The Placebo Effect on Symptoms, Quality of Life, and Functional Outcomes in Patients With Angina Pectoris: A Meta-analysis of Randomized Placebo-Controlled Trials

IMPACT OF THE PLACEBO EFFECT ON SYMPTOMS, QUALITY OF LIFE AND FUNCTIONAL OUTCOMES IN ANGINA PECTORIS

A meta-analysis of randomized placebo-controlled trials

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ABSTRACT

Background

The placebo effect is a well described phenomenon in blinded studies evaluating anti-anginal therapeutics, although its impact on clinical research metrics remains unknown. We conducted a systematic review and meta-analysis to quantify the impact of placebo on endpoints of symptoms, life-quality and functional outcomes in randomized placebo-controlled trials (RCTs) of symptomatic stable coronary artery disease.

Methods

We systematically reviewed MEDLINE, EMBASE, and the Cochrane database for double-blind RCTs of anti-angina therapeutics. Patients randomized to the placebo-arm were the study population. Main outcomes were the changes in exercise performance (exercise treadmill test [ETT] parameters), quality of life (Seattle Angina Questionnaire domains), symptoms (Canadian Cardiovascular Society angina class) and drug usage (nitroglycerin tabs/week) between baseline and following placebo. The primary outcome was ETT total duration time. Data were pooled with a random effect model.

Results

Seventy-eight RCTs (83% drug-controlled, 17% procedure-controlled) were included encompassing 4,925 patients randomized to placebo. ETT total duration time was significantly improved following placebo as compared to baseline (mean [95% confidence interval]: 29.2 [20.6-37.8] seconds) with evidence of high heterogeneity (I 2 = 98%) At subgroup analysis, crossover design was associated with a smaller placebo effect on ETT performance than parallel study design (p for interaction=0.001). A significant placebo effect was observed for all secondary outcomes with overall high heterogeneity.

Conclusion

A substantial placebo effect was present in angina RCTs across a variety of functional and life-quality metrics. High variability in placebo effect size was present, mostly unexplained by differences in study and patient characteristics (PROSPERO CRD42019132797).

KEY WORDS

Placebo; Angina; Randomized controlled trial; Symptom; Quality of life; Coronary artery disease.

BRIEF SUMMARY

The relevance of placebo effect for clinical research metrics of blinded studies evaluating anti-angina therapeutics remains unknown. Among seventy-eight placebo-controlled randomized trials including 4,925 symptomatic stable angina patients receiving placebo, substantial placebo effect was present across a variety of symptoms, life-quality and functional outcomes. High effect size heterogeneity was observed, unaccounted for by differences in study and patient characteristics. Clinical research should focus on more reproducible metrics to promote the experimental characterization of angina treatments.

Introduction

As a result of the general aging population and the decline in mortality from disease-modifying treatments for atherosclerosis, the population of patients with CAD is constantly growing. About 5-10% of this population, accounting for 50,000-100,000 new cases/year in the United States and 30,000-50,000 new cases/year in Europe, experiences disabling symptoms despite state-of-the-art anti-anginal drug therapy and revascularization[1]. The impact in mortality in these patients is now comparable to that of the general stable CAD population[2]. This highlights the ongoing clinical challenge of symptom control in a population with long life expectancy and poor health status[3].

Novel therapeutic options aimed at improving quality of life in this population are emerging; however, for any subjective endpoint the clinical effect results from both a true physical component and a placebo component. Failure to quantify the placebo effect of a therapy complicates the trial design and interpretation of these studies. This is cause for concern in the cardiology community, hampering broad-scale clinical implementation of novel angina therapies with potential benefit in a population burdened by poor quality of life. This observation necessitates randomized placebo-controlled trials to ensure objective outcome assessment and to recommend novel treatments in clinical practice. However, placebo-controlled trial designs testing "soft" (but ever-increasingly important) symptom-related endpoints are challenging due to uncertain magnitudes of anticipated effect size and lack of clarity regarding the most appropriate endpoints to use[4]. Moreover, angina is burdened by several phenomena including its fluctuating nature, the regression to the mean and the Hawthorne effect (i.e. alteration of behavior including the reporting of symptoms by the study participants due to their awareness of being observed) which may further challenge placebo-controlled study design[5]. Of note, placebo interventions may be burdened by a higher than expected placebo-effect that may become clinically significant if applied to subjective endpoints, further complicating trial results interpretation[6].

This systematic review and meta-analysis aims at quantifying the clinical impact of the placebo effect on the most commonly utilized endpoints to assess symptoms, quality of life and functional outcomes in randomized placebo-controlled trials of patients with symptomatic stable angina.

METHODS

Study design

For this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed[7]. The original study protocol was prospectively registered in PROSPERO (CRD42019132797). The primary aim of this study was to assess the clinical impact of placebo effect on symptoms, quality of life and functional outcomes of patients with symptomatic stable CAD.

Studies were deemed eligible if all the following inclusion criteria were respected:

1) Randomized placebo-controlled double-blind design study;
2) All patients included in the study had symptomatic stable angina with suspected or definite diagnosis of obstructive CAD or coronary microvascular dysfunction;
3) At least one of the main study outcomes (see below) was presented.

Studies were excluded if not written in English language or if the main study outcomes were presented in insufficient detail (i.e. reporting central tendency without dispersion measures). Among the selected studies, patients randomized to the placebo-arm of each trial represent the population of interest for this meta-analysis.

Study endpoints

Main outcomes of this analysis were the changes in exercise performance (exercise treadmill test [ETT] parameters), quality of life (Seattle Angina Questionnaire [SAQ] domains), symptoms (Canadian Cardiovascular Society [CCS] angina class) and drug usage (nitroglycerin tabs) between baseline and following placebo. Specifically, the primary outcome was the change between baseline and last follow-up in ETT total duration time (seconds) at either standard or modified Bruce protocol (if high heterogeneity in effect estimates between standard Bruce and modified Bruce protocols

would have been observed, a primary outcome stratification by protocol type was pre-specified). Secondary endpoints were the changes (in seconds) between baseline and last follow-up in ETT time to ST-segment deviation and time to angina; along with changes in each of the SAQ five domains, in CCS class; in the number of nitroglycerin tabs/week use. The impact of placebo on the primary outcome was further evaluated according to study design and patient characteristics by subgroup analysis.

Database Search

Published trials from Embase, MEDLINE/PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) were identified from January 1993 to June 2020. A combination of free-text words were used, including but not limited to the terms *coronary artery disease, angina, chest pain, angor, randomized controlled trial, double-blind, placebo, sham, quality of life, questionnaire, SAQ, exercise, walking test, treadmill, Bruce protocol, Canadian Cardiovascular Society, nitrate,* appropriately linked with the Boolean operators AND or OR. The full search strategy is detailed in the **Supplementary Appendix S1** (page 2). The reference lists of selected articles were also searched manually to identify additional eligible studies. No language restrictions were applied during the search phase.

Study Selection and Data Extraction

The identified studies were screened by 2 independent reviewers (V.R. and M.B.), first based on the title and abstract and subsequently based on the full manuscript. The reasons for excluding studies in the second phase were recorded. The 2 datasets were compared and differences resolved by a third reviewer (F.A.) examining the original study reports. Predefined forms were used to

manually extract information on the study design, populations, and outcomes for each eligible study.

Risk of Bias Assessment

The risk of bias in each study was assessed using the revised Cochrane risk of bias tool (RoB 2.0)[8]. Two investigators (G.G. and L.B.) independently assessed 5 domains of bias for each outcome: the randomization process, deviations from intended interventions, missing outcome data, the measurement of the outcome, and the selection of the reported results. Small study effect was estimated visually by funnel plots and using the weighted regression test of Egger. Details are shown in **Supplementary Figure S1 and S2** in the **Supplementary Appendix S3**.

Data Synthesis and Analysis

The analysis was by aggregated data. Any outcome of interest reported by each study was included and graphically displayed by forest plots. Pooled effect estimates of the outcomes were calculated as weighted mean difference using a random-effects model and presented with 95% confidence intervals (CI). When data were available only as median and interquartile range, mean and standard deviation were calculated, as previously described [9]. When baseline and follow-up data for any endpoint was available, the delta mean value and standard deviation was calculated accordingly to a previously described method (**Supplementary Appendix S2**)[10]. Heterogeneity across studies was assessed using Cochrane Q statistics and I^2 values. I^2 values of less than 25% indicate low heterogeneity, 25% to 50% moderate heterogeneity, and greater than 50% high heterogeneity. Reasons for outliers were explored by re-checking the accuracy of data extraction, then studying the specific clinical trial characteristics in detail. Reasons for heterogeneity among studies in the effect estimate for the primary endpoint were further explored using subgroup

analyses according to the study characteristics (type of placebo, study protocol, exercise test protocol, follow-up length, study publication year) and angina phenotype. Exploratory subgroups analyses based on patient characteristics were carried by dichotomizing studies at the median value of the prevalence of the characteristic of interest in each study. The analyses were conducted using R version 3.2.1.

RESULTS

Of the 1,307 records retrieved, a total of 78 studies fulfilled the inclusion criteria. The consort diagram is shown in **Figure 1**. The bias assessment for each RCT is shown in **Supplementary Figure S1** in the **Supplementary Appendix S3**. Overall, 41 studies were considered at low risk of bias, 35 showed some concerns and 2 studies were at high risk, based on Cochrane Collaboration guidelines. PRISMA checklist is provided in the **Supplementary Appendix S1**.

RCTs and placebo-arm population characteristics

The **Supplementary Tables S1 and S2** in the **Supplementary Appendix S3** shows the main characteristics of each RCT. The aggregated study and clinical characteristics are summarized in **Tables 1** and **2**.

Overall, 64 (82.1%) studies were placebo-drug-controlled and 14 (17.9%) were placebo-procedure controlled, 65 (83.3%) studies enrolled patients with definite CAD at coronary angiography and 13 (16.7%) also patients with suspected CAD, 23 (29.4%) studies enrolled patients with refractory angina exclusively (defined as a chronic condition caused by clinically established reversible myocardial ischemia in the presence of CAD, not adequately controlled by a combination of medical therapy, angioplasty, or coronary artery bypass grafting), 4 (5.1%) studies enrolled patients with microvascular angina exclusively. Regarding study design, 26 (34.1%) studies had more than one active treatment arm, 19 (24.3%) had a crossover design and 23 (29.4%) used a placebo run-in phase. A single study [11] adopted tests for the assessment of true blinding. The median study sample size was 87 participants (interquartile range [IQR] 29-197). In total, 6,190 participants were randomly assigned to receive an active drug and 4,925 were randomly assigned to placebo. Among patients randomized to placebo, the mean age was 63 years (standard deviation [SD] 4) and 75% (SD 24) were males; the median duration of study-level follow-up was 42 days (IQR 14-141), while

the weighted mean duration of follow-up was 81.7 days. Follow-up was available for 4707 (95.6%) placebo-treated patients.

Primary endpoint

The primary endpoint of ETT total duration time (62 studies, 3891 patients) was significantly improved following placebo as compared to baseline (mean difference [95% CI]: +29.2 [20.6-37.8] seconds), with evidence of high heterogeneity (I^2= 98%) among studies (**Figure 2**). Similar results were observed when the analysis was restricted to studies including more than 50 patients in the placebo arm (mean difference [95% CI]: +32.3 [17.9-46.8] seconds, I^2=99%) (**Supplementary Figure S3, Supplementary Appendix S3**).

Secondary endpoints

ETT time to ST-segment deviation (mean difference [95% CI]: +22.2 [14.1, 30.3] seconds) and ETT time to angina (mean difference [95% CI]: +26.0 [17.8, 34.1] seconds) were significantly improved following placebo exposure, with evidence of high heterogeneity among studies for both endpoints (**Supplementary Figure S4**, **Supplementary Appendix S3**). Similarly, a reduction in CCS angina class was observed following placebo (mean difference [95% CI]: -0.5 [-0.9, -0.2] class, I^2=92%). Patient-reported quality of life outcomes were improved following placebo, with each SAQ domain showing a significantly higher score (mean differences [95% CI] for physical limitation: +4.3 [3.1, 5.5] points, I^2=20%; angina stability: +8.4 [4.6, 12.1] points, I^2=93%; angina frequency:+12.7 [9.4, 15.9] points, I^2=94%; treatment satisfaction: +6.1 [4.2, 8.0] points, I^2=44%; quality of life: +8.4 [4.6, 12.1] points, I^2=93%). Similarly, the number of nitroglycerin tabs/week used was significantly reduced following placebo as compared to baseline (mean difference [95% CI]: -0.8 [-1.2, -0.4] tabs/week, I^2=73%) (**Figure 3**).

Sensitivity analyses

Sensitivity analyses limited to RCTs with a low risk of bias showed similar results for all the main outcomes (**Supplementary Figures S5-S6**, **Supplementary Appendix S3**).

Subgroup analyses

Similar effect estimates of the primary endpoint following placebo were observed regardless of study publication year, placebo type (pharmacological vs. procedural), the presence of a run-in phase and follow-up time. No difference in placebo effect between studies using a Bruce versus a modified Bruce protocol was observed (+22.1 [16.6, 27.6] vs. +43.3 [20.4, 66.2], p=0.077). An interaction of crossover study design with the impact of placebo on ETT performance was observed, with no significant placebo effect in RCTs with a crossover design (total ETT duration in crossover vs. no crossover study design: +7.4 [-3.3, -18.1] seconds, I^2=56% vs. +34.8 [22.0, 47.6] seconds, I^2=100%; p for subgroup difference=0.001) (**Table 3** and **Supplementary Figures S7-S9, Supplementary Appendix S3**). Regarding angina phenotype, a more modest placebo effect on ETT performance was observed in RCTs of microvascular angina (total ETT duration increase in microvascular [4RCTs] vs. non-microvascular angina population [74 RCTs]: +6.9 (2.5, 11.2) seconds, I^2=0% vs. +30.3 (18.8, 41.8) seconds, I^2=100%; p for subgroup difference<0.001), while no interaction of the refractory angina and definite CAD status with placebo effect size was observed (**Table 3**). Exploratory subgroup analyses of clinical characteristics are presented in **Supplementary Table S3** in the **Supplementary Appendix S3**. When comparing the baseline study and patient characteristics of the 10 RCTs with the longest ETT total duration versus the others, no differences were observed (**Supplementary Table S4, Supplementary Appendix S3**). Among five studies

carrying serial ETT tests at follow-up, no difference in ETT total duration between the follow-up first and last ETT assessments was observed (**Supplementary Figure S10, Supplementary Appendix S3**)."

DISCUSSION

Cardiovascular mortality from coronary artery disease (CAD) has steadily declined with continuous advances in disease-modifying revascularization and pharmacologic therapies[12,13]. In contrast, the therapeutic approaches for symptoms and quality of life have remained mostly unchanged over the last two decades[4,14]. Data from observational and unblinded randomized studies have shown significant improvements in symptoms, quality of life and functional outcomes with a multitude of pharmacological and non-pharmacological therapeutics in angina[1,14]. However, the reported placebo effect in angina trials represents a challenge to the design and interpretation of clinical efficacy[4,14]. Most of the evidence supporting usage of current guideline-recommended angina treatments results from placebo-controlled trials using endpoints based on validated tools focused on quantification of angina severity, quality of life metrics and exercise time[15,16]. However, the impact of placebo on these metrics and whether these metrics are able to quantitatively reflect the placebo-controlled efficacy of a treatment in the experimental setting remains under-studied. Moreover, while anticipated estimates of the placebo effect size are necessary to inform study power and sample size, no systematic report assessing the effect size of placebo is available. These challenges were recently reflected by the ORBITA trial results, in which percutaneous coronary intervention was reported to have similar effects in exercise time to a placebo-procedure after a run-in phase in which anti-anginal therapy was optimized [11]. Thus, we conducted a systematic review and meta-analysis to quantify the clinical impact of the placebo effect on the commonly used endpoints to assess symptoms, quality of life and functional outcomes in randomized placebo-controlled trials of patients with symptomatic stable angina.

The main findings of our investigation can be summarized as follows:

- Among symptomatic stable angina patients receiving placebo, a substantial placebo effect was present across a variety of endpoints testing symptoms, quality of life and objective functional outcomes
- High variability in the effect size of placebo was observed across the tested outcomes
- Smaller placebo effect was observed for RCTs with a crossover design and in populations of microvascular angina patients
- The observed high variability in placebo effect size persisted at subgroup analysis by study design, placebo type or patient characteristics

This is the first large meta-analysis to formally establish the impact of placebo on functional and quality of life outcomes among symptomatic stable CAD patients enrolled in RCTs. Our meta-analysis provides several original findings deserving consideration in the clinical research field of treatments for angina.

First, our results highlight the challenges in designing angina clinical trials. Indeed, while the need of a placebo is indisputable, a reliable effect size anticipation of placebo effect cannot be established given the variability seen in previous trials. Most pivotal trials of currently established anti-anginal treatments were conducted in an era of limited therapeutic options, frequently with unrevascularised CAD and modest background medical therapy[17]. Moreover, treatment washout was commonly recommended by study protocol. As a consequence, placebo effect size was conceivably negligible relative to the magnitude of the active treatment effect size in the absence of background therapy. Conversely, in modern practice, angina RCTs are conducted with robust guideline-directed background therapy, often accompanied by complete revascularization if feasible. This results in modest incremental treatment effect sizes, for which the absence of a reliable estimate of placebo effect in the control-arm may hamper proper planning of study design,

resulting in uncertainty in the statistical power of the trial with ensuing feasibility and economic implications[18].

The substantial observed heterogeneity was investigated through subgroup analysis to ascertain whether it was due to differences in study characteristics (methodological diversity) or study populations (clinical diversity).

Interestingly, as compared to trials using a parallel study design, the crossover trial design where the patient serves as his/her own control (15 RCTs) was associated with a smaller placebo effect. Crossover trial design has the advantage that there will not be a difference in baseline characteristics between active and placebo treatment that might confound interpretation of results. Moreover, sample size requirements are usually less with a crossover trial design since there is less variability in the placebo group in the measurement parameters. Our findings suggest that this specific study protocol may magnify differences between the active treatment and the control arms. A sound rationale may underlie this finding: a patient just enrolled in a RCT is likely to lean towards positive expectations in regards to the first received treatment (an attitude that is the foundation for the placebo concept itself). Accordingly, in the first study phase, he will likely experience a magnified clinical benefit regardless of treatment allocation. Conversely, the initial positive expectation of the first phase will be counterbalanced, in the second phase, by the perception of treatment withholding. Accordingly, the patient will likely experience a reduced clinical benefit regardless of treatment allocation. This trade-off of expectations between the first and the second study phases may thus account for the observed neutral effect of placebo treatment. Thus, our finding in the context of its plausibility supports the adoption of crossover as the design of choice in angina RCTs (when this protocol is feasible, i.e. in non-placebo-procedure controlled studies) in order to emphasize the active treatment effect. However, for drug approval, assessment of drug

side-effect profile and safety, a parallel trial design is preferable since it minimizes carry-over effects of active treatment and provides a more suitable control group to assess differences.

A non-significant trend for higher ETT total duration with a modified versus standard Bruce ETT protocol was observed, which is likely related to the more gradual protocol, which results, in the same patient, in longer ETT performances. However, both the statistical and the clinical significance of this difference are unlikely to account for the observed much higher overall heterogeneity.

Regarding clinical diversity, we observed an attenuated placebo effect in the subset of microvascular angina. While we have no satisfactory explanation for this finding, we hypothesize that the psychological component, often coexisting in the spectrum of microvascular angina disorders, may play a role in the mitigation of placebo[19]. We also analyzed the interaction of placebo with follow-up length. A significant interaction with apparently shorter ETT duration was observed for RCTs with 3 to 6 months follow-up as compared to those with other follow-up timepoints. This finding might be attributed to a loss of placebo effect over time or to the fluctuating nature of angina that may have spontaneously regressed[5]. However, the absence of a consistent trend in the 6 to 12 months group doesn't allow to exclude that the play of chance may be responsible for it. Of note, since no study presented follow-up data beyond one year, we cannot elaborate on the presence and relevance of placebo effect on the long-term.

Most of the heterogeneity observed in our investigation remains unexplained by methodological and clinical diversity. If the placebo effect is truly independent of CAD-related factors as suggested, then other unmeasured confounders must be responsible for the observed heterogeneity. Several hypotheses not mutually exclusive can be made. First, the specific physical and psychological setting in which functional tests and quality of life self-assessment are carried may influence the patient's output[5,20]. In this regard, a methodological standardization which

includes, beyond technical aspects, recommendations regarding the operator's attitude toward the patient and the modes of questionnaire compilation would be advisable to guarantee reproducibility and comparability[4]. Moreover, the introduction in angina RCTs of objective techniques to quantify the physiological substratum of functional capacity such as cardiopulmonary exercise test (CPET) may in theory provide useful, even if not yet supported by current methodological evidence[21]. From a methodological standpoint, the adoption of adaptive study design allowing for adjustment of sample size based on the observed outcome effect size may further help in this setting characterized by high heterogeneity.

Second, the cyclic nature of angina symptoms described by phenomena such as regression to the mean (nadir bias, i.e. the likelihood that angina will naturally return to its baseline status regardless of the proposed treatment) and hedonic adaptation (i.e. the capacity of patients to self-manage and adapt to their new ischemic threshold) may contribute to high heterogeneity[5,22,23]. Indeed, different enrollment pathways to select patients for inclusion in angina RCTs may be less or more prone to nadir bias and thus to the regression to the mean phenomenon. This is of relevance, as the present analysis assess the combined impact of placebo and time on study outcomes rather than the sole placebo effect. This combined effect of placebo and time is of methodological relevance and is inherent to the placebo-controlled setting (and may thus be practically embedded in the placebo concept) in which it may play an important role in the observed heterogeneity. In this regard, the placebo concept described throughout the manuscript should be intended in a broader perspective which incorporates these inherent and multifaceted phenomena. Third, patients with CAD often have comorbid non-cardiovascular conditions which may modulate the individual's functional threshold: since recorded baseline characteristics in angina RCTs are mostly cardiovascular, an interaction of multisystemic factors with placebo effect size cannot be excluded[24].

Placebo-controlled design is necessary to remove the nocebo effect in the control-arm deriving from the patient's awareness of being untreated, which might itself lead to an apparent although unreal treatment benefit in the active arm. However, while placebo may guarantee that - when observed - a treatment effect is authentic, it might in turn partially obscure a treatment effect, potentially preventing the assessment of the true clinical efficacy of valuable treatments in the experimental setting. Indeed, when a placebo-controlled design is implemented in a study testing life-quality-related endpoints, an implicit assumption is made of a completely additive arithmetic function between the placebo (E_P) and the physiological (E_T) treatment effects in the active treatment arm. However, the functional threshold and the well-being of a patient with CAD is determined by a multifactorial background dependent, beyond the anginal threshold targeted by a therapy, also on other factors such as respiratory capacity, musculoskeletal performance, peripheral artery perfusion and myocardial performance[24]. If the placebo effect is sufficient to blunt the anginal component of an individual functional threshold, then the functional threshold will be determined by non-anginal factors. In this case, E_p and E_T will be dyssynergic and the test – and the associated study endpoint – will not be able to assess the therapeutic effect of the active treatment, which may still be present, but will not emerge.

Taken together, our results underline the limits of study design and of outcomes currently adopted in clinical research of angina treatments and call for more standardized protocols, patient populations and study endpoints. While one of the *a priori* aims of the meta-analysis was to provide a concrete information on anticipated sample size based on the magnitude of the observed placebo effect, the unexpected finding of such high heterogeneity precludes reliable estimates to inform future angina RCTs. Further research is needed to define how to more reproducibly assess angina metrics, and to possibly identify new robust methods and outcomes able to assist the experimental characterization and broad-scale clinical implementation of strongly needed therapeutic options.

LIMITATIONS

The findings of this meta-analysis should be interpreted in the context of some limitations. First, this is a study-level meta-analysis and the findings provide mean study-level effects. Second, even if we selected a broad range of the most commonly adopted endpoints in angina RCTs, some protocols or metrics previously used in angina RCTs (i.e. bicycle ergometer protocols, 6-minute walk test, DASI questionnaire) were not analyzed. Therefore, no inferences can be made regarding the placebo effect in those unstudied settings. Third, the results of the subgroup analyses of clinical characteristics should be considered exploratory and interpreted cautiously owing to study-level estimates and low data counts. Fourth, angina is a complex phenomenon influenced by the interplay of several factors related to both the physical and psychological domains of a patient's well-being. These factors present a temporal dynamic nature which may contribute to the fluctuating symptoms severity and patient's life quality. Accordingly, the presented results are related to both placebo and the effect of time on the study outcomes and should be interpreted in the context of this limitation. Moreover, the design of the present study assesses the measured difference in outcomes in patients receiving placebo, thus investigating the association of placebo with outcomes, rather than the causal nature of this relationship. This is of relevance, since previous studies directly comparing placebo with no-treatment across a range of mostly non-cardiovascular clinical conditions showed small (sometimes undetectable) impact of placebo across several metrics[25,26]. Whether placebo (intended in the stricter definition of a neurobiological psychosomatic mechanism) exerts a direct role in the improvement of functional and life-quality metrics among patients with stable angina remains to be established.

CONCLUSION

Among symptomatic stable CAD patients receiving placebo, a substantial placebo effect was present across a variety of endpoints testing symptoms, quality of life and functional outcomes. High variability in placebo effect size was present, which was mostly unaccounted for by differences in study design, placebo type or patient characteristics. The present findings may affect both evaluation of current published studies and future research.

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FIGURE LEGENDS

Figure 1. Flowchart of the Study Selection Process

RCT = randomized controlled trial

Figure 2. Summary forest plot for the primary study endpoint of ETT total duration time (n=3843 patients)

Figure 3. Summary forest plots for the secondary study endpoints of symptom, quality of life and drug usage parameters

Table 1 – Summary of study characteristics.

Study characteristics	N studies (%)	N pts (%)
Study design		
≥ 1 active treatment arms	26 (34.1)	1455 (29.5)
Crossover design	19 (24.3)	551 (11.2)
Placebo run-in phase	23 (29.4)	1544 (31.3)
Placebo-drug-controlled Placebo-procedure controlled	64 (82.1) 14 (17.9)	4203 (85.3) 722 (14.7)
Study population		
Definite CAD Definite or suspected CAD	65 (83.3) 13 (16.7)	4106 (83.4) 819 (16.6)
Refractory angina	23 (29.4)	784 (15.9)
Microvascular angina	4 (5.1)	220 (4.5)
Study follow-up (days)	42 (14-141)	81.7 (w. mean)

Table 2 – Summary of study-level and patient-level baseline characteristics of patients randomized to placebo

Study characteristics		
	N of studies with available data	Mean/median (SD/IQR)
Demographics		
Male (%)	66	75 (24)
Age (years)	68	63 (4)
Risk factors		
Hypertension (%)	41	50 (44-73)
Dyslipidemia (%)	29	62 (23)
Smoke (%)	33	29 (16-57)
Diabetes mellitus (%)	41	25 (14)
BMI (kg/m^2)	23	27 (3)
CAD history		
Previous MI (%)	42	51 (20)
Previous CABG (%)	34	25 (12-64)
Previous PCI (%)	30	46 (33)
LVEF (%)	17	55 (5)
Anti-ischemic therapy		
Beta-blockers (%)	47	55 (36)
CCB (%)	42	35 (29)
Nitrates (%)	41	44 (33)
Ivabradine (%)	15	0 (0-0)
Ranolazine (%)	16	0 (0-0)

Abbreviations: BMI=body mass index; CABG=coronary artery bypass graft; CAD=coronary artery disease; CCB=calcium channel blocker; IQR=interquartile range; LVEF=left ventricular ejection fraction; MI=myocardial infarction; PCI=percutaneous coronary intervention; SD=standard deviation.

Table 3 – Pooled effect estimates of ETT duration change (seconds) between baseline and following placebo within subgroups of study characteristics and angina phenotypes

Subgroups (n studies)	Pooled effect estimate (95% CI)	p-value for subgroup differences
Type of placebo		
Drug (53)	28.5 (19.5-37.4)	
Procedure (9)	41.7 (20.3-63.0)	0.490
Type of study protocol		
ETT reproducibility as inclusion criteria (33	29.9 (19.5-40.2)	
No ETT reproducibility as inclusion criteria (29)	27.0 (15.1-38.9)	0.726
Placebo run-in (23)	24.5 (15.1-34.0)	
No Placebo run-in (39)	32.7 (17.7-47.7)	0.366
Crossover (15)	6.0 (-6.1-18.1)	
No crossover (47)	34.0 (23.7-44.2)	0.001
Bruce Protocol (46)	22.1 (16.6-27.6)	
Modified Bruce Protocol (15)	43.3 (20.4-66.2)	0.077
Background therapy allowed (36)	31.9 (18.2-45.7)	
Only nitrates allowed (24)	26.1 (14.8-37.4)	0.520
Follow-up length*		
< 14 days (21)	23.3 (11.1-35.6)	0.326
14 days – 3 months (21)	29.7 (18.4-41.0)	0.904
3 – 6 months (4)	10.9 (5.5-16.2)	0.003
6 – 12 months (12)	23.3 (11.1-35.6)	0.406
Study publication year		
1993-2002 (33)	26.9 (16.4-37.5)	
2003-2018 (29)	33.0 (19.2-46.9)	0.491
Angina phenotype		
Definite CAD only (51)	32.3 (15.6-49.0)	
Not only definite CAD (11)	23.1 (12.2-34.1)	0.367
Refractory angina (19)	29.3 (21.0-37.6)	
No refractory angina (43)	27.9 (5.8-50.0))	0.908
Microvascular angina (2)	6.9 (2.5-11.2)	
No microvascular angina (60)	29.9 (20.9-39.0)	<0.001

* p-values for follow-up length refers to the group of interest versus the other three groups.

Abbreviations: CI=confidence interval.