	December 2008	June 2009	April 2011	NA	May 2011	July 2011	October 2011	January 2011	April 2011	2011	NA
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Bayesian
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level
Effect size (95% CI) for MACCE	0.46 (0.24-0.90)	1.16 (0.68–1.96)	NA	1.28 (0.95-1.72)	1.24 (0.93-1.67)	0.55 (0.43-0.70)*	NA	NA	1.20 (0.92-1.56)	1.26 (1.02-1.57)	1.61 (NA), $p<0.001$	NA
Effect size (95% CI) for mortality	NA	1.11 (0.66–1.85)	1.12 (0.80-1.56)*	0.74 (0.43-1.29)	0.72 (0.42-1.24)	0.92 (0.60-1.40)*	0.68 (0.45-1.02)	0.97 (0.81-1.15)	0.81 (0.62-1.06)	0.74 (0.46-1.19)	0.69 (NA), $p=0.05$	1.01 (0.68-1.45)
Effect size (95% CI) for myocardial infarction	NA	NA	0.70 (0.45-1.09)*	0.98 (0.54-1.78)	0.97 (0.54-1.74)	0.67 (0.43-1.05)*	1.07 (0.65-1.76)	NA	1.32 (0.91-1.91)	1.19 (0.69-2.06)	NA	NA
Effect size (95% CI) for stroke	NA	NA	NA	0.15 (0.03-0.67)	0.14 (0.04-0.55)	NA	0.23 (0.09-0.58)	0.29 (0.16-0.51)	0.31 (0.20-0.49)	0.26 (0.10-0.69)	NA	NA
Effect size (95% CI) for repeat revascularisation	NA	4.01 (2.01–7.98)	0.44 (0.32-0.59)*	2.25 (1.54-3.29)	2.17 (1.48-3.17)	0.40 (0.30-0.55)*	3.52 (2.72-4.56)	4.44 (3.42-5.78)	3.73 (2.71-5.14)	1.94 (1.43-2.61)	3.60 (NA), $p<0.001$	NA
Screened studies	823	7,294	NA	254	189	106	472	76	355	1,236	9,120	19
Pooled patients	670	3,773	2,905	1,611	1,611	2,601	5,079	6,992	11,148	1,611	5,674	4,574
Studies included	3 OSs	2 RCTs, 8 OSs	2 RCTs, 8 OSs	4 RCTs	4 RCTs	3 RCTs	3 RCTs, 9 OSs	11 RCTs, 2 OSs	4 RCTs, 23 OSs	4 RCTs	3 RCTs, 13 OSs	4 RCTs, 8 OSs
Gwon et al, *J Kor Med Sci* 2005	No	No	No	No	No	No	No	Yes	No	No	No	No
Lee et al, *J Am Coll Cardiol* 2006	Yes	No	Yes	No	No	No	Yes	No	No	No	Yes	No
Chieffo et al, *Circulation* 2006	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No	Yes
Palmerini et al, *Am J Cardiol* 2006	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No
Sanmartin et al, *Am J Cardiol* 2007	No	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes
Briguori et al, *Am J Cardiol* 2007	No	No	No	No	No	No	No	Yes	No	No	No	No
Lee et al, *Int J Cardiol* 2007	No	No	No	No	No	No	No	Yes	No	No	No	No
Palmerini et al, *Eur Heart J* 2007**	No	No	Yes	No	No	No	No	No	Yes	No	Yes	Yes
Seung et al, *N Engl J Med* 2008	No	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes
Makikallio, *Ann Med* 2008	No	Yes	No	No	No	No	Yes	No	Yes	No	Yes	Yes
Daemen et al, *J Am Coll Cardiol* 2008**	No	No	No	No	No	No	No	Yes	No	No	No	No
Brener et al, *Am J Cardiol* 2008	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Hsu et al, *Int Heart J* 2008	No	No	No	No	No	No	No	No	Yes	No	No	No
White et al, *JACC Cardiovasc Interv* 2008	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes
Wu et al, *Ann Thor Surg* 2008	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes
Buzman, *J Am Coll Cardiol* 2008	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Rodes-Cabau et al, *Circulation* 2008	No	No	No	No	No	No	No	No	Yes	No	No	No
Serruys et al, (abstract) 2008	No	Yes	No	No	No	No	No	No	No	No	No	No
Boudriot et al, (abstract) 2008	No	No	Yes	No	No	No	No	No	No	No	No	No
Cheng et al, *Circ J* 2009	No	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No

Online Table 2. Overlapping meta-analyses on PCI versus CABG in patients with left main coronary artery disease. (Continued)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Buszman et al, *J Am Coll Cardiol* 2009	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	No
Serruys et al, *N Engl J Med* 2009	No	No	Yes	No	No	Yes	No	No	No	No	No	No
Dominguez-Franco et al, *Rev Esp Cardiol* 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Kin et al, *JACC Cardiovasc Interv* 2009**	No	No	No	No	No	No	No	Yes	No	No	No	No
Qiao et al, (abstract) 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Tarantini et al, *Catheter Cardiovasc Interv* 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Ghenim et al, *J Interv Cardiol* 2009	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Liu et al, *Zhonghua Xin Xue Guan Bing Za Zhi* 2009	No	No	No	No	No	No	No	No	Yes	No	No	No
Montalescot et al, *Eur Heart J* 2009	No	No	No	No	No	No	No	No	Yes	No	No	No
Wu et al, *Am J Cardiol* 2010	No	No	No	No	No	No	Yes	No	Yes	No	No	No
Kang et al, *Am J Cardiol* 2010	No	No	No	No	No	No	Yes	No	Yes	No	No	No
Morice et al, *Circulation* 2010**	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Park et al, *N Engl J Med* 2010	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Banning et al, *J Am Coll Cardiol* 2010**	No	No	No	No	No	No	No	Yes	No	No	No	No
Kapur et al, *J Am Coll Cardiol* 2010	No	No	No	No	No	No	No	Yes	No	No	No	No
Kapur et al, *J Cardiovasc Med*, 2010**	No	No	No	No	No	No	No	Yes	No	No	No	No
Yamagata et al, Circ J 2010	No	No	No	No	No	No	No	Yes	No	No	No	No
Chieffo et al, *JACC Cardiovasc Interv* 2010	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Huang et al, *Clin Res Cardiol* 2010	No	No	No	No	No	No	No	No	Yes	No	No	No
Park et al, *J Am Coll Cardiol* 2010***	No	No	No	No	No	No	No	No	Yes	No	No	No
Shimizu et al, *Circ J* 2010	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Boudriot et al, *J Am Coll Cardiol* 2011	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Caggegi et al, *Am J Cardiol* 2011	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No
Park et al, *J Am Coll Cardiol* 2011	No	No	No	No	No	No	No	Yes	Yes	No	No	No
Rittger et al, *Clin Res Cardiol* 2011	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Pepe et al, *Heart Vessels* 2011	No	No	No	No	No	No	No	No	No	No	No	No

For the selection of overlapping meta-analyses of PCI vs. CABG in patients with left main disease we searched PubMed for meta-analyses of randomised controlled trials and/or observational studies published any time using the search terms left main [Title] AND meta-analysis [Title/abstract] AND PCI [Title/abstract] without language restrictions. Effect estimates are reported for the longest follow-up available. * Treatment effects are reported as PCI vs. CABG, except in the meta-analyses by Lee et al and Kajimoto et al, in which treatment effects were reported as CABG vs. PCI. ** subgroup analysis of previously published study. *** extended follow-up evaluation of previously published study. CABG: coronary artery bypass grafting; CI: confidence interval; MACCE: major adverse cardiac and cerebrovascular events; NA: not available; OSs: observational studies; *p*: *p*-value; PCI: percutaneous coronary intervention; RCTs: randomised controlled trials; STEMI: ST-segment elevation myocardial infarction