Title

The role and impact of research agendas on the comparative effectiveness research amongst anti-hyperlipidemics

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Abstract

While it is well-established that funding source influences the publication of clinical trials, relatively little is known about how funding influences trial design. We examined a public trial registry to determine how funding provenance shapes trial design amongst trials involving anti-hyperlipidemics. An automated process was used to identify and analyse 809 trials from a set of 72,564. Three networks were constructed (representing industry, collaborative and non-industry funded trials), each comprising 18 drugs as nodes connected according to the number of comparisons made between them. The results indicated that industry funded trials were more likely to compare across drugs and examine dyslipidemia as a condition, and less likely to register safety outcomes. The provenance of funding for clinical trials had a measurable effect on trial design, which helps quantify differences in research agendas. Improved monitoring of current clinical trials may be used to more closely align research agendas to clinical needs.

Introduction

There is a recognised need to expand comparative effectiveness research (CER) and disseminate its results (1-3). Despite the overwhelming volumes of published evidence for individual therapies (4, 5), a lack of comparative evidence is cited as a current significant problem for clinical decision-making (6-9). A major problem is the apparent mismatch between the agendas of the research community and the evidence needs of clinicians (10). It is not yet known how best to distribute resources to clinical trials to maximise the clinical utility of the evidence produced (11, 12).

Funding source for trials appears to influence the type of evidence sought, thereby shaping the choice of research question and study design, as well as the reported conclusions (13-16). A better understanding of how funding influences clinical trial design may help improve the research endeavour by identifying how the varieties of research agendas match (or do not match) the evidence needs of clinicians and patients.

Clinical trial registries are emerging as a powerful tool to examine the current state of research activity, providing detailed information on study protocols, including the interventions under study, doses and formulations tested, primary and secondary outcomes and the comparators employed (14, 16, 17), regardless of when or if the trial results are published (18). In parallel, network methods have become widely used to understand the structures of social and organisational networks of people (19-21), and the production of scientific research (22-24), and have become a de facto standard for measuring how decentralised systems behave as a whole. This has led to some early methods for applying network analyses to examine CER (25, 26), and is suggestive of the value of applying network theory to the study of clinical trial research.

Focusing on anti-hyperlipidemics, our aims were to examine the role of funding source on trial design, including (i) the preference for active versus placebo comparisons, (ii) the relative concentration of focus on specific pharmacological interventions, and (iii) differences in the conditions and measured outcomes, reflecting the purpose for conducting trials.

Results

Eligible trials

Of the 112,113 clinical trials registered with ClinicalTrials.gov by the 16th of August 2011, 72,564 listed a starting date on or after the beginning of 2006. Of these, 809 include the name (or synonym) of a lipid-modifying drug and 360 specified a condition related to dyslipidemia, cardiovascular conditions such as heart disease or healthy subjects (see Methods). The method of extraction was automated and validated using a manual review. The 18 drugs found in the trials represent all six of the chemical subgroups in the ATC Classifications C10A and C10BA from which the drugs were selected. These two codes represent the set of anti-hyperlipidemics and common combinations used as interventions for dyslipidemia. Study arms contained 373 comparisons against placebo (placebo comparisons), 248 comparisons between two different drugs within the group (active comparisons), and 122 comparisons between two different doses of the same drug (dose comparisons). The distribution of trials, comparisons, outcomes and common interventions are given in Table 1.

Insert Table 1 here

Differences in trial design across the funding spectrum

The majority of trials were for patients with cholesterol-related conditions, as opposed to those categorised as cardiovascular conditions and healthy subjects (Table 1). Industry funded trials were more likely to consider cholesterol-related conditions (79.6% of trials) compared to trials that had collaborative (53.7%) or non-industry (44.6%) funding provenance ($p<0.001$ across groups).

The median enrolment was higher amongst industry funded trials than for otherwise funded trials (Table 1). Median enrolment for industry trials is 196 participants, compared to 60 and 75 participants for collaborative and non-industry funding, respectively. However, despite conducting trials with higher enrolment, industry funded trials started in the period were also more likely ($p<0.001$) to have been completed (70.1%) than collaboratively funded (41.5%) and non-industry (30.8%) funded trials.

Industry funded trials were also more likely ($p<0.001$) to have uploaded summary results to the registry (30.1%), compared to collaborative (7.3%) and non-industry (3.1%) funded trials.

Placebo comparisons were consistently preferred over active and dose comparisons across all funding types, and this was most pronounced for non-industry funded trials (Table 1). Placebo comparisons accounted for 46.1% of all comparisons in industry funded trials and this proportion increases to 56.5% and 55.4% for collaborative and non-industry funded trials, respectively. While placebo comparisons were common across the funding spectrum, active comparisons were more common for industry funded trials (36.1%) when compared to both non-industry (29.5%) and collaboratively (30.4%) funded trials.

Preferences amongst interventions and outcomes

To examine differences between funding groups with respect to the specific interventions chosen in trials, comparative effectiveness networks were constructed, where drugs are represented as single nodes in the network and active comparisons are represented as connections between nodes (see Methods). A visual inspection of the network reveals the focus on atorvastatin and the statin group in general, which is consistent across funding groups (Fig. 1). The proportion of active comparisons involving atorvastatin was not found to differ significantly across funding groups ($p=0.242$ across groups) with proportions ranging from industry (29.1%) to collaborative (23.0%) funding groups. Specific differences that are immediately apparent in the network include the larger number of repeated comparisons between drugs in industry, the greater overall number of comparisons involving atorvastatin in industry funded trials, and the presence of comparisons involving omega 3 preparations in non-industry trials (all omega-3 comparisons had at least partial non-industry funding).

Figure 1 here

Measured outcomes relating to efficacy were more common across the funding spectrum, and trials measuring only efficacy outcomes make up the largest proportion in industry-funded trials (75%) (Table 1). To examine the choice of measured outcomes in more detail, registered primary and secondary outcome measures were examined across the set of drugs (Fig. 2). Amongst the more

commonly examined drugs, non-industry groups tested safety in higher proportions for trials involving ezetimibe, pravastatin and rosuvastatin, and industry groups tested safety in higher proportions for atorvastatin, simvastatin and ezetimibe.

Figure 2 here##

Choice of dose in active and dose comparisons

To examine whether the choice of interventions was different across funding groups, a further set of comparative effectiveness networks were constructed – considering each drug and dose combination as a separate node. In Fig. 3, a section of the industry and non-industry networks are illustrated, comprising all atorvastatin and rosuvastatin interventions. An upward trend was apparent in the dose comparisons involving atorvastatin and rosuvastatin, where registered trials indicate that higher doses of atorvastatin are compared against lower doses of rosuvastatin, as expected given the potency comparison between these two drugs. No apparent differences were found when comparing funding groups by dose comparisons, and the results were generally consistent across the funding spectrum for comparisons between interventions involving other drugs.

Figure 3 here

Discussion

Examination of a large clinical trials registry via comparative effectiveness networks provides a novel method for understanding how the provenance of funding affects trial design. Extending from two recent examples of comparative effectiveness network studies (25, 26) and studies that aggregate and analyse information available on ClinicalTrials.gov (16, 18, 27), we used comparative effectiveness networks to evaluate clinical trials in a large registry. In particular, we looked for differences between funding groups in relation to trial design, choice of intervention (including dose), and measured outcomes. Since the approach examines trials that are often not yet completed or published, the results indicate areas of potential concern about gaps in evidence that will persist into the next few years.

The set of 360 trials collated by the automated extraction and analysis vary widely in design, from large Phase IV trials of 20,000 to early-phase trials involving fewer than ten healthy individuals. While it is likely inappropriate to aggregate (by way of meta-analysis) the results generated by trials with very different designs, the present study shows that it is useful to examine the patterns of how industry and non-industry groups design and undertake trials (often even before results are available or published) and compare these. The contrast between industry and non-industry suggests differences in their research agendas, with implications for the efficiency of the research endeavour and the quality of evidence yet to be published.

Differences in research agendas reflected in the results

Previous studies show that published CER studies are less likely to be funded by industry (1), and it has been suggested that industry has had little incentive to conduct CER studies in the past (28), as only placebo comparisons were required for approval (29). The opposite relationship was demonstrated in an examination of the registrations of clinical trials, where industry-funded trials were found to be more likely to include an active comparison (16). This relationship is confirmed in the present study for anti-hyperlipidemics in the period from January 2006 to August 2011, where industry appears to fund a larger number and proportion of studies comparing interventions. An explanation for why placebo comparisons may be preferred by non-industry groups may be that non-industry groups prefer lower costs, smaller sample size requirements, and a lower risk of unanticipated outcomes (28). The reversal that occurs between registration and publication, where fewer active comparisons are found in published studies of industry-funded trials (1), may be a consequence of publication bias (13-15, 18, 30, 31), or it may reflect a shift in incentives that has occurred since 2006 and is yet to flow into the corpus of published literature (27).

The results also show that industry funds a smaller proportion of trials with measurable outcomes designated as safety issues. Note that the most common registered safety outcomes include terms such as adverse events, serious adverse events, mortality and myopathy – corresponding to both symptoms of the interventions as well as clinical outcomes associated with cardiovascular risk. In addition,

industry groups more often register conditions directly related to dyslipidemia in trial registrations. This finding may also partially explain why a larger proportion of industry-funded trials from the period were already completed, since outcome measures for dyslipidemia are typically observed over shorter periods of time than outcome measures for vascular conditions, which were more commonly listed in non-industry trials. A possible explanation for the above differences is that the research agendas of industry groups are more closely aligned to marketing (32, 33), in which the value of conducting a clinical trial is primarily for establishing efficacy against a surrogate outcome measure rather than detecting safety issues and long-term cost-benefit. While outcome measures relating to lipids are well-established as surrogates for cardiovascular risk (34, 35), more recent negative conclusions for trials involving simvastatin and ezetimibe (36), and torcetrapib (37) for example, suggest that changes in lipids may not necessarily correspond neatly to changes in cardiovascular risk in some instances.

Finally, industry-funded trials started in the period were more likely to have uploaded summary results to the registry. This finding reflects a recent study (27), which indicated that 6.4% of industry sponsored trials and 0.7% of non-industry sponsored trials had uploaded summary results (covering an earlier but partially overlapping time period). The change in registration requirements following the Federal Drug Administration Amendments Act offers a likely explanation for the consistent difference between industry and non-industry, as well as the increased proportions revealed in the present study.

Limitations

The quality of our study is limited by the data quality of the clinical trial registry, and we sought to estimate the degree of error in our information extraction process by conducting a hand analysis of a subset of trials. We found that although free-text insertion of interventions and study arms are detrimental to conducting analysis over a large number of trials, an automated method was able to provide sufficient accuracy in recognising comparisons but a relatively low accuracy when detecting correct doses. The accuracy is reported in the methods. Our recommendation for the design of a

clinical trial registry would be that pharmacological interventions be recorded in a registration as structured information, giving the standard INN name for a drug (where available), the dose (including separately the rate and route) and defined in a hierarchical study arm description indicating the chronology, randomisation approach and the number of patients in each arm.

A similar argument applies to descriptions of the cohorts involved in the trials, especially with regards to pharmacogenetic studies. Trial registrations that involve screening for common polymorphisms are rare in the registry and tend to provide information about cohorts inconsistently, which precludes our ability to provide a trustworthy measurement of the prevalence of pharmacogenomics studies amongst the set. Another similar limitation relates to the meaningfulness of safety and efficacy outcome measurement, which relies heavily on correct specification of measured outcomes in trial registrations. Further examination of the specific measurable outcomes specified, perhaps following Zarin et al. (27), would give a more detailed insight into how different funding groups approach clinical trial design. However, many registered trials specify safety outcomes using general terms such as adverse events, without more detail of the specific nature of the events.

Drugs outside of the ATC Classification for anti-hyperlipidemics (such as cholesterylester transfer protein inhibitors, as well as antihypertensive interventions commonly studied in combination with anti-hyperlipidemics) were not included in the analysis and may have been represented in the set of trials. In addition, observational studies were not included and the less-scripted forms of pragmatic clinical trials (38) were unlikely to be captured, despite the contributions these types of trials may have in providing useful clinical evidence (39).

For the networks reported in the study, the small size precluded the application of many other network metrics, which is a known issue in the area (40, 41). Consequently, we compared these networks using a restricted set of statistical tools and used visual interpretation to examine individual differences between networks. There may be value in using typical network metrics for evaluating larger groups of drugs to determine differences in research agenda bias for more broadly-defined medical conditions.

Conclusions

The results indicate that while industry funded trials are more likely to include active comparisons than their non-industry counterparts, they are also less likely to include measurable outcomes relating to safety, and these are novel results for this class of drugs. Since the results pertain to evidence that is not yet available in the public domain (many of the trials in the period have not yet started, and many more are not yet completed or published), the results are suggestive of how current trial design preferences might manifest in future published evidence, as well as indicating which funding groups are most responsible for comparative effectiveness research on anti-hyperlipidemics.

It is not yet known how best to distribute limited resources to clinical trials in order to maximise clinical utility (11, 12), or how new evidence about outcome measures, drug interactions and pharmacogenetics may change what new evidence may be required in the future (42-44). Improved monitoring of clinical trials registries should substantially enhance our ability to coordinate and direct research priorities that will answer clinically-relevant questions in a trustworthy and efficient manner.

Methods

Data collection and validation

ClinicalTrials.gov is a publicly available registry of clinical trials that includes information about trial design including interventions chosen and outcomes measured, funding and a trial's current status. Clinical trial registrations were selected from ClinicalTrials.gov with a starting date after the 1st January 2006, if they included one or more study arms with one or more lipid-modifying drugs. Drugs were drawn from C10A and C10BA in the Anatomical Therapeutic Code (ATC) Classification, which comprises the five chemical subgroups of lipid-modifying drugs and one group of combination drugs (details in Figs. 1 and 2). The start date was chosen based on the International Committee of Medical Journal Editors (ICMJE) policy, mandating trial registration prior to subject enrolment in order for a trial to be eligible for publication in one of the member journals. Not all registered clinical trials used International Non-proprietary Names (INN) to specify the interventions, so each of the drugs was mapped to an EMBASE term and its associated synonyms. Data from all of the 112,113 clinical trials

registered on ClinicalTrials.gov at the 16th of August 2011 were extracted, including the trial identification number, start date, anticipated or actual enrolment, measured outcomes, condition, funding, trial design and study arm descriptions.

All interventions, defined by a drug in the group described above and an associated dose, were extracted from the study arms of the clinical trial registration. Study arms are provided in free text, which means that the extraction relies on heuristic evaluation of the free text to extract correct doses. Where doses were not found in the study arms, the related information in the intervention section of the registration was used to augment the study arm description. In a random sample of 100 trials, manual validation indicated that the extraction matched the correct dose 73% of the time when an intervention contributed to a comparison.

Classification for trial funding (industry, non-industry or collaborative) was based on information about primary and secondary funding sources in ClinicalTrials.gov. Those with either government or other forms of funding were classified as non-industry funded, and those that included industry as well as government or other forms of funding, were classified as collaborative.

Information available in the trial design and study arms was used to determine which anti-hyperlipidemics were tested and whether comparisons were made between drugs, between one drug and a placebo or between different doses of the same drug. Note that single group assignments and comparisons involving drugs outside of the C10 class do not contribute to the set of comparisons and were not included in the analysis. The condition or conditions registered with the trial were used to further eliminate trials that examined conditions unrelated to cholesterol or cardiovascular conditions.

A random sample of 100 trials was manually evaluated to test the data extraction. The method had 99% accuracy for active comparisons (100% specificity and 90% sensitivity) in trials, 94% accuracy for placebo comparisons (98% specificity and 73% sensitivity) and 95% accuracy for dose comparisons (95% specificity and 100% sensitivity). Correctness was defined for each of the three groups if a trial correctly identified all of the (active, dose or placebo) comparisons for that trial by drug. Partial matches were considered as false negatives. Errors were typically associated with

combination interventions, study arms that include sequences of different interventions or dose titration during the trial, or when a registration included repeated descriptions of the whole trial in each study arm.

Network construction

For the purpose of network construction, individual interventions were defined as unique drug and dose combinations as extracted from the registration of the clinical trials, and for those trials that belonged to the sets defined above. Each drug was also assigned to one of six chemical subgroups, corresponding to the five C10A subgroups and the C10BA group in the ATC Classification. Trials where drugs are present but did not form part of a placebo, dose or active comparison did not contribute to the connectivity of the network. Trials with more than two arms sometimes contribute more than two comparisons.

The first type of network was constructed with interventions aggregated by drug, to illustrate how differences in funding provenance influence active comparisons. The areas of the nodes represent the number of dose and placebo comparisons involving the drug and the thickness of the line is a count of the number of active comparisons between two drugs. Common network metrics such as density, centrality and homophily are not reported because they are misleading metrics for small networks (40, 41).

The second type of network was constructed to highlight dose comparisons and active comparisons between interventions. We chose to illustrate a subset of the network that included all of the interventions associated with two drugs (atorvastatin and rosuvastatin). All placebo comparisons associated with an intervention contribute to the area of the node, active comparisons are represented as connections between two interventions with different drugs and dose comparisons are represented as connections between two interventions of the same drug.

Analysis

We report the trial design characteristics that represent the sets of trials registered on ClinicalTrials.gov in the period between January 1st, 2006 and August 16th, 2011. Kruskal Wallis one way analysis of variance test is used to examine differences between the three funding groups for the condition registered (dichotomous, specifying whether or not a cholesterol-related condition was registered), enrolment (ordinal), and the concentration of comparisons involving atorvastatin (dichotomous, specifying whether or not a comparison involved atorvastatin). Visual interpretation of the constructed networks was used to examine individual differences between funding groups for both the drug-aggregate networks and the intervention networks. Web-crawling, text-mining and analysis were performed in MATLAB® 7.11.1 (The MathWorks, Natick, MA) and network visualisation was performed in Cytoscape 2.8.0 (45), which is available under a general public license.

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Conflict of Interest/Disclosure

The authors declared no conflict of interest.

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Figure Captions

Figure 1. The distribution of placebo and active comparisons by drug and measured outcomes for the set of anti-hyperlipidemics. The drugs are listed from the least to the most number of trials in which an active or placebo comparison was found (top to bottom) and shading and colouring indicate funding source and measured outcomes as given in the key (inset).

Figure 2. Networks illustrating active comparisons as connections between nodes, which represent drugs. The thickness of the connections represents the number of between-drug comparisons (labelled for values greater than one), the colours represent the seven classes of drugs (see Methods) and the area of the nodes represents the number of comparisons against placebo plus between doses of the same drug. The three networks represent different funding groups as labelled.

Figure 3. The industry intervention network (left) and the non-industry intervention network (right) illustrate active comparisons between atorvastatin and rosuvastatin (connections crossing the dotted lines) and dose comparisons (connections that do not cross the dotted lines). Node areas, and widths of lines are as described in Fig. 2.

Figure 4. Data flow for the identification of registered trials and the extraction of comparisons. Numbers in parentheses indicate the number of trials or the number of comparisons as labelled.

Figure 1:

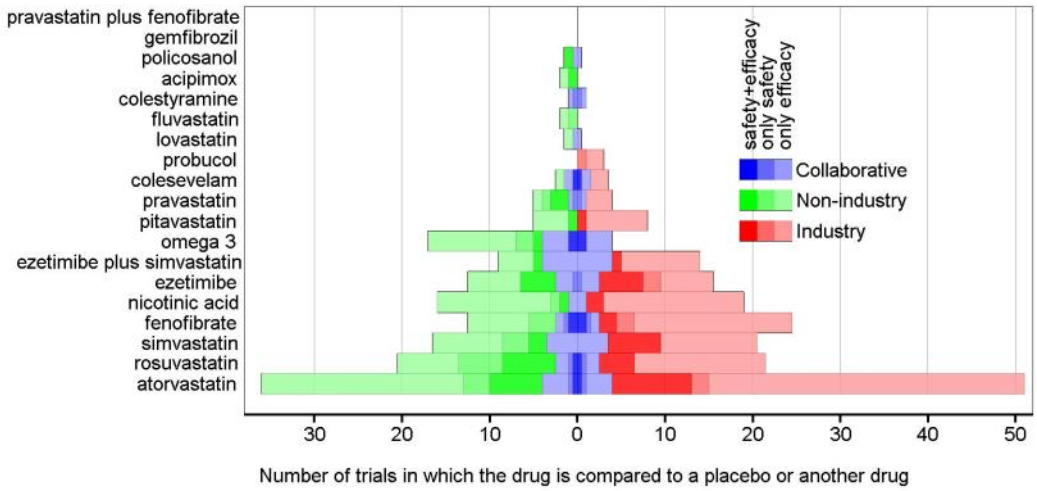


Figure 2:

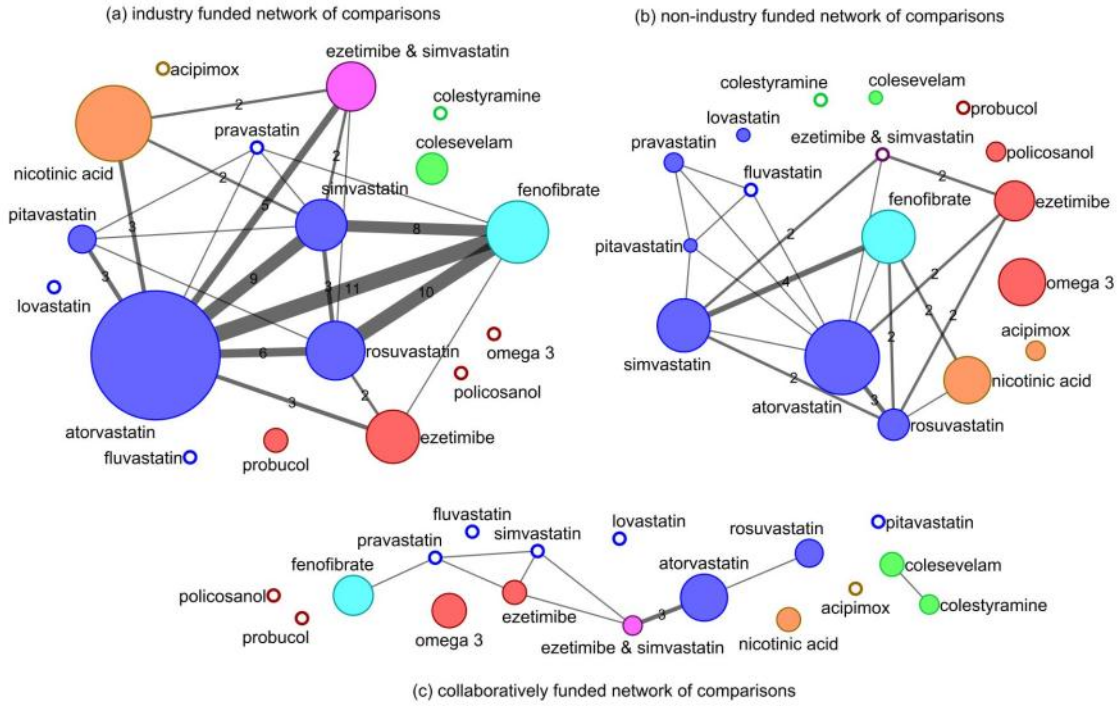


Figure 3:

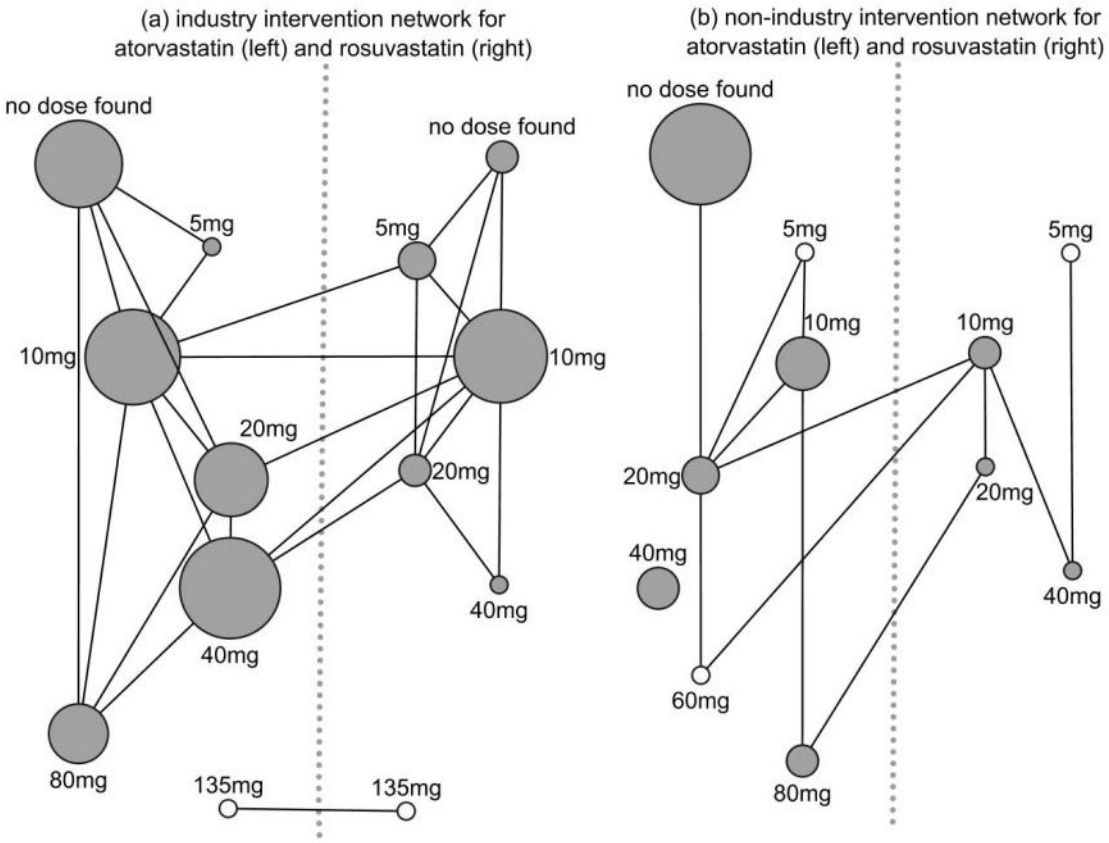
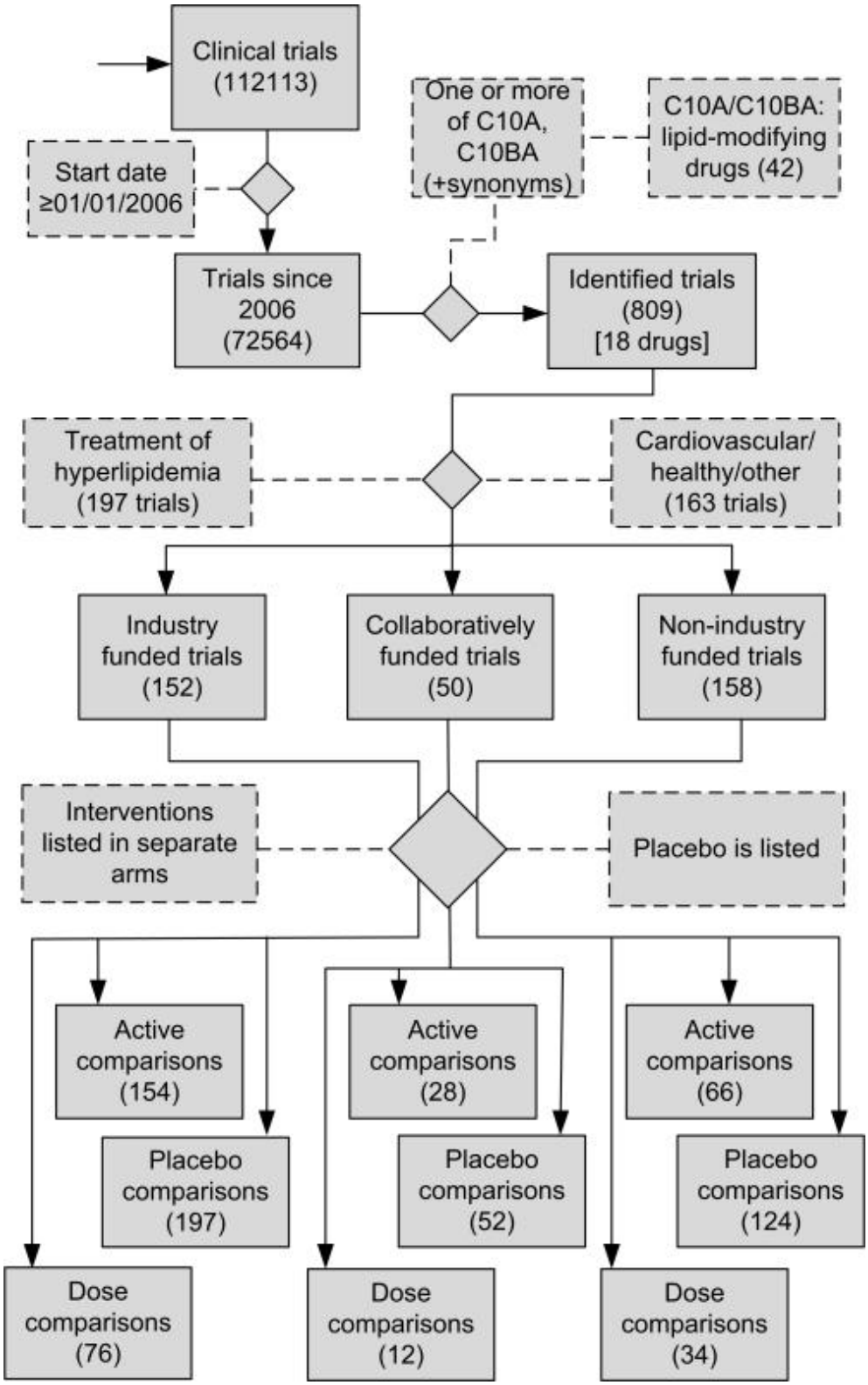

(a) industry intervention network for atorvastatin (left) and rosuvastatin (right)
no dose found
5mg
10mg
20mg
40mg
80mg
135mg
no dose found
5mg
10mg
20mg
40mg
135mg
(b) non-industry intervention network for atorvastatin (left) and rosuvastatin (right)
no dose found
5mg
10mg
20mg
40mg
60mg
80mg
5mg
10mg
20mg
40mg

Figure 4:


Clinical trials (112113)
Start date ≥01/01/2006
One or more of C10A, C10BA (+synonyms)
C10A/C10BA: lipid-modifying drugs (42)
Trials since 2006 (72564)
Identified trials (809) [18 drugs]
Treatment of hyperlipidemia (197 trials)
Cardiovascular/ healthy/other (163 trials)
Industry funded trials (152)
Collaboratively funded trials (50)
Non-industry funded trials (158)
Interventions listed in separate arms
Placebo is listed
Active comparisons (154)
Placebo comparisons (197)
Dose comparisons (76)
Active comparisons (28)
Placebo comparisons (52)
Dose comparisons (12)
Active comparisons (66)
Placebo comparisons (124)
Dose comparisons (34)