



Prognostic impact of secondary prevention medical therapy following myocardial infarction with non-obstructive coronary arteries: a Bayesian and frequentist meta-analysis

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Aims

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinical entity with several causes and patho-physiologic mechanisms. Secondary prevention with medical therapy used in patients with obstructive coronary artery disease has unclear benefits in MINOCA patients.

Methods and results

A literature search was conducted until 8 March 2022. Random-effect frequentist and hierarchical Bayesian meta-analyses were performed to assess the clinical impact of medical therapy [renin–angiotensin–aldosterone system (RAAS) inhibitors, statins, dual antiplatelet therapy (DAPT), β -blockers] in MINOCA patients. Outcomes of interest were all-cause mortality and major adverse cardiovascular events (MACE). A total of 12 663 MINOCA patients among five observational studies were analysed. The mean follow-up ranged from 12 to 90 months across studies. In frequentist meta-analysis, statins and β -blockers were associated with a lower risk of all-cause mortality [pooled adjusted hazard ratios (aHRs) 0.53 and 0.81, with 95% confidence intervals (CIs) (0.37–0.76) and (0.67–0.97), respectively]. Only RAAS inhibitors were associated with a lower risk of MACE [pooled aHR: 0.69, with 95% CI (0.53–0.90)]. Bayesian meta-analysis based on informative prior assumptions offered strong evidence only for the benefit of statins on decreasing the risk of all-cause death [Bayes factor (BF): 33.2] and moderate evidence for the benefit of RAAS inhibitors on decreasing the risk of MACE (BF: 9); assigning less informative prior distributions did not affect the results, yet it downgraded the level of evidence to anecdotal.

Conclusion

In this meta-analysis, statins and RAAS inhibitors were consistently associated with a lower risk of all-cause mortality and MACE, respectively, in patients with MINOCA. Neutral prognostic evidence was demonstrated for β -blockers and DAPT.

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Graphical Abstract

Prognostic Impact of Secondary Prevention Medical Therapy following Myocardial Infarction with Non-Obstructive Coronary Arteries: A Bayesian and Frequentist Meta-Analysis

12,663 MINOCA patients
Meta-analysis of 5 observational studies
Medications analyzed RAAS inhibitors, statins, DAPT, β -blockers
Outcomes of interest <ul style="list-style-type: none"> all-cause mortality major adverse cardiovascular events (MACE)
Statistical methodologies <ul style="list-style-type: none"> Frequentist (classical) Bayesian (probabilistic)
Metric used: Adjusted Hazard Ratio
Mean follow-up: 12 to 90 months

	All-cause mortality		MACE
	β -blockers	Statins	RAAS inhibitors
aHR (Frequentist)	0.81 (0.67-0.97)	0.53 (0.37-0.76)	0.69 (0.53-0.90)
aHR (Bayesian)	0.83 (0.64-1.11)	0.61 (0.47-0.82)	0.74 (0.57-0.93)
Bayes Factor	1.15 (anecdotal)	32.20 (strong)	8.98 (moderate)



Prognostic benefit

- Statins for all-cause mortality
- RAAS inhibitors for MACE



Neutral effect

- β -blockers
- DAPT

Keywords

Myocardial infarction • Non-obstructive coronary arteries • Prognosis • Bayesian • Meta-analysis

Lay summary

- A Bayesian meta-analysis demonstrated the effect of secondary prevention medical therapy on clinical outcomes following myocardial infarction with non-obstructive coronary arteries (MINOCA).
- Statins and renin–angiotensin–aldosterone system inhibitors were associated with a lower risk of all-cause mortality and major adverse cardiovascular events, respectively, in patients with MINOCA.
- β -Blockers and dual antiplatelet therapy had a neutral prognostic effect.

Introduction

Diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) is made following coronary angiography without evidence of obstructive coronary artery disease (CAD) in patients with clinical presentation consistent with an acute myocardial infarct (AMI) after ruling out clinically overt causes for the elevated troponin (e.g. sepsis, pulmonary embolism), clinically overlooked coronary obstructive disease, or subtle non-ischæmic mechanisms of myocyte injury (e.g. myocarditis, Takotsubo's syndrome, other cardiomyopathies).^{1–3} Plaque disruption, epicardial coronary artery spasm, thromboembolism or dissection, and microvascular dysfunction are the major underlying mechanisms of MINOCA.³ Optimal management of patients with MINOCA is challenging given the variability in the pathophysiological mechanisms, generating uncertainty regarding the benefit of conventional secondary prevention therapy in this population.⁴

Currently, there are no evidence-based treatment guidelines for MINOCA.^{5,6} Expert recommendations endorse cause-targeted therapies with a known aetiology¹ while supporting traditional secondary prevention medications used for AMI with CAD.³ However, recent

analyses have suggested that these medications may not offer a significant benefit in MINOCA patients, challenging their routine use in clinical practice.^{7–13} Elucidating the association between treatment options and outcomes may elevate the understanding of underlying mechanisms.

Hence, the question of whether patients with MINOCA derive benefit from the use of conventional cardioprotective medications [dual antiplatelet therapy (DAPT), statins, β -blockers, and renin–angiotensin–aldosterone system (RAAS) inhibitors: angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs)] is of paramount importance. The aim of this meta-analysis was to address this gap in clinical knowledge by examining the impact of secondary prevention medical therapies on long-term outcomes in patients with MINOCA.

Methods

Study design, search strategy, and data extraction

The current systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.¹⁴ The protocol of this meta-analysis has been prospectively registered at the Open Science Framework registries (10.17605/OSF.IO/VF6RE). The literature search was performed independently by two main reviewers (A.B. and D.V.M.) in MEDLINE (PubMed), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases, from inception until 5 May 2022. The basic keywords used in the search strings were 'MINOCA', 'non-obstructive', and 'coronary' in both free text and Medical Subject Headings format (full search strategy detailed in the [Supplementary material online, Appendix](#)). Finally, the reference lists of the eligible studies and relevant reviews were hand-searched to identify further papers not previously detected.

To establish a diagnosis of MINOCA, studies should include patients with positive serum myocardial biomarkers (such as cardiac troponin) with at

least one level rising above the 99th percentile of the upper limit of normal.³ Clinical evidence of AMI, indicated by ischaemic symptoms, new electrocardiographic changes (ST-segment, left bundle-branch block, pathological Q waves) or imaging evidence of loss of viable myocardium, new regional wall motion abnormalities, or an intracoronary thrombus, should be present. Signs of significant obstructive CAD (epicardial coronary lesions of >50% stenosis) on coronary angiography, as well as detection of any overt alternative diagnosis to explain the clinical presentation, rule out the diagnosis of MINOCA.³

Either observational (cohort, case-control, and cross-sectional) studies or randomized controlled studies reporting adjusted hazard ratios (aHRs) were included in the meta-analysis if they investigated and reported the specific risk of adverse clinical outcomes by the administration or not of a secondary prevention medication among adult individuals with MINOCA. These medications included: DAPT, statins, β -blockers, and RAAS inhibitors. Exclusion criteria of the meta-analysis were the following: (i) case reports, reviews, editorials, and practice guidelines or publications in languages other than English; (ii) studies with follow-up period shorter than 6 months; (iii) studies not specifically reporting rates of events or hazard ratio and 95% confidence intervals (CIs) for the primary outcome; and (iv) studies lacking a control group not receiving secondary prevention medications, which would not allow calculation of aHRs.

Two investigators independently screened the studies, and disagreements were resolved by consensus with a third author (A.S.). For each eligible study, the risk for bias was assessed through the Quality In Prognosis Studies (QUIPS) tool.¹⁵ Publication bias was assessed with a visual inspection of funnel plots. We did not use any test for assessing funnel plot asymmetry since we included <10 studies in the meta-analysis and the power of the tests was considered to be too low to distinguish random deviations from real asymmetry. Moreover, we used the GRADE checklist via the GRADEpro software (<http://tech.cochrane.org/revman/grade>) to rate the quality of evidence and the strength of our recommendations.¹⁶

Descriptive data and definitions were collected from the screened reports using piloted forms. Clinical outcome measures were extracted at the longest available follow-up including trial-defined major adverse cardiovascular events (MACE) and particularly all-cause death rates. Covariates used in each multivariable survival analysis have been recorded for each included study.

Data synthesis and analysis

Rates of events and aHRs have been documented for both case (MINOCA patients receiving secondary prevention medication) and control (MINOCA patients not receiving medication) groups. Random-effect meta-analyses of the study outcomes were first conducted using a frequentist approach. Results are reported as pooled aHRs with corresponding 95% CIs. Inconsistency in associations among the trials was quantified using the I^2 statistic. P values for heterogeneity were derived using the Cochran Q statistic. Frequentist analyses were conducted using the R metafor and dmetar packages (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) in the RStudio software (Version 1.4.1106).

Meta-analyses were also performed following a random-effect Bayesian approach with the R metaBMA package using the RStudio software. Bayesian (probabilistic) and frequentist (classical) approaches constitute two well-known statistical methodologies that can lead to different findings, despite rarely differing in the direction or treatment rankings. A frequentist P value is an expectation of a long-run frequency, whereas a Bayesian analysis emerges as a suitable approach to analyse new data in light of prior probabilities to correct the faulty intuitions that may arise when the pre-existing body of evidence (e.g. clinical knowledge based on other ACS patients or prior evidence on MINOCA mechanisms) is ignored and not integrated with the quantitative results.¹⁷ Hence, a Bayesian analysis always requires the specification of prior beliefs about the population-level parameters to inform the posterior distribution. We used normal prior distributions for all population means and rather informative prior distributions for all variances using a distribution $[N(0,0.35)]$ for the effect size (logHR), centred at the null value with small dispersion [$\text{Half-Cauchy HC}(-1.975, 0.67)]$ for between-study heterogeneity. The selection of rather informative priors was based on current clinical knowledge and the presumed benefit deriving from the

administration of those secondary prevention medications in patients with MI.

To check whether the choice of informative priors meaningfully affected our results, we also fitted models with uniform weakly informative priors $[N(0,1)$ and $\text{HC}(0, 0.5)]$ to allow the observed data, rather than the prior distributions, to have a stronger influence on the results. The mean and 95% credible intervals (CrIs) of each posterior distribution were calculated. To measure the strength of the evidence uninfluenced by the selection of priors, we calculated meta-analytic Bayes factors (BFs), which are likelihood ratios expressing a comparison of how well the alternative hypothesis (H1) or the null hypothesis (H0) predict the outcome according to the following relation: 'Prior odds of $H1 \times \text{BF}_{10} = \text{Posterior odds of } H1$ '; where $\text{BF}_{10} = [\text{Probability}(\text{data, given } H1)] / [\text{Probability}(\text{data, given } H0)]$. We interpreted the BFs using Jeffreys' evidence categories.¹⁸ Particularly, BF_{10} represents how many times more likely the data are under the alternative hypothesis (H1—presence of an effect) than under the null hypothesis (H0—no effect). In general, a BF_{10} of ≤ 1 would provide evidence that the medication assessed does not have a significant beneficial impact; a BF_{10} of 1–3 or 3–10 would provide anecdotal or moderate-substantial evidence for the prognostic effect of the medication; while BF_{10} may provide strong evidence at values 10–30; very strong evidence at values of 30–100 and decisive evidence at values >100.¹⁹

Sensitivity analyses

Multiple leave-one-out meta-analyses were performed by excluding successively one study at each analysis to investigate the influence of each study on the overall effect size estimate and to identify influential studies.

Results

Study selection and characteristics

The study selection process is summarized in [Figure 1](#). After screening 10 725 articles initially retrieved, five studies were deemed eligible for our meta-analysis^{7–9,13,20} ([Figure 1](#)).

The patient sample size added up to a total of 12 663 MINOCA patients (pooled mean age 64.8 ± 10.8 years, 51.1% female, mean follow-up range from 12 to 90 months). Of them, 20% had diabetes mellitus, 62% had hypertension, 54% had hyperlipidaemia, 28% were smokers and 14% had a family history of CAD. The mechanism of MINOCA was reported in only two studies.^{9,20} The duration of DAPT after hospital discharge was not reported. The design and key characteristics of the selected studies are presented in [Supplementary material online, Table S1](#).

Quality assessment

Results of the risk of bias assessment via the QUIPS tool for the included studies are presented in [Supplementary material online, Table S2](#). Included studies showed overall high or moderate quality.

Association of outcomes with secondary prevention medication according to the frequentist approach

[Table 1](#) displays the results of the frequentist analyses, and [Figure 2](#) summarizes the corresponding forest plots of comparison. The administration of statins and β -blockers was independently associated with decreased risk of all-cause mortality, while the administration of RAAS inhibitors was significantly associated with decreased risk of MACE occurrence. All outcomes displayed mild or moderate heterogeneity, except for the analyses on the prognostic impact of statin administration (significant heterogeneity).

Sensitivity analyses

The sensitivity leave-one-out analysis performed for the study outcomes with more than two eligible studies for meta-analysis (see

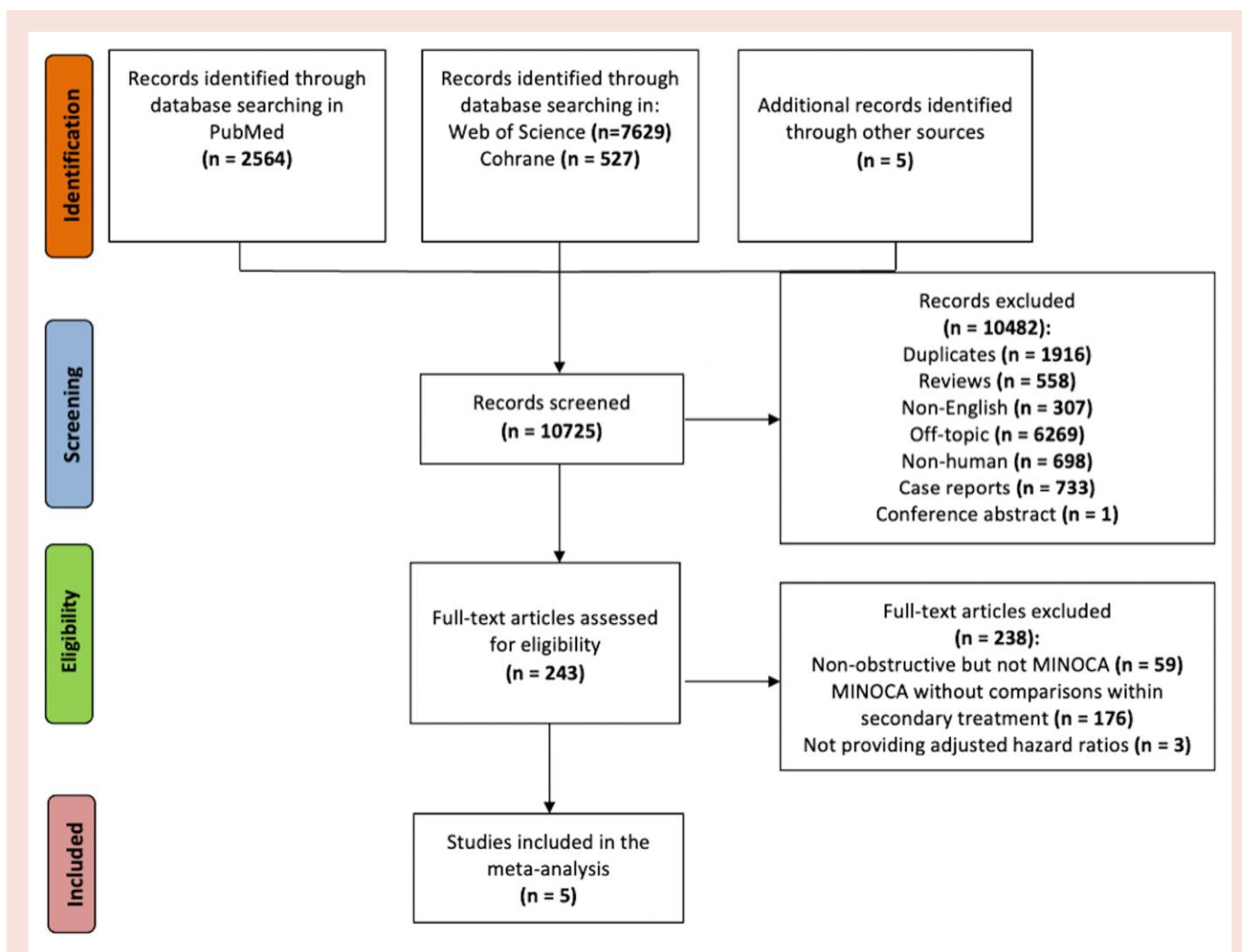


Figure 1 Study selection process. A flow diagram illustrating literature search and the study selection process.

Table 1 Results deriving from the random-effect frequentist meta-analyses

Frequentist outcome assessed	Random-effect analysis Pooled aHR (95% CI)	Heterogeneity I^2 (%)
DAPT MACE	1.10 (0.52–2.33)	42
β -Blockers MACE	0.80 (0.62–1.04)	57
Statins MACE	0.59 (0.32–1.10)	91
RAASi MACE	0.69 (0.53–0.90)	43
β -Blockers death	0.81 (0.67–0.97)	0
Statins death	0.53 (0.37–0.76)	61
RAASi death	0.74 (0.53–1.03)	48

aHR, adjusted hazard ratio; CI, confidence interval; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events; RAASi, renin–angiotensin–aldosterone system inhibitors.

Association of outcomes with secondary prevention medication according to the Bayesian approach

The results of the random-effect Bayesian analyses with informative prior assumptions are reported in [Table 2](#) and the posterior distributions are illustrated in [Figure 3](#). [Supplementary material online, Table S3](#) and [Figure S2](#) present the analysis using weakly informative prior assumptions.

Both Bayesian analyses offered consistent results regarding the association of statin and RAAS inhibitor administration with decreased rates of all-cause mortality and MACE, respectively. The rather informative approach yielded strong evidence (BF: 32.20) for the benefit of statins in decreasing the risk of all-cause death (aHR = 0.61, 95% CrI: 0.47–0.82) and moderate evidence (BF: 8.98) for the benefit of RAAS inhibitors on decreasing the risk of MACE (aHR = 0.74, 95% CrI: 0.57–0.93). The level of evidence deriving from weakly informative prior assumptions was anecdotal for both outcomes ($0.33 < \text{BF} < 3$). No benefit was shown from DAPT and β -blockers in both approaches. A graphical illustration of Bayesian analyses with informative prior assumptions according to BF is provided in [Figure 4](#).

GRADE assessment

The assessment of our findings based on the GRADE checklist is illustrated in the [Supplementary material online, Table S4](#). Briefly, the level

[Supplementary material online, Figure S1](#)) did not identify major sources of discrepancies regarding the effect of statins and RAAS inhibitors on all-cause mortality and MACE occurrence, respectively.

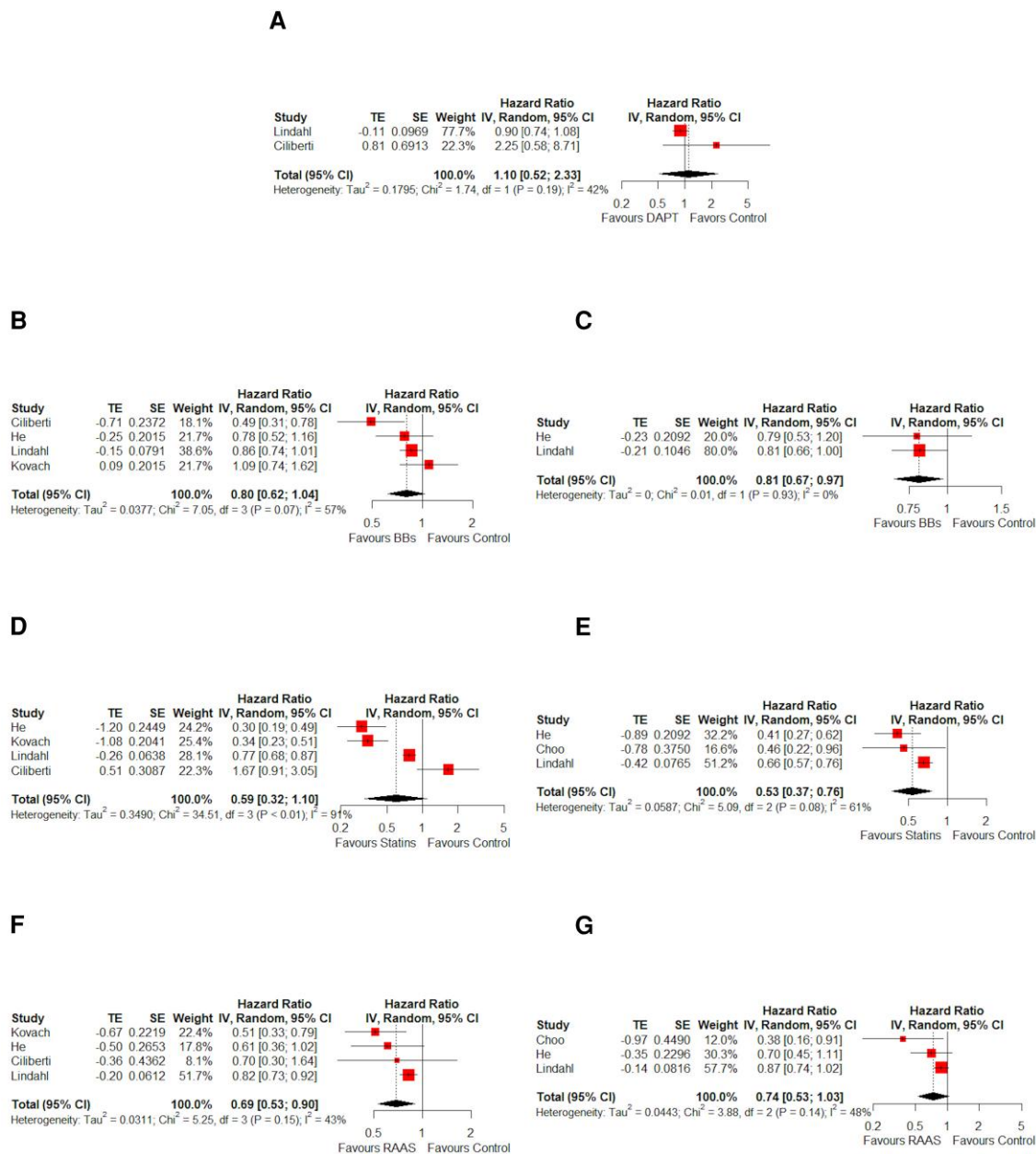


Figure 2 Forest plots of comparison in adverse outcome cumulative incidence among myocardial infarction with non-obstructive coronary arteries patients receiving or not dual antiplatelet therapy (A, major adverse cardiovascular events), β -blockers (B, major adverse cardiovascular events, C, all-cause mortality), statins (D, major adverse cardiovascular events, E, all-cause mortality), and renin-angiotensin-aldosterone system inhibitors (F, major adverse cardiovascular events, G, all-cause mortality). Abbreviations as in Table 1.

of certainty on the association of statins or DAPT with MACE, and the association of β -blockers or RAAS inhibitors with all-cause death is estimated to be 'low'. The level of certainty on the association of statins with all-cause death and the association of β -blockers or RAAS inhibitors with MACE occurrence is deemed 'moderate'.

Discussion

This meta-analysis evaluated the benefit of medical therapy for secondary prevention in patients with MINOCA. Among 12 663 patients with

MINOCA and using both frequentist and Bayesian analysis, RAAS inhibitors and statins were associated with a lower risk of MACE and all-cause death, respectively. β -Blockers showed mortality benefit in frequentist analysis which was not confirmed by Bayesian analysis, while the effect of DAPT was neutral.

Most studies have demonstrated that patients with MINOCA have better short- and long-term outcomes than patients with MI and significant CAD.^{5,6,21} Still, patients with MINOCA are at higher risk of short- and long-term mortality and risk of recurrent events compared with the general population.²² The role of secondary

Table 2 Results deriving from the random-effect Bayesian analyses based on rather informative prior assumptions

Bayesian Outcome assessed	Informative prior assumptions		
	aHR (95% CrI)	Bayes factor ₁₀ (level of evidence)	t
DAPT MACE	0.96 (0.70–1.38)	0.47 (anecdotal)	0.162
β-Blockers MACE	0.83 (0.66–1.04)	1.54 (anecdotal)	0.161
Statins MACE	0.71 (0.48–1.13)	2.30 (anecdotal)	0.480
RAASi MACE	0.74 (0.57–0.93)	8.98 (moderate)	0.157
β-Blockers death	0.83 (0.64–1.11)	1.15 (anecdotal)	0.138
Statins death	0.61 (0.47–0.82)	32.20 (strong)	0.173
RAASi death	0.80 (0.61–1.04)	1.84 (anecdotal)	0.153

Abbreviations as in Table 1.

preventive medications in MINOCA is not well established.^{3,23} Parallel to that, long-term use of conventional secondary prevention medications is less common in patients with MINOCA compared with patients with MI-CAD.²⁴

A recent meta-analysis by De Filippo et al.²⁵ investigating a similar research question as in our study, concluded that β-blockers, statins, and DAPT are associated with a survival benefit, while ACE inhibitors/ARB reduce the risk of MACE among MINOCA patients. The aforementioned meta-analysis has some major inaccuracies and limitations. The authors reported that they included only adjusted observational studies.²⁵ However, one of the included studies comprised results from univariate Cox regression analysis,¹⁰ while a second one reported odds ratios instead of hazard ratios.¹² Moreover, our study included two eligible studies that were not used in the meta-analysis by De Filippo et al.^{8,20} Finally, the aforementioned meta-analysis utilized only a frequentist method for statistical purposes. Our study, nevertheless, filtered the results of the frequentist analysis through several Bayesian re-analyses, taking into account the posterior probabilities of the prognostic benefit of secondary prevention medications.¹⁷ This substantially improved the accuracy of evidence. Thus, the novelty of our study originates from the fact that it (i) is based on more reliable, optimal study selection criteria, (ii) has a more robust, refined statistical methodology, and (iii) provides more specific and robust conclusions, compared with the study by De Filippo et al.

Statins

Treatment with statins has been consistently associated with improved secondary and primary prevention outcomes in randomized controlled trials of patients with CAD.²⁶ The results of our meta-analysis suggest a strong benefit in MINOCA patients as well. Statins slow down the progression of the atherosclerotic process and promote plaque stabilization.²⁷ This could explain the benefits of statins in patients with MINOCA, particularly in cases where plaque disruption from non-significant plaques is the responsible pathophysiological mechanism.²⁸ Statins improved prognosis in patients with epicardial coronary spasm,²⁹ which is a major MINOCA subgroup, and have also demonstrated anti-inflammatory properties in CAD, which could be playing a role in MINOCA.³⁰ Furthermore, prior studies have suggested that statins may improve endothelial dysfunction, which has been proposed as one of the underlying pathophysiological mechanisms in MINOCA.³¹

Renin–angiotensin–aldosterone system inhibitors

Renin–angiotensin–aldosterone system inhibitors show beneficial effects not only in patients with MI and heart failure with reduced ejection fraction³² but also in patients with CAD without impaired left ventricular function.³³ In our meta-analysis, RAAS inhibitors were associated with decreased rates of MACE and showed potential association with decreased risk of mortality. Renin–angiotensin–aldosterone system inhibitors have pleiotropic effects and various pathophysiological pathways on the cardiovascular system, which could explain their benefit in patients with MINOCA.³⁴ Specifically, RAAS inhibitors demonstrate anti-atherosclerotic and anti-thrombotic effects, lower blood pressure, and produce sympathetic inhibition by blocking the ACE-mediated formation of angiotensin II and the linkage of Ag II to receptor Type 1 in the circulation and peripheral tissues.³⁵ Inhibiting the renin–angiotensin system can decrease plaque size, cholesterol content, and macrophage accumulation, which could result in plaque stabilization.³⁶ Since non-obstructive coronary artery lesions may cause a significant number of MIs, RAAS inhibitors could decrease the occurrence of major cardiac events in MINOCA patients.²⁸ Another beneficial effect of ACE inhibitors is the increase of bradykinin bioavailability, which improves non-endothelial and endothelial-dependent coronary microvascular function, and has a protective role on the cardiomyocyte.³⁷

β-Blockers

The frequentist association of β-blockers with a lower risk of all-cause mortality was not confirmed by our Bayesian analysis. Evidently, the role of β-blockers in patients without systolic left ventricular dysfunction after MI is uncertain.³⁸ Most studies on β-blockers have not shown a significant association with outcomes in patients with MINOCA, too.^{7,8,10,12,13} The use of β-blockers was associated with a reduction in recurrences in patients affected by spontaneous coronary artery dissection.³⁹ On the other hand, even higher risk of all-cause mortality in patients with MINOCA was shown in a prior meta-regression analysis.⁵ However, the aforementioned study suffered from notable limitations. Our findings suggest that the role of β-blockers in patients with MINOCA has to be further investigated.

Dual antiplatelet therapy

Dual antiplatelet therapy decreases the risk of adverse events following acute MI⁴⁰ and is recommended for at least 1 year.⁴ In patients with MINOCA, recent consensus documents suggested using long-term low-dose aspirin for secondary prevention.³ However, synthesis of the data in our Bayesian meta-analysis demonstrated that treatment with DAPT was not associated with decreased occurrence of MACE.

Our findings are in accordance with the findings that treatment with DAPT or single antiplatelet therapy in recent observational studies had neutral^{7,8,10,12,20} or even detrimental¹³ effects on outcomes in patients with MINOCA. However, the population analysed in these cohort studies was highly heterogeneous and may have included cases of myocarditis and Takotsubo syndrome.⁴¹ A *post hoc* analysis of the CURRENT-OASIS 7 randomized clinical trial comparing high vs. Standard doses of clopidogrel even indicated that high-dose clopidogrel could be potentially harmful in patients with MINOCA as contrasted with patients with MI and obstructive CAD.⁴²

The rather neutral prognostic impact of antiplatelets in patients with MINOCA could be partially explained by the fact that MINOCA is a highly heterogeneous clinical entity including various pathophysiological mechanisms other than plaque disruption, such as coronary epicardial vasospasm and microvascular spasm, that are not directly benefited from intense antiplatelet prophylaxis.^{3,43} Unfortunately, the included studies did not report a breakdown of the MINOCA pathophysiology

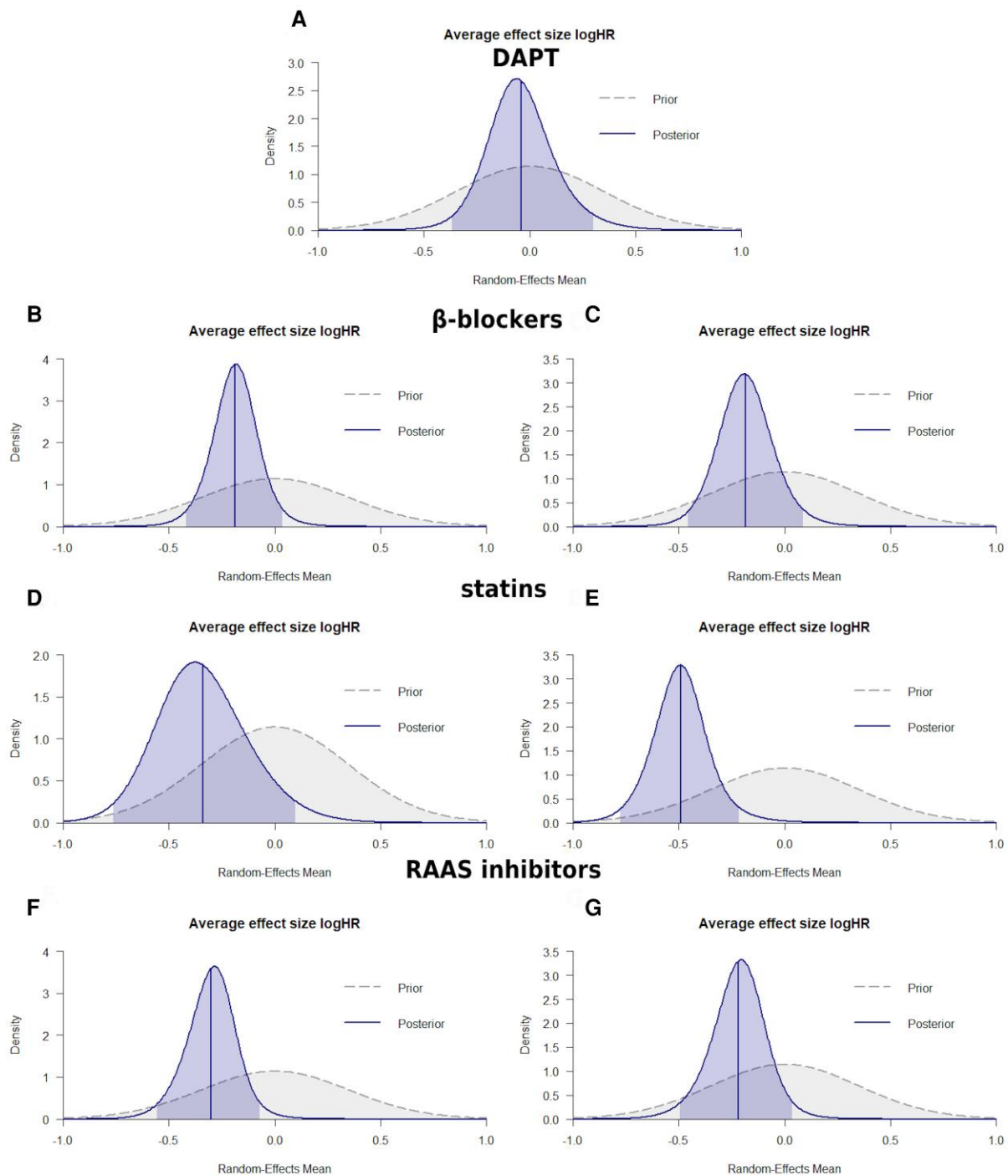
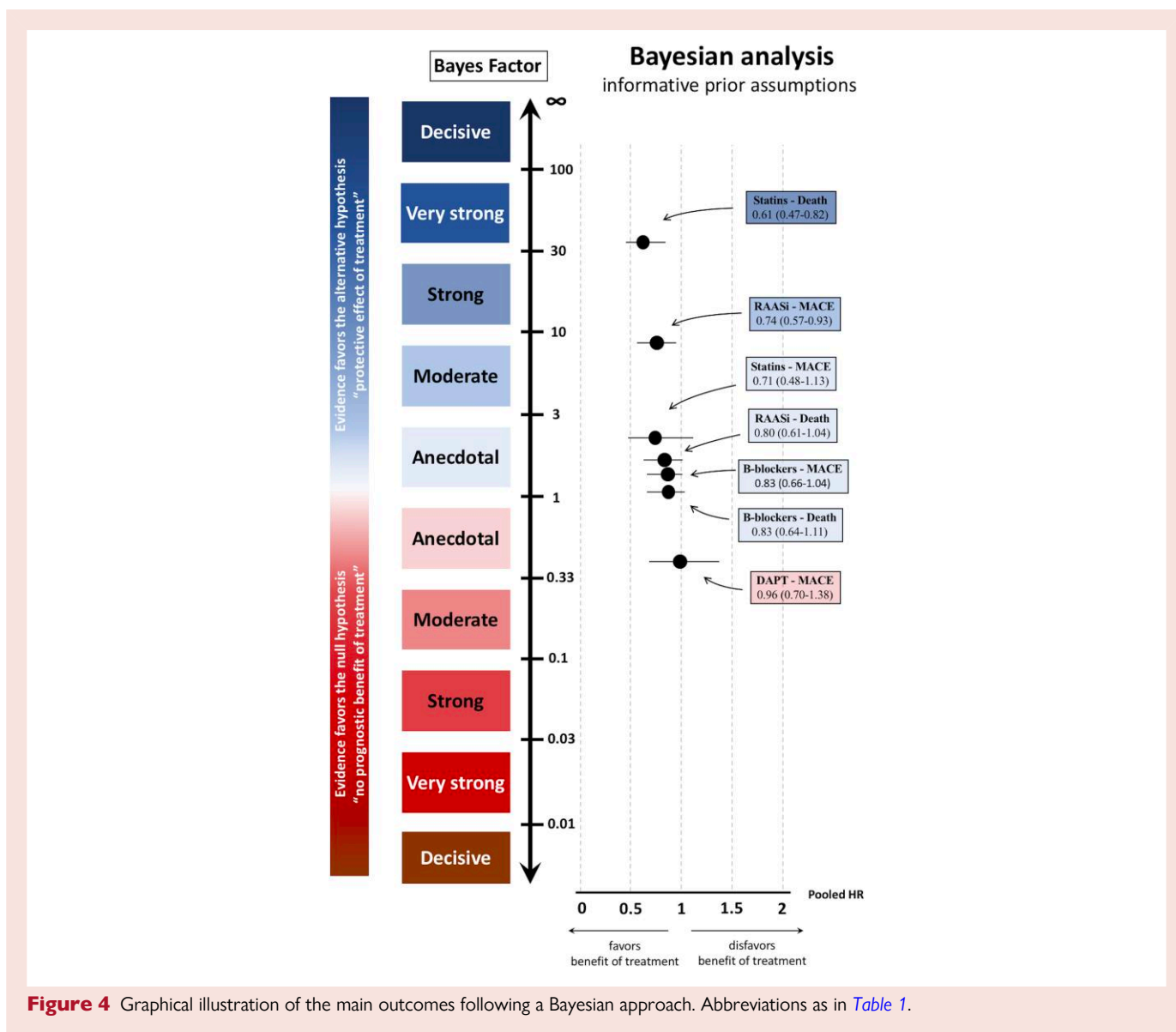


Figure 3 Posterior distributions of the Bayesian random-effect meta-analyses following informative prior assumptions among myocardial infarction with non-obstructive coronary arteries patients receiving or not dual antiplatelet therapy (A, major adverse cardiovascular events), β -blockers (B, major adverse cardiovascular events, C, all-cause mortality), statins (D, major adverse cardiovascular events, E, all-cause mortality), and renin–angiotensin–aldosterone system inhibitors (F, major adverse cardiovascular events, G, all-cause mortality). Abbreviations as in Table 1.

mechanisms in included patients. The inefficacy of antiplatelet therapy in the absence of obstructive coronary atherosclerosis could also be speculated by the results of recent trials that failed to demonstrate a prognostic benefit of aspirin among high-risk patients⁴⁴ and healthy elderly individuals.⁴⁵

Bayesian and frequentist analysis

The present study concurs with several Bayesian re-analyses of frequentist analyses, which demonstrated that the observed differences may not be accurate,⁴⁶ mainly because the weight of evidence against the null hypothesis is not nearly as strong as the magnitude of the



P value suggests. Moving to BFs might relieve us of the flawed conceptual framework and improper view of the scientific method that travels with the *P*-value. However, BFs must be used with prior odds to calculate the posterior probability. For instance, if a serious sceptic estimated that there was only a 1:100 chance of decreased mortality with statin administration in MINOCA, then a BF of 30 should not change his/her mind. Nevertheless, the Bayesian analyses based on rather informative prior assumptions can be particularly relevant in our case since those secondary prevention medications might have been a priori expected not to harm patients with MINOCA; hence, a clinician might have been predisposed towards a more beneficial impact of their administration (i.e. more informative prior assumption of the aHR with mean aHR = 1 and standard deviation = $e^{0.35}$).

Limitations

Our study has some potential limitations that should be discussed: (i) systematic pooling of observational studies, which carry different baseline patient characteristics and suffer from selection bias, may affect results. However, after assessing the quality of methodology of the

included studies, we found an overall high quality across studies; (ii) a limited number of the eligible studies; (iii) inherent heterogeneity regarding aetiology of mechanism that resulted in MINOCA. Cardiac magnetic resonance was not systematically performed in the studies, which could result in the inclusion of cases of non-ischaemic myocyte injury that should otherwise be excluded. An incomplete understanding of the underlying MINOCA mechanism can lead to suboptimal secondary prevention measures.²¹ Therefore, both ESC guidelines and AHA Scientific Statement highlight the role of cause-targeted therapies in MINOCA, suggesting that these patients should be treated according to the underlying pathophysiological diagnosis.^{3,4} (iv) The diagnostic criteria to define MINOCA are evolving, emphasizing a diagnostic algorithm based on invasive or non-invasive imaging to differentiate 'true' MINOCA from alternative diagnoses.⁴⁷ Hence, the results of this meta-analysis should be interpreted cautiously, bearing in mind that the definition of MINOCA across the included studies may be inconsistent given that it was based on previous guidelines/expert consensus; (v) heterogeneity regarding presenting features and outcomes across studies could raise concerns. However, we performed leave-one-out sensitivity analyses, which showed that sequential omissions did not affect

the positive prognostic impact of statins and RAAS inhibitors; (vi) the classical argument of Bayesian subjectivity owing to the choice of priors.⁴⁸ However, we applied different priors yielding similar results, and, thereby, confirming the robustness of the main analysis. We also checked the convergence of the Markov Chain Monte Carlo algorithm to validate the posterior samples of our analyses.

Conclusions

This meta-analysis evaluated the impact of secondary prevention treatment on outcomes in patients with MINOCA. The synthesis of data from observational studies revealed a therapy-related benefit in patients with MINOCA by RAAS inhibitors and statins. Using a Bayesian approach to improve the accuracy of evidence assessment against the null hypothesis, we found a neutral prognostic effect of the administration of β -blockers and DAPT. Given that the different pathophysiologic facets of MINOCA probably explain differences in the efficacy of treatment, this meta-analysis highlights the need for careful diagnostic evaluation such as multimodality imaging,⁴³ management optimization, and intense clinical surveillance in patients with MINOCA.

Lead author biography



Athanasios Samaras, MD, graduated from the Medical School of the Aristotle University of Thessaloniki, where he is currently a PhD candidate and, also, an MSc student in Health Statistics & Data Analytics. He completed a research fellowship at the Cardiology Department of Aarhus University Hospital, Denmark. He is currently working as a Cardiology Resident in Hippokraton General Hospital of Thessaloniki, Greece. His research areas of interest are cardiovascular disease, digital health, artificial intelligence, and data analytics.

Data availability

The data generated in this research will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Author contributions

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