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A systematic review of analytical methods used to study subgroups in (individual patient data) meta-analyses

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Abstract

Objectives: To determine whether individual patient data meta-analyses (IPDMA) are used to perform subgroup analyses and to study whether the analytical methods regarding subgroup analyses differ between IPDMA and conventional meta-analyses (CMA).

Study Design and Setting: IPDMA were identified with a comprehensive literature search, subsequently, CMA on similar research questions were traced. Methods for studying subgroups were compared for IPDMA and CMA that were matched with respect to domain, type of treatment, and outcome measure.

Results: Of all 171 identified IPDMA and 102 CMA, 80% and 45% presented subgroup analyses, respectively. For 35 IPDMA and 37 ''matched'' CMA, subgroup analytic methods could be compared. The number of performed subgroup analyses did not differ between IPDMA and CMA. Both IPDMA and CMA often do not report adequate information on methods of analyses. Interaction tests were often not performed in IPDMA (69%) and individual patient data was often not directly modelled (74%).

Conclusion: Many IPDMA performed subgroup analyses, but overall treatment effects were more emphasized than subgroup effects. To study subgroups, a wide variety of analytical methods was used in both IPDMA and CMA. In general, the use and reporting of appropriate methods for subgroup analyses should be promoted. Recommendations for improvement of methods of analyses are provided.

Keywords: Individual patient data; Meta-analysis; Methodology; Published data; Subgroup analysis; Review

1. Introduction

One of the main aims of a meta-analysis is to pool results of similar studies quantitatively to produce a single and more precise overall estimate of the average effect [1,2]. The direction and magnitude of the average effect of meta-analyses are intended to guide decisions regarding clinical practice for a wide range of patients. Most physicians, however, would like to use the specific characteristics of a patient to decide on patients' individual treatment [3−5]. The application of trial results in clinical practice, therefore, requires discrimination between subgroups of patients who do and do not benefit from the intervention [6−8].

Compared to randomized trials, meta-analyses offer a better basis for subgroup analysis because they have a larger sample size [9]. In conventional meta-analyses (CMA) based on published data differences in treatment effects between groups of study participants can be assessed by relating outcome to some characteristic (of treatment or study participant) on a continuous or ordered scale by meta-regression analyses [1]. When subgroup analyses are repeated in either randomized trials or meta-analyses, they do, however, often not confirm earlier findings [1].

Systematic reviews and meta-analyses that use individual patient (i.e., raw) data (IPDMA) rather than simply the summary results of each trial have been proposed as a major improvement in subgroup analyses. The advantages of using raw data are that more exact information is available on individual patient level about subgroup status, and it offers the opportunity to recode variables (i.e., making them more comparable between trials); to include all randomized patients; and to improve the overall follow-up. IPDMA usually have greater statistical power to carry out informative subgroup analyses, especially for patient-level subgroups (e.g., age or diabetic status), allowing a more thorough assessment as to whether differences are spurious or not [4,6,10−13]. They may enhance the flexibility and

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precision of subgroup analyses and thereby allow more informative subgroup analyses.

Previous studies showed that the main effects of IPDMA and CMA were comparable [10,14−18]. To date, however, no systematic study has been performed that studied whether IPDMA are indeed used to perform subgroup analyses and whether the methodology used for subgroup analyses differs between IPDMA and CMA. We, therefore, performed such a systematic review in which we compared the methods used for studying subgroup effects between IPDMA and CMA.

2. Methods

2.1. Search

A comprehensive literature search in PubMed, Embase, the Cochrane library, and Web of Science was conducted to identify all IPDMA of randomized controlled trials. For this search, keywords from the systematic catalog or alphabetic index were used (detailed search strategy is presented in Appendix A available on the journal's web site at www.elsevier.com/locate/jclinepi). The last search was conducted on April 24, 2006. To identify CMA on the same objective, a ''related articles'' search in PubMed was conducted for every identified IPDMA (detailed search strategy is presented in Appendix B on the journal's web site at www.elsevier.com/locate/jclinepi).

2.2. Selection

In first instance, titles and abstracts were screened to identify eligible IPDMA. Selection of potential eligible IPDMA was not restricted to particular treatments or disease outcome. Full text papers were retrieved when meta-analytic techniques for raw data (i.e., individual patient data) of randomized trials were used. Potential eligible titles for CMA were included when the objective was comparable with the IPDMA (i.e., similar for the research question, for example when the effect of treatment X on outcome Y was studied in population Z), and meta-analytic techniques for published randomized trials were used. If obvious duplicate papers were available, only the most recent published paper was included.

To compare the analytical methods used to study subgroups in IPDMA and CMA, only those IPDMA and CMA that both performed subgroup analyses could be included. Moreover, only those CMA were included that could be ''matched'' to IPDMA on domain (certain type of patients in certain situations for which the objective is studied [19]), type of treatment, and outcome measure.

2.3. Data extraction and analysis

Data from all included IPDMA and CMA were extracted with respect to specific characteristics, that is, publication year, number of included trials and patients, duration of follow-up, domain, type of treatment, outcome measured, effect measure, heterogeneity tests, fixed- or random-effect analysis, number and types of subgroups studied, and methods for subgroup analysis. All subgroups considered as such in the original meta-analyses were counted as subgroups. Appropriate tests that were counted to study heterogeneity were Chi square, I square, Q statistic, and Breslow Day. We also recorded whether an appropriate interaction test was performed, that is, whether an interaction term (=treatment × subgrouping variable) was included in a regression model.

The methods for studying subgroup effects were counted and described for IPDMA and CMA. These methods were compared for all IPDMA and their ''matched'' CMA. Differences in frequencies (e.g., the difference in number of studies included in IPDMA and CMA) and the corresponding 95% confidence interval (CI) were calculated [20].

3. Results

3.1. Search

In the search for IPDMA, 1,808 potential eligible papers were identified. Another 39 potential eligible titles were found, while searching for CMA. They represent several medical fields, but the majority of the papers regard oncology and cardiovascular diseases. After studying the abstracts, full text was retrieved of 302 papers for detailed evaluation; 171 papers were finally included in the analyses. The remaining 1,676 papers were excluded for one of the following reasons: published instead of raw data; IPDMA on cohort studies, case−control studies, or case reports instead of randomized controlled trials; only one treatment arm evaluated; methodological review; or duplicate publication (Fig. 1).

The ''related articles'' search for CMA identified 11,149 potential eligible papers. After studying the abstracts, full text was retrieved of 362 papers for detailed evaluation; 102 papers were finally included in the analysis. The remaining 11,047 papers were excluded for one of the following reasons: raw instead of published data; CMA on cohort studies, case−control studies, or case reports instead of randomized controlled trials; only one treatment arm evaluated; methodological or tutorial review; research question was not similar between IPDMA and CMA; or duplicate publication (Fig. 2).

3.2. Summary of all IPDMA and CMA that studied the same research question

The 171 IPDMA papers were published between 1993 and 2006. In 136 (80%) IPDMA subgroup, analyses were presented. Of these, 35 could be ''matched'' to a CMA that also studied subgroups (Fig. 1). The 102 identified CMA were published between 1990 and 2005. In 46 (45%)

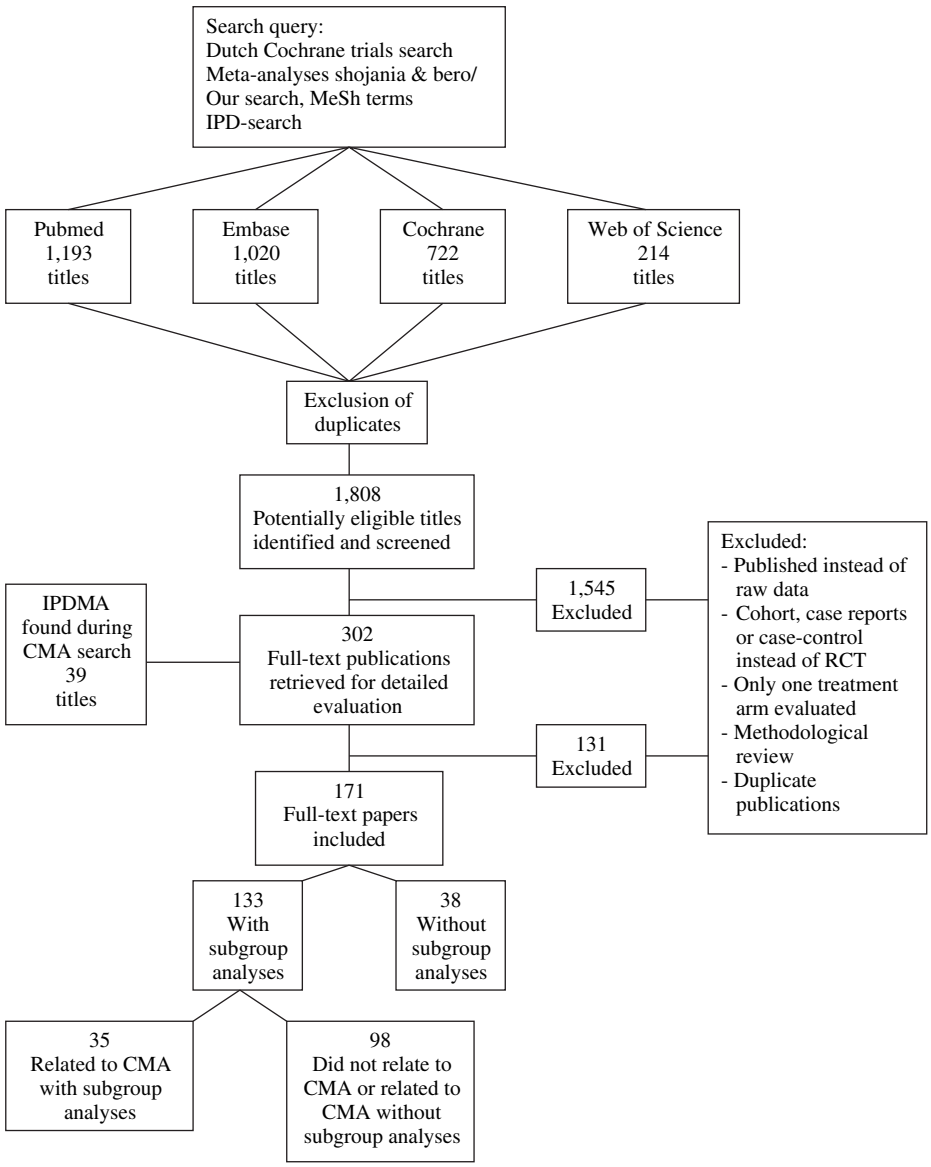

Fig. 1. Flowchart of the inclusion of IPDMA.

CMA subgroup analyses were presented. Of these, 37 could be ''matched'' to an IPDMA that also studied subgroups (Fig. 2). The risk difference (RD) of performing subgroup analyses in IPDMA and CMA (i.e., the risk of studying subgroups for IPDMA minus the risk of studying subgroups for CMA) was 34% (95% CI: 23, 46).

Table 1 shows the characteristics of the methods used for studying subgroups in IPDMA and CMA. They used a wide variety of methods to study subgroups, but often do not report adequate information about the use of heterogeneity tests ($N_{IPDMA} = 69$ (51%); $N_{CMA} = 21$ (46%)), fixed- or random-effect models ($N_{IPDMA} = 78$ (57%); $N_{CMA} = 15$ (33%)), and definition of subgroups before data analyses ($N_{IPDMA} = 27$ (20%); $N_{CMA} = 12$ (26%)). Moreover, direct modelling of IPD and interaction tests was rarely reported ($N = 29$ (21%)), and finally random-effect meta-analyses were only occasionally reported ($N_{IPDMA} = 12$ (9%); $N_{CMA} = 10$ (22%)).

3.3. Comparison of methods of subgroup analyses in the "matched" IPDMA and CMA

In total, 37 CMA could be ''matched'' with 35 IPDMA. The analytical methods used to study subgroups in both the IPDMA and their ''matched'' CMA are showed in Table 2. Small differences were seen between IPDMA and CMA in both the (median) number of studies ($N_{IPDMA} = 8$; $N_{CMA} = 12$) and the (median) number of patients included ($N_{IPDMA} = 2{,}045$; $N_{CMA} = 4{,}008$). The (median) duration of follow-up in IPDMA ($N = 24$ months) was twice compared to CMA ($N = 12$ months). Even though on average IPDMA have a longer follow-up period, the publication dates

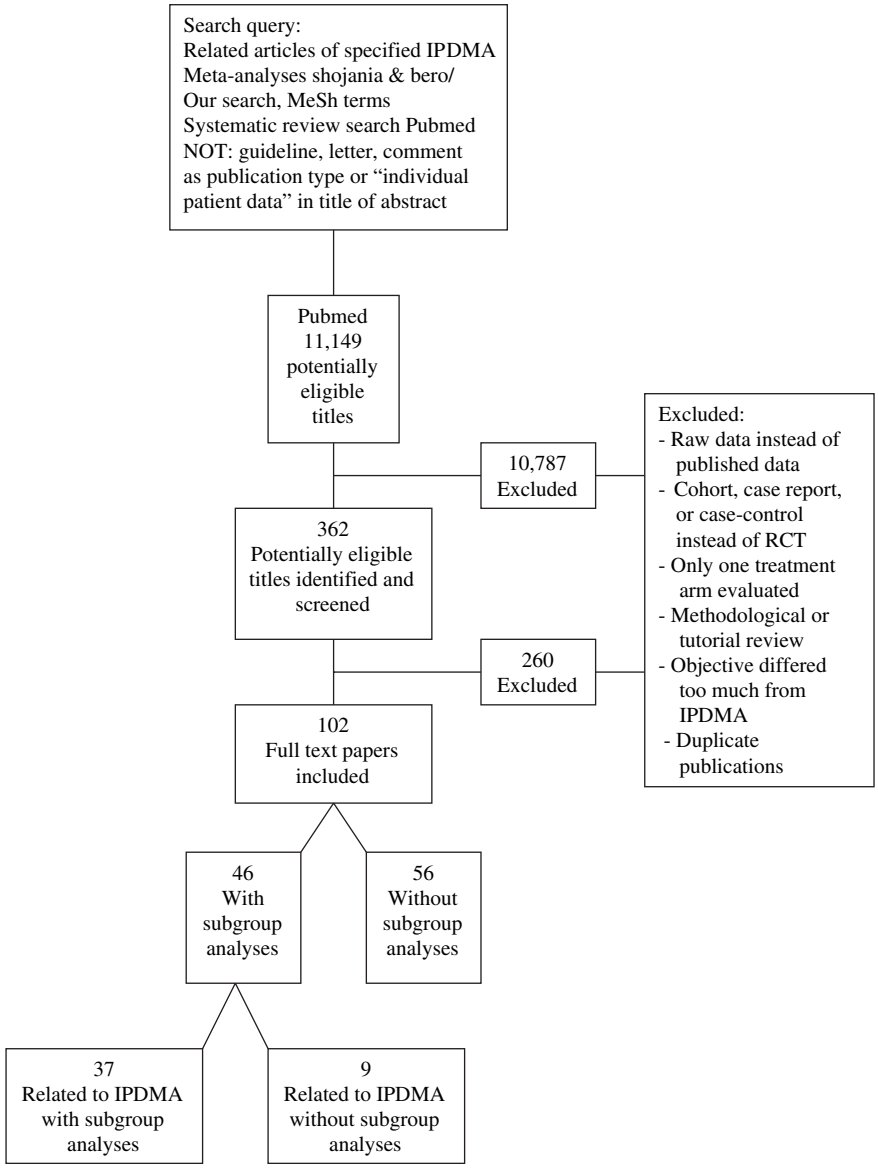

Fig. 2. Flowchart of the inclusion of CMA.

of the included IPDMA and CMA do not differ, (median publication date 2000 with a quartile range [1998; 2004] and 2001 [1998; 2003], respectively). A small difference in (median) number of subgroups studied ($N_{\text{IPDMA}} = 3$; $N_{\text{CMA}} = 2$) was seen. There were minor differences in time of defining subgroups between IPDMA ($N_{\text{a priori}} = 22$ (63%); $N_{\text{a posteriori}} = 3$ (9%)) and CMA ($N_{\text{a priori}} = 25$ (68%); $N_{\text{a posteriori}} = 3$ (8%)). More IPDMA ($N = 11$ (31%)) than CMA ($N = 1$ (3%)) performed an interaction test. More CMA ($N = 34$ (92%)) than IPDMA ($N = 26$ (74%)) stratified their analysis per trial before pooling the results (i.e., two-stage method). The use of meta-regression to study subgroups was reported in eight CMA (22%). Compared to CMA, IPDMA expressed their measure of effect more often as a hazard ratio ($N_{\text{IPDMA}} = 11$ (31%); $N_{\text{CMA}} = 4$ (11%)) and less often as a relative risk ($N_{\text{IPDMA}} = 8$ (23%); $N_{\text{CMA}} = 4$ (11%)) or a RD ($N_{\text{IPDMA}} = 1$ (3%); $N_{\text{CMA}} = 5$ (14%)). However, CMA bears serious problems extracting hazard ratios from published reports [21]. More IPDMA reported the use of Breslow Day ($N_{\text{IPDMA}} = 1$ (3%); $N_{\text{CMA}} = 0$) as heterogeneity test, whereas more CMA reported the use of Chi square ($N_{\text{IPDMA}} = 12$ (34%); $N_{\text{CMA}} = 16$ (43%)) and Q statistic ($N_{\text{IPDMA}} = 1$ (3%); $N_{\text{CMA}} = 5$ (14%)) as heterogeneity test. More CMA reported the use of random-effect models ($N_{\text{IPDMA}} = 1$ (3%); $N_{\text{CMA}} = 9$ (24%)), whereas more IPDMA reported the use of fixed-effects models ($N_{\text{IPDMA}} = 14$ (40%); $N_{\text{CMA}} = 12$ (32%)). Finally, both IPDMA and CMA often do not report adequate information about the use of heterogeneity tests ($N_{\text{IPDMA}} = 21$ (60%); $N_{\text{CMA}} = 17$ (46%)),

Table 1
Characteristics of the methods of studying subgroups in IPDMA and CMA

Characteristics	IPDMA ($N = 136$)	CMA ($N = 46$)
Number of studies included (median; quartile range)	7 (4; 14)	12 (7; 22)
Number of patients included (median; quartile range)	2,045 (1,144; 4,953)	3,075 (1,397; 5,805)
Follow-up in months (median; quartile range)	26 (6; 60)	12 (6; 41)
Number of subgroups studied (median; quartile range)	3 (1; 6)	2 (1; 5)
Time of defining subgroups (*N*, %)		
A priori	101 (74)	31 (67)
A posteriori	6 (4)	3 (7)
Both	2 (2)	—
No adequate information available	27 (20)	12 (26)
Interaction test (*N*, % yes)[a]	38 (28)	1 (2)
Stratification per trial (*N*, % yes)[b]	107 (79)	42 (91)
Meta-regression (*N*, %)	—	11 (24)
Effect measure (*N*, %)[c,d]		
Difference/change score Ratio	16 (6)	11 (24)
Relative risk	39 (29)	18 (39)
Odds ratio	54 (40)	18 (39)
RD	7 (5)	6 (13)
Hazard ratio	37 (27)	5 (11)
Poisson	2 (1)	–
Heterogeneity (*N*, %)[c,e]		
Breslow Day	2 (1)	1 (2)
Chi square	58 (43)	18 (39)
I square	9 (7)	2 (4)
Q statistic	5 (4)	8 (17)
No adequate information available	69 (51)	21 (46)
Analyses (*N*, %)[e]		
Random	12 (9)	10 (22)
Fixed	41 (30)	17 (37)
Both	5 (4)	4 (9)
No adequate information available	78 (57)	15 (33)

[a] Interaction test, i.e., interaction term (=treatment × covariate/factor/subgroup) included in a regression model.
[b] Stratification per trial, i.e., two-stage method.
[c] In most articles the use of fixed or random models, use of effect measures, and testing of heterogeneity is not stated specific for the subgroup analysis.
[d] Nineteen IPDMA and 12 CMA presented two effect measures.
[e] Eight IPDMA and 4 CMA presented two heterogeneity tests.

fixed- or random-effect models ($N_{IPDMA} = 18$ (51%); $N_{CMA} = 12$ (32%)), and definition of subgroups before data analyses ($N_{IPDMA} = 9$ (26%); $N_{CMA} = 9$ (24%)).

The type of subgroups studied varied between the compared IPDMA ($N = 35$) and CMA ($N = 37$): 23 (66%) IPDMA and 10 (27%) CMA studied patient characteristics (RD, 39%; 95% CI: 17, 60), for example, age or gender; 24 (69%) IPDMA and 14 (38%) CMA studied disease characteristics (RD, 31%; 95% CI: 9, 53), for example, severity or staging; 15 (43%) IPDMA and 27 (73%) CMA studied treatment-related subgroups (RD, −30%; 95% CI −52, −8), for example, regimen or dose; 4 (11%) IPDMA and 13 (35%) CMA studied outcome-related subgroups (RD, −24%; 95% CI −42, −5), for example timing; and 10 (27%) CMA studied subgroups related to the quality of included trials (RD, −27%, 95% CI −41, −13), for example concealment of allocation, blinding, or completeness of follow-up.

4. Discussion

In 136 (80%) of the full set of 171 IPDMA assessed, subgroup analyses were performed to examine whether certain patients benefit more from a specific treatment than others. In total 35 IPDMA and 37 ''matched'' CMA could be compared with respect to subgroup analytic methods. A wide variety of methods was used to study subgroups in both IPDMA and CMA, and the methods to study these subgroups were not reported appropriately. It was often not reported which heterogeneity test was used, whether random- or fixed-effects models were used, and at what time subgroups were defined.

Some of our findings deserve further discussion. First, we identified 171 IPDMA, which is much more than expected. However, this still represents only about 2% of the total of over 8,600 systematic reviews published since 1996 (Bastian, Glasziou Cochrane Colloquium, 2005). The majority addressed cardiovascular diseases and oncology, which agree with the overall available literature in the medical field. A rather small group of IPDMA could be compared to CMA with respect to subgroup analytic methods. This is due to the small number of CMA that reported subgroup analysis, and the limited number of CMA that could be ''matched'' to IPDMAs.

Second, although many IPDMA performed subgroup analyses, the overall treatment effect was usually the main focus of the paper. Only occasionally the subgroup analyses were emphasized. The general lack of differences between subgroups with respect to treatment effects found, may explain this tendency. Other reasons could include the exploratory nature of the subgroup analyses or the absence of formulated hypotheses. It is generally accepted that subgroups should be defined before data analyses because post hoc analyses are known to be sensitive to spurious associations being found [22,23]. Nevertheless, around 30% of both IPDMA and CMA did not define their subgroups a priori. In IPDMA, subgroups were often based on patient and disease characteristics, whereas treatment- or outcome-related subgroups were studied more frequently in CMA. Patient or disease characteristics should be studied using raw data rather than aggregated data because these provide more statistical power to detect patient-level interactions [11,24]. Moreover, IPDMA offer the opportunity to stratify

Table 2
Characteristics of the methods of studying subgroups within the compared IPDMA and CMA

Characteristics	IPDMA ($N = 35$)	CMA ($N = 37$)	RD % (95% CI)
Number of studies included (median; quartile range)	8 (4; 13)	12 (8; 18)	—
Number of patients included (median; quartile range)	2,045 (1,093; 9,387)	4,008 (1,570; 6,116)	—
Follow-up in months (median; quartile range)	24 (5; 63)	12 (5; 48)	—
Number of subgroups studied (median; quartile range)	3 (1; 7)	2 (1; 5)	—
Time of defining subgroups (*N*, %)			
A priori	22 (63)	25 (68)	−5 (−27; 17)
A posteriori	3 (9)	3 (8)	1 (−12; 14)
Both	1 (3)	—	3 (−3; 9)
No adequate information available	9 (26)	9 (24)	2 (−18; 22)
Interaction test (*N*, % yes)[a]	11 (31)	1 (3)	28 (12; 44)
Stratification per trial (*N*, % yes)[b]	26 (74)	34 (92)	−18 (−35; −1)
Meta-regression (*N*, %)	—	8 (22)	−22 (−35; −9)
Effect measure (*N*, %)[c,d]			
Difference/change score	6 (17)	6 (16)	1 (−16; 18)
Ratio			
Relative risk	7 (20)	18 (49)	−29 (−50; −8)
Odds ratio	15 (43)	14 (38)	5 (−18; 28)
RD	1 (3)	5 (14)	−11 (−24; 2)
Hazard ratio	11 (31)	4 (11)	20 (2; 38)
Heterogeneity (*N*, %)[c,e]			
Breslow Day	1 (3)	—	3 (−3; 9)
Chi square	12 (34)	16 (43)	−9 (−31; 13)
I square	2 (6)	2 (5)	1 (−10; 12)
Q statistic	1 (3)	6 (16)	−13 (−26; 0)
No adequate information available	21 (60)	17 (46)	14 (−9; 37)
Analyses (*N*, %)[c]			
Random	1 (3)	9 (24)	−21 (−36; −6)
Fixed	14 (40)	12 (32)	8 (−14; 30)
Both	2 (6)	4 (11)	−5 (−18; 8)
No adequate information available	18 (51)	12 (32)	19 (−3; 41)

[a] Interaction test, i.e., interaction term (=treatment × covariate/factor/subgroup) included in a regression model.
[b] Stratification per trial, i.e., two-stage method.
[c] In most articles the use of fixed or random models, use of effect measures, and testing of heterogeneity is not stated specific for the subgroup analysis.
[d] Five IPDMA and 10 CMA used two different effect measures.
[e] Two IPDMA and 4 CMA used two different heterogeneity tests.

the subgroup analyses instead of using ''mean'' covariates, which may lead to ecological bias [13].

Third, a variety of methods to study subgroup effects is used. Meta-regression was expected to be the main form of subgroup analysis in CMA. However, only 22% of the CMA reports the use of meta-regression analyses. Even when original papers reported the use of meta-regression, most papers did not clearly define how the covariates were incorporated in the meta-regression, for example, just one paper reported the use of ''mean'' covariates, and three papers reported categorized covariates. Most other CMA used stratification methods whereby subgroup data that were available in all trials were pooled, or dummy variables were made for specific variables, for example, average age of participants above or below median age for all trials.

Fourth, to reduce the chance of false positive and false negative findings, only subgroup effects for which significant interactions were found, should be studied [25]. However, of those performing subgroup analyses, nearly half (45%) of IPDMA did not report such an interaction test. Furthermore, many of the interaction tests reported in the papers, for example likelihood ratio tests, Chi-square tests, or comparisons of hazard ratios are inappropriate. As a result, the number of meta-analyses using appropriate interaction test (28%) is actually much smaller.

Fifth, most IPDMA (74%) stratified their analyses by trial, that is, the ''two-stage'' method [26], where each trial is analyzed separately using its raw data before the summary results from each trial are pooled and analyzed using a fixed- or random-effect meta-analysis. This practice is aimed at adjustment for residual confounding by study, which is generally accepted [27,28]. However, if many trials are included in the meta-analysis, unstable estimates might be produced using fixed trials effect or stratified models [14]. We, therefore, believe that the two-stage method negates many advantages of using individual patient data, and consider it possible to adjust for possible confounding by direct modelling of IPD and including a dummy for study [14, 30–32]. When IPD meta-analyses are stratified according to trial, random-effect models are rarely

used. This was unexpected, because in general heterogeneity is not exclusively explained by random variation.

Sixth, in many IPDMA and CMA the methods on subgroup analyses were not reported appropriately, notably whether a heterogeneity test was used, whether random- or fixed-effect models were used, and at what time subgroups were defined. This practice triggered us to provide some recommendations on how analyses should be handled at the end of this article.

4.1. Limitations and strengths

To appreciate our findings, certain limitations and strengths should be discussed. Our search for CMA may not have been optimal, as due to practical reasons we used a ''related articles'' search, instead of a complete CMA search. It is therefore possible that we have missed some CMA. It is, however, unlikely that eligible CMA were systematically missed. Moreover, only one person (L.K.) extracted the data, which might have led to misclassification of the results. We, however, believe this misclassification to be minimal as in case of uncertainty the papers were discussed with two other researchers (G.v.d.H., M.M.R.). Furthermore, the proportion of CMA that included subgroup analysis is probably an overestimation. It is more likely to find a related CMA that reports subgroup analyses because IPDMA are often performed when subgroup effects, for instance based on results of a meta-regression performed in CMA, are expected. Finally, the small number of IPDMA and CMA that could be included in the direct comparison on subgroup analytic methods might not be representative of all identified IPDMA. We therefore compared the characteristics of the small groups of ''matched'' IPDMA and CMA with the characteristics of all identified IPDMA and CMA that presented subgroup analyses. This comparison revealed no differences with respect to time of defining subgroups, the use of interaction test, stratification, and meta-regression (data not shown).

The major strengths of this study are that, with the developed search strategy, we identified many more IPDMA than expected, which confirms that our search strategy was very effective. Furthermore, this is the first article that compared the analytical methods to study subgroups between IPDMA and CMA systematically and directly. Our findings are in agreement with Simmonds et al. [26]. They described analytical methods used in 44 IPDMA published in 1999−2001, and also found evidence of poor reporting, rare use of direct pooling of IPD, and rare reporting of random-effect meta-analyses. They finally concluded that the statistical methodology varied substantially.

4.2. Recommendations

As shown in this article, a variety of methods were used to study subgroups. To improve the analyses and results of future IPDMA, certain standards should be developed. We would like to give some recommendations on how analyses should be handled.

First, besides using appropriate methods to study main and subgroup effects of specific treatments, it is also important to report them appropriately.

Second, to decide whether pooling of different studies is justified, heterogeneity should be tested using the I square, which describes the percentage of total variation across studies that can be attributed to heterogeneity rather than chance [29].

Third, if the raw data are available for all studies, we recommend direct pooling of this raw data instead of the two-stage method. A dummy variable for study should be included to adjust for possible confounding [14,30−32].

Fourth, when possible the performance of subgroup analyses should be specified a priori in the study protocol.

Fifth, prognostic modelling techniques should be used to select subgrouping variables because this method is shown to maintain statistical power, while preventing multiple testing [33].

Sixth, before stratified analyses can be performed, an interaction term (treatment × subgrouping variable) should be included in a regression model, and should reach statistical significance [8,23,25,33,34].

5. Conclusion

We showed that many IPDMA performed subgroup analyses, but the overall treatment effects were more frequently emphasized than the subgroup effects. To study subgroups, a wide variety of analytical methods were used in both CMA and IPDMA. In general, the use and reporting of appropriate methods for subgroup analyses should be promoted. So far, it has been shown that, when possible, subgroups should be defined before data analyses, and appropriate interaction tests should be used to identify relevant subgroups. Nevertheless, this study shows that the principles and methods of studying subgroups in IPDMA need further study.

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[32] Whitehead A, Omar RZ, Higgins JP, Savaluny E, Turner RM, Thompson SG. Meta-analysis of ordinal outcomes using individual patient data. Stat Med 2001;20(15):2243−60.
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Appendix A. Search strategy

Search strategy IPDMA shown per database

Search strategy IPDMA		
Database	Search strategy	Number
PubMed	#1 Shojania & Bero	
	#2 Our search	
	#3 Dutch Cochrane trial search	
	#4 Individual patient data	
	#5 #1 OR #2	
	#6 #5 AND #3 AND #4	1193
Embase	MeSH terms: trials, meta-analysis, individual patient data	1020
Web of science	#1 Meta-analysis (topic)	
	#2 Trial (topic)	
	#3 Individual patient data (topic and/or title)	
	#4 #1 AND #2 AND #3	214
Cochrane library	#1 Individual patient data from 1800–2004 [all products]	
	#2 Meta-analysis	
	#3 Clinical trials	
	#4 Controlled clinical trials	
	#5 Randomized controlled clinical trials	
	#6 #1 AND #2 AND (#3 OR #4 OR #5)	722

Search strategy CMA shown per database

Search strategy CMA		
Database	Search strategy	Number
PubMed	#1 Shojania & Bero	
	#2 Our search	
	#3 Meta-analysis MeSH	
	#4 Related article search specific IPD-article	
	#5 Systematic review search PubMed for #4	
	#6 #4 AND #1	
	#7 #4 AND #2	
	#8 #4 AND #3	
	#9 #5 OR #6 OR #7 OR #8 NOT guideline[pt]	
	NOT editorial[pt] NOT comment[pt] NOT letter[pt]	11149

Shojania & Bero—meta-analysis (1)

(((meta-analysis [pt] OR meta-analysis [tw] OR meta-analysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt]))

Our search—meta-analysis

(‘‘Meta-Analys is’’[MH] OR ‘‘Review Literature’’[MH] OR ‘‘meta-analysis’’[pt] OR ‘‘meta-anal*’’[tw] OR ‘‘meta-anal*’’[tw] OR ‘‘quantitativ* review*’’[tw] OR ‘‘quantitative* overview*’’[tw] OR ‘‘systematic* review*’’[tw] OR ‘‘systematic* overview*’’[tw] OR ‘‘methodologic* review*’’[tw] OR ‘‘methodologic* overview*’’[tw] OR ((‘‘review’’[pt] OR ‘‘review’’[tw]) AND (‘‘medline‘‘[tw] OR ‘‘cinahl’’[tw] OR ‘‘embase’’[tw] OR ‘‘excerpta’’[tw] OR ‘‘odds ratio’’[tw] OR ‘‘pooled’’[tw] OR ‘‘pooling’’[tw]))) NOT (letter[pt] OR editorial[pt] OR comment[pt] OR in vitro[mh] OR (‘‘animal’’[mh] NOT (‘‘human’’[mh] AND ‘‘animal’’[mh])))

Dutch Cochrane trials search—trials (2)

randomized controlled trial[PTYP] OR randomized controlled trials OR controlled clinical trial[PTYP] OR clinical trial[PTYP] OR clinical trials OR (clinical AND trial) OR random allocation OR random* OR double blind method OR single blind method OR (singl* OR doubl* OR trebl* OR tripl*) OR blind* OR mask* OR placebo* OR placebos OR research design OR comparative study OR evaluation studies OR follow up studies OR prospective studies OR control OR controlled OR prospectiv* OR volunteer* (‘‘individual patient data‘‘[All Fields] OR ‘‘individual patient data meta‘‘[All Fields] OR ‘‘individual patient data meta analysis‘‘[All Fields])

Individual patient data

‘‘individual patient data’’[All Fields] OR ‘‘individual patient’’[All Fields] OR ‘‘patient data’’[All Fields] OR ‘‘individual data’’[All Fields] OR ‘‘individual patient data meta’’[All Fields] OR ‘‘individual patient data meta analysis’’[All Fields] OR ‘‘individual patient’s data’’[All Fields] OR ‘‘original patient data’’[All Fields] OR ‘‘original data’’[All Fields]) OR ‘‘individual data analysis’’[All Fields] OR ‘‘raw data’’[All Fields] OR ‘‘raw patient data’’[All Fields] OR ‘‘raw data analyses’’[all Fields])

Embase MeSH terms

(‘randomized controlled trials’/exp OR ‘randomized trials’ OR ‘controlled trials’ OR ‘clinical trials’/exp OR (clinical AND trial) OR ‘random allocation’/exp OR random* OR ‘double blind method’/exp OR blind* OR mask* OR placebo* OR ‘research design’/exp OR comparative

study'/exp OR evaluation studies' OR 'followup studies'/exp OR 'prospective studies'/exp OR control* OR prospective*) AND ('meta analyses'/exp OR 'review literature'/exp OR 'meta analyses' OR review/exp OR 'quantitative review' OR 'qualitative review' OR 'systematic review'/exp OR pooled OR pooling OR evidence) AND ('individual patient data' OR 'individual patient' OR 'patient data'/exp OR 'individual data')

Meta-analysis MeSH

MeSH descriptor Meta-analysis in MeSH products AND MeSH descriptor review in MeSH products

Clinical trials

MeSH descriptor Clinical trials in MeSH products

Controlled clinical trials

MeSH descriptor Controlled clinical trials in MeSH products

Randomized controlled trials

MeSH descriptor Randomized controlled trials in MeSH products

References

(1) Shojania KG, Bero LA. Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. Eff Clin Pract 2001;4(4):157−62.
(2) Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using Pubmed. Int J Epidemiol 2002;31(1):150−53.

Appendix B. References of the comparison of IPDMA and their "matched" CMA

Number IPDMA	Number CMA	Pub date	Reference
31		1997	Schalm SW, Hansen BE, Chemello L, Bellobuono A, Brouwer JT, Weiland O, et al. Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. Meta-analysis of individual patient data from European centers. J Hepatol 1997;26(5):961−6.
	1M	2002	Kjaergard LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. Cochrane Database Syst Rev (Online: Update Software) 2002; (2):CD002234.
	3M	2001	Cummings KJ, Lee SM, West ES, Cid-Ruzafa J, Fein SG, Aoki Y, et al. Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C. Previously nonresponsive to interferon: a meta-analysis of randomized trials. JAMA 2001;285(2):193−9.
34		2000	Cornu C, Boutitie F, Candelise L, Boissel JP, Donnan GA, Hommel M, et al. Streptokinase in acute ischemic stroke: an individual patient data meta-analysis: The Thrombolysis in Acute Stroke Pooling Project Stroke 2000; 31(7):1555−60.
	17M	2003	Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev (Online: Update Software) 2003; (3):CD000213.
84		2001	Should all patients with Type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001;134(5):370−9.
	99M	2004	Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 2004;329(7470):828.
85		1996	Nicolucci A, Carinci F, Graepel JG, Hohman TC, Ferris F, Lachin JM. The efficacy of tolrestat in the treatment of diabetic peripheral neuropathy. a meta-analysis of individual patient data. Diabetes Care 1996;19(10):1091−6.
	104M	1996	Nicolucci A, Carinci F, Cavaliere D, Scorpiglione N, Belfiglio M, Labbrozzi D, et al. Meta-analysis of trials on aldose reductase inhibitors in diabetic peripheral neuropathy. The Italian Study Group. The St. Vincent Declaration. Diabet Med 1996;13(12):1017−26.
95		1998	Hughes MD, Daniels MJ, Fischl MA, Kim S, Schooley RT. CD4 cell count as a surrogate endpoint in HIV clinical trials: a meta-analysis of studies of the AIDS Clinical Trials Group. AIDS 1998;12(14):1823−32.
	123M	1995	Ioannidis JP, Cappelleri JC, Lau J, Skolnik PR, Melville B, Chalmers TC et al. Early or deferred zidovudine therapy in HIV-infected patients without an aids-defining illness. Ann Intern Med 1995;122(11):856−66.
	189M	1997	Staszewski S, Hill AM, Bartlett J, Eron JJ, Katlama C, Johnson J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. AIDS 1997;11(4):477−83.
111		2000	Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS Studies. Antiarrhythmics vs Implantable Defibrillator Study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21(24):2071−8.

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Appendix B. Continued

Number IPDMA	Number CMA	Pub date	Reference
	137M	2003	Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41(9):1573−82.
	138M	2003	Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 2003;138(6):445−52.
124		2004	Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. Int J Geriatr Psychiatry 2004;19(7):624−33.
	149M	2003	Lanctot KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety of cholinesterase inhibitors in alzheimer's disease: a meta-analysis. CMAJ 2003;169(6):557−64.
	150M	2003	Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev (Online: Update Software) 2003;(3):CD001190.
133		2002	Radiotherapy for early breast cancer. Cochrane Database Syst Rev (Online: Update Software) 2002;(2):CD003647.
	177M	2004	Van de Steene J, Vinh-Hung V, Cutuli B, Storme G. adjuvant radiotherapy for breast cancer: effects of longer follow-up. Radiother Oncol 2004;72(1):35−43.
	294M	2000	Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol2000;18(6):1220−9.
134		2000	Darbyshire J, Foulkes M, Peto R, Duncan W, Babiker A, Collins R, et al. Immediate versus deferred zidovudine (AZT) in asymptomatic or mildly symptomatic HIV infected adults. Cochrane Database Syst Rev (Online: Update Software) 2000;(2):CD002039
	123M	1995	Ioannidis JP, Cappelleri JC, Lau J, Skolnik PR, Melville B, Chalmers TC, et al. Early or deferred zidovudine therapy in HIV-infected patients without an AIDS-defining illness. Ann Intern Med 1995;122(11):856−66.
137		2000	Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Cochrane Database Syst Rev (Online: Update Software) 2000;(4):CD002805.
	193M	2001	Meert AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallot F, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2001;1(1):5.
138		2000	Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ 2000;321(7260):531−5.
	268M	2000	Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. Br J Cancer 2000;82(11):1789−94.
146		2000	Chemotherapy for non-small cell lung cancer. Non-Small Cell Lung Cancer Collaborative Group. Cochrane Database Syst Rev (Online: Update Software) 2000;(2):CD002139.
	224M	1995	Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer 1995;76(4):593−601.
150		1997	Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. Lancet 1997;350(9089):1417−24.
	235M	1997	Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation 1997;96(9):2823−9.
156		1994	Krogsgaard K, Bindslev N, Christensen E, Craxi A, Schlichting P, Schalm S, et al. The Treatment effect of alpha interferon in chronic hepatitis B is independent of pre-treatment variables. Results based on individual patient data from 10 clinical controlled trials. European concerted action on viral hepatitis (Eurohep). J Hepatol 1994;21(4):646−55.
	112M	1993	Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Ann Intern Med 1993;119(4):312−23.
159		1997	Clahsen PC, van de Velde CJ, Goldhirsch A, Rossbach J, Sertoli MR, Bijnens L, et al. Overview of randomized perioperative polychemotherapy trials in women with early-stage breast cancer. J Clin Oncol 1997;15(7):2526−35.
	247M	2000	Colleoni M, Bonetti M, Coates AS, Castiglione-Gertsch M, Gelber RD, Price K, et al. Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. J Clin Oncol 2000;18(3):584−90.

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Appendix B. Continued

Number IPDMA	Number CMA	Pub date	Reference
163		1998	Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97(22):2202−12.
	256M	2003	Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. Am J Med 2003;115(6):473−9.
166		2000	Pignon JP, Bourhis J, Domenge C, Designe L. chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. meta-analysis of chemotherapy on head and neck cancer. Lancet 2000;355(9208):949−55.
	265M	2001	Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. Head Neck 2001;23(7):579−89.
168		2000	Poynard T, McHutchison J, Davis GL, Esteban-Mur R, Goodman Z, Bedossa P, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. Hepatology 2000;32(5):1131−7.
	1M	2002	Kjaergard LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. Cochrane Database Syst Rev (Online: Update Software) 2002;(2):CD002234.
175		2001	Koch A, Ziegler S, Breitschwerdt H, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: meta-analysis based on original patient data. Thromb Res 2001;102(4):295−309.
	282M	2002	Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database Syst Rev (Online: Update Software) 2002;(4):CD000305.
	288M	1992	Nurmohamed MT, Rosendaal FR, Buller HR, Dekker E, Hommes DW, Vandenbroucke JP, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet 1992;340(8812):152−6.
176		2001	Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral Triptans (Serotonin 5-HT(1B/1D) Agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358(9294):1668−75.
	33M	2001	Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia 2001;21(2):129−36.
	37M	2000	Cady RK, Sheftell F, Lipton RB, O'Quinn S, Jones M, Putnam DG, et al. Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. Clin Ther 2000;22(9):1035−48.
178		2002	Mathurin P, Mendenhall CL, Carithers RL Jr, Ramond MJ, Maddrey WC, Garstide P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002;36(4):480−7.
	291M	1990	Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Ann Intern Med 1990;113(4):299−307.
184		2002	Barden J, Edwards JE, Moore RA, McQuay HJ. Ibuprofen 400 Mg is effective in women, and women are well represented in trials. BMC Anesthesiol 2002;2(1):6.
	62M	2004	Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. BMC Fam Pract 2004;5(1):10.
198		1998	D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. BMJ 1998;316(7140):1275−85.
	115M	2004	Liberati A, D'Amico R, Pifferi, Torri V, Brazzi L. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev (Online: Update Software) 2004;(1):CD000022.
208		2000	Human immunodeficiency virus Type 1 RNA Level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. HIV Surrogate Marker Collaborative Group. AIDS Res Hum Retroviruses 2000;16(12):1123−33.
	189M	1997	Staszewski S, Hill AM, Bartlett J, Eron JJ, Katlama C, Johnson J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. AIDS 1997;11(4):477−83.
210		1993	Nystrom L, Rutqvist LE, Wall S, Lindgren A, Lindqvist M, Ryden S, et al. Breast cancer screening with mammography: overview of swedish randomised trials. Lancet 1993;341(8851):973−8.
	329M	2002	Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. preventive services task force. Ann Intern Med 2002;137(5 Part 1):347−60.
	330M	2001	Olsen O, Gotzsche PC. Screening for breast cancer with mammography. Cochrane Database Syst Rev (Online: Update Software) 2001;(4):CD001877.

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Appendix B. Continued

Number IPDMA	Number CMA	Pub date	Reference
216		2004	Gill S, Loprinzi CL, Sargent DJ, Thome SD, Alberts SR, Haller DG, et al. Pooled analysis of fluorouracil-based adjuvant therapy for Stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22(10):1797−806.
	26M	1996	Zalcberg JR, Siderov J, Simes J. The role of 5-fluorouracil dose in the adjuvant therapy of colorectal cancer. Ann Oncol 1996;7(1):42−6.
233		2005	Adachi JD, Rizzoli R, Boonen S, Li Z, Meredith MP, Chesnut CH III. Vertebral fracture risk reduction with risedronate in post-menopausal women with osteoporosis: a meta-analysis of individual patient data. Aging Clin Exp Res 2005;17(2):150−6.
	345M	2003	Cranney A, Waldegger L, Zytaruk N, Shea B, Weaver B, Papaioannou A, et al. Risedronate for the prevention and treatment of postmenopausal osteoporosis. Cochrane Database Syst Rev 2003;(4):CD004523.
234		2005	Veldt BJ, Hansen BE, Eijkemans MJC, De Knegt RJ, Stijnen T, Habbema JDF, et al. Dynamic decision analysis to determine optimal treatment duration in chronic hepatitis C. Aliment Pharmacol Ther 2005;21(5):539−47.
	1M	2002	Kjaergard LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. Cochrane Database Syst Rev (Online: Update Software) 2002; (2):CD002234.
235		2005	Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. J Clin Oncol 2005;23(22):5074−87.
	347M	2005	Horan JT, Liesveld JL, Fernandez ID, Lyman GH, Phillips GL, Lerner NB, et al. Survival after HLA-identical allogeneic peripheral blood stem cell and bone marrow transplantation for hematologic malignancies: meta-analysis of randomized controlled trials. Bone Marrow Transplant 2003;32(3):293−98.
238		2005	Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables H, et al. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. J Thorac Cardiovasc Surg 2005;130(2):512−9.
	349M	2005	Bakhai A, Hill RA, Dundar Y, Dickson R, Walley T. Percutaneous transluminal coronary angioplasty with stents versus coronary artery bypass grafting for people with stable angina or acute coronary syndromes. Cochrane Database Syst Rev 2005;(1):CD004588.
243		2004	Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. Osteoporos Int 2004.
	345M	2003	Cranney A, Waldegger L, Zytaruk N, Shea B, Weaver B, Papaioannou A, et al. Risedronate for the prevention and treatment of postmenopausal osteoporosis. Cochrane Database Syst Rev 2003;(4):CD004523.
334		2003	Jafar TH, Schmid CH, Stark PC, Toto R, Remuzzi G, Ruggenenti P, et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. Nephrol Dial Transplant 2003;18(10):2047−53.
	298M	1997	Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. angiotensin-converting-enzyme inhibition and Progressive Renal Disease Study Group. Ann Intern Med 1997;127(5):337−45.
342		2002	Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52(12):1166−74.
	353M	2002	Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 2002;180:396−404.
352		2006	Auperin A, Le Pechoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol 2006;17(3):473−83.
	224M	1995	Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer 1995;76(4):593−601.
354		2006	Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 2006;64(1):47−56.
	357M	2004	Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004;22(22):4604−12.