Enhancing statistical power in lipid-lowering therapy studies through optimization of the MACE endpoint composition: a model-based meta-analysis approach

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Abstract

A quantitative tool was developed to optimize the composite MACE endpoint (an assessment following statin and anti-PCSK9 therapies), by minimizing the sample size required to achieve a statistically significant therapeutic effect, following meta-regression modeling of single MACE components.

Introduction

- Major adverse cardiac events (MACE) is a commonly used composite endpoint for clinical cardiovascular research, with no standard definition of its individual components making up the endpoint – the very definition of MACE may thus vary across clinical trials [1].
- While composite endpoints such as MACE may improve statistical efficiency, they also present limitations, eg increased complexity and potential masking of treatment benefits. A careful balance of statistical efficiency, clinical relevance, and component compatibility is essential for achieving optimal patient benefits in clinical trials.

Methods

- PubMed and ClinicalTrial were searched to identify randomized controlled studies of dyslipidemia with statins or PCSK9 inhibitors where MACE and individual MACE components and dynamics of biomarkers were reported (Figure 1).
- A meta-regression model of individual MACE components was built with a stepwise covariate search approach, on top of base models with *therapy type* as a default predictor. Missing covariate values were imputed using the multiple imputation approach, assuming that the values were missing at random.
- Model-predicted averages of the effect size for a composite outcome and a population of interest, along with event frequencies in the control group, uncertainty in model parameters and pre-defined trial durations were used to calculate minimal sample size of clinical studies required to achieve statistical significance in the risk ratio (RR) reduction and as defined by the upper bound of the 95% confidence interval (CI) of the weighted mean being less than zero.

Demographic characteristics

Prevention type, presence of patients with severe renal disease (RD), age, body mass index, males (%), hypertension (%), diabetes (%), smokers (%)

Baseline dyslipidemia biomarkers

- low-density lipoprotein cholesterol (LDLc)
- high-density lipoprotein cholesterol (HDLc)
- triglycerides (TG)
- remnant cholesterol (remC)

Study design

- type of treatment
- follow-up duration

Treatment-related change in lipid biomarkers

Baseline- and comparator-adjusted measurements of LDLc (ΔLDLc), HDLc, TG and remC:

$$\Delta Biom = (Biom - Biom_{BL})_{TRT} - (Biom - Biom_{BL})_{COMP}$$

Records identified through database searches:
- PubMed: **550**
- ClinicalTrials.gov: **210**

Total records: **760**

→ Duplicates removed (**414**)

Records after duplicates were removed: **346**

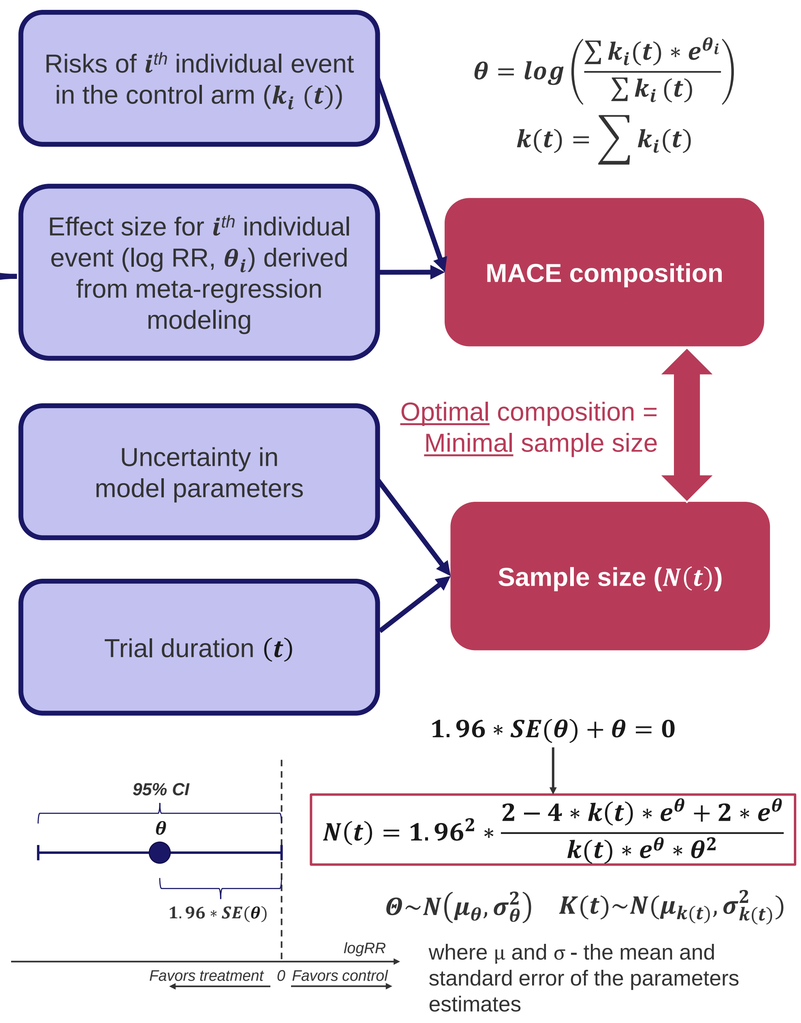
→ Records excluded on the basis of titles and abstracts (**286**):
- non-relevant treatment type (**63**)
- less than 100 participants per arm (**102**)
- without control (**9**)
- meta-analyses (**17**)
- follow-up period less than 1.5 years (**27**)
- without published results (**68**)

Full-text articles assessed for eligibility: **60**

→ Records excluded on the basis of full text (**6**):
- non-relevant MACE (**5**)
- non-relevant biomarkers (**1**)

54 studies included in meta-analysis (**N = 270471**)

FIGURE 1. PRISMA flow diagram of study screening and selection



Results

- 54 studies including 270,471 patients were collected, reporting 15 different single cardiovascular events, e.g. mortality from different causes, stroke and its subtypes, myocardial infarction and its subtypes, and others (Figure 2).
- Treatment-mediated decrease in LDLc, baseline levels of remC and HDLc as well as non-lipid population characteristics and type of therapy were identified as significant covariates for 10 of the 15 outcomes (Table 1).

TABLE 1. Final meta-regression model for each individual endpoint

Individual components	Covariates
nfMI	***Therapy* + *ΔLDL* + *ΔLDL* : *RD***
CR	***Therapy* + *ΔLDL***
CM	***Therapy* + *ΔLDL***
HF	***Therapy* + *remC***
MI	***Therapy* + *HDL***
TM	***Therapy* + *HDL***
CVM	***Therapy* + *HDL***
ST	***Therapy* + *Age* : *Prevention***
fST	***Therapy* + *Renal Disease***
iST	***Therapy* + *Hypertension,%***

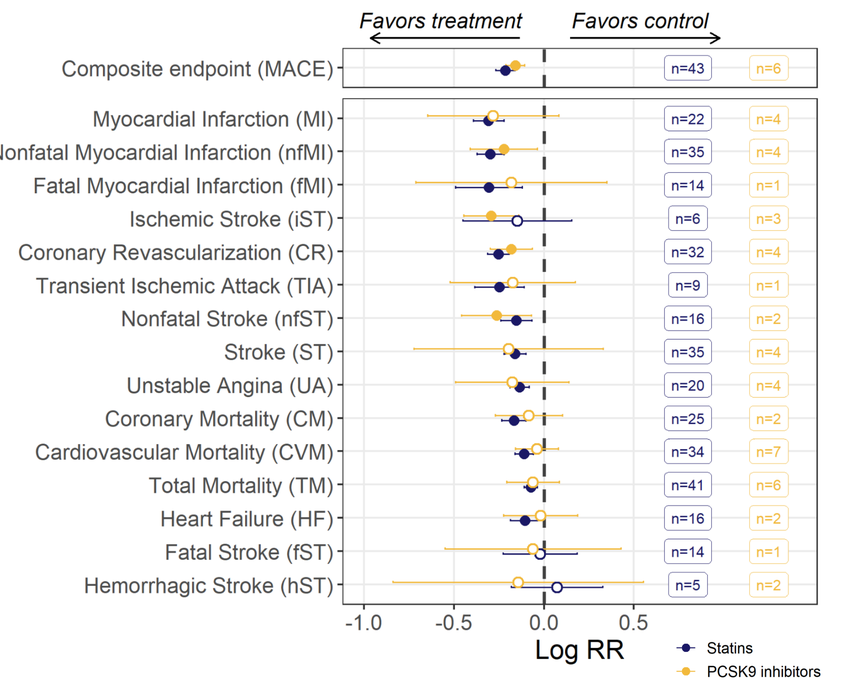


FIGURE 2. RR (mean with 95% CI) of MACE and individual MACE components as assessed by random-effects meta-analysis modeling.
n – the number of trials; open dots – non-significant risk reduction

- Optimal MACE composition based on required sample size depends on patient characteristics and does not directly correlate with the number of included components. Since the effect size for a composite endpoint is represented by the weighted average of the treatment benefit per incorporated single event, including frequently occurring events with low effect sizes (e.g. HF) may dilute the overall therapeutic gain of composite outcome (Figure 3).

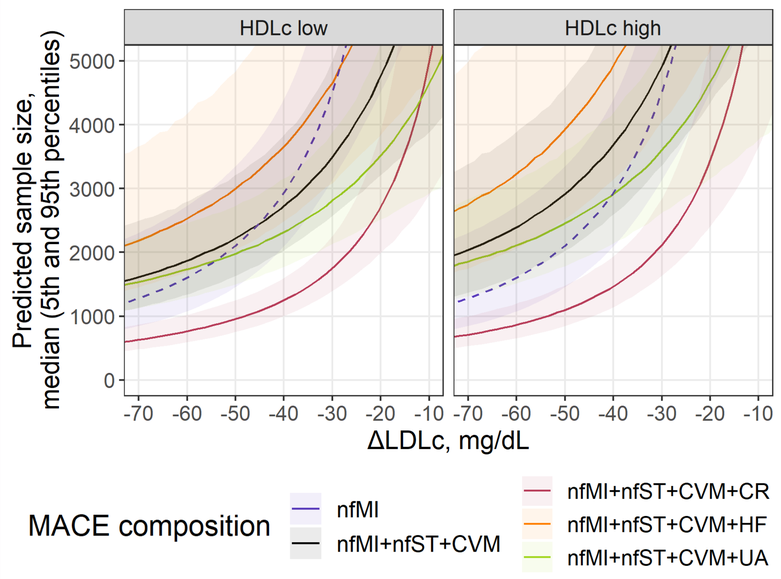


FIGURE 3. Sample size prediction for a statin treatment trial with single (dashed) or composite MACE (solid) as an endpoint.
HDLc correspond to the 25th and 75th percentiles, follow-up duration: 4 years

Conclusions

- **Treatment-mediated decrease in LDLc, high baseline remC and HDLc levels, and the absence of renal impairment were associated with the decreased relative risks of MACE components.**
- **A quantitative tool was developed and used to benchmark different MACE compositions for statins and anti-PCSK9 therapies based on the minimum population size.**
- **Rather than standardizing MACE composition, it is recommended to redefine composite outcome for each population and mechanism of action, in order to achieve greater power.**

References

1. Armstrong PW, Westerhout CM. Composite End Points in Clinical Research: A Time for Reappraisal. Circulation. 2017;135(23):2299-2307. doi:10.1161/CIRCULATIONAHA.117.026229

Funding

Supported by the Ministry of Science and Higher Education of the Russian Federation, (Agreement 404 075-10-2021-093, Project MMD-RND-2266) and Modeling & Simulation Decisions FZ - LLC, 405 Dubai, UAE.

32nd PAGE Meeting, Jun 2024,
Poster II-098

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