GUSTAVO BUSCH JUSTINO

EARLY INITIATION OF PCSK9 INHIBITOR THERAPY VERSUS PLACEBO IN PATIENTS WITH ACUTE CORONARY SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

Trabalho apresentado à Universidade Federalde Santa Catarina, como requisito para a conclusão do Curso de Graduação em Medicina.

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DEDICATÓRIA

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Early Initiation of PCSK9 Inhibitor Therapy versus Placebo in Patients with Acute Coronary Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

In patients with stable atherosclerotic cardiovascular disease, PCSK9 inhibitors (PCSK9i) have shown a 50-60% reduction in LDL-C from baseline, added to high-intensity statin therapy. However, less is known about the impact of PCSK9i in the setting of an acute coronary syndrome (ACS). Therefore, we performed a systematic review and meta-analysis comparing PCSK9i with placebo in the setting of ACS, added to guideline directed high-intensity or maximally tolerated statin therapy. We included randomized controlled trials (RCTs) with initiation of PCSK9i or placebo within 1 week of presentation or percutaneous coronary intervention for ACS. PubMed, EMBASE, and Cochrane Central were searched. This study followed Cochrane and PRISMA recommendations. Six RCTs were included, totalizing 996 patients of whom 503 (50.5%) received PCSK9i. Mean follow-up ranged from 4 to 52 weeks. LDL-C (MD -44 mg/dL; CI -54.3 to -33.8; $p<0.001$) and Lp(a) levels (MD -24.0 nmol/L; CI -43.0 to -4.9; $p=0.01$) were significantly lower at follow-up with PCSK9i. Similarly, total cholesterol (MD -49.2 mg/dL; CI -59 to -39.3), triglycerides (MD -19 mg/dL; CI -29.9 to -8.2) and Apo B (MD -33.3 mg/dL; CI -44.4 to -22.1) were significantly reduced with PCSK9i. In conclusion, in patients with ACS, early initiation of PCSK9i, added to statin, significantly reduces LDL-C and Lp(a) as compared with placebo. Whether the differences in these atherogenic lipoproteins translate into a reduction in clinical endpoints is yet to be determined.

Patients with acute coronary syndromes (ACS) are at high risk for recurrent ischemic events in the early stages after the index event, leading to a 20% increase in the recurrence rate within 3 years.[1,2] Previous randomized trials have shown that early lipid-lowering therapy with high intensity statin rapidly reduces recurrent atherosclerotic events.[3–5] The European Society of Cardiology (ESC) Guidelines recommend lowering low-density lipoprotein cholesterol (LDL-C) levels to <55 mg/dL and ≤50% from baseline, whereas the American Heart Association/American College of Cardiology (AHA/ACC) recommends lowering LDL-C levels to <70 mg/dL and ≤50% from baseline.[6–8] This should happen in a stepwise approach that includes maximally-tolerated statin therapy and, if needed, non-statin therapy, including proprotein convertase subtilisin/kexin 9 inhibitors.[6–8] Recently, the ACC Expert Consensus stated that adults with clinical atherosclerotic cardiovascular disease (ASCVD) at very high risk on statin regimen should aim LDL-C levels <55 mg/dL.[9] In patients with stable atherosclerotic disease, evolocumab significantly reduced the risk of any coronary revascularization by 22% and complex revascularizations by 29%, as compared with placebo, over a median follow-up of 2.2 years.[10,11] In patients with a history of ACS within the prior 1 to 12 months (median 2.6 [1.7-4.4] months) of trial enrolment, there was a significant 15% reduction in the risk of major cardiovascular events among those treated with alirocumab in the ODYSSEY OUTCOMES trial.[12] Less is known, however, about the use of PCSK9 inhibitors in patients soon after a presentation with ACS. There is some evidence of greater plaque regression in patients treated with PCSK9 inhibitors immediately after a presentation with ACS.[13,14] Recent randomized controlled trials have investigated the role of PCSK9i administration in the acute setting of ACS. Therefore, we aimed to perform a systematic review and meta-analysis comparing the impact of PCSK9i and statin therapy on atherogenic lipoprotein levels with statin monotherapy in patients presenting with ACS.

METHODS

We systematically searched Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed from inception to January 12, 2023, for studies published in English with the following medical subject heading terms: ‘acute coronary syndrome’, ‘ACS’, ‘proprotein convertase subtilisin/kexin type 9 inhibitor’, ‘PCSK9 inhibitor’, ‘alirocumab’, ‘evolucumab’, ‘angiography’, ‘postinfarction’, ‘percutaneous coronary intervention’ and ‘PCI’. Additionally, we evaluated the references of included trials for additional studies and contacted authors for unpublished data. We performed the systematic review and meta-analysis in agreement with the recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[15,16] This study is registered with PROSPERO (CRD42022364868).

We included studies that met the following criteria: (1) randomized controlled trials (RCTs) comparing PCSK9i with placebo; in (2) patients presenting with ACS; (3) with initiation of PCSK9i therapy within 1 week of presentation for PCI or ACS; and (4) reporting any of the outcomes of interest - serum levels of LDL-C, Lp(a), HDL-C, triglycerides, total cholesterol and apolipoprotein B (Apo B). We excluded nonrandomized studies and studies that administered the first dose of PCSK9i or placebo more than 1 week after ACS presentation or PCI.

Two authors (G.B.J. and L.B.J.) independently extracted relevant data following predetermined methods of search, quality assessment and data extraction. Disagreements were resolved by consensus between authors (G.B.J., L.B.J. and M.E.M.).

Risk of bias and quality assessment of individual studies were analyzed with the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (RoB 2).[15] The RoB2 tool ranks RCTs as high, low, or unclear risk of bias based on five domains: selection,

performance, detection, attrition, and reporting biases. Funnel plots of individual study weights against point estimates were used to check for evidence of publication bias.

Treatment effects were compared using pooled odds-ratios (ORs) and mean differences (MDs) with 95% confidence intervals (CIs) for dichotomous and continuous endpoints, respectively. We evaluated heterogeneity with Cochran Q test and I^2 statistics; P values inferior to 0.10 and I^2 >25% were considered significant for heterogeneity. We used a fixed-effect model for endpoints with I^2<25% (low heterogeneity). DerSimonian and Laird random-effects model was assessed in pooled outcomes with high heterogeneity. P values of <0.05 were considered statistically significant. Statistics were analyzed with Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

As described in Figure 1, our initial search strategy yielded 1,260 results. After exclusion of duplicate records and studies based on title and abstract, 24 trials were thoroughly reviewed for the inclusion and exclusion criteria. Finally, 996 patients from 6 RCTs were included in the systematic review and meta-analysis, of whom 503 (50.5%) received PCSK9i therapy.[13,14,17–20] Characteristics of each study are detailed in Table 1. Among the intervention group, 317 (63%) participants received evolocumab and 186 (37%) received alirocumab. Mean time from presentation to administration of first dose ranged from 3.6 hours to 6.5 days.

After a mean follow-up ranging from 4 to 52 weeks, LDL-C was significantly lower in those who received an early administration of PCSK9i compared with placebo (MD -44.0 mg/dL; 95% CI -54.3 to -33.8 mg/dL; p<0.001; Figure 2A). The percent change of this lipoprotein from baseline was significantly greater in patients who received PCSK9i therapy relative to placebo (MD -38.0%; 95% CI -46.5 to -29.7%; p<0.001; Figure 2B). Lp(a) levels

were also significantly reduced in those who received either evolocumab or alirocumab therapy (MD -24.0 nmol/L; 95% CI -43.0 to -4.9 nmol/L; p=0.01; Figure 2C). Similarly, serum levels of total cholesterol (MD -49.2 mg/dL; 95% CI -59 to -39.3 mg/dL; p<0.001; Figure 3A), triglycerides (MD -19.0 mg/dL; 95% CI -29.9 to -8.2 mg/dL; p<0.001; Figure 3B) and Apo B (MD -33.3 mg/dL; 95% CI -44.4 to -22.1 mg/dL; p<0.001; Figure 3C) were significantly lower at follow-up in the intervention group as compared with control. HDL cholesterol levels were marginally higher in patients treated with PCSK9i therapy (MD 2.5 mg/dL; 95% CI 0.9 to 4.2 mg/dL; p=0.003; Figure 3D).

The proportion of patients who achieved an LDL-C <55 mg/dL and <70 mg/dL was 91% and 96%, respectively, for patients treated with PCSK9i therapy, as compared with 20% and 44%, respectively, of those in the placebo group (Figures 3E and 3F).

Adverse events of any cause happened in 44% of the participants treated with PCSK9i and in 48% of those in the placebo group, with no statistical significance (OR 0.85; 95% CI 0.64 to 1.13; p=0.27; Figure 4). Myalgia and local injection site reactions were the most common reported adverse events, accounting for 5.6% and 3.9% of cases in the PCSK9i and placebo groups, respectively.

Quality appraisal of each RCT is detailed in eTable 1 in the Supplement. Overall, studies were classified as low for the risk of bias. Albeit restricted by the small number of trials, funnel plot analysis indicated no evidence of publication bias (eFigure 2 in the Supplement). We performed sensitivity analyses by systematically excluding each study from the pooled outcomes, which showed consistency among results.

DISCUSSION

In this systematic review and meta-analysis of six studies and 996 patients, we compared early administration of PCSK9i with placebo in patients presenting with ACS. The

main findings were as follows: (1) the levels of LDL-C were reduced by approximately 45 mg/dL among those who received an early administration of PCSK9i compared with placebo (75.5% vs. 39.0%, respectively; MD -44.0 mg/dL; p<0.001); (2) Lp(a) levels were significantly lower in participants treated with either alirocumab or evolocumab therapy over a follow-up period of 4 to 52 weeks (MD -24.0 nmol/L; 95% CI -43.0 to -4.9 nmol/L; p=0.01); (3) this improvement was also observed for total cholesterol, and triglycerides levels (p<0.01); and (4) patients receiving PCSK9i therapy exhibited slightly higher levels of serum HDL cholesterol.

Individuals presenting with ACS are at an increased risk of recurrent cardiovascular events. Multisociety European and American guidelines on prevention and lipid management recommend high-statin therapy (or maximally-tolerated statin) to achieve strict LDL-C goals after ACS (≤50% from baseline and <55 mg/dL or <70 mg/dL).[6–9] If this level is not achieved in up to 6 weeks despite maximally tolerated statin therapy, additional lipid lowering therapy should be added, which now includes a gamut of options for oral and injectable medications. Despite these recommendations, it is well known that reaching optimal levels of LDL-C remains challenging in these very-high-risk patients, which delays the benefits of secondary prevention.[2] PCSK9i reduce mortality in patients with a history of ACS, when initiated 1-12 months after an ACS for patients with LDL-C ≥70 mg/dL.[12,21] Therefore, an early administration of PCSK9i within 4 weeks of an ACS may help to achieve guideline LDL-C goals quicker and ultimately reduce recurrent cardiovascular events in this population, although the latter remains to be determined.

PCSK9 inhibitors have also been shown to reduce percent atheroma volume relative to placebo in patients with stable coronary artery disease and in those with acute myocardial infarction.[13,22] PACMAN-AMI evaluated the effects of biweekly administration of alirocumab added to rosuvastatin compared with statin therapy alone on coronary plaque composition,

evolution and phenotype, among patients with acute myocardial infarction.[13] Alirocumab was administered within 24 hours of PCI of the culprit lesion. There was a statistically significant reduction in mean percent atheroma volume in the alirocumab group from baseline to week 52 (-2.13% vs. -0.92%; p<0.001). This reduction was greater than the one achieved by the GLAGOV trial, which enrolled patients with stable CAD (0.05% vs. -0.95%; p<0.001).[22] Moreover, in PACMAN-AMI, maximum lipid core burden index within 4 mm was significantly lower in the PCSK9i group (−79.42 vs. −37.60; p=0.006) and fibrous cap thickness was significantly increased in the same population (62.67 μm vs. 33.19 μm; p=0.001).[13] These findings suggest that the early initiation of PCSK9i may be beneficial in secondary prevention not only by reducing lipid serum levels, but also by modifying coronary plaque phenotype.

The ODYSSEY OUTOMES and FOURIER trials demonstrated clinical efficacy and safety of PCSK9i in individuals with a more stable phenotype of atherosclerotic disease, enrolled no sooner than 1 month after ACS.[11,12] Our systematic review and meta-analysis extend the findings of these clinical trials in lipid endpoints to the more acute setting, early after presentation with ACS (within one week). The EPIC-STEMI trial aimed to evaluate not only the degree of reduction of LDL-C, but also the time interval in which the effects of PCSK9i therapy were seen. Within the first 24 hours after PCI for STEMI, those who received alirocumab experienced a slightly higher rate of reduction in LDL-C (-0.001 mmol/L/h; p=0.032). Ultimately, 92% of the participants in the PCSK9i group reached ESC/EAS recommended LDL-C levels of <55 mg/dL, as opposed to 57% in the placebo group, over a median follow-up of 45 days (p=0.002).[20] In our study, 4 trials assessed the number of patients who achieved guideline recommended goals of LDL-C at 4 weeks after ACS;[17–20] 91% of patients who underwent PCSK9i therapy achieved mean values of LDL-C <55 mg/dL as compared with only 20% of those who received statin monotherapy (p<0.001).

The target of LDL-C <70 mg/dL was achieved by 96% in the PCSK9i group compared with 44% in the placebo group (p<0.001).

Lp(a) is also a key determinant of atherosclerotic risk.[23,24] This lipoprotein carries cholesterol, oxidized phospholipids and limits thrombolysis by competing with plasminogen at the fibrin binding site.[25–27] Patients with elevated levels of Lp(a) also tend to experience great absolute risk reductions from PCSK9i therapy.[28,29] In patients with stable coronary heart disease, evolocumab reduces Lp(a) levels by 20-30%.[28] In the setting of an ACS, there is a significant increase in Lp(a) levels in the placebo group as early as 24 hours after the index event, particularly in those with elevated Lp(a) at baseline.[30,31] Evolocumab may blunt this increase in Lp(a) during an acute myocardial infarction by inhibiting mature PCSK9.[30] In our meta-analysis, PCSK9i lowered Lp(a) levels by approximately 8%; however, Lp(a) increased by 18% in the placebo group (MD -24.0 nmol/L; 95% CI -43.0 to -4.9 nmol/L; p=0.01).

Our study has limitations. First, the individual studies and their pooled results in this meta-analysis are not powered to detect a significant difference in clinical outcomes between groups. EVOLVE-MI (ClinicalTrials.gov: NCT05284747) and AMUNDSEN (ClinicalTrials.gov: NCT04951856) are two ongoing multicenter, open-label, RCTs that aim to evaluate early and long-term effects of evolocumab in patients who present with ACS. Second, only 2 of the included RCTs had a longer follow-up of 52 weeks. And, finally, the absence of patient-level data from most of the studies precluded detailed subgroup analyses, such as exploring the effects in patients who were previously on statin vs. statin-naïve.

In conclusion, in this meta-analysis of RCTs, patients who were treated with PCSK9i therapy within one week of an ACS had lower levels of LDL-C and Lp(a) as compared with statin monotherapy. To the extent that lower levels of these atherogenic lipoproteins are associated with improved clinical outcomes, these findings provide support for early

treatment with PCSK9 inhibitors in patients who present with ACS. Cardiovascular outcome trials are warranted to evaluate clinical endpoints in this patient population.

DISCLOSURES

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FIGURE LEGENDS

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) Flow Diagram

Figure 2. Primary Outcomes

Figure 2A. LDL-C was significantly reduced with PCSK9 inhibitor therapy relative to placebo (mg/dL).

Figure 2B. The relative change in LDL-C from baseline was significantly greater with PCSK9 inhibitor therapy relative to placebo (%).

Figure 2C. Lp(a) was significantly reduced with PCSK9 inhibitor therapy relative to placebo (nmol/L).

Figure 3. Secondary Outcomes

Figure 3A. Total cholesterol was significantly reduced with PCSK9 inhibitor therapy relative to placebo (mg/dL).

Figure 3B. Triglycerides were significantly reduced with PCSK9 inhibitor therapy relative to placebo (mg/dL).

Figure 3C. Apo B levels were significantly reduced with PCSK9 inhibitor therapy relative to placebo (mg/dL).

Figure 3D. HDL-C was significantly increased with PCSK9 inhibitor therapy relative to placebo (mg/dL).

Figure 3E. The number of patients who achieved LDL-C <55 mg/dL at 4 weeks was significantly higher in those treated with PCSK9i as compared with placebo.

Figure 3F. The number of patients who achieved LDL-C <70 mg/dL at 4 weeks was significantly higher in those treated with PCSK9 inhibitors as compared with placebo.

Figure 4. The incidence of any adverse events was not significantly different in those treated with PCSK9 inhibitors as compared with placebo.

Table 1. Baseline Characteristics of Included Studies

	Number of patients, n	PCSK9i, n (%)	Time to first dose of PCSK9i, ± SD	Males, n (%)	Mean age, ± SD (years)	ACS PCSK9i, n (%)	ACS placebo, n (%)	Previous statin treatment, n (%)[b]	HTN, n (%)	DM, n (%)[c]	Previous MI, n (%)	Previous PCI, n (%)	Follow-up (weeks)
EVOPACS 2019	308	Evolocumab: 155 (50.3) Placebo: 153 (49.7)	<72h after NSTE-ACS < 24h after STEMI	Evolocumab: 128 (83) Placebo: 123 (80)	Evolocumab: 60.5 ± 12 Placebo: 61 ± 10.7	NSTE-ACS: 88 (57) STEMI: 67 (43)	NSTE-ACS: 107 (70) STEMI: 46 (30)	Evolocumab: 31 (20) Placebo: 36 (24)	Evolocumab: 79 (51) Placebo: 85 (56)	Evolocumab: 23 (15) Placebo: 24 (16)	Evolocumab: 24 (15) Placebo: 19 (12)	Evolocumab: 25 (16) Placebo: 23 (15)	8
EVACS I 2020	57	Evolocumab: 30 (50) Placebo: 27 (50)	<24h after presentation	Evolocumab: 22 (73) Placebo: 11 (41)	55 ± 13	NSTEMI: 30 (100)	NSTEMI: 27 (100)	34 (60)	NA	NA	NA	NA	4.3
Okada 2020	102	Evolocumab: 52 (51) Placebo: 50 (49)	<24h after PCI	Evolocumab: 43 (82) Placebo: 47 (94)	Evolocumab: 66.4 ± 13.1 Placebo: 63.4 ± 14	NSTEMI: 4 (7.6) STEMI: 48 (92)	NSTEMI: 9 (18) STEMI: 41 (82)	Evolocumab: 14 (26) Placebo: 12 (24)	Evolocumab: 31 (59) Placebo: 33 (66)	Evolocumab: 17 (32) Placebo: 14 (28)	Evolocumab: 1 (1.9) Placebo: 5 (10)	Evolocumab: 4 (7.6) Placebo: 10 (20)	4
PACMAN-AMI 2022	300	Alirocumab: 148 (49.3) Placebo: 152 (50.7)	<24h after PCI	Alirocumab: 124 (83.8) Placebo: 119 (78.3)	Alirocumab: 58.4 ± 10 Placebo: 58.6 ± 9.4	NSTEMI: 70 (47.3) STEMI: 78 (52.7)	NSTEMI: 72 (47.4) STEMI: 80 (52.6)	Alirocumab: 17 (11.5) Placebo: 20 (13.2)	Alirocumab: 60 (40.5) Placebo: 70 (46.1)	Alirocumab: 12 (8.1) Placebo: 19 (12.5)	Alirocumab: 2 (1.4) Placebo: 5 (3.3)	Alirocumab: 2 (1.2) Placebo: 5 (3.3)	52
EPIC-STEMI 2022	68	Alirocumab: 38 (55.9) Placebo: 30 (44.1)	Prior to PCI. Time from symptom onset to PCI: 3.65h ± 2.25	Alirocumab: 27 (71) Placebo: 28 (93.3)	Alirocumab: 61.4 ± 11 Placebo: 63.6 ± 10.4	STEMI: 38 (100)	STEMI: 30 (100)	Alirocumab: 8 (21) Placebo: 8 (26.7)	NA	Alirocumab: 5 (13.16) Placebo: 1 (3.33)	Alirocumab: 3 (7.9) Placebo: 3 (10)	NA	12
HUYGENS 2022	161	Evolocumab: 80 (49.7) Placebo: 81 (51.3)	6.5 days[a]	Evolocumab: 60 (75) Placebo: 55 (67.9)	Evolocumab: 60.9 ± 10.0 Placebo: 60.2 ± 9.2	NSTEMI: 80 (100)	NSTEMI: 81 (100)	Evolocumab: 75 (93.8) Placebo: 78 (96.3)	Evolocumab: 45 (56.3) Placebo: 33 (40.7)	Evolocumab: 13 (16.3) Placebo: 14 (17.3)	Evolocumab: 5 (6.3) Placebo: 9 (11.1)	Evolocumab: 9 (11.3) Placebo: 12 (14.8)	52

[a]Mean time from NSTEMI to baseline imaging was 2.3 days. Mean time from baseline imaging to randomization was 4.2 days;
[b]Low/moderate and high intensity statin;
[c]Patients with and without insulin treatment;
ACS = acute coronary syndrome;
DM = diabetes mellitus;
HTN = hypertension;
MI = myocardial infarction;
n = number of patients;
NA = not available;
NSTE-ACS = non-ST-segment elevation acute coronary syndrome;
NSTEMI = non-ST-segment-elevation myocardial infarction;
PCI = percutaneous coronary intervention;
PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor;
STEMI = ST-segment-elevation myocardial infarction.

FIGURES

Figure 1

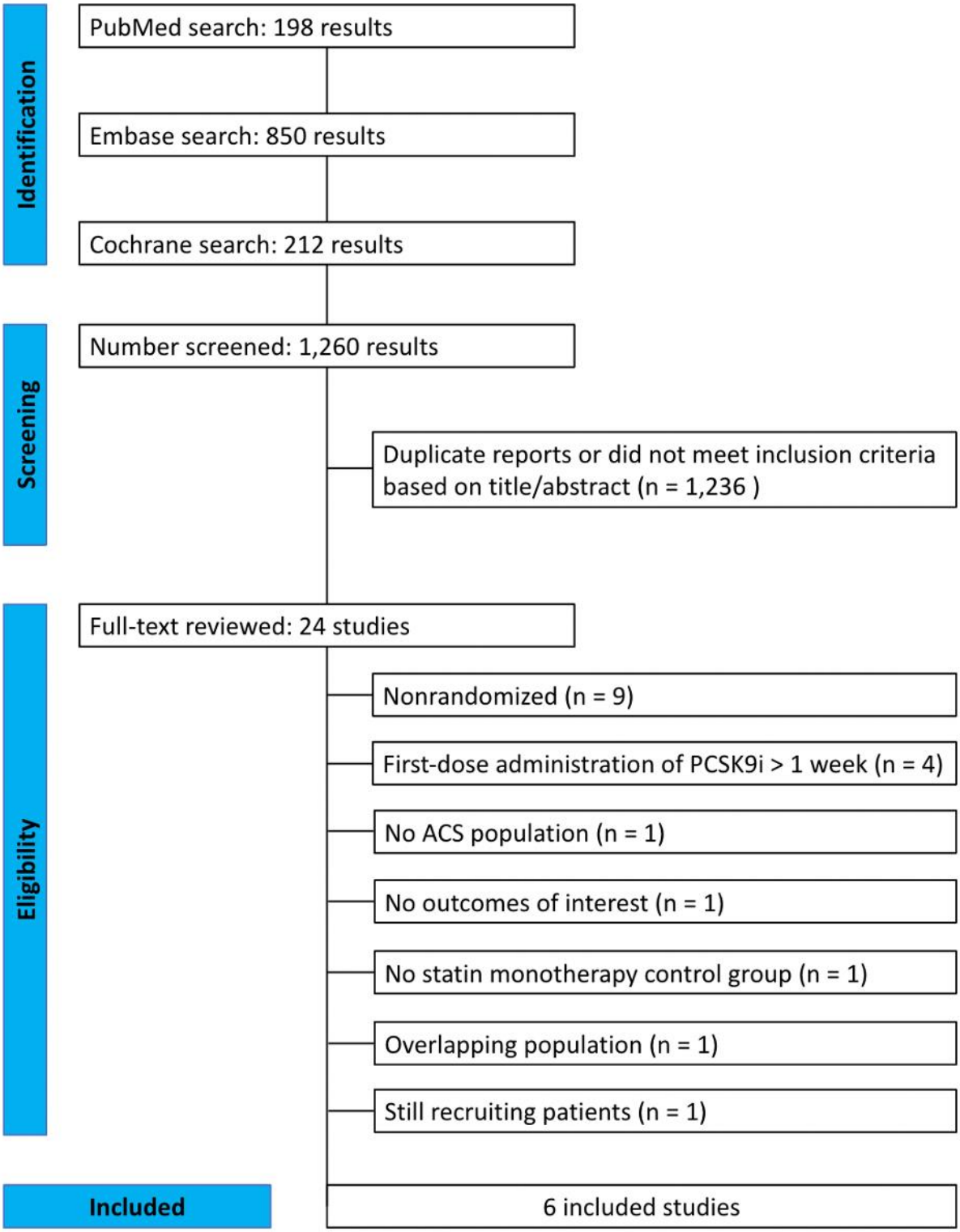

Figure 2

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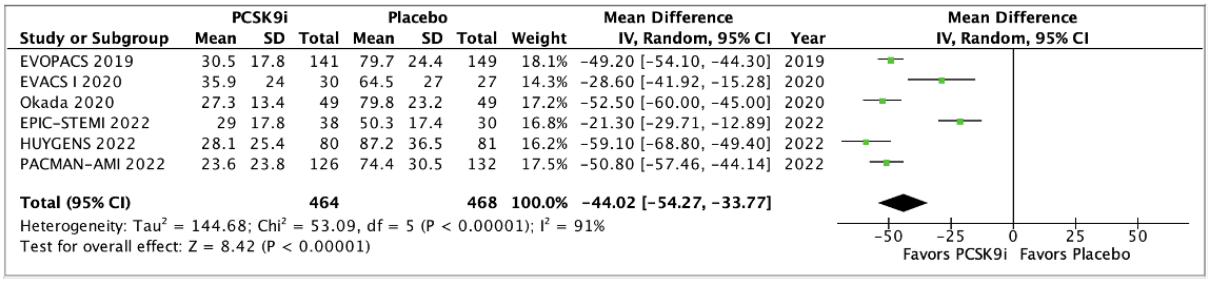

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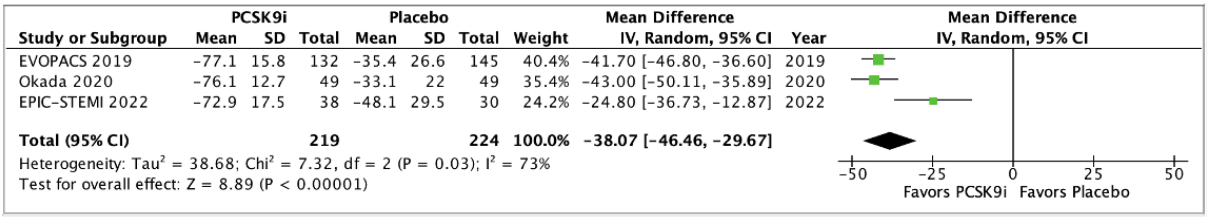

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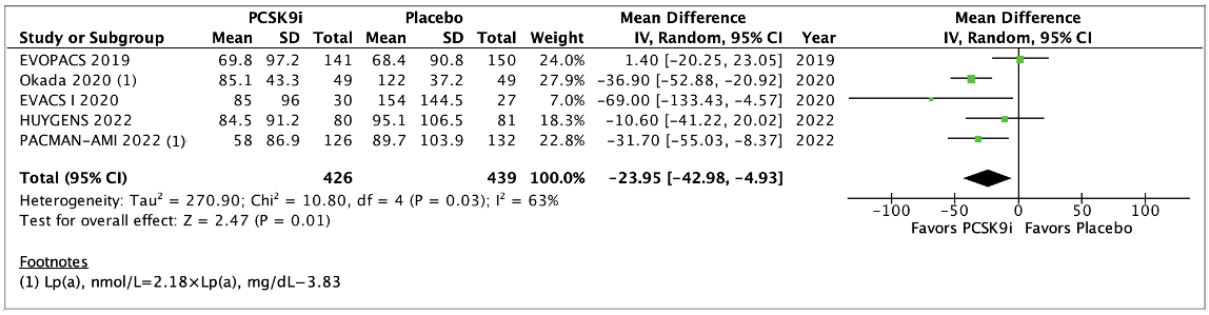

Figure 3

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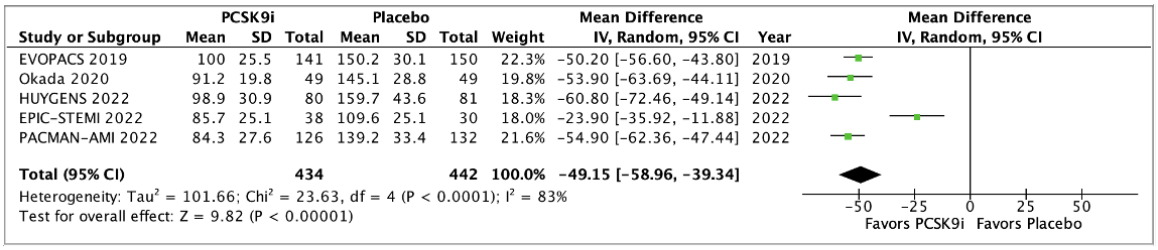

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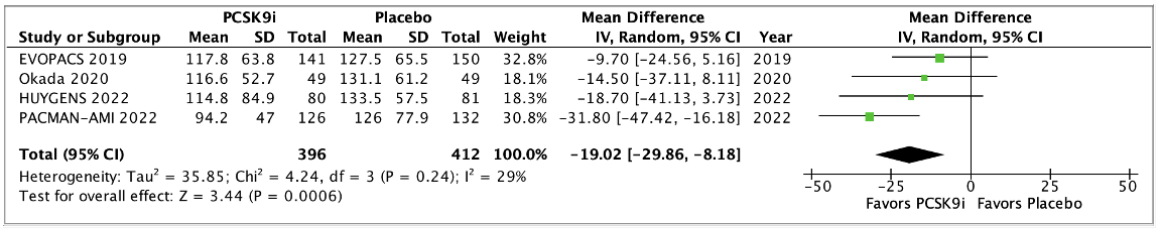

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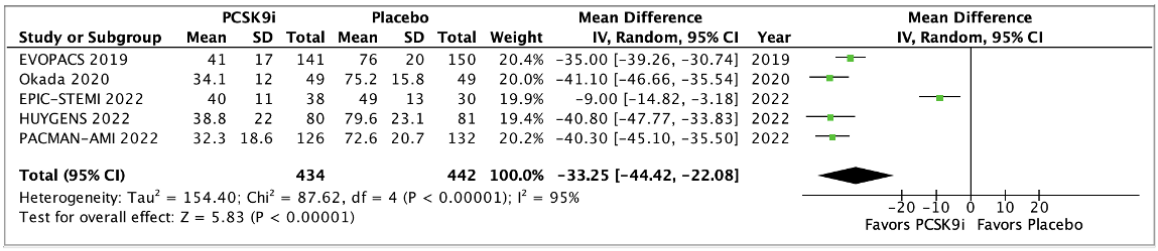

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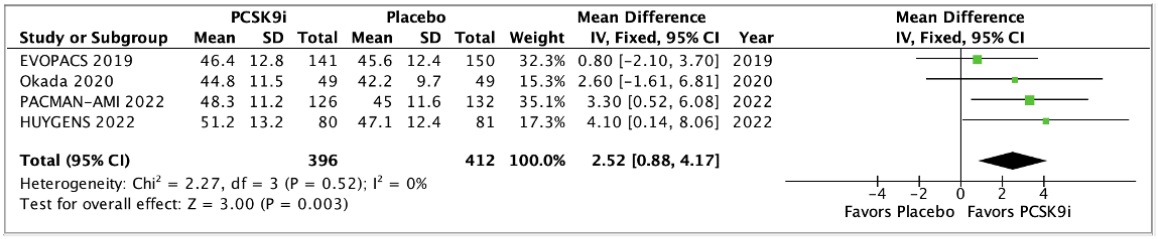

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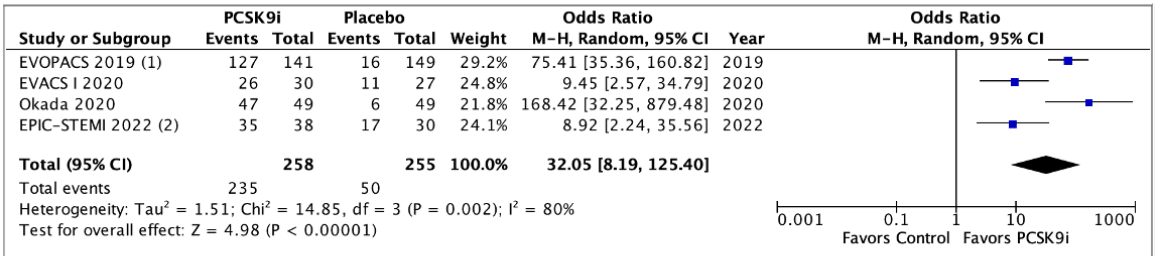
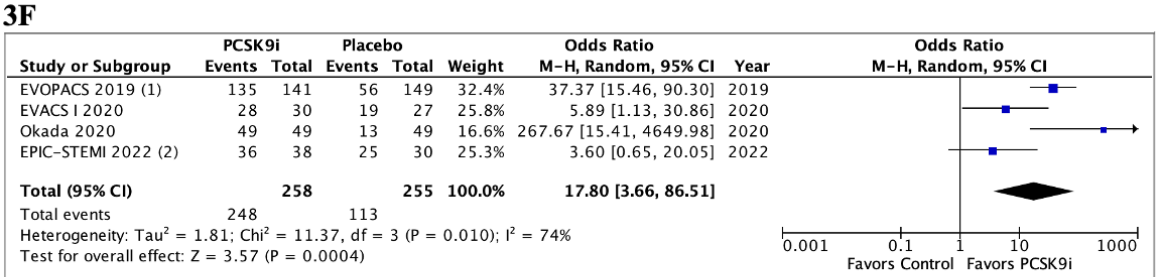


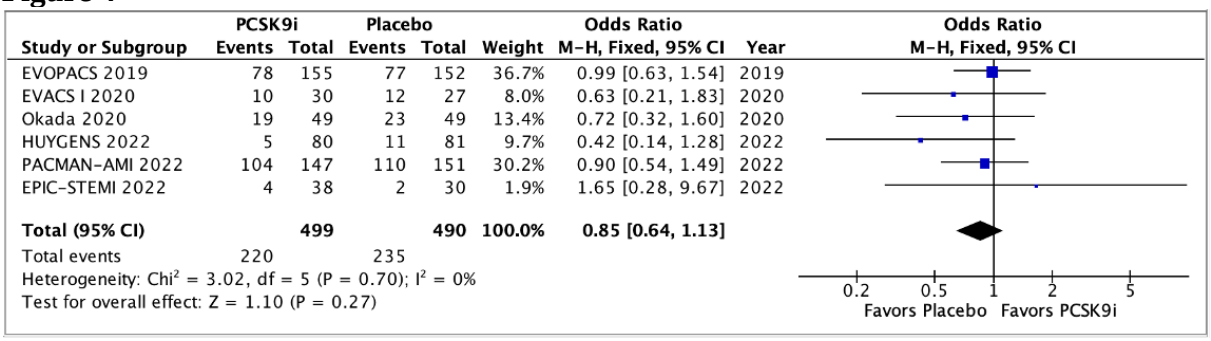
Footnotes
(1) 8 weeks
(2) ≤55 mg/dL; Median follow-up of 45 days

3F



Footnotes
(1) 8 weeks
(2) ≤70 mg/dL; Median follow-up of 45 days

Figure 4


PCSK9i
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
EVOPACS 2019 78 155 77 152 36.7% 0.99 [0.63, 1.54] 2019
EVACS I 2020 10 30 12 27 8.0% 0.63 [0.21, 1.83] 2020
Okada 2020 19 49 23 49 13.4% 0.72 [0.32, 1.60] 2020
HUYGENS 2022 5 80 11 81 9.7% 0.42 [0.14, 1.28] 2022
PACMAN-AMI 2022 104 147 110 151 30.2% 0.90 [0.54, 1.49] 2022
EPIC-STEMI 2022 4 38 2 30 1.9% 1.65 [0.28, 9.67] 2022
Total (95% CI) 499 490 100.0% 0.85 [0.64, 1.13]
Total events 220 235
Heterogeneity: Chi² = 3.02, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
0.2
0.5
1
2
5
Favors Placebo
Favors PCSK9i

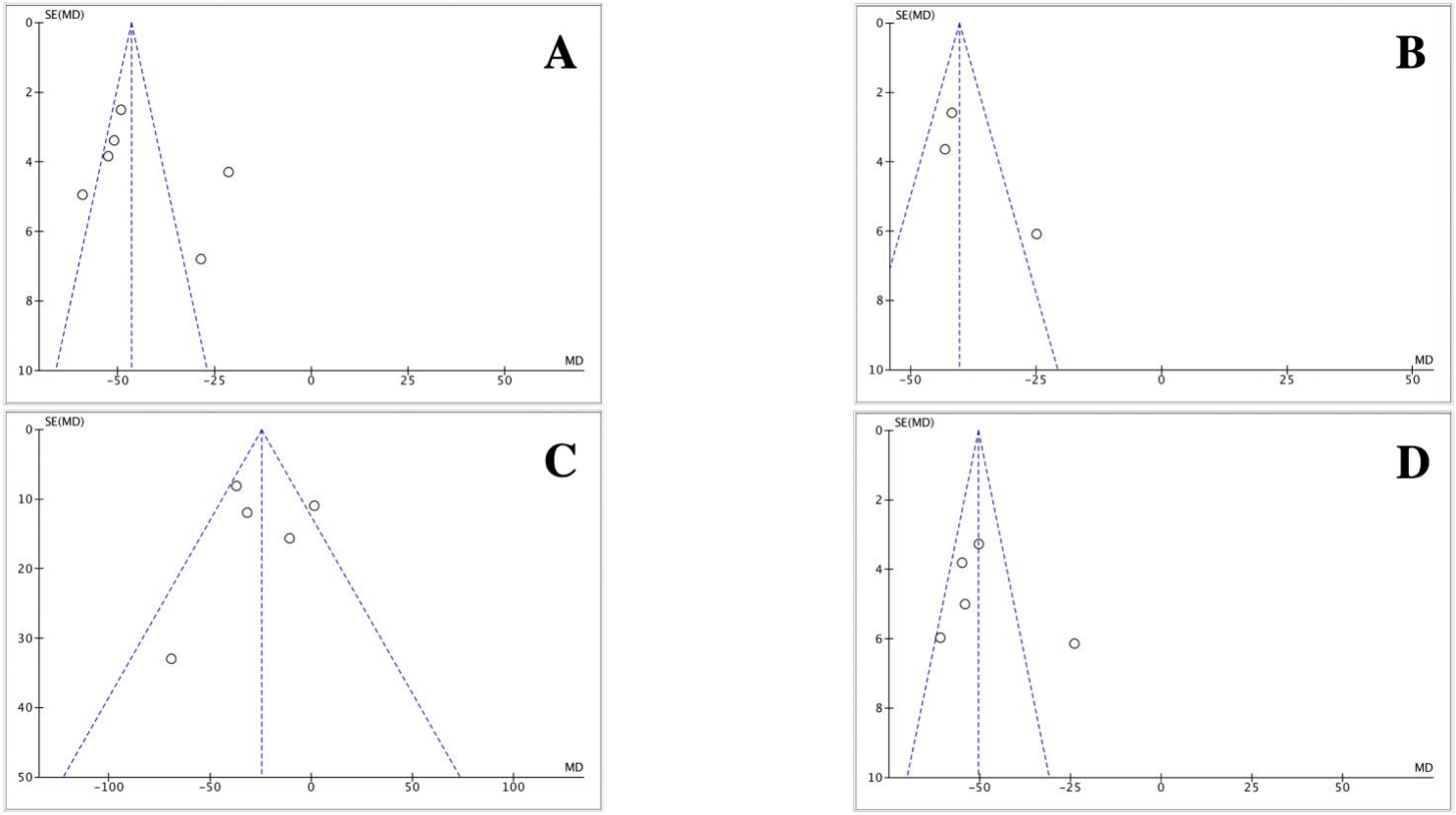
APÊNDICE

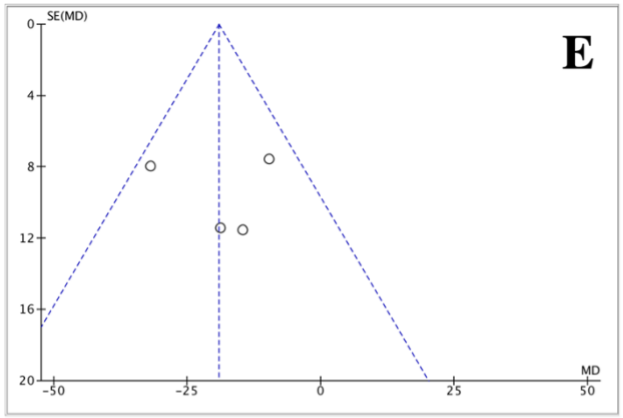
eTable 1. Risk of bias summary for randomized studies (RoB 2).

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
EVOPACS, 2019	Low	Low	Low	Low	Low	Low
EVACS I, 2020	Low	Low	Some concerns[a]	Some concerns[a]	Low	Some concerns
Okada, 2022	Low	High	Low	Low	Low	High
PACMAN-AMI, 2022	Low	Low	Low	Low	Low	Low
EPIC-STEMI, 2022	Low	Low	Low	Low	Low	Low
HUYGENS, 2022	Low	Low	Low	Some concerns	Low	Some concerns

[a] No published information available

eFigure 1. Funnel plots for LDL-C levels at follow-up (1A), % change of LDL-C from baseline (1B), Lp(a) levels at follow-up (1C), total cholesterol levels at follow-up (1D), triglycerides levels at follow-up (1E), Apo B levels at follow-up (1F), HDL-C levels at follow-up (1G), number of participants with LDL-C <55 mg/dL at 4 weeks (1H), and number of participants with LDL-C <70 mg/dL at 4 weeks (1I) and adverse events of any cause (1J) showed no definitive evidence of publication bias.

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16
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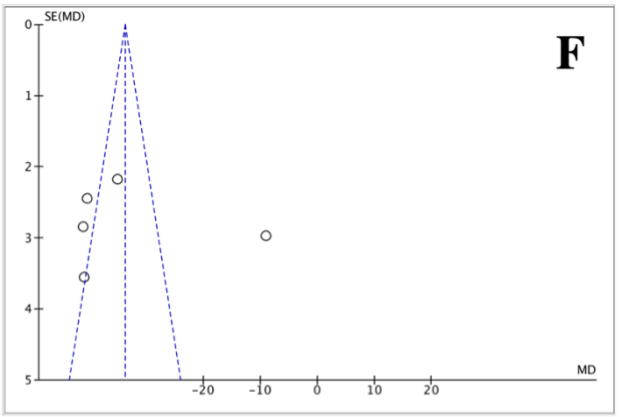
MD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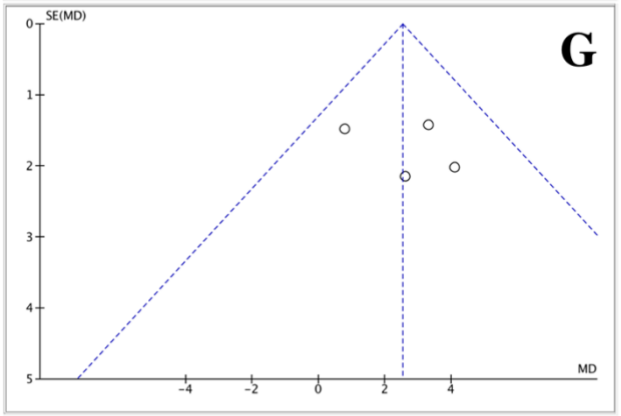
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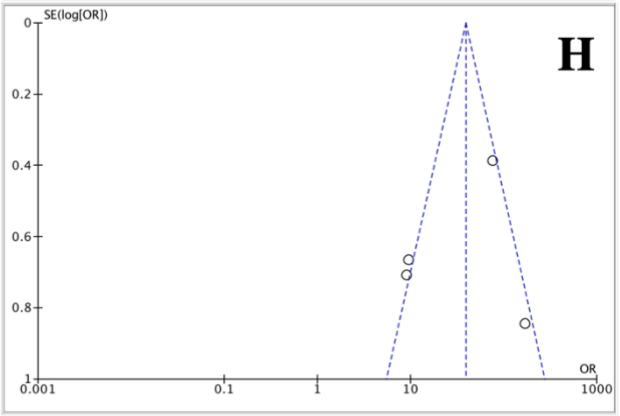
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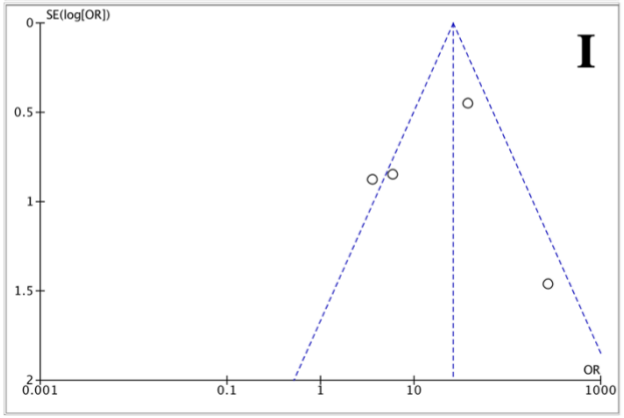
OR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0.1
1
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1000
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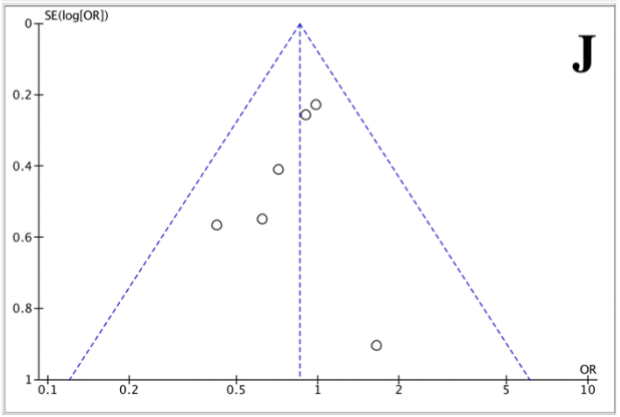
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0.2
0.4
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0.8
1
0.1
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OR

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