Huseyin Naci

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Evidence-based prescribing: Combining network meta-analysis with multi-criteria decision analysis to choose among multiple drugs

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Authors:

Huseyin Naci PhD [1, 2], Gert van Valkenhoef PhD [3], Julian PT Higgins PhD [4, 5], Rachael Fleurence PhD [6], and AE Ades PhD [7]

Author affiliations:

1. LSE Health, London School of Economics and Political Science, London, UK.
2. Drug Policy Research Group, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA.
3. Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
4. School of Social and Community Medicine, University of Bristol, Bristol, UK.
5. Centre for Reviews and Dissemination, University of York, York, UK
6. Program on Comparative Effectiveness Research Methods and Infrastructure, Patient-Centered Outcomes Research Institute, Washington DC, USA.
7. School of Social and Community Medicine, University of Bristol, Bristol, UK.

Correspondence:

Huseyin Naci, LSE Health, Office 301, Cowdray House, London School of Economics and Political Science, 20 Houghton Street London WC2A 2AE, UK. E-mail: h.naci@lse.ac.uk; Tel: +44 (0) 20 7955 6840; Fax: +44 (0) 20 7955 6803.

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The challenging nature of evidence-based decision-making

"What is the drug of choice for condition x?" is among the most commonly asked questions in primary care.[1] Reflecting the complexity of prescribing decisions, answering this question requires a difficult trade-off between the benefits and harms of multiple drugs for a given condition.

The principles of evidence-based medicine suggest that prescribing decisions should be guided by an objective benchmark, namely scientific evidence.[2] Such evidence is particularly important when choosing a first-line treatment among multiple alternatives. Unfortunately, existing clinical evidence on benefits and harms is rarely adequate to inform prescribing decisions. A randomized controlled trial comparing all relevant drugs would provide such information. However, clinical trials are often designed for regulatory purposes and therefore include selective patient populations and do not include all available comparator drugs.[3,4] In order to obtain insight into the comparative benefits and harms of multiple drugs, prescribers turn to summaries of evidence to discern the most promising drugs from their less effective comparators.

Recent methods used to synthesize existing evidence provide much-needed information on the comparative benefits and harms of multiple drugs. Network meta-analysis is one such method that allows for the combination of direct and indirect evidence from randomized trials, facilitating the comparison of all relevant drugs even when they are not directly compared to each other in clinical trials.[5] The recent surge in the number of network meta-analyses in the general medical literature is a testament to the increasing need for comparative evidence in prescribing decisions.[6] Even when comparative evidence from network meta-analyses exists, however, making sense of it remains a challenge. In particular, prescribers and patients often struggle to weigh the relative benefits and harms of multiple alternatives.

In this proof-of-concept study, we discuss the important yet challenging role of comparative clinical evidence in guiding prescribing decisions in clinical practice. Using a recent systematic review and network meta-analysis of statins as an example, we highlight the need to adopt a more formal framework to help prescribers and patients in identifying a first line drug among multiple alternatives. We call for combining network meta-analysis methods with decision analytic approaches such as multi-criteria decision analysis to encourage and facilitate shared decision-making between prescribers and patients.

Synthesizing existing evidence: Insights from the quarter-century history of statins

Statins are among the most widely prescribed classes of drugs, used to prolong survival by reducing the risk of heart attacks and strokes.[7-10] In addition to their benefits, statins are generally safe with rare adverse events.[11,12] Although a large number of randomized controlled trials compared statins head-to-head, until recently, findings of these active-comparator trials were neither systematically identified nor combined with the findings of placebo-controlled trials. Previous meta-analyses were pairwise in nature, which, by definition, compared two alternatives at a time. Even previous attempts at analyzing the comparative benefits and harms of multiple statins did not identify and include active-comparator trials.[13-17] Over the past 25 years, there has not been any comprehensive review of the existing literature evaluating whether individual statins (irrespective of their cholesterol-lowering effects) are different in terms of their benefit and harm profiles. Despite the absence of comparative evidence demonstrating its superiority to other statins in terms of its benefit and harm profile, utilization rates of five statins trailed behind those of atorvastatin (Lipitor®)[18] making it the best-selling medication in history.[19]

A recent review of the clinical trial literature[20] – set out to help prescribers in selecting a first-line statin – highlighted the essential role of network meta-analysis methods in synthesizing the existing evidence on statins. First, network meta-analysis methods allowed for the combination of both placebo-controlled and active-comparator trials, incorporating the entirety of relevant evidence. Second, these methods allowed for ranking individual statins with comparable LDL cholesterol lowering effects on the basis of

clinically meaningful benefit and harm outcomes. Similarity or interchangeability of statin doses was established by a statistical analysis of LDL cholesterol lowering effects at different doses.[21] Long-term benefit outcomes included all-cause mortality, major coronary events, and major cerebrovascular events. Short- to intermediate-term tolerability and harm outcomes were discontinuations due to adverse events, myalgia, and creatine kinase and hepatic enzyme elevations.

Insofar as this review provided much-needed answers regarding the comparative effects of individual statins, it also highlighted the challenging nature of making sense of the existing evidence on harms and benefits of multiple alternatives, and their trade-offs. First, this comprehensive review including almost 200 clinical trials did not conclusively distinguish between individual statins. Perhaps unsurprisingly, individual statins differed in terms of their comparative effects on benefit and harm outcomes (**Supplemental Table**). Based on the available evidence on major coronary events, for example, fluvastatin had the most favorable efficacy profile, followed by atorvastatin (**Figure 1**).[22] In terms of adverse outcomes, pravastatin had the most favorable tolerability profile, i.e., the highest probability of ranking best in terms of its effect on discontinuations due to adverse events.[23]

Second, considering additional benefit and harm outcomes further complicated the decision around which statin should be preferred as the first drug of choice. Simvastatin ranked higher than other statins in reducing the risk of all-cause mortality and major cerebrovascular events.[24] However, it was associated with relatively high rates of creatine kinase elevations, indicating potential muscle damage. While atorvastatin ranked high in terms of major coronary outcomes, it had a high probability of ranking last in terms of hepatic enzyme elevations, which indicate hepatotoxicity.

In many ways, this review underscored the challenges facing prescribers who are charged with not only making sense of a disparate set of findings, but also basing their prescribing decisions on the existing evidence. Complicating matters further, there was no clear way to identify the winner among statins, leaving it up to the prescriber to decide whether – and to what extent – long-term clinical benefits outweighed more intermediate-term harms for any given statin.

Making sense of existing evidence using multi-criteria decision analysis

The complexity of prescription drug therapy stems from the difficulty in making trade-offs between the benefits and harms of two or more options. Frustrating for prescribers, there is a lack of a conceptual framework with regard to balancing the benefits and harms of prescription drugs. A more formal approach is needed to help prescribers and patients in identifying a first line drug among multiple alternatives. One such approach is multi-criteria decision analysis,[25] which is a formal framework for analysis of complex decision problems involving trade-offs between multiple outcomes.[26] An attractive feature of multi-criteria decision analysis is that it applies qualitative or quantitative preferences on different outcomes, allowing for a transparent judgment on their relative importance.[27-29]

When applied to prescription drug therapy, multi-criteria decision analysis consists of four key elements.[26] First is choosing the alternatives to be appraised (e.g., multiple drugs in a given class). Second is deciding on the criteria against which the alternatives are appraised (e.g., different benefit and harm outcomes). Third is estimating the comparative performance of each alternative on each criterion (e.g., comparative effects of each drug on different benefit and harm outcomes). Finally, fourth is determining the criteria weights that indicate the relative importance of each criterion as compared to others (e.g., preferences about the relative importance of different benefit and harm outcomes).

Recently, multi-criteria decision analysis was considered alongside network meta-analysis, thereby greatly improving the interpretability of existing evidence by making explicit the difficult trade-offs between outcomes.[30] To illustrate the promise of this combined approach, we revisited the recent systematic review of statins and combined information on multiple outcomes using qualitative preference statements in a proof-of-concept study (**see below for the methods of combining network meta-analysis and multi-criteria decision-analysis**). When combining the evidence on multiple outcomes, we adopted simple preference statements about the relative importance of different outcomes and considered the effect of statins on preventing mortality to be more important than either major coronary or cerebrovascular events, which were in turn more important than any one of the

tolerability or harm outcomes. This assumption was justified in the case of statins where side effects are generally not severe,[31] and clinical practice guidelines emphasize total mortality as more important than non-fatal coronary and cerebrovascular outcomes.[32,33]

Methods of combining network meta-analysis and multi-criteria decision analysis

Applying weights to different criteria, multi-criteria decision analysis allows trade-offs between different outcomes of interest. To determine the weights, the decision maker is first asked to rank the importance of improving each outcome from its worst possible value to its best – such that the weight for outcome B (e.g., major coronary events) must be greater than that for outcome A (e.g., all-cause mortality). Various elicitation methods can be applied to make this information more precise, or even assign fixed values to the weights. Since the weights are subsequently used to compare specific numeric values for different outcomes, it is important to take into account the scales on which the outcomes have been measured when constructing the preference information.

For the recent systematic review of the statin trials, we took into account the evidence for the previously assessed benefit and harm outcomes, as obtained from separate network meta-analyses. To enable a meaningful comparison between the outcomes, we calculated absolute risks by multiplying the odds ratios obtained from network meta-analysis with the average odds of events across the control arms of included trials, thereby placing all outcomes on the same scale.[30,34] We then applied a structured benefit-risk model that allows evidence on multiple outcomes to be combined using qualitative preference statements.[25,30,35] This benefit-risk model took into account the probability distributions of all outcomes of interest and quantified the uncertainty around a decision, while keeping outcome measurements and value judgments clearly separated.[25]

Specifically, we sampled from the posteriors for the absolute risk on each outcome, which were translated to a partial utility between 0 and 1 (where 1 was best possible and 0 the worst possible value) for all alternative treatments and for all outcomes. For each such sample, there was a

corresponding set of criteria weights (preferences), which summed to one. Instead of using fixed criteria weights, we sampled them from all possible weights that were compatible with the ordinal preference information. The utility for each alternative statin was the weighted sum of the partial utilities. The structured benefit-risk model was based on 10,000 iterations to create a sample from the posterior distribution for the utilities, which was subsequently used to generate Figure 2 (to rank individual statins).

Many multi-criteria decision analysis methods require exact values to be assigned to the weights. The method we applied handled qualitative preference statements by randomly sampling from all weightings compatible with the preference information.[29,35] The final ranking thus incorporated two sources of uncertainty: uncertainty about the effects of the treatments, and uncertainty due to the imprecision of the preference information. In some cases, the uncertainty due to imprecision of the preferences can be substantial, but in this case our analysis showed that most of the uncertainty in the ranking was due to uncertainty of the treatment effects.

Ranking individual statins using decision analytic approaches

Figure 2 shows the distribution of ranking probabilities. In this figure different colors show different ranks, with darker colors showing better ranks. Using this figure, a decision-maker would want to choose the statin with the highest probability of best ranks (i.e., highest distribution of dark colors). According to Figure 2, fluvastatin has a considerable probability of both being the best (41%) and worst (12%) statin (based on the combination of benefits and harms), highlighting the uncertainty in its evidence base. In contrast, both simvastatin and atorvastatin have a high probability of better ranks, with a negligible probability of ranking worst.

One way of interpreting the existing evidence, then, would be to conclude that atorvastatin and simvastatin have the most favorable benefit and harm profiles. Of course, this interpretation is dependent on our set of qualitative preferences on the relative importance of different outcomes

(assuming that the effect of statins on preventing mortality is important than either major coronary or cerebrovascular events, which are in turn more important than any one of the tolerability or harm outcomes). Others may consider tolerability and harm outcomes to be equally or even more important than benefit outcomes. Indeed, differing preferences regarding the relative importance of different outcomes should be taken into account in prescribing decisions. One of the advantages of combining network meta-analysis with multi-criteria decision analysis is that this combined approach allows prescribers and patients to weight different outcomes differently and see how drug rankings change accordingly. Another key advantage of this approach is that it is patient-centered: Patient preferences can be used to determine the relative importance of different benefit and harm outcomes. This is important as individual patients differ in terms of their preferences for different outcomes.[36] For example, some patients may even prefer death to severe disability following stroke. Considering patient values would facilitate shared decision-making between patients and prescribers in choosing among multiple drugs.

Evidence-based prescribing: are we there yet?

Although the methodological standards for conducting and reporting systematic reviews and meta-analyses have improved substantially over the last two decades, they offer little guidance for making trade-offs between multiple benefit and harm outcomes. We envision a future where summaries of existing clinical literature are frequently combined with patient preferences, and considered alongside the knowledge and clinical expertise of prescribers when making prescribing decisions. For example this might take the form of a patient decision support tool that relies on the findings of published network meta-analyses, which can then be considered in light of patient preferences. If presented in an accessible, easy-to-use, and understandable format, patients could, for example, work through the evidence-based information in their own time, and then discuss with their clinician before finalizing their decision. Several patient decision aid tools already exist that aim to facilitate shared decision-making.[37] Existing evidence suggests that using such tools improve patients' knowledge; manage their expectations

regarding drug therapy, and allow patients to make decisions that are more consistent with their informed values.[38]

Such a future rests on the assumption that existing evidence, as well as its reviews and syntheses, are valid and reliable. As with any other method, network meta-analysis is not without its limitations, and these should be carefully investigated and addressed. Although the validity of the statistical methods underlying network meta-analysis is widely accepted,[39,40] there is concern about the combination of direct and indirect evidence *post-hoc* from published data. The validity of network meta-analysis depends on the distribution of relative treatment effect modifiers across comparisons (e.g., age, baseline disease severity).[41] An imbalance in the distribution of relative treatment effect modifiers across treatment comparisons can bias the results of network meta-analysis, and should be explored using meta-regressions and subgroup analyses.[42] To ensure valid findings, both pairwise and network meta-analyses should be reserved for sets of trials conducted in relatively homogeneous clinical populations. Selective publication of randomized trials with favorable findings, often termed publication bias, may also pose a threat to the validity of evidence syntheses.[43]

Similarly, more research is needed on the application of multi-criteria decision analysis in health care decisions. First, it is important to consider how to gauge patient preferences in clinical practice settings and beyond. An important question to consider is: which preference elicitation techniques would work best for different populations of patients? Second, whether existing utility instruments, such as the EQ-5D can be used to rank different outcomes using population-level preferences should be investigated. Although existing utility measures are suitable for calculating quality-adjusted life-years in the context of cost-effectiveness analysis, they may not be particularly sensitive to individual patient preferences and trade-offs between different outcomes. In addition, seeking individual patient input (as opposed to population-level utilities) would be desirable because patient preferences are intrinsically different at the individual level, and vary over time due to external factors.[44]

A related challenge is the "granularity" and applicability of the existing evidence. Generalizing the findings of randomized controlled trials to individual patients seen in clinical practice remains a challenge. Although the findings of randomized controlled trials – or their syntheses in meta-analyses – may be particularly helpful for the "average" patient or population, patients often do not respond uniformly to therapies. In addition, randomized controlled trials are often short-term; do not report important harm outcomes; and include selective patient populations, which may differ greatly in terms of their age, gender, and co-morbidity profiles from those seen in clinical practice.[45] Despite much enthusiasm for tailoring decisions for individual patients, existing clinical evidence is not detailed enough to individualize treatment options.

In the case of statins, despite their quarter-century history, there is still inadequate evidence for a meaningful comparison of individual drugs in primary and secondary prevention. For instance, there is no available all-cause mortality data on simvastatin among individuals without established coronary heart disease; no data on the effect of fluvastatin and simvastatin on major coronary events in primary prevention; and no data on the effect of fluvastatin and rosuvastatin on major coronary events in secondary prevention. In addition, there is a paucity of information on populations that are most likely to receive statins, such as those 75 years of age and older that are eligible for statin therapy for the secondary prevention of coronary heart disease.[22,23]

Given the absence of adequate effectiveness data on sub-groups by racial, ethnic, genetic, and co-morbidity profiles of patients, a synthesis of all randomized controlled trials of statins constitutes the current best evidence on the comparative benefits and harms of drugs, and should form the basis of prescribing decisions – alongside clinical expertise and patient preferences – about the care of individual patients.

Conclusion

After two decades of "evidence-based medicine" incorporating scientific evidence into prescribing decisions remains challenging. The combination of network meta-analysis with multi-criteria decision

analysis holds the promise to introduce more transparency to the decision-making process and potentially increase the relevance and informative value of existing evidence for prescribing decisions. This combined approach would have important advantages. First, prescribing decisions would take into account multiple benefit and harm outcomes on all relevant alternatives. Second, such an approach would make explicit the qualitative preferences and trade-offs between these outcomes. Third, patient values and choices can be considered alongside the knowledge and expertise of prescribers, making shared decision-making a reality in clinical practice. Taken together, this combined approach has the potential to improve prescribing decisions.

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Figure Legends

Figure 1 – Distribution of ranking probabilities for individual statins.

Figure 2 – Comparative benefit-harm profiles of individual statins on the basis of placebo-controlled and active-comparator trials.

Figure 1: Distribution of ranking probabilities for individual statins. Ranking for each treatment indicates the probability of being the best treatment, the second best, the third best, and so on. For simplicity, this figures provides the relative ranking probabilities for only two outcomes. Tolerability depicts discontinuations due to adverse events whereas efficacy refers to primary and secondary prevention of major coronary events. Based on this figure, fluvastatin has the most favorable efficacy profile, followed by atorvastatin. In terms of adverse outcomes, pravastatin has the most favorable tolerability profile.

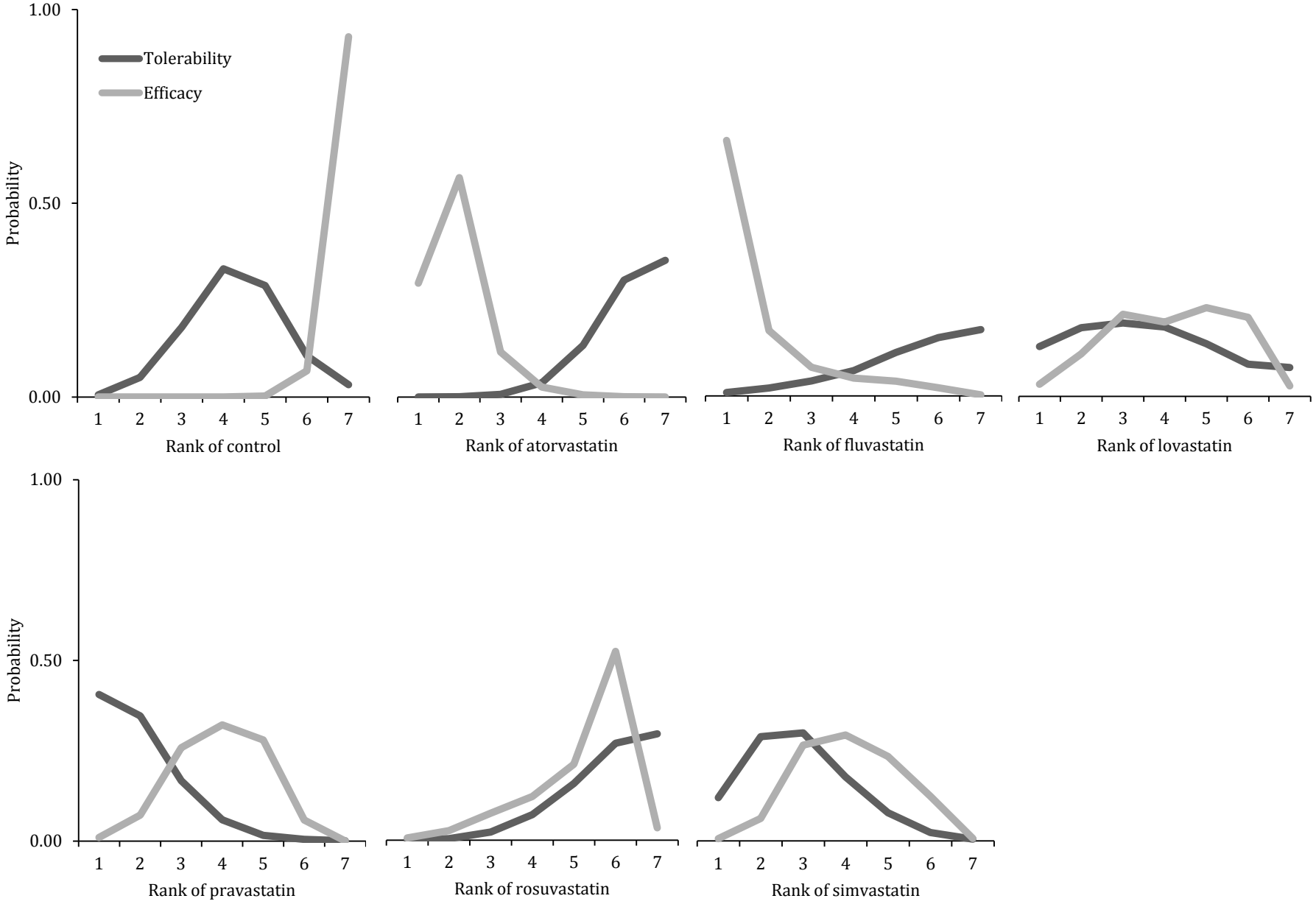

Figure 2: Comparative benefit-harm profiles of individual statins on the basis of placebo-controlled and active-comparator trials. This figure combines the overall benefit (all-cause mortality, major coronary events, and major cerebrovascular events) and harm (discontinuations due to adverse events, myalgia, transaminase elevation, and creatine kinase elevation) outcomes for each statin, estimated based on probability distributions for absolute effect sizes. The figure shows the distribution of ranking probabilities for both benefit and harm outcomes, taking into account the qualitative preference statements about the relative importance of different outcomes (all-cause mortality assumed to be more important than either major coronary or cerebrovascular events, which were in turn assumed to be more important than any of the harm outcomes). Based on this figure, fluvastatin has a considerable probability of both being the best (41%) and worst (12%) statin, highlighting the uncertainty in its evidence base. In contrast, both simvastatin and atorvastatin have a high probability of better ranks, with a negligible probability of ranking worst.