Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments

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.Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments.

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ABSTRACT

Objective To evaluate the impact of searching clinical trial registries on including the results of additional randomized controlled trials (RCTs) in systematic reviews (ie, eligible RCTs not originally included in the systematic review classified as completed or terminated in the registry).

Design 1) We identified systematic reviews of RCTs assessing pharmaceutical treatments published between June 2014 and January 2015. 2) For all systematic reviews that did not report a trial registry search but reported the information to perform it, we searched the World Health Organization International Trials Registry Platform (WHO ICTRP Search Portal) for completed or terminated RCTs not originally included in the systematic review. 3) We searched the results for all completed or terminated RCTs identified and 4) performed meta-analyses when additional data were retrieved.

Data source MEDLINE and WHO ICTRP Search Portal

Data extraction For each systematic review, two researchers independently extracted the outcomes analyzed, the number of patients included and the treatment effect estimated. For each RCT identified, two researchers independently determined whether the results were available (ie, posted, published or available on the sponsor website) and extracted the data.

Results Among 223 selected systematic reviews, 116 (52%) did not report a search of trial registries; 21 of these did not report the information to perform the search (key words, search date). We performed the search for 95 systematic reviews; for 54/95 (57%), we found no additional RCTs and for 41/95 (43%) we identified 122 additional RCTs. The search allowed for increasing the number of patients by more than 10% in 19 systematic reviews, 20% in 10, 30% in 7, and 50% in 4. Moreover, 63 RCTs had results available; the results for 45 could be included in a meta-analysis. We reanalyzed 14 systematic reviews including 45 RCTs. The weight of the additional RCTs in the re-calculated meta-analyses ranged from 0% to 58% and

was greater than 10% in 5 of 14 systematic reviews, 20% in 3, and 50% in 1. The change in summary statistics ranged from 0% to 29% and was greater than 10% for 5 of 14 systematic reviews and greater than 20% for 2. However, none of the changes to summary effect estimates led to a qualitative change in the interpretation of the results once the new trials were added.

Conclusions Trial registries are an important source for identifying additional RCTs. The additional number of RCTs and patients included if a search were performed varied across systematic reviews.

INTRODUCTION

Systematic reviews are considered to provide the highest level of evidence[1,2]. They are widely used by clinical practice guideline developers, granting health agencies and journal editors [3–6]. A major challenge of systematic reviews is to identify all relevant randomized controlled trials (RCTs), whatever their publication status[7–13]. Indeed, results for half of RCTs are never published and the publication status is affected by the nature and direction of results, which may bias the results of the systematic review[14]. In some cases, the importance of unpublished trials can be considerable; for example, the addition of unpublished data in the updated Cochrane review assessing the efficacy of neuraminidase inhibitor for influenza modified the conclusion[15,16]. Initiatives aimed at reducing publication bias include the trial registration policy initiated by the International Committee of Medical Journal Editors (ICMJE) in 2005[17]. In 2007, the US Food and Drug Administration Amendments Act (FDAAA) required the posting of clinical trial results at ClinicalTrials.gov no later than one year after the date of final collection of data for the pre-specified primary outcome, for all phase II to IV trials of drugs, biologic treatments and devices having at least one site in the United States[18,19]. The research community has embraced this policy, and there was a marked increase in trial registration around the time of implementation of the ICMJE policy[20]. In April 2016, about 90,000 completed experimental studies were registered at ClinicalTrials.gov (the largest registry), and 16,500 have results posted.

When performing systematic reviews, the search of trial registries is now considered an essential tool [3,21–23]. Previous studies showed that clinical trial registry search is not systematically reported by authors of systematic reviews [24–26], but to our knowledge, none had systematically performed a trial registry search to quantify the impact of searching trial registries. The objectives of this study were to 1) describe whether and how clinical trial

registries were searched in published systematic reviews of pharmaceutical treatments and 2) evaluate the impact of searching trial registries on the identification of additional RCTs (ie, eligible completed or terminated RCTs not included in the systematic review). For this purpose, we identified a sample of systematic reviews of RCTs assessing pharmaceutical treatments indexed in PubMed and recorded whether a search of clinical trial registries was performed. Then, for all systematic reviews not reporting a search in clinical trial registries but reporting the information to perform it, we systematically performed the search.

METHODS

Identification of systematic reviews

Search strategy

We systematically searched MEDLINE via PubMed for all systematic reviews of RCTs assessing pharmaceutical treatments that were published in English between June 1, 2014 and January 31, 2015 by searching for "Meta-Analysis[ptyp] AND ("2014/06/01"[PDAT]: "2015/01/31"[PDAT]) AND English[lang] appearing in the title, abstract or keywords (date search: March 16, 2015)

Inclusion and exclusion criteria

One researcher screened all titles and abstracts of citations retrieved to identify all reports of systematic reviews of RCTs with at least one meta-analysis including at least two RCTs and assessing pharmaceutical treatment (ie, drug, health-related biological product or biologic supplementation). We excluded updates of previously published systematic reviews and systematic reviews of diagnostic test accuracy, prognosis, economics evaluations, genetics, non-RCT studies, network meta-analyses, indirect comparison meta-analysis as well as individual patient data meta-analyses. The full-text of potentially relevant citations was obtained. As a quality control procedure, another researcher independently screened 20% of the citations and confirmed the eligibility of all systematic reviews included. Discrepancies were discussed to reach consensus.

Data extraction

From the published reports and supplementary appendices when available, two researchers independently recorded the following:

1) the general characteristics of the systematic review (ie, the type of journal: general medical journal, specialty journal or Cochrane review), the funding source (none-profit, for-profit, not reported or unclear), and the number of RCTs and participants included in the systematic review.
2) the reporting of the clinical trial registry search (ie, whether a search in a clinical trial registry was reported, the name and type of registries searched, and whether the results of the search were reported (the number and identification of RCTs identified from the clinical trial registry search).

Any disagreement was resolved by discussion and consensus.

Impact of searching clinical trial registries

For each systematic review that did not report a search in clinical trial registries, we systematically performed a search reproducing the conditions of the original search reported in the systematic review, particularly taking into account the date of the search and the inclusion criteria of the systematic review.

We screened the retrieved records and identified all eligible RCTs classified in the registries as completed (i.e., RCTs that ended normally) or terminated (i.e., RCTs that stopped recruiting or enrolling participants early and would not start again) that were not initially included in the systematic reviews

Search strategy

Our search strategy followed the same search and selection process described by the authors of the published systematic reviews.

1) From the selected full-text articles and all available supplementary materials, we systematically recorded the search terms related to the condition and interventions

used by authors and the date of last electronic search. Systematic reviews that did not provide search terms or the date of search were excluded from this analysis.

2) We searched the World Health Organization International Trials Registry Platform (WHO ICTRP Search Portal). We chose this portal (i.e., a portal provides access to a central database containing the trial registration data sets provided by several registries) because it includes 16 national and international primary registries including ClinicalTrials.gov. In the advanced search window of the WHO ICTRP Search Portal (http://apps.who.int/trialsearch/), we entered the search terms recorded in the "condition" and "intervention" fields with Boolean operators. We chose "all" in the "recruitment status" field and "Search for clinical trials in children" when appropriate. Details of the search strategies and keywords for each systematic review are available in Appendix 1.

Identification of completed or terminated RCTs

For each search, we downloaded all the citations retrieved and identified all studies with a recruitment status recorded as "completed" or "terminated" registered before the date of the last search reported in the systematic review and

For each systematic review, two researchers independently screened the records retrieved and selected all completed or terminated RCTs not already included in the systematic review that fulfilled the systematic review eligibility criteria in terms of participants, interventions, and comparator. We systematically verified in the history or archives of the registry that the recruitment status was recorded as "completed" or "terminated" before the date of the search (Appendix 2). Any disagreements were resolved by consensus. A third researcher screened all selected records to confirm their inclusion.

Availability of RCT results

For each selected RCT, two researchers independently determined whether the trial results were available (ie, posted, published or available on the sponsor website). We searched for 1) results posted on clinical trial registries and 2) publications referenced on the trial registry and 3) performed an electronic search of PubMed and Google and searched the sponsor website. All trials with results available were screened, and we selected only trials for which the results became available before the last electronic search of the systematic review.

Inclusion of the RCT results in meta-analyses

We recorded the number of meta-analyses reported in the systematic review, the number of meta-analyses that could include the additional RCTs, and the number of meta-analyses for which all the RCTs identified had available results and could be included in the meta-analysis.

Finally, we determined the impact of including the RCTs on treatment effect estimates. For this purpose, we used an algorithm to select one meta-analysis in which at least one RCT with results available could be included.

We proceeded as follows:

1. For each systematic review, we recorded all the outcomes of the meta-analysis reported in the systematic review report.

2. For each eligible RCT with results available, we determined whether the RCT could be included in the meta-analyses previously recorded, i.e., the RCT reports included the following:

    a. For continuous outcomes: sample size, mean and one measure of dispersion (standard deviation, standard error or confidence interval) by group. Standard errors and confidence intervals were converted in standard deviations to

perform the meta-analyses. When results were given for separate subgroups, we pooled the results, the pooled sample size being the sum of the subgroup sample sizes, the pooled mean being the weighted mean of the subgroups and the pooled standard deviation combined[3].

b. For binary outcomes: sample size and number of events by group.

c. For time-to-event outcomes: hazard ratio and 95% confidence interval or median survival times and confidence intervals by group[27].

3. When RCT(s) could be included in several meta-analyses, we selected only one meta-analysis according to the following order of outcomes analyzed: 1) the primary efficacy outcome of the systematic review, 2) the primary safety outcome, 3) the patient-important outcome such as mortality, quality of life or morbidity outcome. If several of these outcomes could be used to include new RCT(s), we selected the first meta-analysis reported. If none of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported.

For each meta-analysis selected, we extracted from the RCTs identified the outcome data (ie, number of events and number of patients in each group, means, standard deviations, etc). When the outcome data were available in several sources, we considered in priority the data reported 1) in the registry, 2) in a published report and 3) on the sponsor website.

Data analysis

Statistical analyses involved use of R v3.1.0 (http://www.R-project.org, the R foundation for statistical Computing, Vienna, Austria). Qualitative variables are represented by percentages. Quantitative variables are represented by medians (quartile 1–quartile 3 [Q1–Q3]). In a post-hoc analysis, we used a chi-square test to compare the proportion of reviews reporting a trial

registry search according to the type of systematic review (Cochrane vs non-Cochrane) and funding source (not-for-profit funding or not funded vs for-profit funding, funding not reported or unclear).

For the meta-analysis selected for recalculation (one per selected systematic review), we calculated summary statistics (risk ratios, odds ratios, hazard ratios, mean differences or standardized mean differences) and the I^2 statistic (measure of heterogeneity) with and without trials retrieved by a trial registry search. We reported the magnitude of the change in the result of the meta-analysis as a percentage change in the summary statistic after including the RCTs retrieved. We re-analysed the published meta-analyses by using the same statistical method (Peto, Mantel-Haenszel, inverse variance), analysis model (fixed v random effects), and measure of effect (risk ratio, odds ratio, weighted mean difference) used by the original authors. For all meta-analyses, we assessed heterogeneity by calculating the I^2 statistic and τ^2 (DerSimonian-Laird estimate).

RESULTS

Identification and characteristics of reports

Among the 2,249 citations retrieved, we included 223 reports of systematic reviews with meta-analyses (fig 1). The characteristics of the included systematic reviews are in table 1. One-third (35%) were Cochrane reviews; the median [Q1-Q3] number of RCTs included in systematic reviews was 10 [6-18] and the median [Q1-Q3] number of patients was 1,594 [614-5027].

Reporting of clinical trial registry search in systematic reviews

Among the 223 systematic review reports included, 107 (48%) reported searching at least one clinical trial registry: 48 of these (45%) reported searching only individual registries, 11 (10%) only portals and 44 (41%) a combination of individual registries and portals. The portal and individual register most frequently searched were the WHO ICTRP Search Portal (n=53/107, 50%) and ClinicalTrials.gov (n=89/107, 83%), and for 40 studies (37%), both were searched. In only 47 of the 107 (21%) reports were the results of the clinical trial registry search clearly described (i.e., with a description of the number and identification of RCTs found from the search) (fig 1, table 1): 16 of these 47 reviews (34%) did not retrieve any eligible RCTs, 11 (23%) retrieved only ongoing studies, 13 (28%) retrieved at least one completed or terminated RCT without results available and 7 (15%) retrieved at least one completed or terminated RCT with results identified. Of these last 7, 3 included RCTs in at least one meta-analysis.

A search of a trial registry was more frequent in Cochrane than non-Cochrane reviews [65/77 (84%) vs 42/146 (29%), p<0.001] and not-for-profit funding or no funding than for-profit funding, funding not reported or unclear [79/139 (57%) vs 28/84 (33%), p<0.001].

Impact of searching clinical trial registries

Identification of completed or terminated RCTs

Among the 116 systematic reviews not reporting a search in trial registries, for 21 (18%), we were not able to perform the clinical trial registry search because the search date or the keywords were not reported. Therefore, we performed the search for 95 systematic reviews. Among the 15,282 records screened (median [Q1-Q3] records screened for each systematic review = 23 [6-150]), we identified 122 eligible RCTs terminated or completed (involving 52,743 patients) not originally included in the systematic review. Among the 122 RCTS, 104 (85%) were classified as completed and 18 (15%) as terminated. Among the 18 RCTs classified terminated, 3 had results available and were included in meta-analyses, 2 were stopped early because of adverse events and 1 was stopped early because of futility. The remaining 15 RCTs had no results available and no information on the reason for stopping early.

Availability of RCT results

Overall, the trial registry searches identified at least one eligible RCT for 41 of 95 (43%) systematic reviews, with a median [Q1-Q3] of 9% [4-18] additional patients per systematic review (fig 2, table 2, Appendix 3). Among these 41 systematic reviews with additional RCTs identified, the number of patients included was increased by 10% in 19, 20% in 10, 30% in 7, and 50% in 4.

We identified results for 63 of 122 RCTs (52%) involving 42,202 patients, and 45 of 122 (37%) involving 21,358 patients could be included in the quantitative analyses (i.e., reported sufficient data to be included in at least one meta-analysis of the systematic review). The 18 remaining RCTs with results could not contribute to the quantitative analysis because of differences in definition or metrics used between the outcome reported in the RCT and the outcome of the systematic review or outcome reporting bias.

The results of the RCTs identified were 1) posted (n=41/63, 65%); 2) published as identified by a reference reported on the registry (n=21/63, 33%) or from a complementary search (n=10/63, 16%); or 3) were available on the company's Web site (n=31/63, 49%). The results were available in one (n= 29/63, 46%), two (n=27/63, 43%) or three sources (n= 7/63, 11%).

For 14 systematic reviews, the trial registry searches allowed for identifying RCTs with results (n= 45) that could contribute to the quantitative analysis. Among the 73 meta-analyses reported in these 14 systematic reviews; the search in trial registries retrieved additional results that could be included in 59 meta-analyses. Overall, 31 of 59 (53%) meta-analyses were considered complete (ie, all the RCTs identified had available results and could be included in the meta-analysis).

Inclusion of the RCT results in meta-analyses

Finally, we recalculated the effect estimates for the selected meta-analyses from the 14 systematic reviews including RCTs that could contribute to the quantitative analysis. Among the 14 meta-analyses selected, 6 involved safety outcomes and 8 efficacy outcomes. In the meta-analysis without additional RCTs, results for 12 of 14 outcomes significantly favoured the experimental treatment and results for 2 did not differ from the comparator.

The weight of the eligible RCTs included ranged from 0% to 58% and was greater than 10% for 5 of 14 systematic reviews, 20% for 3, and 50% for 1. The change in summary statistics ranged from 0% to 29% and was greater than 10% for 5 of 14 systematic reviews and greater than 20% for 2. For example, in the meta-analysis with a 29% change in summary effect, the mean difference changed from -0.35 [-0.51; -0.19] to -0.45 [-0.55; -0.36], for a larger effect after inclusion of the new RCTs. However, including the RCTs identified by a trial registry search did not change the statistical significance or direction of the results. Detailed descriptions of the 14 meta-analyses are provided in table 2.

DISCUSSION

Summary of findings

Despite recommendations [23], about half of the published systematic reviews performed a trial registry search and only one-fifth reported the results of the search. When we performed the search, we identified additional studies for 43% of the systematic reviews. However, because of the lack of data availability, data for half of the eligible RCTs retrieved could not be included in systematic reviews. We re-analyzed 14 meta-analyses to include data from RCTs retrieved by the trial registry search. The weight of the eligible RCTs included ranged from 0% to 58% and the change in summary statistics from 0% to 29%. The addition of data from registries mainly adds to the precision of summary estimates, but none of the changes led to a qualitative change in the interpretation of the results once the new trials were added.

Comparison with other studies

Our results are consistent with other studies showing that the search for unpublished trial data is still often lacking in systematic reviews[24–26,28,29] as in a random sample of 300 recent systematic reviews indexed in MEDLINE in February 2014 of which 19% reported searching trial registries[30]. A previous study by Hart in 2012 aimed to re-analyze meta-analyses by adding unpublished trial outcome data obtained from the US Food and Drug Administration (US FDA) to published meta-analyses[31]. The study documented that the addition of unpublished trial data obtained from the US FDA could change the magnitude of the effect size or in a few cases the statistical significance of meta-analyses. Moreover, in a systematic review by Golder in 2016, aiming at quantifying the impact of the underreporting of adverse events in systematic reviews showed that the inclusion of unpublished data may reduce the imprecision of pooled effect estimates in meta-analysis of adverse events[32]. However, to

our knowledge, the impact of searching trial registries in terms of identifying trials and their inclusion in the analysis when results are available has never been evaluated.

Limitations

Our study has some limitations. First, we searched only the WHO ICTRP Search Portal using the keywords reported by authors for their electronic search. Consequently, we cannot claim that we identified all RCTs. However, this portal brings together 16 national and international primary registries including ClinicalTrials.gov. Furthermore, in a previous study, the overlap between ICTRP and ClinicalTrials.gov was good, because all records identified in ClinicalTrials.gov were also identified in ICTRP[33]. Second, we did not account for eligibility criteria related to trial quality. The quality assessment of data recorded from trial registries is difficult and some trials could secondarily be excluded because of insufficient quality. Third, we did not attempt to contact investigators of the unpublished trials to obtain results. In fact, we aimed to reproduce the condition the authors encountered and it would not be appropriate to ask authors for results after such a delay. Further, we did not search for additional data presented in conference abstracts or searched US FDA and EMA websites. Therefore, the number of systematic reviews with trials identified by a search of clinical trial registries and the amount of data from RCTs retrieved from clinical trial registries may be underestimated. Fourth, we choose to include only one meta-analysis per systematic review to make the workload manageable. Finally, we focused on only systematic reviews of pharmaceutical treatment and cannot extrapolate to non-pharmaceutical treatments because the regulation for trial registration and posting of results is less stringent with these treatments.

Implications for clinicians and policy makers

Clinical trial registries have been developed and their use enforced by editors and policy makers to reduce waste in research and publication bias. They have been considered an important step toward more transparency and increasing research value.

Searching clinical trial registries is recommended when performing systematic reviews. In our study, the addition of new RCTs in meta-analyses affected treatment effect estimates but did not change the statistical significance of the results or the direction of the treatment effect, although it increased precision.

Nevertheless, searching clinical trials registers remains an essential recommendation for the conduct of systematic reviews and should be enforced. In fact, the objective of systematic reviews is to collate all empirical evidence [3]. However, overall, results for only about half of clinical trials are published, and searching only electronic bibliographic databases gives access to only the "tip of the iceberg" [24–26]. In our study, searching clinical trials registries allowed for finding new evidence for almost half of the systematic reviews (41/95), and this new evidence was usable in at least one meta-analysis in one-third of these systematic reviews (14/41). Finally, searching trial registries in general represented a low burden. The median (Q1-Q3) number of records to screen by systematic review was low (23 [6-150]). The results for 41 of 63 trials were posted at ClinicalTrials.gov and therefore immediately available. Furthermore, a previous study showed that the reporting of results was more complete at ClinicalTrials.gov than in published reports[34]. Of course, one important limitation of this search is the lack of availability of the results for completed trials and the low level of details on the methodologic quality recorded in the registries. Some initiatives to facilitate the access to clinical trial results, such as the 2007 FDAAA, which requires the posting of clinical trial results[18] or pharmaceutical company policies[35], have been implemented. Some

researchers have developed an intervention to improve posting, such as emailing a reminder of the FDAAA 801 requirement to responsible parties[36]; other interventions are necessary. Recently, the new rules of trial registration at ClinicalTrials.gov requires submission of a full protocol and statistical analysis plan at the same time as submission of results [37]. Registries could be an even more important source of results in the future."

CONCLUSION

Searching clinical trial registries is essential for identifying additional trials that could increase the value of systematic reviews. However, the lack of availability of RCT results limits the value of the search. Trial registry searching should be promoted and enforced, as should the posting of trial results.

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Contributions

Conceived, designed and experiments: MB, AY, IB, PR, Wrote the first draft:
MB, IB, AY Contributed to the writing of the manuscript: AY, IB, EP, PR
Data analyses MB, AY, EP and IB.

Transparency declaration

AY affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

AY and IB had access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

All data from this study—including literature searches, additional explanatory material, and data extraction forms—are available on request.

Conflicts of interest

None of the authors have conflicts of interest to declare.

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This study received no funding.

TABLES

Table 1 Characteristics of included systematic reviews and registry searches

Table 2 Effect of adding randomized controlled trials retrieved from clinical trial registries on meta-analyses

FIGURES

Fig 1 Study flow diagram

Fig 2 Identification of trials by searching trials registries

APPENDIX

Appendix 1 Verification of the recruitment status according to the registry

Appendix 2 Keywords, date of search and detection in the WHO ICTRP Search Portal

Appendix 3 Systematic reviews for which data could not be added to the meta-analysis

Appendix 4 Impact of trial registry searches on summary statistics

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29

Figure 1: Study flow diagram

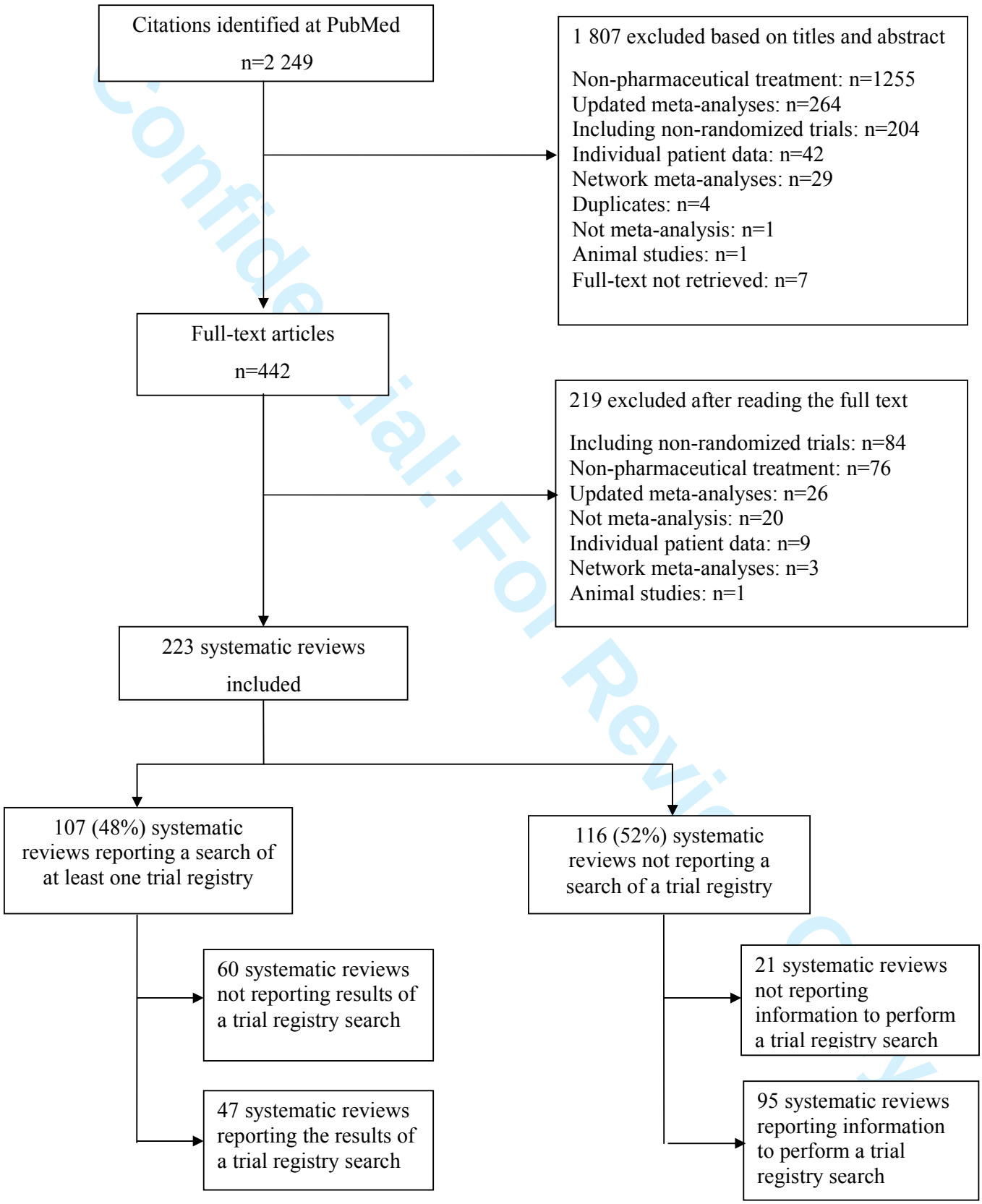
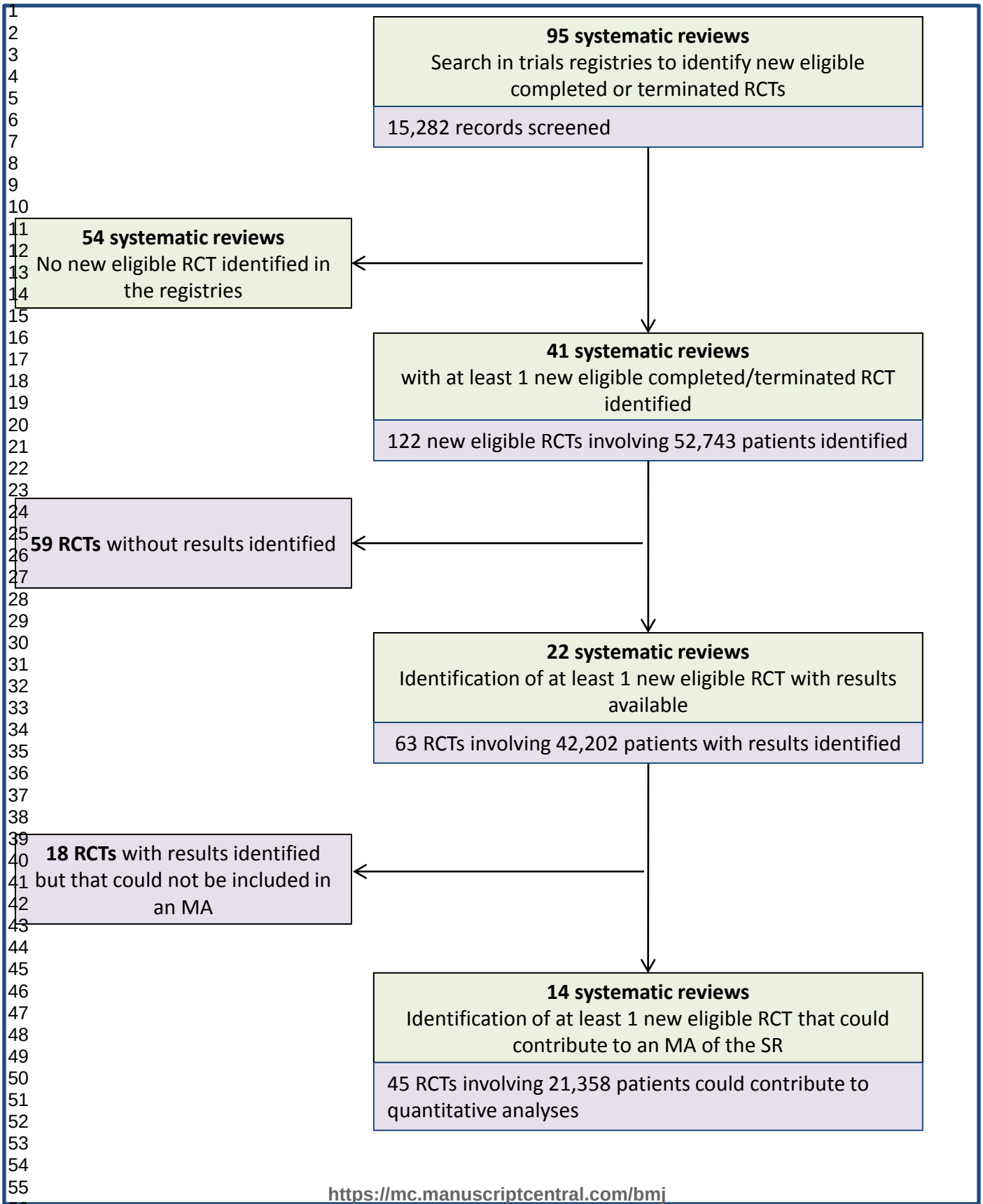


Figure 2: Identification of trials by searching trials registries (WHO ICTRP Search Portal)



MA= meta-analysis, IQR= Interquartile range, Med= median, RCT = randomized controlled trial

The RCTs could not contribute to the quantitative analyses because outcomes of interest were not reported

Table 1: Characteristics of included systematic reviews and registry searches

Characteristics of the systematic reviews		Systematic reviews n=223 (%)
Type of review	- Cochrane reviews	77 (35)
	- Non-Cochrane reviews	146 (65)
Funding	- Not-for-profit	106 (47.5)
	- For-profit	3 (1.3)
	- No funding	33 (14.8)
	- Not reported or unclear	81 (36.3)
Number of RCTs included in the systematic reviews	Median [Q1-Q3]	10.0 [6.0-18.0]
	Min-max	2-158
Number of patients included in the systematic reviews *	Median [Q1-Q3]	1,594.0 [614.0-5,027.0]
	Min-max	47-102,607
Clinical trial registry search (yes)		**107 (48.0)**
Characteristics of registry search		**n=107 (%)**
Search portal (at least one portal searched)		57 (53.3)
- WHO ICTRP		53 (49.5)
- MetaRegister of Current Controlled Trials		15 (14.0)
- International Federation of Pharmaceutical Manufacturers and Associations		1 (0.9)
Individual clinical trial registries approved by the WHO or ICMJE (at least one searched)		93 (86.9)
- ClinicalTrials.gov		89 (83.2)
- International Standard Randomised Controlled Trial Number Register		22 (20.6)
- EU Clinical Trials Register		5 (4.7)
- Australian New Zealand Clinical Trials Registry		5 (4.7)
- Japan Primary Registries Network		3 (2.8)
- Chinese Clinical Trial Registry		1 (0.9)
Non-approved or unclear individual clinical trial registries		11 (10.3)

RCTs: Randomized controlled trials
[Q1-Q3] : Interquartil range
WHO ICTRP: World Health Organization International Trials Registry Platform
** Number of patients included was unclear or missing in 9 non-Cochrane systematic reviews*

Table 2 Effect of adding randomized controlled trials retrieved from clinical trial registries on meta-analyses

ID[1]	Number of RCTs[2] (and patients) included in the original SR[3]	Number of RCTs (and patients) retrieved from trial registry search	Number of RCTs (and patients) retrieved with results that could contribute to at least one MA[4]	Description of the selected[5] outcomes (type of outcome: PO, SO or U[6])	Summary statistic of the selected meta-analysis in the original SR	Summary statistic of the selected meta-analysis with new RCTs included	Weight of the new RCTs included in the selected meta-analysis (%)	Change in summary statistic (%)	Direction of change in summary statistic	Change in statistical significance
Efficacy outcomes										
1	18 (9952)	1 (73)	1 (73)	Atrial fibrillation (PO)	OR[7] 0.51 [0.36 ; 0.70]	OR 0.53 [0.38 ; 0.73]	1.9	6	Decrease efficacy	No
4	9(11390)	2 (355)	1 (322)	PASI 75[8] (PO)	RR[9] 18.28 [12.76 ; 26.17]	RR 14.20 [10.72 ; 18.81]	37.6	9	Decrease efficacy	no
3	20 (8225)	8 (1806)	2 (1400)	Overall survival (U)	HR[10] 0.87 [0.82 ; 0.91]	HR 0.88 [0.84 ; 0.93]	14.8	8	Decrease efficacy	No
4	6 (2264)	1 (1029)	1 (1029)	Overall survival (U)	HR 0.89 [0.80 ; 0.99]	HR 0.90 [0.83 ; 0.98]	34.8	10	Decrease efficacy	No
5	12 (6297)	2 (340)	1 (102)	Overall survival (U)	HR 0.99 [0.90 ; 1.09]	HR 0.99 [0.90 ; 1.08]	3.5	0	No change	No
6	32 (6812)	8 (3831)	5 (2942)	Neuropsychiatric inventory total score (U)	SMD[11] -0.21 [-0.29 ; -0.12]	SMD -0.19 [-0.28 ; -0.11]	9.0	10	Decrease efficacy	No

7	9 (2857)	1 (514)	1 (514)	UPDRS[12] scale (U)	MD[13] -1.77 [-2.13 ; -1.41]	MD -1.66 [-1.99 ; -1.32]	16.1	6	Decrease efficacy	No
8	23 (18980)	28 (14733)	21 (11298)	HbA1c[14] (U)	MD -0.35 [-0.51 ; -0.19]	MD -0.45 [-0.55 ; -0.36]	58.3	29	Increase efficacy	No
Safety outcomes										
9	14 (42602)	1 (166)	1 (166)	Major bleeding (U)	OR 0.88 [0.79 ; 0.99]	OR 0.88 [0.79 ; 0.98]	0.2	0	No change	No
10	70 (32054)	4 (2039)	4 (2039)	Opportunistic infection (PO)	OR 1.79 [1.17 ; 2.74]	OR 1.52 [1.04 ; 2.23]	18.7	28	Less harm	No
11	9 (11007)	4 (810)	2 (550)	Withdrawal due adverse event (SO)	RR 0.83 [0.74 ; 0.93]	RR 0.85 [0.76 ; 0.94]	0.2	13	More harm	No
12	16 (33958)	1 (129)	1(129)	Major bleeding (PO)	RR 0.79 [0.52 ; 1.19]	RR 0.80 [0.54 ; 1.20]	1.5	5	More harm	No
13	19 (101801)	2 (317)	2 (317)	Treatment discontinuation due to all cause (PO)	RR 1.40 [1.08 ; 1.82]	RR 1.37 [1.06 ; 1.75]	8.6	6	Less harm	No
14	43 (16011)	7 (943)	2 (477)	Fatal adverse event (U)	RR 1.63 [1.32 ; 2.01]	RR 1.62 [1.32 ; 2.99]	1.2	1	Less harm	No

[1] ID = Identification of the systematic review, corresponding to appendix 4
[2] RCT = randomised controlled trial
[3] SR = systematic review
[4] MA = meta-analysis

[5] For each systematic review, we selected one meta-analysis in which at least one RCT with results available could be included according a predefined hierarchical order of outcomes analyzed as follows: 1) the primary efficacy outcome, 2) the primary safety outcome, and 3) the most clinically relevant outcome. If none of these meta-analyses could include an RCT, we selected the meta-analysis that could include at least one RCT that was reported first.
[6] PO = the outcome was defined as primary in the SR, SO = the outcome was defined as secondary in the SR, U = primary and secondary outcome were not pre specified in the SR
[7] OR = odds ratio
[8] PASI 75 = 75% reduction in the Psoriasis Area Severity Index
[9] RR = Risk ratio
[10] HR = hazard ratio
[11] SMD = standardized mean difference
[12] UPDRS scale = Unified Parkinson Disease Rating Scale
[13] MD = mean difference
[14] HbA1c = glycated hemoglobin

APPENDIX

Appendix 1: Verification of the recruitment status according to the registry

ClinicalTrials.gov

We systematically verified the Last Verified date recorded in the registry (ie, the most recent date on which all of a clinical study's information on ClinicalTrials.gov was confirmed as accurate and current).

If the Last Verified date was before the date of the search, the trial was included.

If the Last Verified date was after the date of the search, we verified in the archives of the registry Web site when the status was modified and we excluded trials that were recorded as "completed" or "terminated" after the date of search.

UMIN registry:

We systematically verified the "Date of last update". If this date was before the date of the search, the trial could be included.

If the" Date of last update" was after the date of search, we verified that the "date trial data considered complete" and the "date analysis concluded" was before the date of the search and we verified in the history of the registry that these dates were recorded before the date of search; if not, the trial was excluded.

ISRCTN:

We systematically verified the "Last edited" date. If this date was before the date of the search, the trial could be included.

If the" Last edited" date was after the date of the search, we verified the "Recruitment end date" and the "Overall trial end date."

Because this registry did not give access to archives, if additional identifiers with a ClinicalTrials.gov number was provided, we searched this registry.

ANZCTR:

We systematically verified the timing of the registration status in the history.

The history reported the timing of the modification with the reason for the modification.

Eudract:

We downloaded the full trial details; we checked the trials status and the date on which this record was first entered in the EudraCT database

Appendix 2: Keywords, date of search and finding in the WHO ICTRP Search Portal

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
1	stomach neoplasms OR gastric cancer OR carcinosis	paclitaxel OR S-1 OR fluorouracil		30/11/2013	350
2	HIV OR antiretroviral naïve	tenofovir OR gs4331 OR gs 4331 OR gs-4331		31/10/2013	344
3	Sleep Bruxism			31/08/2014	23
4	constipation OR fecal impaction	polyethylene glycol OR laxative		10/02/2014	48
5		perphenazine		31/10/2013	14
6	food hypersensitivity OR food allergy	probiotics OR bifidobacterium OR lactobacillus		30/09/2013	10
7	coronary angiography	statin OR atorvastatin OR rosuvastatin OR cerivastatin OR simvastatin OR pravastatin OR lovastatin OR Hydroxymethylglutaryl-CoA reductase inhibitors OR HMG-CoA reductase inhibitors		31/01/2014	321
8	Myelodysplastic Syndromes OR refractory anemia OR Preleukemia OR refractory cytopenia OR Refractory anemia excess blasts OR Thrombocytopenia	Romiplostim OR eltrombopag		28/02/2014	64
9	hypertension OR blood pressure	abitesartan OR azilsartan OR candesartan OR elisartan OR embusartan /// eprosartan OR forasartan OR irbesartan OR losartan OR milfasartan OR olmesartan OR saprisartan OR tasosartan OR telmisartan OR valsartan OR zolasartan OR KT3-671 OR atacand OR teveten OR avapro OR cozaar OR benicar OR micardis OR diovan		15/01/2014	909
10	thrombosis OR embolism OR thromboembolism	new oral anticoagulants OR direct coagulation OR Xa inhibitor OR IIa inhibitor OR thrombin inhibitor OR rivaroxaban OR dabigatran OR apixaban OR edoxaban		28/02/2014	106
11	alcoholic pancreatitis OR chronic pancreatitis	antioxidant OR ascorbic acid OR bilirubin OR butylated hydroxyanisole OR butylated hydroxytoluene OR canthaxanthin OR carotenoids OR catalase OR ergothioneine //// grape seed extract OR melatonin OR nordihydroguaiaretic acid OR probucol OR propyl gallate OR pyrogallol OR quercetin OR selenium OR silymarin OR thioctic acid OR tocopherols /// tocotrienols OR uric acid OR vitamin OR alpha-		31/03/2010	6

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
		tocopherol OR beta-tocopherol OR gamma-tocopherol OR zeta carotene OR beta-carotene OR curcumin OR methionine OR allopurinol OR oxidizing agent			
12	chronic kidney disease AND hyperuricemia			15/11/2012	11
13	acute coronary syndromes OR ST-elevation myocardial infarction OR non-ST-elevation myocardial infarction OR unstable angina	bivalirudin OR angiomax OR hirulog OR stent OR percutaneous coronary		09/04/2014	71
14	atrial fibrillation	atorvastatin		30/04/2014	12
15	arterial compliance OR pulse wave OR vascular siffnesss OR applanation tonometry OR arterial stiffness OR pulse	antioxydants OR ascorbic acid OR vitamin E OR vitamin A OR vitamin C OR tocopherol OR carotene OR dietary supplements		31/12/2013	5
16		fluphenazine		01/05/2010	6
17		Nalbuphine OR en2234a OR en 2234a OR nubain		31/07/2013	10
18	colon OR rectum OR colorectal	Biological agent OR Biological therapy OR VEGF-A OR VEGFA OR EGF receptor OR bevacizumab OR cetuximab OR panitumumab OR aflibercept OR regorafenib		5/31/2013	684
19		new oral anticoagulant OR oral thrombin inhibitor OR factor Xa inhibitor OR dabigatran OR rivaroxaban OR apixaban	01/01/2001	23/03/2014	217
20	cystic fibrosis OR CF OR mucovicidosis	appetite stimulants OR cyproheptadine OR prednisolone OR progestational agents OR progestins OR anabolic agents OR megesterol OR megace OR mirtazapine OR antidepressive agents OR antidepressants OR cannaboids OR tetrahydrocannabinol /// antihistamines OR histamine antagonists OR corticosteroids OR prednisone OR steroids OR hormone therapy OR growth hormone OR hormones OR dronabinol OR pizotyline OR pizotifen OR risperidone OR olanzapine		08/04/2014	4
21	colorectal cancer OR colon cancer OR rectal cancer	panitumumab OR vectibix		31/03/2014	122

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
22	breast cancer	gonadotropin releasing hormone OR GnRH analogue OR GnRH agonist OR triptrorelin OR goserelin OR leuprolide OR busselin OR nafarenlin		31/03/2014	84
23		haloperidol		01/05/2010	82
24		metformin AND (repaglinide OR novonorm)		30/11/2013	11
25		trifluoperazine		01/05/2010	3
26	contrast induced acute kidney injury OR CIN OR contrast induced nephropathy OR contrast nephropathy OR AKI OR acute kidney injury OR ARF OR acute renal failure	statin OR 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor OR HMG-CoA OR CI AKI OR CI-AKI OR		10/02/2014	1
27		rivaroxaban OR dabigatran OR apixaban OR new oral anticoagulant OR oral thrombin inhibitors OR oral factor Xa inhibitors	01/01/2001	15/09/2013	180
28	tonsillectomy OR adenotonsillectomy	ketamine OR analgesics OR opioid		01/02/2013	1
29	gastrointestinal cancer OR gastric cancer OR colorectal cancer OR colon cancer OR rcetal cancer	S-1 OR 5-fluorouracil		31/12/2013	631
30	dermatitis OR eczema OR atopy OR atopic	probiotics OR prebiotics OR synbiotics OR lactobacillus OR lactobacilli bifidobacteria OR bifidobacterium		31/12/2013	42
31	heart failure AND congestive	adrenergic beta-antagonists		31/12/2013	6
32					
33	agitation OR delirium	sevaflurane OR dexmedetomidine		15/03/2014	49
34	thyroid cancer	recombinant human thyroid hormone stimulating hormone OR thyroid hormone withdrawal		31/08/2013	2
35	hypertension portal	propranolol AND carvedilol		31/03/2013	0
36	cancer OR tumour OR carcinoma OR neoplasm	vitamin D OR cholecalciferol OR ergocalciferol		4/30/2014	197
37	inflammation OR high-sensitivity C-reactive protein OR high-sensitive C-reactive protein OR hs-CRP	vitamin D OR cholecalciferol		28/02/2014	18
38	Embolism OR Thrombosis OR Postoperative Complications OR Intraoperative Complications OR deep venous thrombosis OR DVT OR pulmonary embolism OR thrombosis OR thrombotic OR emboli OR thromboemboli OR thromboprophyla OR bleed OR hemorrhag OR complication	Anticoagulants OR heparin OR UFH OR LMWH OR warfarin OR coumadin OR vitamin K antagonist OR VKA OR aspirin OR ASA OR factor Xa inhibitor OR fondaparinux OR rivaroxaban OR apixaban OR thrombin inhibitor OR dabigatran		6/30/2013	289
39		dabigatran OR BIBR 1048		08/12/2013	76

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
40	operable advanced breast cancer OR locally advanced breast cancer	neoadjuvant OR trastuzumab OR lapinib OR pertuzumab		31/03/2014	20
41	contrast medium OR contrast OR radiography OR angiocardiography OR angiography OR heart catheterization OR cardiac catheterization OR kidney diseases OR kidney failure OR nephritis OR kidney disease OR nephrotoxicity OR nephrotoxic OR contrast nephropathy	hydroxyl methylglutaryl coenzyme A reductase inhibitor OR HMG-CoA reductase inhibitor OR statins OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR cerivastatin OR fluindostatin OR fluvastatin	1/1/1950	1/31/2014	65
42	gastric cancer OR stomach cancer	S-1 OR fluouracil		20/02/2014	201
43	peri-operative period OR postoperativeperiod OR surgery OR surgical OR operation OR surgical procedures OR operative procedures	melatonin		30/09/2013	9
44	“chronic obstructive pulmonary disease” OR “COPD”	“tiotropium” AND “fluticasone propionate/salmeterol” et “tiotropium” AND “fluticasone–salmeterol”		31/12/2013	3
45	cancer	“bevacizumab” OR “avastin” OR “aflibercept” OR “VEGFR-TKIs” OR “sorafenib” OR “nexavae” OR “sunitinib” / “sutent” OR “SU1248” OR “vandetanib” OR “caprelsa” OR “ZD6474” OR “axitinib” OR “pazopanib” OR “votrient” OR “GW786034” OR “regorafenib” OR “apatinib” OR “ramucirumab” OR “angiogenesis inhibitors”	01/01/2004	28/02/2014	2680
46	“Kashin-Beck disease” or “KBD” or “Urov”	“hyaluronic acid” or “hyaluronan” or “hyaluronate” or “HA”		30/11/2013	1
47	Parkinson’s disease OR Parkinson’s OR PD	extended-release pramipexole OR ropinirole prolonged-released OR rotigotine transdermal patch		10/02/2013	3
48	non-small-cell lung cancer OR EGFR wild-type OR EGFR mutation-negative	epidermal growth factor receptor inhibitors OR erlotinib OR gefitinib		31/07/2013	362
49	Gestational diabetes OR gestational diabetes mellitus OR diabetes pregnancy	Metformin OR hypoglycemic drugs OR Hypoglycemic Agents OR Antidiabetic		31/12/2012	664
50	schizophrenia	chlorpromazin		30/06/2013	6
51	(‘‘malignant glioma’’ or ‘‘high-grade glioma’’ or ‘‘GBM’’ or ‘‘HGG’’	‘‘herpes simplex virus thymidine kinase’’ or ‘‘HSV-tk’’ or ‘‘gene therapy’’ or ‘‘genetic therapy’’		30/11/2013	1
52	nonalcoholic fatty liver disease OR NAFLD OR nonalcoholic steatohepatitis OR NASH	pentoxifylline		31/01/2013	2
53	add-back OR HRT OR GnRHa OR GnRH-a OR GnRH agonist OR GnRH analogues		01/01/1998	28/02/2013	12
54	Clonidin OR Catapres OR Dexmedetomidine			06/02/2013	12

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
55	"alfusosin" OR "doxazosin" OR "tamsulosin" OR "terazosin" OR "silodosin" OR "fiansteride" OR "dutasteride" OR "sildenafil" OR "tadalafil" OR "vardenafil" OR "oxybutynin" OR "tolterodine" OR "trospium chloride" OR "darifenacin" OR "solifenacin" / "fesoterodine" OR "mirabegron" / "serenoa" OR "Adrenergic alpha-Antagonists" OR "5-alpha reductase inhibitors" OR "phosphodiesterase 5 inhibitors" OR "cholinergic antagonists" OR "2-(2-aminothiazol-4-yl)-4′-(2-((2-hydroxy-2-phenylethyl)amino)ethyl)acetanilide" OR "serenoa"			31/01/2013	104
56	local analgesia OR "intra-articular analgesia			31/08/2013	1
57	chemotherapy OR per-formance status			31/07/2013	274
58	ovarian cancer	systematic chemotherapy OR pegylated liposomal doxorubicin	01/01/2000	31/01/2013	41
59	rheumatoid AND arthritis	infliximab OR etanercept OR adalimumab OR certolizumab OR golimumab OR anakinra OR abatacept OR tocilizumab OR rituximab		6/24/2013	581
60		ranibizumab OR bevacizumab	01/01/2004	31/03/2013	215
61		axitinib OR cabozantinib OR erlotinib OR gefitinib OR lapatinib OR pazopanib OR regorafenib OR sorafenib OR sunitinib OR vandetanib		3/31/2013	3576
62		statin		31/07/2013	0
63	Erectile dysfunction OR Lower urinary tract symptoms OR Benign prostatic hyperplasia OR ED OR LUTS OR BPH	alpha-blockers OR doxazosin OE alfuzosin OR tamsulosin OR PDE5 OR sildenafil OR tadalafil OR vardenafil OR udenafil		30/11/2013	52
64	malignant OR neoplasms OR cancer OR oncology	palonosetron AND (antineoplastic agents OR neoplastic OR chemotherapy OR chemoradiotherapy)		30/06/2013	9
65		hypotonic AND isotonic		31/01/2013	3
66	body fat OR body weight OR fat free mass OR fat mass OR adiposity OR fat distribution OR body fat regulation OR BMI OR weight loss OR body composition.	vitamin D OR vitamin D supplementation	01/01/1995	31/03/2013	51
67	cardiac surgery OR cardiopulmonary bypass OR heart surgery	steroid OR corticosteroid glucocorticoid OR dexamethasone OR prednisolone OR prednisone OR methylprednisolone OR hydrocortisone	1996	30/04/2013	9

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
68	cardiovascular disease OR coronary OR myocardial ischemia OR stenosis OR restenosis OR revascularization OR coronary OR coronary intervention OR cerebrovascular OR percutaneous disease OR stroke	folic acid OR folate OR multivitamin	1966	30/09/2013	109
69	Multiple Sclerosis	Serotonin Uptake Inhibitors OR SSRI OR fluoxetine OR citalopram OR dapoxetine OR escitalopram OR fluvoxamine OR indalpine OR paroxetine OR sertraline OR vilazodone OR zimeldine		20/03/2013	8
70	postoperative pain OR postoperative nausea vomiting	nicotine		31/07/2012	2
71	chronic obstructive pulmonary disease OR chronic bronchitis OR pulmonary emphysema OR COPD	NAC OR acetylcysteine		01/08/2013	12
72	hyperglycemia OR stroke	intravenous insulin	1966	15/02/2013	3
73		gonadotropin-releasing hormone agonist OR luteinizing-hormone releasing hormone agonist OR triptorelin OR goserelin	01/01/1992	30/08/2013	258
74	bacterial vaginitides OR bacterial vaginoses OR bacterial vaginitis OR bacterial vaginosis.	Probiotics OR lactobacillus OR bifidobacterium OR lactobacilli OR lactic acid bacteria.		31/05/2013	18
75	Erectile Dysfunction OR Impotence	Mirodenafil OR 5-ethyl-2-(5-(4-(2-hydroxyethyl)piperazine-1-sulfonyl)-2-propoxyphenyl)-7-propyl-3,5-dihydro-4H-pyrrolo(3,2-d)pyrimidin-4-one OR SK3530	1966	31/03/2013	6
76		Lidocaine AND (opioid OR fentanyl OR remifentanil OR sufentanil OR alfentanil)		31/03/2013	36
77	myocardial infarction OR percutaneous coronary intervention OR acute coronary syndrome	cangrelor		30/04/2013	7
78	arthroscopic OR postoperative pain	bupivacaine		30/04/2013	76
79	anaesth OR anaesth OR nerve block	dexamethasone		16/05/2014	3
80		miralax and gatorade OR		31/01/2014	3
81	rhinoplasty			28/02/2014	12
82	atrial fibrillation OR atrial tachycardia OR atrial tachyarrhythmia OR AT OR atrial flutter	catheter ablation OR radiofrequency ablation		14/03/2014	107

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
83	Alzheimer disease OR AD	cholinesterase inhibitors OR donepezil OR galantamine OR rivastigmine OR metrifonate OR tacrine OR antipsychotics OR haloperidol OR thioridazine OR thiothixene OR chlorpromazine OR acetophenazine OR clozapine OR olanzapine //// risperidone OR quetiapine OR aripiprazole OR antidepressants OR setraline OR fluoxetine OR citalopram OR trazodone OR mood stabilizers OR valproate OR carbamazepine OR lithium OR anticonvulsants OR benzodiazepines OR memantine OR psychotropic drugs		31/12/2013	227
84	cardiac surgery OR valve surgery OR coronary surgery OR cardiopulmonary bypass OR extracorporeal circulation	glucocorticoid OR steroid OR hydrocortisone OR dexamethasone OR methylprednisolone"		31/08/2013	7
85	CPR OR cardio-pulmonary resuscitation OR cardio-arrest	vasopressine OR epinephrine OR adrenaline		20/08/2013	0
86		DPP-IV inhibitors OR vildagliptin OR sitagliptin OR saxagliptin OR alogliptin OR linagliptin OR dutogliptin OR metformin OR sulfonylureas		1/31/2013	1661
87	carotenoids and visual function OR visual performance OR visual acuity OR vision OR contrast sensitivity OR glare sensitivity OR AMD OR age-related maculopathy OR choroidal neovascularization OR geographic atrophy	lutein OR zeaxanthin OR xanthophyll		30/04/2014	27
88	psoriasis OR pustulosis of palms OR pustulosis of soles	ustekinumab OR CNTO-1275 OR interleukin 12/23 monoclonal antibody OR sterala		01/08/2013	26
89		lapatinib		28/02/2014	325
90	prostat	hormone therapy OR intermittent androgen OR androgen antagonists /// hormone blockade OR androgen deprivation OR continuous androgen OR hormone deprivation OR LHRH OR luteinising hormone-releasing hormone OR flutamide OR bicalutamide OR cyproterone OR buserelin OR goserelin OR leupro OR triptorelin OR nilutamide		4/30/2013	303
91	Premature OR infant OR newborn OR low birth weight OR neonate OR premature OR neurodevelopment OR neuroprotection OR neurobehavioral development OR neurological development OR neural development	Erythropoietin OR epo OR epogen OR epoetin OR rhuepo		30/11/2012	11

ID	Key words used in "Conditions" field	Key words used in "Interventions" field	First limit of search	Last electronic search	Citation findings
92	spastic colon OR irritable colon OR irritable bowel OR functional bowel OR colonic disease OR colonic diseases OR IBS OR gastrointestinal sydrome	peppermint oil OR mintoil OR colpermin		28/01/2013	2
93		tramadol AND ondansetron		18/08/2014	1
94	colorectal OR neoplasms	cetuximab		16/02/2014	665
95		nicergoline		16/08/2013	3

Appendix 3: Systematic reviews for which data could not be added to the meta-analysis

	Number of RCT[i]s (and patients) included in the original SR[ii]	Number of RCTs (and patients) retrieved from WHO ICTRP search	Number of RCTs (and patients) retrieved with results that could contribute to at least one MA[iii]
1	21 (12242)	2 (1587)	0
2	10 (1052)	4 (274)	0
3	7 (27024)	1 (60)	0
4	10[iv]	7 (15613)	0
5	5 (4155)	1 (9)	0
6	5 (613)	1(400)	0
7	25 (1599)	3 (132)	0
8	9 (2812)	4 (745)	0
9	10 (924)	2 (162)	0
10	24 (1794)	1 (100)	0
11	6 (1268)	1 (50)	0
12	7 (2340)	1 (8)	0
13	6 (1420)	1 (217)	0
14	128[v]	1 (66)	0
15	23 (24370)	5 (3291)	0
16	12 (1268)	2 (490)	0
17	8 (4855)	1 (501)	0
18	18 (2305)	2 (80)	0
19	3 (130)	1 (20)	0
20	9 (662)	1 (80)	0
21	11 (2587)	1 (240)	0
22	9 (765)	2 (430)	0
23	12 (1304)	1 (70)	0
24	11 (1481)	2 (142)	0
25	8 (1176)	2 (181)	0
26	15 (8332)	1 (688)	0
27	7 (523)	1 (22)	0

[1]RCT = Randomized controlled trial; [2] SR = Systematic review; [3] MA = Meta-analysis; [4 5] Number of patients included was unclear or missing in two SRs

Appendix 4: Results of the trials registries searches and their impact on summary statistics

October 19, 2016

Contents

1 Systematic review 1

1.1 Title of the systematic review

The preventive effect of atorvastatin on atrial fibrillation: a meta-analysis of randomized controlled trials

1.2 Inclusion criteria

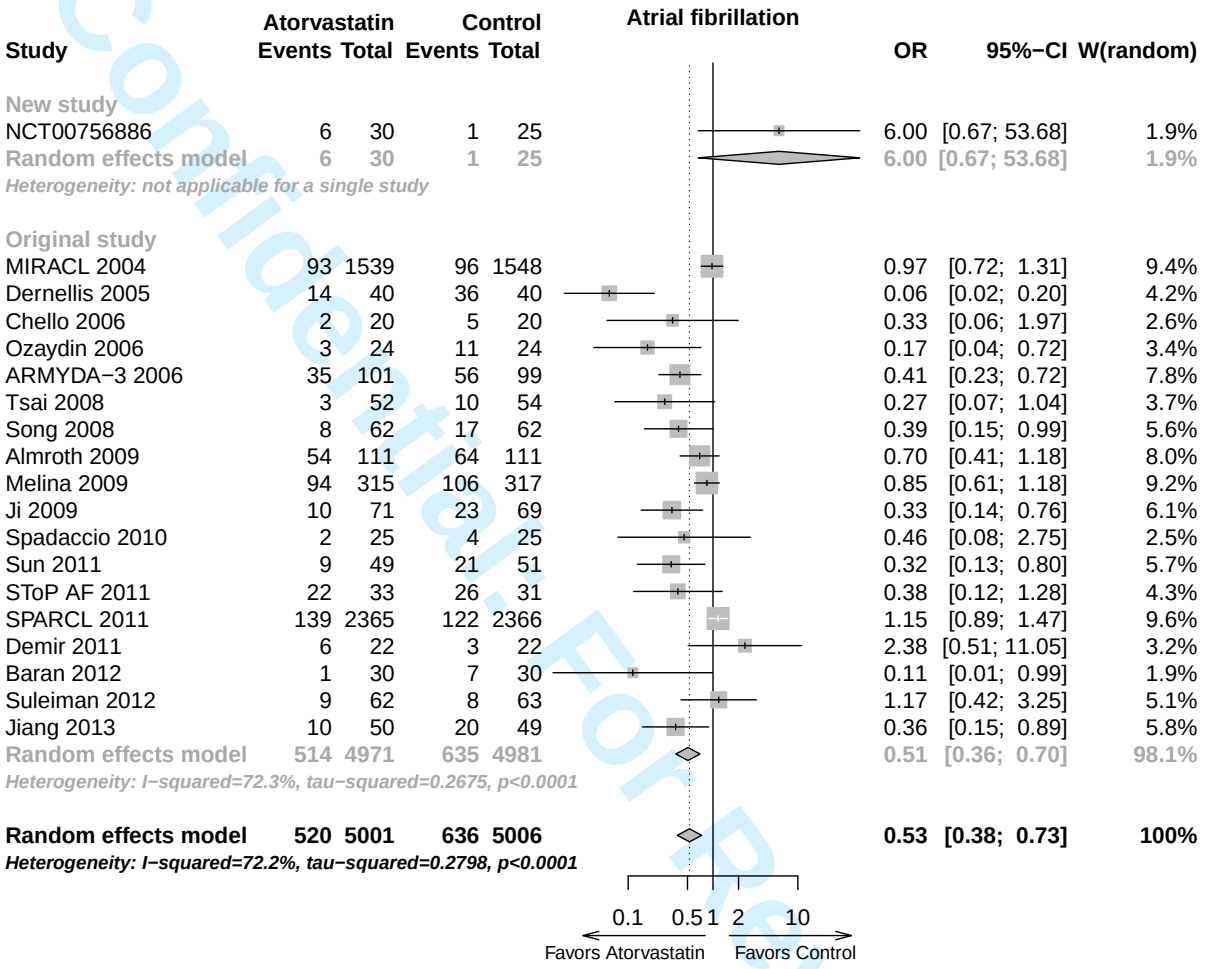
Studies that met the following specified criteria:

- comparison of atorvastatin with placebo or control treatment, regardless of the background therapy;
- randomized controlled human trials;
- new-onset AF or recurrent AF in each group as an outcome.

1.3 Comparison assessed

	Experimental	Control
NCT00756886	Atorvastatin	Placebo

1.4 Results



2 Systematic review 2

2.1 Title of the systematic review

Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis

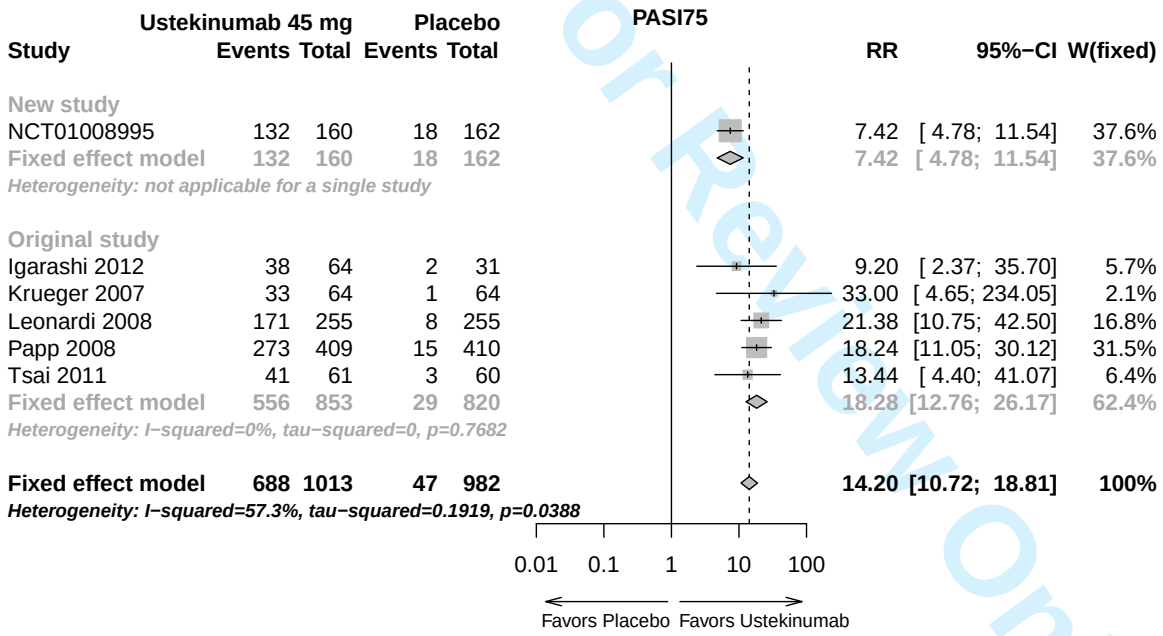
2.2 Inclusion criteria

Firstly, the RCTs had to include patients with a proven diagnosis of plaque psoriasis for at least 6 months. Exclusion criteria for patients included known malignancy (except treated basal cell skin cancer or squamous cell skin cancer of at least 5 years duration) or recent serious systemic or local infection. Exclusion criteria for controls included systemic use of corticosteroids, immunosuppressants or agents specifically targeting IL-12 or IL-23 with a withdrawal time of < 2 weeks. Thirdly, articles lacking original data for meta-analysis and review articles were excluded.

2.3 Comparison assessed

	Experimental	Control
NCT01008995	Ustekinumab	Placebo

2.4 Results



3 Systematic review 3

3.1 Title of the systematic review

The role of biological therapy in metastatic colorectal cancer (mCRC) after first-line treatment : a meta-analysis of randomised trials

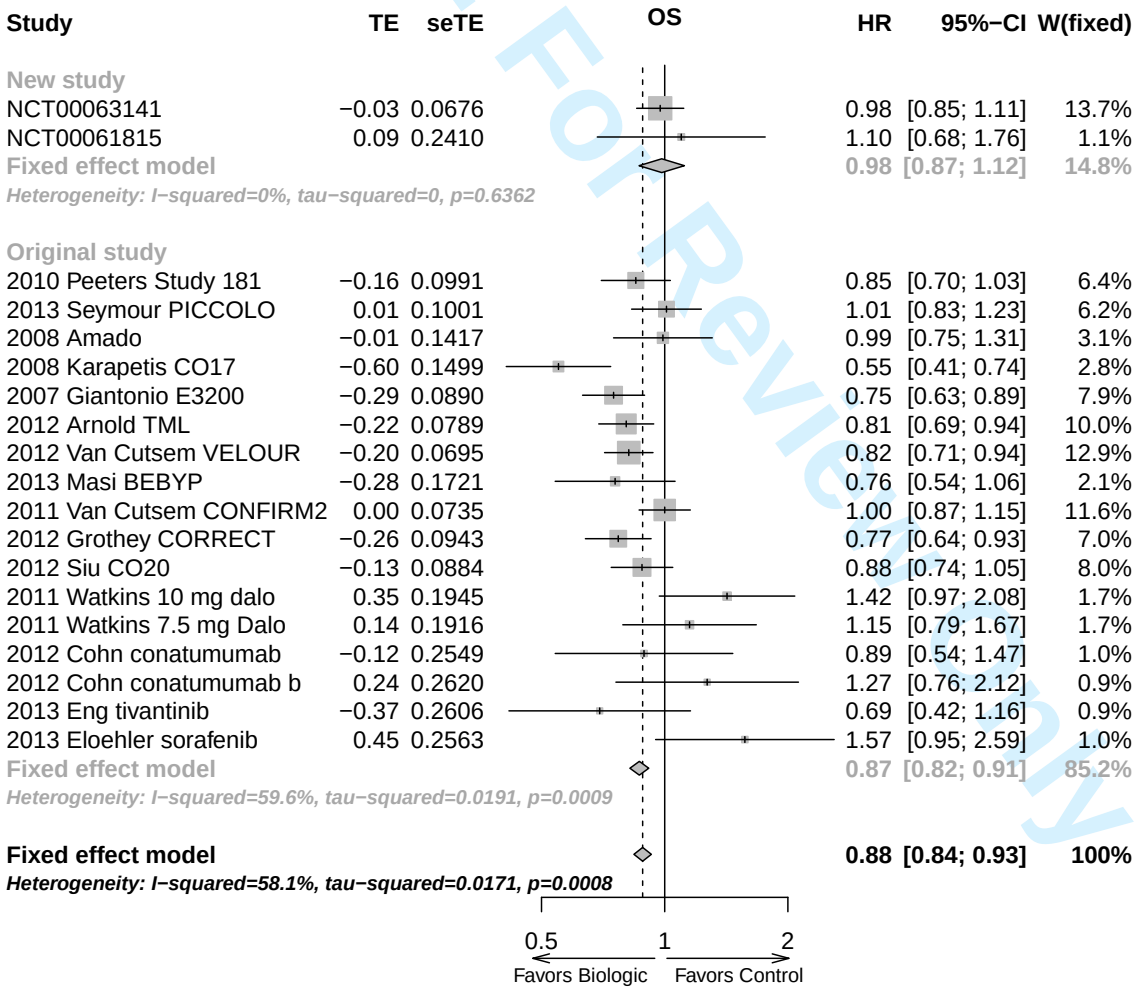
3.2 Inclusion criteria

Studies included were registered RCTs evaluating second- or third line (or beyond) therapy for mCRC, which reported at least one of the following: OS, PFS, ORR and toxicity.

3.3 Comparison assessed

	Experimental	Control
NCT00063141	Cetuximab+Irinotecan	Irinotecan
NCT00061815	Cetuximab+FOLFOX4	FOLFOX4

3.4 Results



4 Systematic review 4

4.1 Title of the systematic review

S-1-based versus 5-FU-based chemotherapy as first-line treatment in advanced gastric cancer: a meta-analysis of randomized controlled trials

4.2 Inclusion criteria

Studies meeting the following inclusion criteria were included:

- patients suffering from histological confirmed, inoperable, advanced, or recurrent adenocarcinoma of the stomach or gastroesophageal junction at baseline;
- phase II or phase III RCT;
- trials comparing S-1-based with 5-FU-based regimens given as first-line palliative chemotherapy and not confounded by additional agents or interventions;
- if there were multiple articles based on similar patients, only the largest or the most recently article was included.

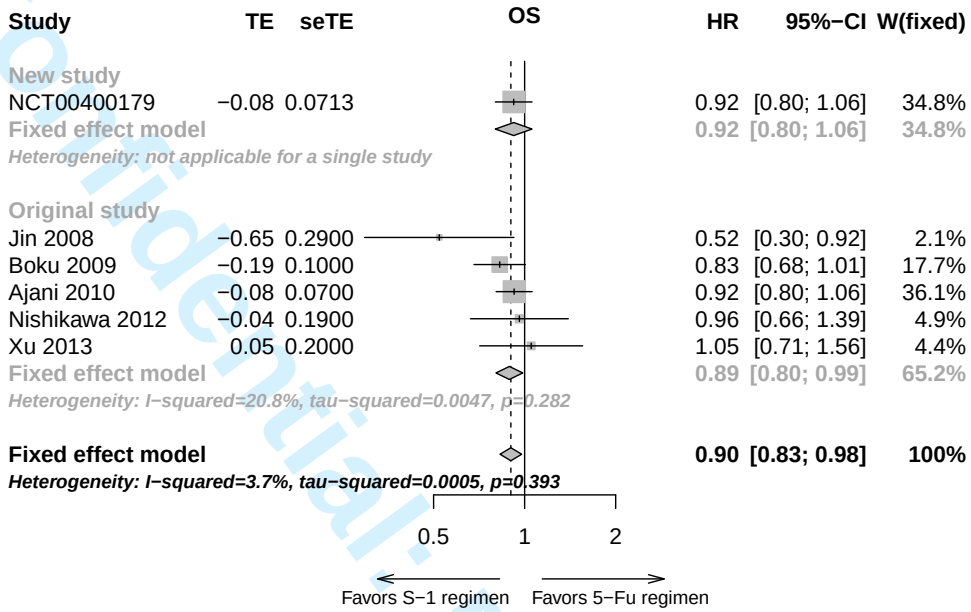
Exclusion criteria included the following:

- letters, reviews, case reports, editorials, and expert opinion;
- non-prospective trials.

4.3 Comparison assessed

	S-1-based regimen	5-FU-based regimen
NCT00400179	S-1/Cisplatin	5-FU/cisplatin

4.4 Results



5 Systematic review 5

5.1 Title of the systematic review

Efficacy and toxicity of adding cetuximab to chemotherapy in the treatment of metastatic colorectal cancer: a meta-analysis from 12 randomized controlled trials

5.2 Inclusion criteria

Studies that met the following criteria were considered for inclusion:

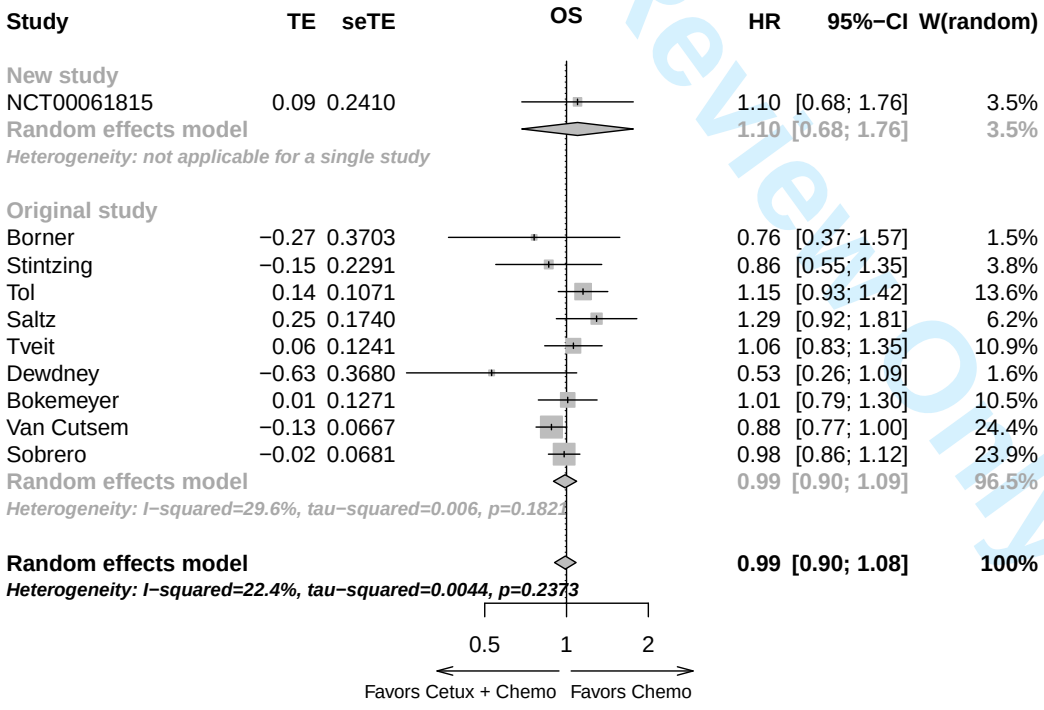
- randomized controlled trials;
- the study population of patients aged ≥18 years;
- eligible patients with histologically or cytologically confirmed mCRC;
- randomized allocation to cetuximab plus chemotherapy group or chemotherapy group;
- results reported data on efficacy and safety.

Reports were excluded from the final analysis if they described studies with a single-arm design or randomized controlled trials that assigned cetuximab into the two treatment arms.

5.3 Comparison assessed

	Experimental	Control
NCT00061815	Cetuximab+FOLFOX4	FOLFOX4

5.4 Results



6 Systematic review 6

6.1 Title of the systematic review

Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis

6.2 Inclusion criteria

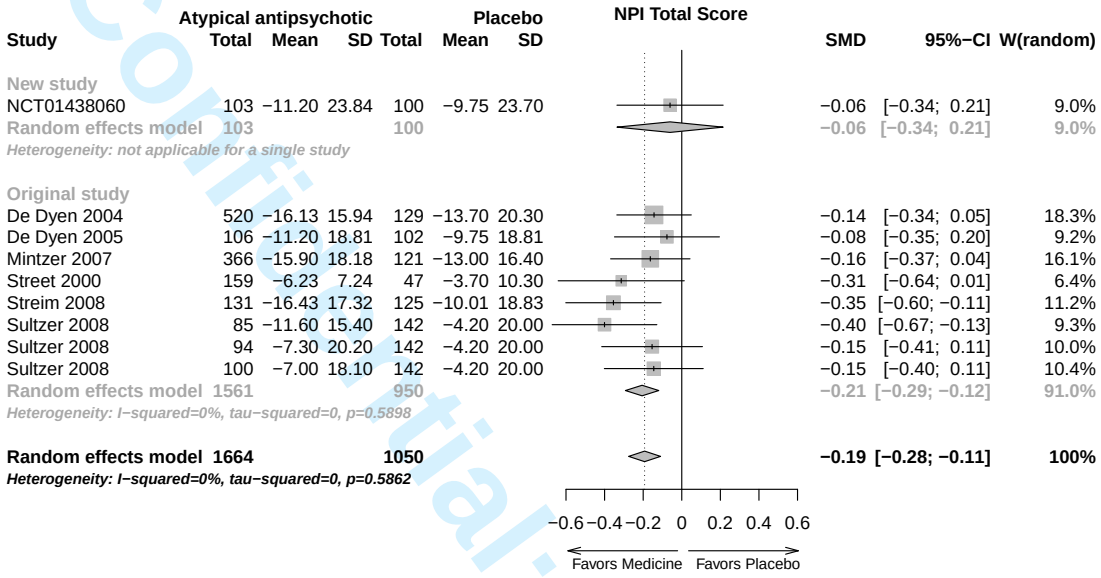
Trials were selected for inclusion if they met all of the following criteria:

- double-blind, placebo controlled, randomised controlled trials (RCTs);
- the design of the trial was either parallel or crossover; for a crossover trial, it had a washout period greater than 1 week;
- patients enrolled were diagnosed as probable or possible AD according to the Diagnostic and Statistical Manual of Mental Disorders?Fourth Edition or the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer?s Disease and Related Disorders Association;
- studies compared any medicine at any dose with placebo, with any treatment durations;
- neuropsychiatric outcomes were measured with the most common neuropsychiatric scales Neuropsychiatric Inventory (NPI) (NPI-10 or NPI-12) or Neuropsychiatric Inventory-Nursing Home version (NPI-NH).

6.3 Comparison assessed

	Medicine	Placebo
NCT01438060	Aripiprazole	Placebo

6.4 Results



7 Systematic review 7

7.1 Title of the systematic review

Meta-analysis of the efficacy and safety of long-acting non-ergot dopamine agonists in Parkinson's disease

7.2 Inclusion criteria

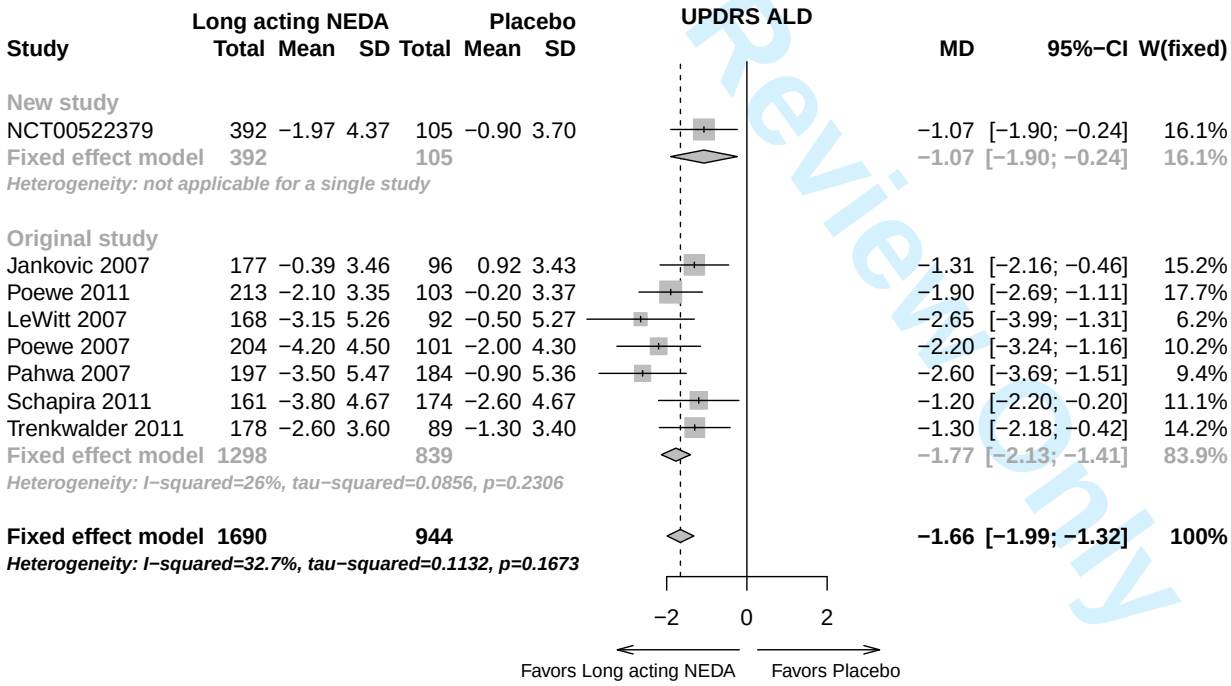
Trials were included in the study if they met all of the following criteria:

- RCT,
- study participants were required to have a clinical diagnosis of PD,
- intervention therapies consisting of long-acting NEDA versus placebo,
- assessment of the efficacy data in the form of Unified Parkinson's Disease Rating Scale (UPDRS) scores, "off" time and/or "on" time without troublesome dyskinesia measured by patient diaries, tolerability data in the form of withdrawals, and safety data in the form of adverse events.

7.3 Comparison assessed

	Long-acting NEDA	Control
NCT00522379	Rotigotine	Placebo

7.4 Results



8 Systematic review 8

8.1 Title of the systematic review

The long-term efficacy and safety of DPP-IV inhibitors monotherapy and in combination with metformin in 18 980 patients with type-2 diabetes mellitus a meta-analysis

8.2 Inclusion criteria

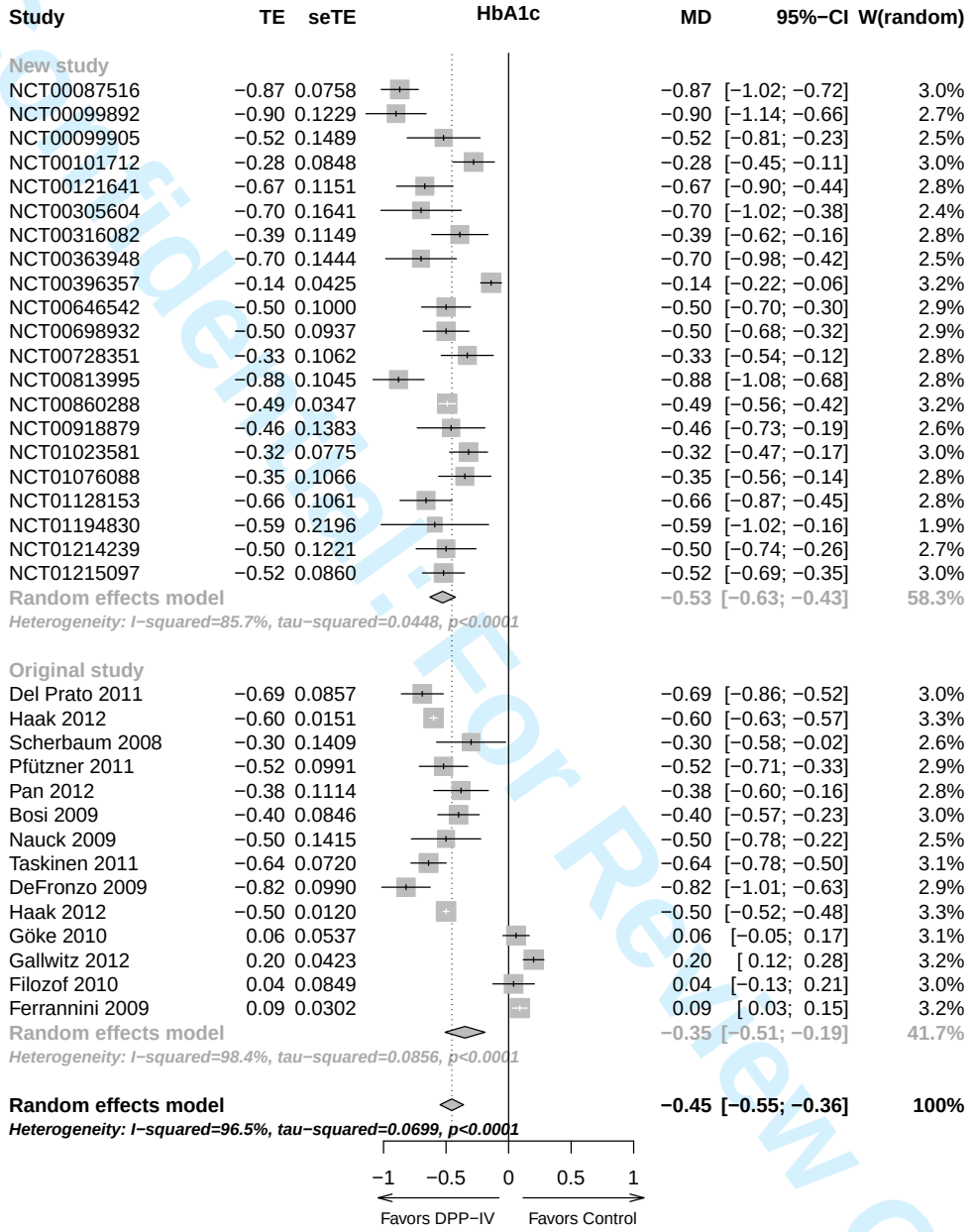
Studies were deemed eligible for inclusion in pooled analysis if they met the following criteria:

- were phase 3 or later, prospected and randomized controlled trials of $\geq$ 24 weeks' duration,
- enrolled adult patients with T2DM,
- were comparing DPP-IV inhibitors with placebo, DPP-IV inhibitors +metformin with metformin and DPP-IV inhibitors + metformin with sulphonylureas + metformin and
- have at least 50 subjects in every arm of the studies.

8.3 Comparison assessed

	Experimental	Control
NCT00087516	Sitagliptin	Placebo
NCT00099892	Vildagliptin	Placebo
NCT00099905	Vildagliptin	Placebo
NCT00101712	Vildagliptin	Placebo
NCT00121641	Saxagliptin	Placebo
NCT00305604	Sitagliptin	Placebo
NCT00316082	Saxagliptin	Placebo
NCT00363948	Sitagliptin	Placebo
NCT00396357	Vildagliptin	Placebo
NCT00646542	Vildagliptin	Placebo
NCT00698932	Saxagliptin	Placebo
NCT00728351	Vildagliptin	Placebo
NCT00813995	Sitagliptin	Placebo
NCT00860288	Vildagliptin or Sitagliptin	Placebo
NCT00918879	Saxagliptin	Placebo
NCT01023581	Alogliptin alone or in combination with metformin	Metformin or Placebo
NCT01076088	Sitagliptin alone or in combination with metformin	Metformin or Placebo
NCT01128153	Saxagliptin	Placebo
NCT01194830	Linagliptin	Placebo
NCT01214239	Linagliptin	Placebo
NCT01215097	Linagliptin	Placebo

8.4 Results



9 Systematic review 9

9.1 Title of the systematic review

Dabigatran Etexilate and Risk of Myocardial Infarction, Other Cardiovascular Events, Major Bleeding, and All-Cause Mortality: A Systematic Review and Meta-analysis of Randomized Controlled Trials

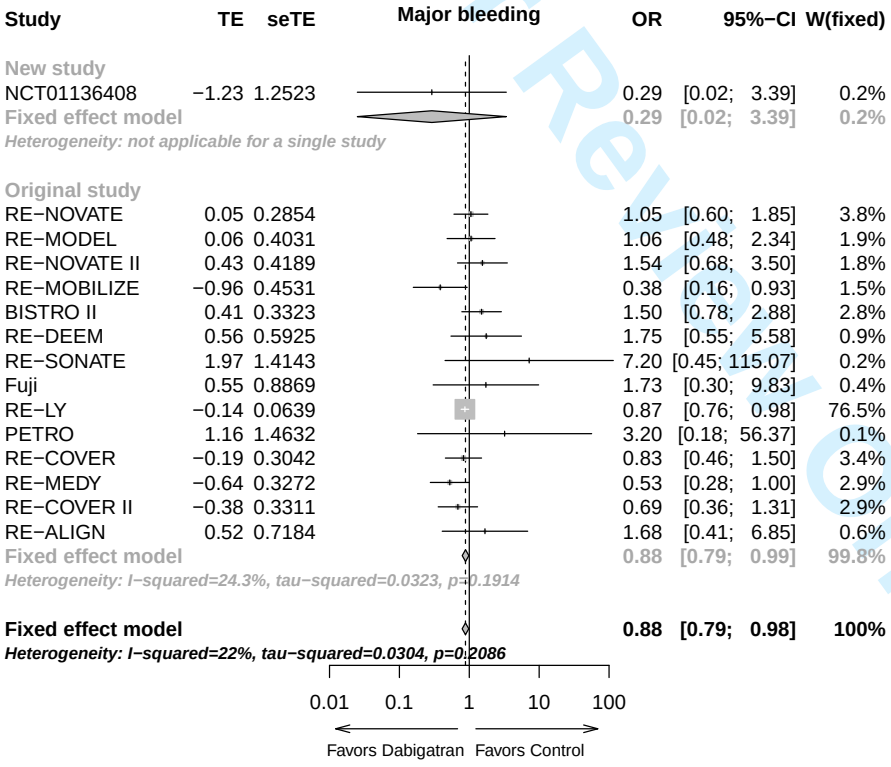
9.2 Inclusion criteria

To be included in the meta-analysis, clinical trials should present the following criteria: (1) it should be an RCT and (2) the follow-up should have been the same between the different groups. In addition, (3) the control groups should receive a placebo or the reference treatment when applicable. This meant (3a) warfarin was the reference treatment in patients with NVAF and in the treatment of venous thromboembolism (VTE) or pulmonary embolism; (3b) enoxaparin was the reference treatment for the prevention of VTE events in patients undergoing total hip or knee surgery; and (3c) placebo was used for the prevention of recurrence of coronary events in patients receiving antiplatelet therapy or for the prevention of recurrence of VTE events in patients who had completed a first period of anticoagulant therapy.

9.3 Comparison assessed

	Experimental	Control
NCT01136408	Dabigatran Etexilate	Warfarin

9.4 Results



10 Systematic review 10

10.1 Title of the systematic review

Biologic Therapies in Rheumatoid Arthritis and the Risk of Opportunistic Infections: A Meta-analysis

10.2 Inclusion criteria

A randomized trial of a biologic agent was considered eligible if it fulfilled all of the following conditions:

- randomized patients with RA,
- randomized Food and Drug Administration?approved biologic agents for treatment of RA,
- compare the effect of a biologic agent with that of a control drug, and,
- provided safety data to calculate ?1 outcome of interest.

The control arm included either placebo or disease-modifying antirheumatic drugs/conventional therapy. Low-dose corticosteroids (<10 mg equivalent to prednisolone) were permitted in all arms.

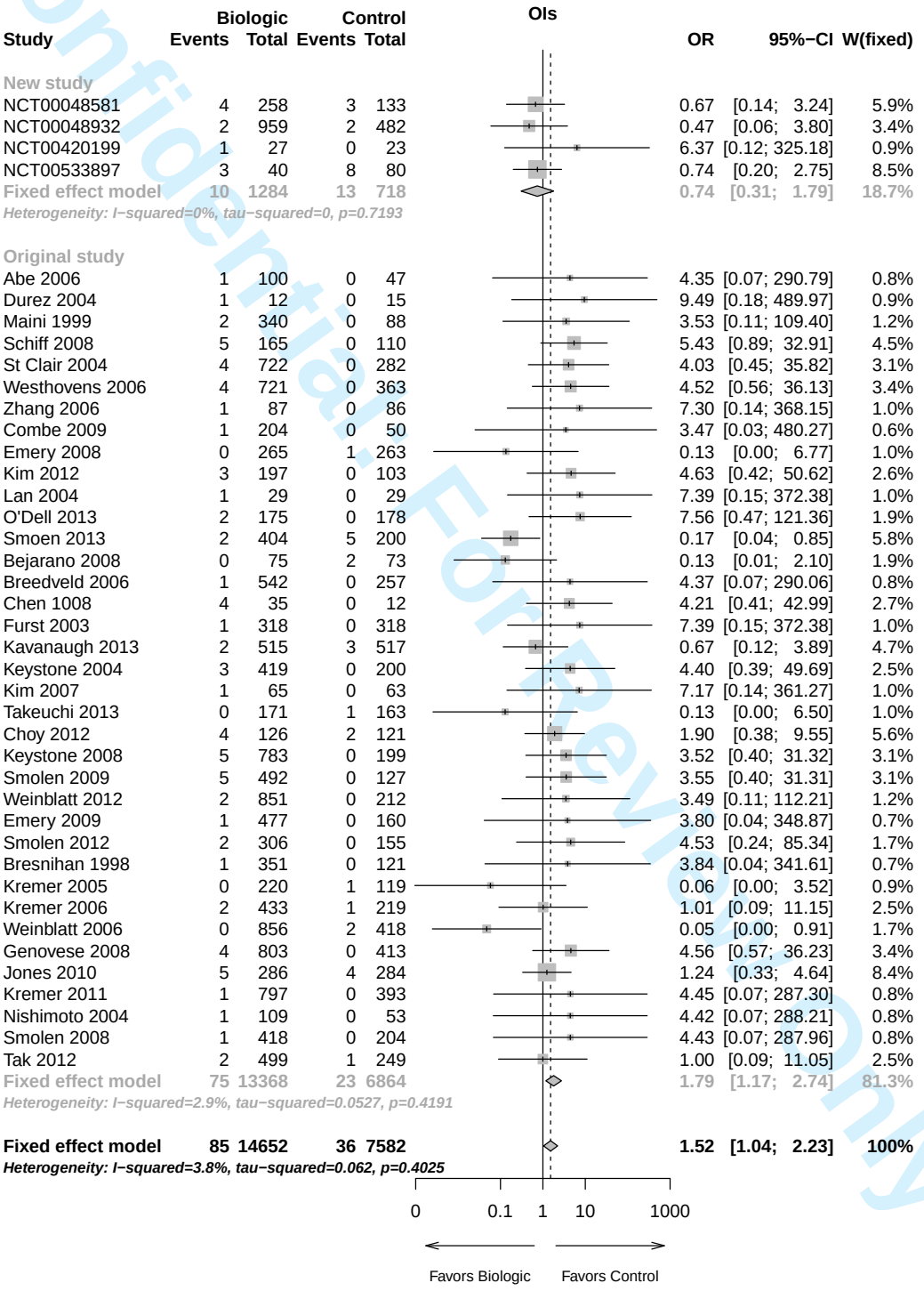
A study was considered ineligible if it included

- no data on OIs;
- compared different dosing, schemes, or routes of the same biologic agent;
- randomized 2 biologic agents;
- or included agents not approved for RA.

10.3 Comparison assessed

	Biologic	Control
NCT00048581	Abatacept	Placebo
NCT00048932	Abatacept	Placebo
NCT00420199	Abatacept + MTX	Placebo + MTX
NCT00533897	Abatacept	Placebo

10.4 Results



11 Systematic review 11

11.1 Title of the systematic review

Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension

11.2 Inclusion criteria

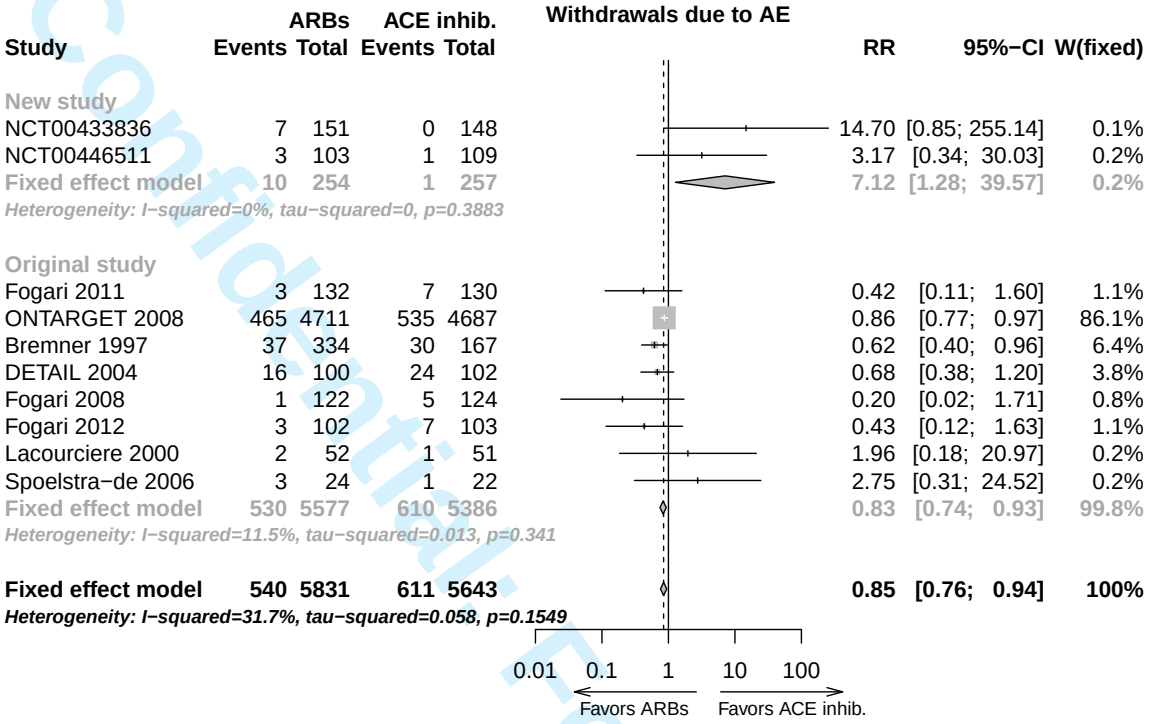
Studies:

- directly compared an ACE inhibitor and an ARB;
- randomized participants to the ACE inhibitor group or the ARB group;
- had the same protocol regarding continuation or discontinuation of pre-study blood pressure lowering therapy in both arms;
- had the same protocol for adding background blood pressure lowering therapy during the trial in both arms;
- had a prespecified duration of at least one year;
- were double blinded when included for WDAE.

11.3 Comparison assessed

	ARBs	ACE inhibitors
NCT00433836	Valstartan	Enalapril
NCT00446511	Valstartan	Enalapril

11.4 Results



12 Systematic review 12

12.1 Title of the systematic review

Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials

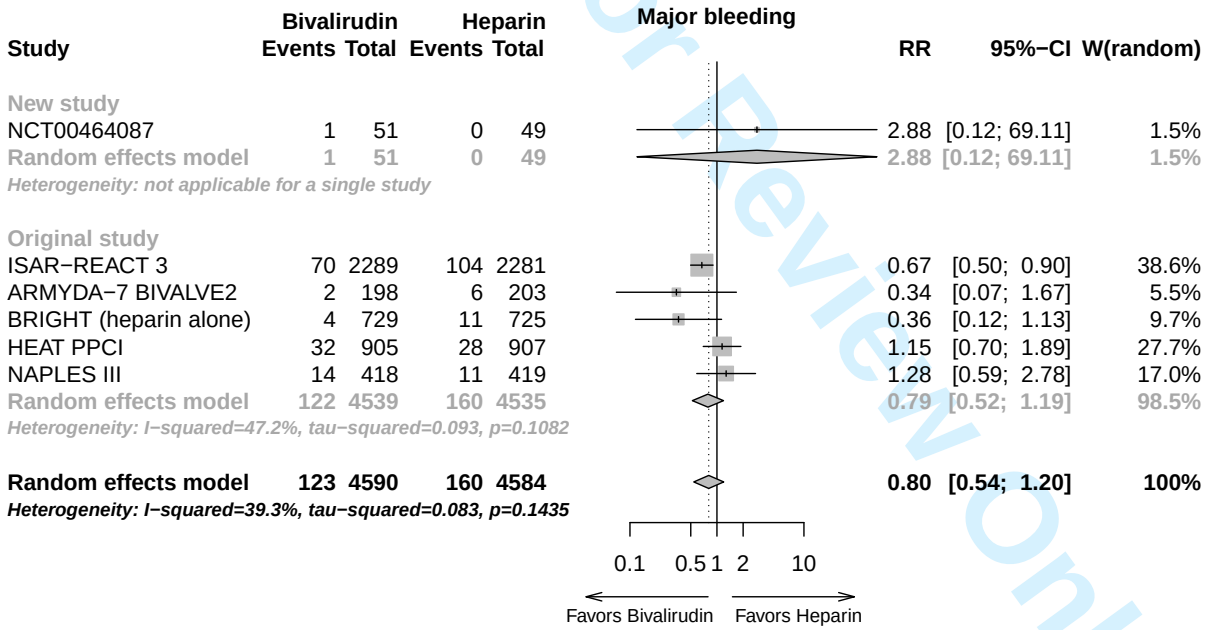
12.2 Inclusion criteria

Trials were included if they enrolled individuals with planned PCI and randomly assigned patients to treatment with bivalirudin (using the approved dosing regimen) or heparin (mostly unfractionated heparin [UFH], but also low-molecularweight heparin) with or without a GPI. Trials that did not report clinical outcomes, involved fi brinolytics, were done before coronary stenting was available, or compared bivalirudin with anticoagulant regimens other than heparin or low-molecular-weight heparin were excluded from the analysis.

12.3 Comparison assessed

	Experimental	Control
NCT00464087	Bivalirudin	Heparin

12.4 Results



13 Systematic review 13

13.1 Title of the systematic review

Treatment Discontinuations With New Oral Agents for Long-term Anticoagulation: Insights from a Meta-Analysis of 18 Randomized Trials Including 101 801 patients.

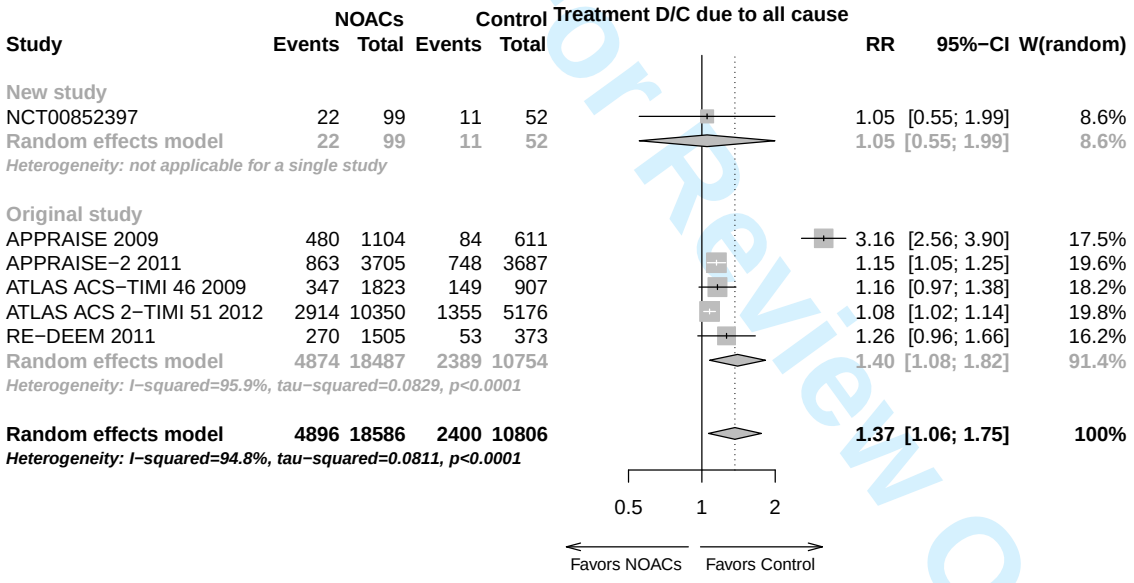
13.2 Inclusion criteria

Studies included compared NOACs with conventional anticoagulants or placebo for the treatment of VTE/pulmonary embolism (PE), ACS, and stroke prevention in patients with AF. The included studies had to have at least 12 weeks of follow-up. Studies of orthopedic operations were not included. Both double-blind and open-label trials were eligible for inclusion.

13.3 Comparison assessed

	NOACs	Control
NCT00852397	Apixaban	Placebo

13.4 Results



14 Systematic review 14

14.1 Title of the systematic review

Safety and efficacy of addition of VEGFR and EGFR-family oral small-molecule tyrosine kinase inhibitors to cytotoxic chemotherapy in solid cancers: A systematic review and meta-analysis of randomized controlled trials

14.2 Inclusion criteria

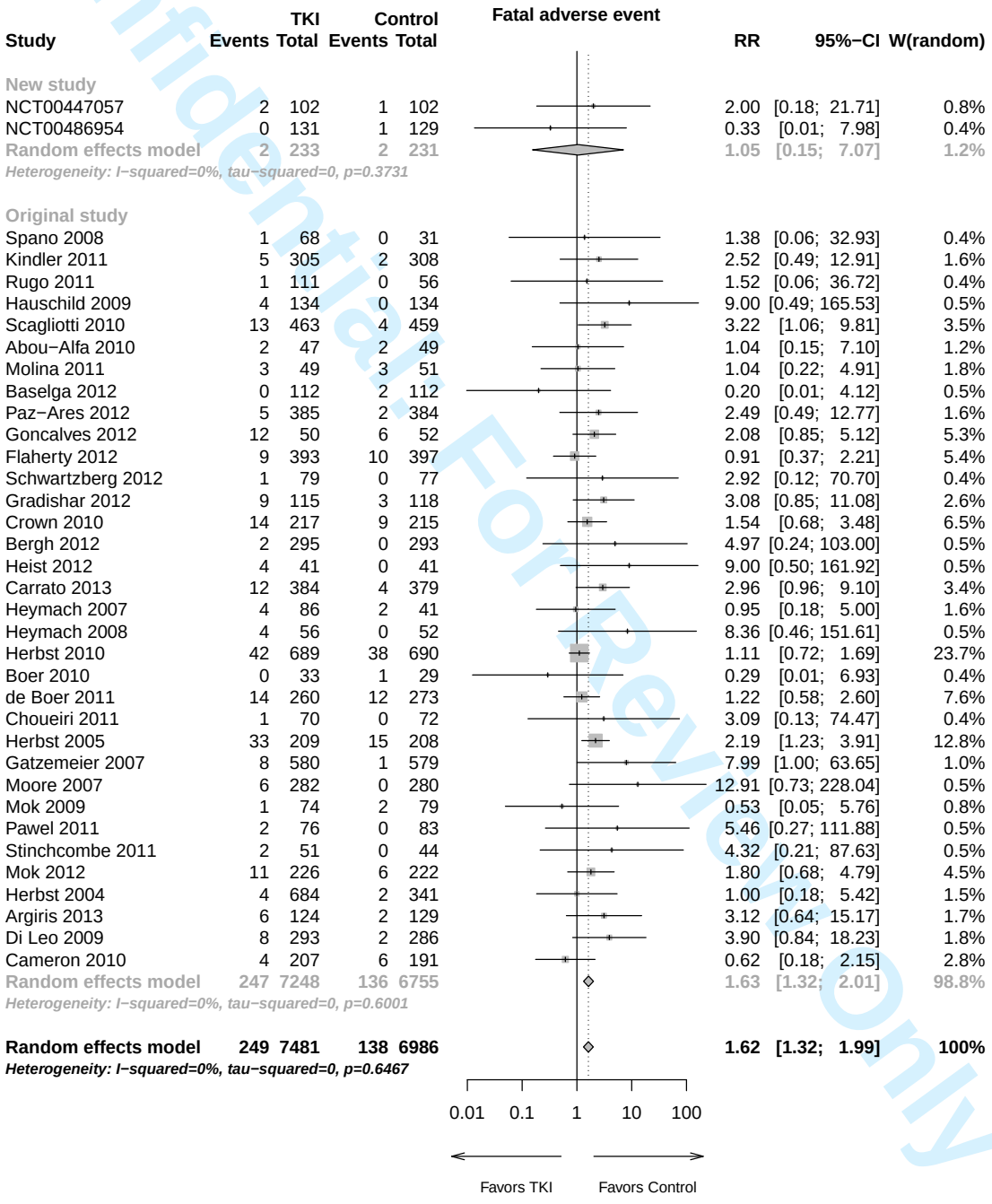
Clinical trials that met the following criteria were included:

- phase II and III trials in patients with solid cancers;
- random assignment of participants to treatment with chemotherapy plus VEGFR or EGFR-targeted TKI or chemotherapy alone;
- reporting data for at least one of the safety or efficacy outcomes.

14.3 Comparison assessed

	TKI	Control
NCT00447057	Pemetrexed + Erlotinib	Pemetrexed
NCT00486954	Paclitaxel + Lapatinib	Paclitaxel

14.4 Results



15 Summary

Systematic Review	Proportion of patients added in meta-analysis (%)	Summary statistic		Change in summary statistic (%)	Direction of change
		Without new studies	With new studies		
1	1	OR 0.51 [0.36 ; 0.70]	OR 0.53 [0.38 ; 0.73]	6	Decrease
2	19	RR 18.28 [12.76 ; 26.17]	RR 14.20 [10.72 ; 18.81]	9	Decrease
3	19	HR 0.87 [0.82 ; 0.91]	HR 0.88 [0.84 ; 0.93]	8	Decrease
4	51	HR 0.89 [0.80 ; 0.99]	HR 0.90 [0.83 ; 0.98]	10	Decrease
5	2	HR 0.99 [0.90 ; 1.09]	HR 0.99 [0.90 ; 1.08]	0	No change
6	8	SMD -0.21 [-0.29 ; -0.12]	SMD -0.19 [-0.28 ; -0.11]	10	Decrease
7	23	MD -1.77 [-2.13 ; -1.41]	MD -1.66 [-1.99 ; -1.32]	6	Decrease
8	112	MD -0.35 [-0.51 ; -0.19]	MD -0.45 [-0.55 ; -0.36]	29	Increase
9	0	OR 0.88 [0.79 ; 0.99]	OR 0.88 [0.79 ; 0.98]	0	No change
10	10	OR 1.79 [1.17 ; 2.74]	OR 1.52 [1.04 ; 2.23]	28	Less harm
11	5	RR 0.83 [0.74 ; 0.93]	RR 0.85 [0.76 ; 0.94]	13	More harm
12	1	RR 0.79 [0.52 ; 1.19]	RR 0.80 [0.54 ; 1.20]	5	More harm
13	1	RR 1.40 [1.08 ; 1.82]	RR 1.37 [1.06 ; 1.75]	6	Less harm
14	3	RR 1.63 [1.32 ; 2.01]	RR 1.62 [1.32 ; 2.99]	1	Less harm

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