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Statins and risk of thromboembolism:

A meta-regression to disentangle the efficacy-to-effectiveness gap using observational and trial evidence

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Abstract

Background and aims

Meta-analyses of randomised controlled trials (RCTs) and observational studies indicate a lower risk of venous thromboembolism (VTE) associated with statin treatment. We aimed to compare the effect of statin therapy in these two settings and to identify and quantify potential factors to explain statin efficacy and effectiveness.

Methods and Results

We electronically searched on December 11th, 2018, articles reporting on first VTE events in RCTs (statin vs placebo) and in observational studies (participants exposed vs non-exposed to statin). We performed Knapp-Hartung random-effect meta-analyses to calculate pooled relative risks (RRs) of VTE events associated with statin treatment, separately for RCTs and observational studies; and estimated the ratio of the relative risk (RRR) comparing RCTs vs observational studies using meta-regressions, progressively adjusted for study-level characteristics. Twenty-one RCTs (115,107 participants; 959 events) and 8 observational studies (2,898,096 participants; 19,671 events) were included. Pooled RRs for RCTs and observational studies were 0.82 (95% confidence interval (CI): 0.67 to 1.00; I^2 19.2%) and 0.60 (95% CI: 0.42 to 0.86; I^2 86.3%), respectively. In meta-regressions, the unadjusted RRR indicated a nonsignificant 23% smaller benefit in RCTs (RRR 0.77; 95% CI: 0.52 to 1.13); accounting for age, sex, geographical region, and duration of follow-up, there was a sensible change of the RRR which resulted 0.30 (95% CI: 0.13 to 0.68).

Conclusion

Differences in the characteristics between patients included in RCTs and those in observational studies may account for the differential effect of statins in preventing VTE in the two settings.

Keywords: Venous thromboembolism; statin; meta-analysis; meta-regression; clinical trials; observational study; real-world evidence

Acronyms: RCT - Randomised Controlled Trial; VTE - Venous thromboembolism

Introduction

Statin treatment is recommended for the primary and secondary prevention of cardiovascular diseases.[1] In the last two decades, post-hoc observational investigations of randomised controlled trials (RCTs) and pre-clinical studies have demonstrated that the cardiovascular effects of statins are not exclusively mediated by their lipid-lowering properties. In particular, their anti-inflammatory and anti-platelet properties could complement their lipid-lowering effects (statin pleiotropy).[2] Because inflammation and platelet hyperactivity are involved in the pathophysiology of venous thromboembolism (VTE),[3] several studies have also investigated the effect of statin treatment on the risk of VTE events. These studies have been recently summarised in meta-analyses which, overall, indicate a reduced risk of VTE events in people treated with statins;[4, 5] they also suggest, however, a possible difference in the magnitude of the effect when comparing RCTs with observational studies. Whether such differences are related to study design, characteristics of included participants, or precision of estimates (i.e., RCTs reported lower events as they rarely included VTE events as a pre-specified endpoint) remains uncertain.

To date, there is no systematic and quantitative evaluation of a possible heterogeneous effect of statins between the two study settings - RCTs and observational studies; in particular, whether and to what extent potential effect modifiers explain the heterogeneous treatment effects is unknown. Clarifying these uncertainties is relevant for two main reasons. First, the importance of observational and “real-world” evidence, its complementarity to RCTs, and the identification of sources of dissimilarities between the two study settings is essential for a better understanding of the efficacy and effectiveness of a treatment.[6] Second, exploring potential effect modifiers of a treatment facilitates the implementation of a precision (stratified) approach to everyday clinical patients.[7]

Within this context, we aimed to quantitatively compare the efficacy of statin treatment in RCTs vs observational, real-world studies and to explore to what extent potential factors influencing statin effect could contribute to the heterogeneous effects observed in these two settings.

Methods

Search strategy and study selection

We performed a systematic review and meta-analysis following a registered protocol and reported results in line with standard guidelines (checklist in the **Supplemental Material**). On 11th December 2018, we updated two previous searches [4, 8] using ISI Web of Science, PubMed, and Cochrane Library to identify new observational studies or RCTs (open or blinded trials enrolling 100 or more participants) reporting incident VTE events (deep vein thrombosis and pulmonary embolism, regardless of their assessment) in people randomised to statin treatment or placebo and in people exposed vs non-exposed to statin (observational studies). Details of the search terms used are provided in the supplementary material (**Supplemental Material Figure S1**). RCTs were eligible for inclusion if they reported first VTE events, included adults from a general population, and lasted at least 24 weeks. Observational cohort studies were eligible for inclusion if they reported first VTE events in adults from the general population. Reference lists of selected studies were manually scanned for additional reports.

Data extraction and quality assessment

For eligible studies, we extracted data on: first author, year of journal publication, PubMed identification number, study design, population included, geographical region, sex, mean/median age and follow-up duration, total number of participants and cases of VTE for statin and no statin/placebo, and confounders accounted for in observational studies. The quality of studies was assessed using Cochrane's risk of bias tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies.[9, 10] With the Cochrane's tool, the risk of bias is judged high, low, or unclear for six items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The NOS score, ranging from 3 to 9 with higher score indicating an observational study of higher quality, is the sum of the score for three items: selection of the participants (i.e., representativeness of the cohort and ascertainment of the exposure; score 1 to 4), comparability of

the non-exposed participants (1 to 2), and assessment of outcome (i.e., record linkage vs self-reported; duration of follow-up; 1 to 3).[10] The process of study selection, data extraction, and quality assessment were performed independently by two authors, with discrepancy solved by consensus or arbitration.

Statistical methods

Following Cornfields rare disease assumption, odds ratios and hazard ratios were assumed to approximate the relative risk (RR).[11] For RCT trials with zero events in one of the arms, the RR was calculated with the 'opposite-arm' continuity correction.[12] A random-effect meta-analysis of the association between statin use and VTE events was performed separately for observational studies (most-adjusted estimates) and RCTs; we used the Knapp-Hartung method, instead of the widely used Der Simonian-Laird estimator, as the former is considered an improved alternative for random effects meta-analyses.[13, 14] Heterogeneity was assessed using the I^2 statistic and publication bias was graphically evaluated with funnel plots and formally quantified with Egger's test.

We calculated the ratio of the relative risk (RRR) comparing RCTs and observational studies with meta-regressions: models were progressively adjusted for potential study-level characteristics, including age, sex, geographical region (continent), and duration of follow-up. Ratios of the relative risks lower than 1 indicate an effect of statins in preventing VTE which is smaller in RCTs than in observational studies.

Stata 15.0 (Stata Corp, College Station, TX, USA) was used for all analyses; we considered $p < 0.05$ as statistically significant.

Results

Characteristics of included studies

The updated search found an additional observational study and no additional RCTs meeting the inclusion criteria (**Figure S1**);[15] references of the included studies are reported in the **Supplementary Material**.

Overall, 115107 (median: 4574; range: 108-20536) participants reporting 959 VTE (19; range: 1-346) events were included in 21 RCTs and 2898096 (16930; range: 289-2004692) participants with 19671 (136; 20-12199) events in 8 observational studies (**Table 1**).

Weighted mean age and follow-up were 63 (range: 51-75) and 3.6 (1.0-5.6) years, respectively, in RCTs and 58 (42-73) and 5.9 (1.1-10.0), respectively, in observational studies. Men were 66.8% in RCT and 49.2% in observational investigations; all observational studies and 10 out of 21 (47.6%) RCT were conducted in Europe or North America.

In RCTs, the risk of bias was considered low, high, and unclear in 65.1%, 4.8%, and 30.1% of the cases, respectively; high or unclear domain-specific bias was lowest for “random sequence generation” (0%) and highest for “incomplete outcome data” (19/21; 90.5%; **Table S1**). In observational investigations, six studies had a score greater or equal than six out of a maximum nine (**Table S2**).

Meta-analyses and meta-regressions

The results of the meta-analysis indicated a lower risk of VTE combining RRs from RCTs, with a reduction of 18% in participants randomised to statins (pooled RR: 0.82; 95% CI: 0.67 to 1.00; **Figure 1**) and low variability across RCTs (I^2 19.2%). The corresponding pooled RR for observational studies was 0.60 (95% CI: 0.42 to 0.86) with a larger heterogeneity (I^2 86.3%). There was evidence of publication bias in observational ($p=0.034$) but not randomised ($p=0.729$) studies (**Figure S2**).

In meta-regressions, the unadjusted RRR comparing RCTs with observational studies indicated a nonsignificant 23% smaller benefit in RCTs: RRR 0.77 (95% CI: 0.52 to 1.13; **Figure 2**); the RRR was similar upon adjustment for age (0.66; 95% CI: 0.41 to 1.06). Progressive adjustment for study-level

characteristics resulted in lower RRRs, which was 0.30 (95% CI: 0.13 to 0.68) accounting for age, sex, geographical region, and duration of follow-up (**Figure 2**).

Discussion

In this analysis, we observed differences comparing RCTs and observational studies in the reduction of VTE events associated with statin treatment. These differences are in part explained by the heterogeneous characteristics of participants between RCTs and observational studies, such as age and sex, which are key determinants of VTE risk.

The debate about the relative pros and cons of RCTs vs observational evidence has reignited in the last few years as a consequence of an increased interest in “real-world” evidence, which is commonly defined as the observational evidence from data collected for purposes other than research (i.e., electronic health records).[6] The growing interest is exemplified by several studies investigating the effectiveness of treatments using real-world data,[16-18] in line with the Food and Drug Administration and the European Medicines Agency guidance about the use of real-world data to support regulatory decision-making.[19, 20] In parallel with regulatory advances, there is also an increasing research interest in analytical tools to simulate randomised experiments using non-randomised data, in particular to account for the baseline imbalance of risk factors which could act as confounders on the association between treatment and outcome.

The problem of confounding is well-known in observational research and still represents one of the major criticisms to reliably quantifying treatment effects using observational data.[21] The impossibility of controlling for unknown or unmeasured confounders, which are intrinsically balanced in a RCT, may result in a biased estimate. However, in the context of statins and risk of VTE, previous real-world evidence from Smeeth L et al. suggests the effects of statins were comparable with findings observed RCTs;[22] these results indicate that an appropriate epidemiological model can largely control for covariate imbalances between exposed and non-exposed participants and that the absence of randomisation may not be the most important limiting factor in the analysis of observational data. Smeeth L et al.’s findings have been confirmed in our study: we did not find evidence in the unadjusted analysis of a differential effect between pooled estimates of RCTs and observational studies. However, accounting for potential confounders

between studies, the RRRs progressively changed: from a RRR of 0.77 in the unadjusted model to 0.66 (i.e., 14% relative difference) accounting only for age and 0.39 (i.e., 50% relative difference) accounting also for sex. While recognizing that the confidence intervals of these estimates are partly overlapping, the changes in the RRRs would suggest that the heterogeneous effects between randomised and observational studies could, at least in part, be related to the inclusion of heterogeneous participants, above and possibly beyond the unbalanced confounders which have been accounted for within each observational study.

Our results, indicating a possible role of heterogeneous patients' characteristics in the heterogeneous risk reduction between RCTs and observational studies, have important ramifications. It is well recognised that RCT's participants are poorly representative of the real-world population; therefore, it is difficult to accurately quantify the effect of a treatment for everyday patients.[23] This knowledge gap could be reduced in two complementary ways. Investigators could "mimic" one study type in another: for example, one could assess whether the treatment effect is similar between participants of a RCT and those of an observational study with RCT-like participants;[24] or, symmetrically, between participants of an observational study and those of a RCT with observational study-like participants (i.e., pragmatic RCTs).[25] In addition, trialists and observational epidemiologists should investigate in detail whether the effect of a treatment differs according to baseline patients' characteristics (i.e., interaction analysis).[7] In observational studies, this is easily implementable in pre-planned, protocol-based analyses; conversely, in RCTs the limited statistical power for interaction,[26] the improper analytical methods frequently used to assess it and,[27] most importantly, the absence of a real interest in identifying groups of participants in which the treatment could be more (or less) effective, has hampered so far a better identification of patients who could benefit more from treatments. Notably, conducting such an investigation would be in line with the much-promoted personalized medicine and,[28] at the same time, would likely reduce the difference between the efficacy and effectiveness of a treatment. These considerations, however, do not negate the relevance of other factors as potential explanations for the differences between RCTs and

observational studies: among them, exposure and outcome definitions and ascertainment and concomitant diseases and therapies are likely relevant; furthermore, in the context of statins and VTE, a potential heterogeneous effect of different statin types on VTE should be considered and balanced against the impact of other factors (particularly age and sex) on the risk of VTE.[8]

Our study has several strengths. To our knowledge, this is the first investigation to explore whether the effect of statins on VTE differs between RCTs and observational studies; to identify potential factors behind such discrepancy; and to quantify their relevance. These questions were addressed in this updated meta-analysis which followed current guidelines for conducting and reporting systematic reviews and meta-analyses. There are also some limitations. Outcome data could not be further phenotyped (provoked or unprovoked VTE; pulmonary embolism or deep vein thrombosis). All RCTs, except one, [29] have been designed to investigate the effect of statins on major cardiovascular outcomes or surrogate endpoints of atherothrombosis; therefore, each RCT was not individually powered to demonstrate an effect of statin on VTE outcomes. We could not extract detailed information on how VTE events were assessed in the included RCTs, limiting the possibility to account for this information in the analysis. However, it is likely that their definitions and diagnostic algorithms were heterogeneous both within and between RCTs. A similar limitation applies to real-world studies, where VTE events were mostly extracted from medical records. Lastly, the direction of the association between study-level characteristic and the outcome could be different when explored at individual (i.e., within a study) or aggregate level.[30]

In conclusion, these results would indicate that the differences in the prevention of VTE events with statin treatment observed comparing RCTs and observational studies are partly related to patient characteristics and partly related to dissimilarities in study design. Future approaches whereby (i) RCTs are more frequently complemented by observational/real-world data and (ii) investigators more extensively explore whether the treatment effect depends on patients' characteristics could help decipher the dissimilarities observed between the two research settings and assist health care professionals in a personalised approach to treatments.

Competing interests

SS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly, and Boehringer Ingelheim.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi–Aventis and Lilly.

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi–Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi–Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

FZ, JM and SKK have nothing to disclose.

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Author Contribution

KK, FZ, SKK: study idea and design; FZ, SKK, SS: literature search and data extraction; JM, FZ: data analysis; FZ: first draft; all Authors: study critical revision and manuscript draft. All authors provided final approval of the version to publish. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data access and sharing

Databases and statistical codes are available on request from the corresponding author (FZ).

Ethics

This article does not contain any study with human participants performed by any of the authors.

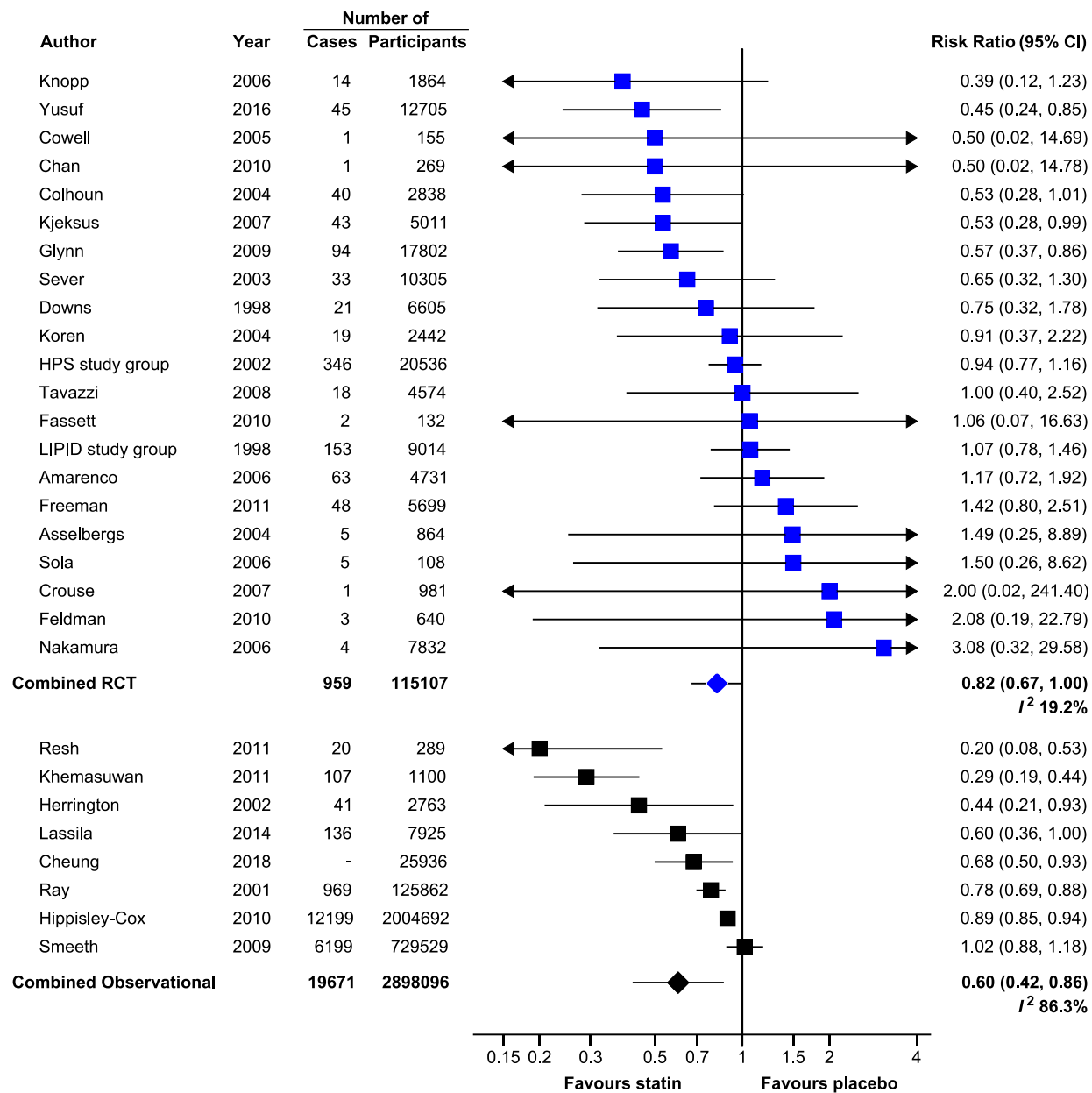
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FIGURES LEGEND

Figure 1: Effect of statin therapy on venous thromboembolism

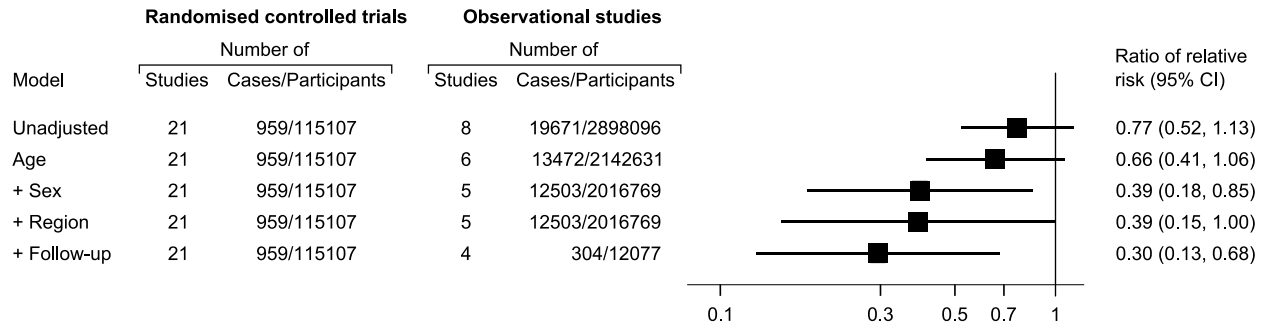


Legend: Study-specific and overall estimate are reported separately for randomised controlled trials (blue) and observational studies (black), comparing statin vs no-statin: values <1 indicate a reduced risk of venous thromboembolism events associated with statin use. *I*² indicates how the results of studies are consistent,

with larger values indicating higher heterogeneity. Cases and participants indicate study-specific number of venous thromboembolism events and participants.

- indicates not available. RCT: randomised controlled trial; VTE: venous thromboembolism.

Figure 2: Progressively adjusted ratios of the relative risks



Legend: Ratios of the relative risks <1 indicate an effect of statins in preventing venous thromboembolism events which is smaller in randomised controlled trials than in observational studies (i.e., statin use associated with a greater reduction of venous thromboembolism events in observational studies). Cases and participants indicate the combined number of venous thromboembolism events and participants for the specific meta-regression. Meta-regressions are progressively adjusted (top-bottom) for study-level characteristics.