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Predictors of Long-Term Mortality in Patients with Myocardial Infarction and Nonobstructed Coronary Arteries: A Systematic Review and Meta-Regression Study

Francesco Pelliccia, MD, PhD,[a] Vincenzo Pasceri, MD, PhD,[b] Giampaolo Niccoli, MD, PhD,[c] Gaetano Tanzilli, MD,[a] Giulio Speciale, MD,[b] Carlo Gaudio, MD,[a] Filippo Crea, MD,[c] Paolo G Camici, MD[d]

[a]*Department of Cardiovascular Sciences, Sapienza University, Rome, Italy;* [b]*Interventional Cardiology Unit, San Filippo Neri Hospital, Rome, Italy;* [c]*Department of Cardiology, Catholic University, Rome, Italy;* [d]*San Raffaele Hospital and Vita e Salute University, Milan, Italy*

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Correspondence to:

Francesco Pelliccia, MD, PhD,

Department of Cardiovascular Sciences,

Sapienza University,

Viale del Policlinico 155, 00166 Rome - IT

Tel.: +39 348 3392006; Fax: +39 06 330 62516;

E-mail: *f.pelliccia@mclink.it*.

ABSTRACT

BACKGROUND: The long-term mortality of patients with myocardial infarction and non-obstructed coronary arteries (MINOCA) remains poorly defined. This study aimed to determine long-term mortality of patients with MINOCA and identify potential prognostic determinants of long-term outcome.

METHODS: We searched Pubmed, Embase and Cochrane databases and reviewed cited references up to December 31, 2018 to identify studies with > 6 months follow-up data.

RESULTS: We selected 44 studies including 36,932 patients (20,052 women and 16,880 men). During a median follow-up of 25 months (interquartile range: 23-39 months), 1,409 patients had died (3.8%). Overall, annual mortality rate was 2.0% (95% CI: 1.5% to 2.4%) with significant heterogeneity (I^2=80%, P<0.001). Meta-analysis of the 26 studies comparing patients with MINOCA with those with myocardial infarction and obstructive coronary artery disease showed that annual rates of long-term total mortality were 2.2% (95% CI: 1.7-2.7%) and 5.0% (95% CI: 4.1-5,9%) respectively, with a significant difference between the two groups (Relative Risk: 0.60, 95% CI: 0.46-0.78, p<0.001). Meta-regression analysis demonstrated that normal ejection fraction (p=<0.0001) and normal coronary arteries at angiography (p=0.004) were inversely related to long-term mortality whilst use of beta-blockers during follow-up (p=0.010) and ST depression on the admission electrocardiogram (p=0.016) were directly related with worse outcome.

CONCLUSIONS: The long-term mortality after MINOCA is lower than that in patients with myocardial infarction and obstructive coronary artery disease, but it is not trivial. Reduced ejection fraction, non-obstructive coronary artery disease, use of beta-blockers during follow up and ST depression on the admission electrocardiogram are

significant predictors of long-term prognosis. (PROSPERO registration number CRD42019117042)

Keywords: Coronary artery disease; myocardial infarction; MINOCA; prognosis.

INTRODUCTION

Myocardial infarction with non-obstructed coronary arteries (MINOCA) is a syndrome with different causes, characterized by clinical evidence of myocardial infarction with angiographically normal or near-normal coronary arteries (stenosis<50%).[1,2] Despite recent progress in the understanding of its pathophysiology and clinical correlates,[3,4] the long-term outcome of MINOCA patients remains controversial. Smilowitz et al. reported a more favorable prognosis for patients with MINOCA compared with patients with myocardial infarction and obstructive coronary artery disease,[5] although Pasupathy et al. demonstrated that the prognosis of MINOCA is less benign than previously thought with in-hospital and 1-year mortality rates of 0.9% and 4.7% respectively.[6] Furthermore, in a retrospective analysis of a multicenter trial, Planer et al. showed that patients with MINOCA had a higher adjusted risk of mortality at 1 year compared with patients with non-ST elevation myocardial infarction and coronary artery disease (5.2 vs. 1.6%).[7] Along with the current uncertainty about the long-term prognosis of MINOCA, it is also unclear whether, as suggested by Montone et al.,[8] any of the clinical features at admission could be used to predict the subsequent long-term prognosis.

Based on an updated systematic review and meta-regression analysis of studies including patients with MINOCA, we aimed to determine the long-term mortality of these patients and identify potential prognostic determinants of their long-term outcome.

METHODS

This systematic review was conducted according to current guidelines, including the Cochrane Collaboration and Meta-analysis Of Observational Studies in

Epidemiology,[9] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocols.[10] The review protocol was registered on the PROSPERO international prospective register of systematic reviews (Centre for Reviews and Dissemination, University of York, registration number CRD42019117042).[11] Also, the protocol was approved (No. 2018/D/411) by the Institutional Review Board Committee of the Department of Cardiovascular Sciences of the Sapienza University, Rome, Italy.

Search Strategy

We searched PubMed, Embase, and Cochrane databases up to December 31st, 2018. Multiple search key-words were used, including 'myocardial infarction', 'heart attack', 'normal coronary arteries', 'non obstructive', 'coronary stenosis', 'arteriosclerosis'. A full search through the bibliography of published trials, meta-analyses and reviews was also performed, including studies presented or published in other languages. In addition, we searched the presentations at major cardiovascular scientific sessions, including meetings of the American College of Cardiology, American Heart Association and European Society of Cardiology.

Inclusion and Exclusion Criteria

The definition of MINOCA implied clinical evidence of myocardial infarction and angiographic demonstration of non-obstructive coronary artery disease, i.e. coronary stenosis less than 50% of luminal diameter. Studies were selected according to the following pre-specified inclusion criteria: (a) diagnosis of myocardial infarction, based on typical symptoms, elevation of at least one necrosis biomarker and ST-segment or T-wave changes on the 12-lead electrocardiogram (12); (b) invasive coronary

angiography for a comprehensive anatomic characterization of the epicardial coronary arteries (i.e. presence vs. absence of obstructive coronary artery disease). Exclusion criteria were: (a) coronary angiography not available at the time of the initial diagnosis; (b) diagnosis of Takotsubo syndrome; (c) follow-up duration<6 months; (d) duplicate reporting, in which case the manuscript reporting the largest sample of patients with MINOCA was selected, or, if equal, the study with the largest number of patients. To avoid possible overlap between patient cohorts, multicenter international registries were excluded. Single case reports and previous systematic reviews on MINOCA were also excluded.

Study Selection

Two un-blinded reviewers (FP and VP) first screened retrieved citations independently. Studies identified as potentially relevant based on title or abstract were selected for full review. The reviewers independently assessed these investigations for eligibility based on the above-mentioned inclusion and exclusion criteria. Disagreement was resolved by consensus with third party adjudication. After excluding duplicates, studies were screened to identify potentially suitable articles that should be assessed for eligibility as full-text.

End-Points

The primary objectives of this study were: (a) overall mortality during long-term follow-up; (b) clinical features at presentation, including age, sex, cardiovascular risk factors, co-morbidities, biomarkers, electrocardiographic findings, ejection fraction and pharmacologic treatment. Accordingly, data for these end points were collected from each selected study. Absolute numbers were re-calculated when percentages

were reported. Data were extracted onto standard spreadsheets which included date of study publication, years of enrolment, duration of follow-up, demographics, clinical characteristics at admission, and clinical outcome, as previously defined. Methodological study quality was assessed using the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) checklist of 22 items.[12]

Statistical Analysis

Continuous variables were reported as means ± standard deviation, while skewed data were described as medians ± interquartile range. Statistical analyses were performed with R software 3.4.0 (The R Foundation for Statistical Computing) using the Metafor Package.[13] We tested heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I^2 statistics (significant heterogeneity was considered present for p values <0.10 and/or an I^2>50%).[14] Random effects meta-regression analysis was carried out to measure the impact of baseline characteristics on the effect size for the pre-specified outcome (i.e. long-term total mortality).[15] We used a random effects method since it did not assume that a true effect is common to all studies. Sensitivity analysis included a leave-one-out analysis to assess whether the pooled results were influenced by a single investigation. We performed several sub-group analyses to take into account the following parameters: (1) study sample size (large if >100 patients or small if <100 patients); (2) different geographical areas; (3) duration of follow-up (those with a follow-up<5 years as opposed to those with a mean follow-up>5 years); (4) year of publication (those published in 2008-2018 as opposed to those published more than 10 years ago, i.e. 2007 or earlier). Presence of publication bias was estimated using

the Rucker test (with arcsine transformation) which is best suited for binary outcomes and funnel plot graph.[16] Statistical significance was set at $p< 0.05$ (two-tailed).

RESULTS

Search Results

The process of study selection (Figure 1) allowed identification of 44 studies that were suitable for the meta-analysis (Supplemental references). These studies were published between 1995 and 2018 and included patient cohorts from North America, Europe, Asia, and Australia. Quality assessment by STROBE checklist disclosed a moderate quality in 25 studies and a high quality in 19 studies. Sample size ranged from 21 to 13,172 participants. Overall, 36,932 patients were included in the systematic review (Table 1). Of these 20,052 were women (54%) and 16,880 men (46%). Age of the study populations ranged from 32 to 71 years.

Clinical Characteristics

Cardiovascular risk factors were available in most studies (Supplemental table 1). Family history of cardiovascular disease, hypertension, dyslipidemia, diabetes mellitus and smoking were present in 25%,45%, 37%, 12%, and 21% of MINOCA patients, respectively. A previous myocardial infarction had occurred in 6% of patients, whereas a previous stroke or transient ischemic attack had occurred in 3% of cases. The majority of studies reported the prevalence of co-morbidities, i.e., peripheral vascular disease (1%), chronic kidney disease (2%), lung diseases (9%) as well as malignancy (3%).

Presenting features at admission were available in several studies (Supplemental table 2). ST elevation myocardial infarction was diagnosed in 20% of patients, and

non ST elevation myocardial infarction in 57% whilst in the remaining 23% the type of myocardial infarction was not reported. Markers of myocardial injury were above upper limits of normal in all studies. The mean values of troponin T or I ranged from 0.2 to 20,8 μg/L. Mean values of left ventricular ejection fraction ranged from 46% to 69% (median: 58%; 95% CI: 55% to 60%). Coronary angiography showed normal coronary arteries in 46% of patients whereas non-obstructive coronary artery disease was present in 54%. Treatment during follow-up included antiplatelet agents (acetylsalicylic acid and/or a P2Y12 receptor antagonist) in 51% of cases, beta-adrenoceptor blocking agents in 46%, angiotensin converting enzyme inhibitor/angiotensin receptor blockers in 38%, and statins in 43%.

Main Clinical Outcomes

All the 44 studies assessed post-discharge outcome for a minimum of 6 months. Follow-up ranged from 6 to 125 months (median: 25 months; interquartile range: 23-39 months). Overall, 1,409 out of 36,932 patients died (3.8%)(Table 1). Annual mortality rate was 2.0% (95% CI: 1.5% to 2.4%) with significant heterogeneity amongst studies (I^2=80%, P<0.001)(Figure 2).

In the 26 studies comparing outcome in patients with MINOCA vs. those with myocardial infarction and obstructive coronary artery disease, annual mortality rates were 2.2% (95% CI: 1.7% to 2.7%) in MINOCA and 5.0% (95% CI: 4.1% to 5,9%) in patients with myocardial infarction and obstructive coronary artery disease (Supplemental table 3), resulting in a significant difference between the two groups (Relative Risk: 0.60, 95% confidence intervals: 0.46 to 0.78, p<0.001)(Figure 3).

Meta-Regression

Meta-regressions analysis demonstrated: (1) an inverse relation between long-term mortality and both ejection fraction (p=<0.0001; coefficient: -0.001; 95% CI: from 0.000 to 0.001) and the angiographic finding of normal coronary arteries (p=0.004; coefficient: 0.001; 95% CI: from -0.000 to 0.001); and, (2) a direct relation between higher mortality and both beta-blocker therapy during follow-up (p=0.010; coefficient: 0.000; 95% CI: from -0.000 to 0.001) and occurrence of ST depression at admission (p=0.016; coefficient: 0.000; 95% CI: from 0.000 to 0.001)(Figure 4). Conversely, no association was found between long-term mortality and age, sex, cardiovascular risk factors, chronic kidney disease, and duration of follow-up (Table 2).

Sensitivity and Funnel Plot Analyses

The leave-one-out analysis showed that pooled results were not influenced by a single trial, not even the larger studies by Johnston et al.,[17] Nordenskjold et al.,[18] Baineyet al.,[19] and Dey et al.[20] In addition, none of the parameters considered in the sub-analyses (duration of follow-up, age> 60 years, sample size, geographical areas, or year of publication) was found to affect the results of the meta-analysis. Rucker's test did not suggest publication bias (P=0.48 for long-term mortality). Funnel plot analysis showed no asymmetry suggesting a significant risk of publication bias, and that the long-term mortality did not depend on the size of the studies (Figure 5).

DISCUSSION

The present analysis provides long-term mortality data in the largest series of patients with MINOCA reported so far. Indeed, our systematic review of 44 investigations allows to describe the long-term post-discharge outcome of patients experiencing an episode of MINOCA in a very large cohort of patients (>36,000)

pooled from observational studies carried out in North America, Europe, Asia, and Australia. The study's main findings were a) long-term mortality rates in patients with MINOCA are not trivial; b) some presenting features, i.e. reduced ejection fraction at presentation, angiographic evidence of non-obstructive coronary artery disease, indication to beta-blockers at discharge, and electrocardiographic evidence of non-ST elevation at admission, are significantly associated with an unfavorable long-term prognosis.

Long-Term Outcome

Annual rate of mortality for the MINOCA patients during a median follow-up period of 25 months was 2.0%, a figure which is lower than that reported in a previous meta-analysis where one-year mortality was 4.7%.[6] Our findings, conversely, are in line with several previous reports. Bugiardini et al. reported a 2% yearly mortality rate in a large cohort of patients with acute coronary syndromes without obstructive coronary artery disease that were included in a series of international multicenter studies.[21] Similar findings have been reported in large-scale trial sub-studies on MINOCA, such as CRUSADE (2% rate of death or recurrent myocardial infarction) and PURSUIT (2.2% rate of death or recurrent myocardial infarction at six months).[22] Therefore, the common assumption that non-obstructive coronary artery disease carries a good prognosis is incorrect. Indeed, the yearly mortality rate in MINOCA is considerably higher than the annual mortality of 0.3% in patients with chronic angina and angiographically non-obstructed coronary arteries.[23] In addition, Andersson et al. have recently reported that patients with MINOCA had a worse short- and long-term survival compared with people in the general population matched for age and sex.[24] These results, therefore, suggest that patients with non-obstructive coronary artery

disease, particularly with premature myocardial infarction, warrant careful clinical surveillance.

More difficult is to compare the prognosis of patients with MINOCA as opposed to those with myocardial infarction and obstructive coronary artery disease, also in view of the different underlying pathophysiologic mechanisms. MINOCA patients form a heterogenic population with different underlying mechanisms in contrast to myocardial infarction due to coronary artery disease for which the athero-thrombotic mechanism prevails. In our study, annual mortality rates were significantly lower in patients with MINOCA as compared to those with myocardial infarction and obstructive coronary artery disease (2.2 vs 5.0%). This finding is in line with the study by Nordenskjöld et al. showing that MINOCA patients have better short and long-term prognosis than patients with myocardial infarction associated with significant coronary artery disease.[18] This is similar to what observed in patients with myocardial infarction and coronary artery disease as reported in the SWEDEHEART registry.[25] Nevertheless, the rate of long-term serious cardiovascular events are of concern considering that MINOCA patients tend to be younger and have less co-morbidities than patients with myocardial infarction related to coronary artery disease.[6,26]

Factors Associated With Long-Term Outcome

Left ventricular ejection fraction was the factor most closely related to a poor prognosis. Although this is a novel finding for MINOCA patients, it is in keeping with the well-recognized predictive role of cardiac dysfunction after myocardial infarction. In the HORIZONS-AMI cohort, predictors of new-onset heart failure at two years were a history of myocardial infarction, ejection fraction, female sex and diabetes.[27]

Similarly, in the CARE and VALIANT trials, predictors of poor prognosis were age, diabetes, renal insufficiency, left ventricular ejection fraction, and Killip class.[28,29] Our meta-regression analysis indicates that angiographic evidence of normal 'smooth' coronary arteries is associated with a better prognosis. This is in line with previous reports showing that, among patients without obstructive coronary artery disease, those with normal coronary arteries may carry a lower risk than the subjects with atherosclerotic disease albeit non-obstructive.[30,31] The latter group might represent a different population of younger patients with a possible tendency for spontaneous thrombosis and other etiologies leading to coronary artery disease (i.e., variant angina pectoris, microvascular dysfunction, and coronary vasospasm).[3,6,32] Our results differ from the ASPECT[33] and ADAPT[34] data showing that, despite being more likely to have cardiovascular risk factors, those with non-obstructive coronary artery disease were no more likely to have adverse events than those with normal angiograms. Similarly, Rossini et al. studied unselected consecutive patients presenting with acute coronary syndrome and found no differences in the incidence of major acute cardiac events between patients with normal coronary arteries (0% stenosis) and those with mild coronary artery disease (stenosis<50%) at long-term follow-up.[35] Conversely, our results are in agreement with previous studies demonstrating that prognosis in patients with MINOCA depends on the angiographic findings at index hospitalization, with very few ischemic events at long-term follow-up in those having non diseased vessels.[30,31] This might relates to the total atherosclerotic burden which, however, is often overlooked at conventional angiography with respect to assessment with newer computed tomography angiography.[36,37] In MINOCA patients with documented myocardial scar tissue at cardiac magnetic resonance, Aldrovandi et al. reported coronary artery disease in

84% of cases.[36] Also, Amhadi et al. showed that mortality rates in patients with MINOCA were related to the type of atherosclerotic plaques, i.e. calcified plaque (1.4%), mixed plaque (3.3%) and non-calcified plaque (9.6%).[37]

In our series, use of beta-blockers was associated with a worse outcome. This finding might couple with the evidence that a poor left ventricular function, which constitutes a class I indication to beta-blocker agents, was of prognostic significance. Of interest, we found a very low utilization of conventional cardioprotective medications, [38] with only 38% of patients receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blockers and 43% having statins. These two pharmacologic classes have been shown in a recent Swedish observational study to be the most effective pharmacologic treatments in reducing cardiac events in MINOCA, with dual antiplatelet therapy showing only a neutral effect.[25] Thus, the possibility exists that patients with lower ejection fraction were also more likely to be treated with a beta-blocking agent.

Limitations

Our study has limitations intrinsic to any study-level meta-analysis. Duplicate reporting of data is a potential methodological limitation that was seriously considered. Multicenter international registries were excluded in order to avoid overlap between cohorts. Observational investigations may suffer from selection biases and systematic pooling of studies with different baseline patients' characteristics might affect results. Despite these limitations, we assessed the quality of methodology of the included studies, with the majority resulting of high quality. In addition, observational studies deal with real world populations and therefore can provide reliable scientific information. The lack of control groups including healthy

subjects or patients with acute coronary syndrome does not allow one to draw definite conclusions about differences in long term outcome between MINOCA patients and the general population or patients with chronic coronary artery disease. A major concern in the clinical definition of MINOCA is that the majority of the included studies did not carry out special diagnostic investigations to rule out the potential role of microcirculation as a cause of myocardial acute injury, nor were diagnostic tests carried out to assess the atherosclerotic burden.[8,9] Meta-analysis showed that there was significant heterogeneity in presenting features and outcome among the studies. Indeed, studies selected for this meta-analysis differ in multiple aspects (i.e. baseline characteristics, sample size, length of follow-up, etc.). However, in order to evaluate the stability of the results, we performed a 'leave-one-out' sensitivity analysis and were able to show that omission of each study did not change overall results.

Conclusions

Our update analysis of patients with a diagnosis of MINOCA shows that long-term mortality rates are not trivial, and that some presenting features (a reduced ejection fraction, malignancy, the use of beta-blockers, and the finding of ST depression) are significantly associated with an unfavorable long-term prognosis.

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Legends for figures

Figure 1. PRISMA diagram of study selection. The flow diagram demonstrates the study selection process in the systematic review and meta-analysis.

Figure 2. Forest plot showing individual and overall incidence for annual rate of total mortality - The black squares represents the weighted estimate of incidence for each single study. The sky blue diamond represents the overall estimated incidence. The vertical line represents the pooled averaged incidence estimate. Horizontal bars indicate 95% confidence intervals.

Figure 3. Forest plot of risk ratios for yearly rate of overall mortality in patients with MINOCA vs. patients with myocardial infarction associated with coronary artery disease. Markers represent point estimates of risk ratios, marker size represents study weight. Horizontal bars indicate 95% confidence intervals.

Figure 4. Meta-regression graphs showing the inverse association between long-term mortality and both ejection fraction at presentation (upper left panel) and the angiographic finding of normal coronary arteries (upper right panel), as well as the direct relation of a higher mortality with beta-blocker therapy during follow-up (lower left panel) and the electrocardiographic finding of ST depression at admission (lower right panel). Each circle size represents a study, telescoped by its weight in the analysis. The x axis shows the prevalence of each covariate. The y axis shows the incidence of long-term mortality. The regression line is calculated by the meta-regression model.

Figure 5. Funnel plot for long-term mortality. The analysis showed no asymmetry suggesting a significant risk of publication bias, and that the long-term mortality did not depend on the size of the studies.

Predictors of Long-Term Mortality in Patients with Myocardial Infarction and Nonobstructed Coronary Arteries: A Systematic Review and Meta-Regression Study

CLINICAL SIGNIFICANCE

- The long-term mortality after myocardial infarction and non-obstructed coronary arteries (MINOCA) is not trivial.
- Left ventricular ejection fraction, non-obstructive coronary artery disease, use of beta-blockers during follow up and ST depression on the admission electrocardiogram are significant predictors of long-term prognosis.
- MINOCA should not be regarded as a benign condition and therefore patients should receive the same clinical attention as patients with myocardial infarction due to coronary artery disease.

Table 1. Demographics and rates of long-term outcome in the overall population

n	Author	Year	Reference	Country	Patients (n)	Female sex (n)	Mean age (years
1.	William MJA	2018	Heart 2018 Sep 29	New Zealand	897	487	63
2.	Ciliberti G	2018	Int J Cardiol 2018;267:41-45	Italy	150	63	63
3.	Montenegro Sá	2018	Coron Artery Dis 2018;29:511-515	Portugal	114	67	64
4.	Safdar B	2018	J Am Heart Assoc 2018; 28;7	U.S.	290	269	46
5.	Raparelli V	2018	Can J Cardiol 2018;34:468-476	Canada	82	34	49
6.	Bainey KR	2018	Int J Cardiol 2018;264:12-17	Canada	2092	1108	59
7.	Nordenskjöld AM	2018	Int J Cardiol 2018;261:18-23	Sweden	9092	5637	65
8.	Montone RA	2018	Eur Heart J 2018;39:91-98	Italy	80	40	63
9.	Andersson HB	2018	Eur Heart J 2018;39:102-110	Denmark	554	212	60
10	Barr PR	2018	Heart Lung Circ 2018;27:165-174	New Zealand	302	151	56
11	Rallidis LS	2017	Am J Cardiol 2017; 120:740-746	Greece	60	-	32
12	Ohlow MA	2015	Am J Emerg Med 2015;33:150–154	Germany	272	134	62
13	Johnston	2015	Am J Cardiol2015;115:1661-1666	Sweden	13172	7324	62
14	Aldous S	2015	Heart Lung Circ 2015;24:869-78	New Zealand	351	185	56
15	Planer D	2014	CircCardiovascInterv 2014;7:285–293	International	197	105	54
16	Manfrini O	2014	Am J Cardiol 2014;113:1628–1633	U.K.	350	114	71
17	Larsen AI	2013	Am J Cardiol 2013;111:643-648	International	127	38	57
18	Rossini R	2013	Am J Cardiol 2013;112:150-155	Italy	318	173	66
19	Collste O	2013	J Intern Med 2013; 273: 189e196.	Sweden	176	112	58
20	Gerbaud E	2012	Int J Cardiov Imaging 2012; 28: 783e794	France	130	63	54
21	Sun J	2012	Coron Artery Dis 2012;23:162–166	China	51	20	57
22	Rhew SH	2012	Chonnam Med J 2012;48:39–46	Korea	100	41	58
23	Abid L	2012	Intern Med 2012;51:1959–1967	Tunisia	21	2	45
24	Hansen KW	2012	Eur J PrevCardiol 2012;19:746–754	Denmark	1595	834	62
25	Mahmoudi M	2012	Br J Radiol 2012; 85: e461-6	U.K.	91	54	53
26	Kang WY	2011	Int J Cardiol 2011;146:207–212	Korea	372	145	59
27	Chopard R	2011	Arch Cardiovasc Dis 2011; 104: 509-517	France	87	52	53
28	Ramanath VS	2010	ClinCardiol 2010;33:36–41	U.S.	123	66	58
29	Frycz-Kurek AM	2010	Kardiol Pol 2010; 68:1211-1217	Poland	972	436	58
30	Cortell A	2009	Rev Esp Cardiol 2009;62:1260–1266	Spain	64	37	60
31	Dey S	2009	Heart 2009;95:20–26	International	2031	921	-
32	Dwyer JP	2008	Int J Cardiol 2008;129:394–398	Australia	29	10	59

33	Eitel I	2008	Eur Heart J 2008; 29: 2651-2659	Germany	59	53	70
34	Ahmar W	2008	Int J Cardiol 2008; 128:131-133	Australia	41	12	44
35	Terefe YG	2007	Coron Artery Dis 2007;18:621–626	U.S.	58	31	55
36	Bugiardini R	2006	Arch Intern Med 2006;166:1391–1395	International	701	372	58
37	Christiansen JP	2006	Am J Cardiol 2006; 97: 768-771	New Zealand	23	8	54
38	Dokainish H	2005	J Am Coll Cardiol 2005;45:19–24	U.S.	32	16	60
39	Germing A	2005	Int J Cardiol 2005;99:19–23	Germany	76	22	53
40	Larsen AI	2005	Am J Cardiol 2005;95:261–263	Canada	725	103	49
41	Golzio PG	2004	Ital Heart J 2004;5:732–738	Italy	53	10	45
42	Da Costa A	2001	Eur Heart J 2001;22:1459–1465	France	91	34	50
43	Ammann P	2000	Chest 2000; 117: 333-338	Switzerland	21	6	42
44	Zimmerman FH	1995	J Am Coll Cardiol 1995; 26: 654-661	U.S./Canada	720	271	-

F/U: Follow-up; mo.: months; n.: number.

Table 2. Meta-regression analysis of the effects of presenting features on long-term mortality

Variable	Coefficient	95% C.I.	P
Follow-up duration	0.001	-0.001 0.001	0.115
Female sex	0.022	-0.000 -0.000	0.81
Age	0.001	-0.000 - 0.001	0.180
Family history	0.000	-0.000 -0.000	0.990
Hypertension	0.000	-0.000-0.001	0.340
Hyperlipidemia	0.000	-0.001 -0.000	0.740
Diabetes mellitus	0.000	-0.000-0.001	0.320
Smoking	0.000	-0.000 - 0.000	0.850
Previous MI	-0.001	-0.001 -0.001	0.990
Previous stroke/TIA	0.001	-0.001 -0.002	0.520
Peripheral vascular disease	-0.001	-0.002 -0.001	0.280
Chronic kidney disease	0.000	-0.001 -0.001	0.920
Lung disease	0.000	0.001-0.003	0.380
Malignancy	0.003	0.000 - 0.007	0.400
STEMI – ST elevation	0.000	-0.001-0.000	0.290
NSTEMI – ST downsloping	0.000	0.000-0.001	0.016
Ejection fraction	-0.001	0.000-0.001	<0.0001
Troponin	0.000	-0.001 -0.002	0.620

Coronary stenosis<50%	0.001	-0.001 -0.001	0.004
ASA and/or P2Y12 blocker	0.000	-0.000-0.000	0.100
Beta-blockers	0.000	-0.000 - 0.001	0.010
ACE-I or ARB	0.000	-0.000-0.001	0.080
Statin	0.001	-0.000- 0.000	0.330

ACE-I= Angiotensin converting enzyme-inhibitors; ARB= Angiotensin receptor blocker; ASA= acetylsalicylic acid; C.I.= confindence interval; MI= myocardial infarction; NSTEMI= Non ST elevation myocardial infarction; STEMI= ST elevation myocardial infarction; TIA= transient ischemic attack.

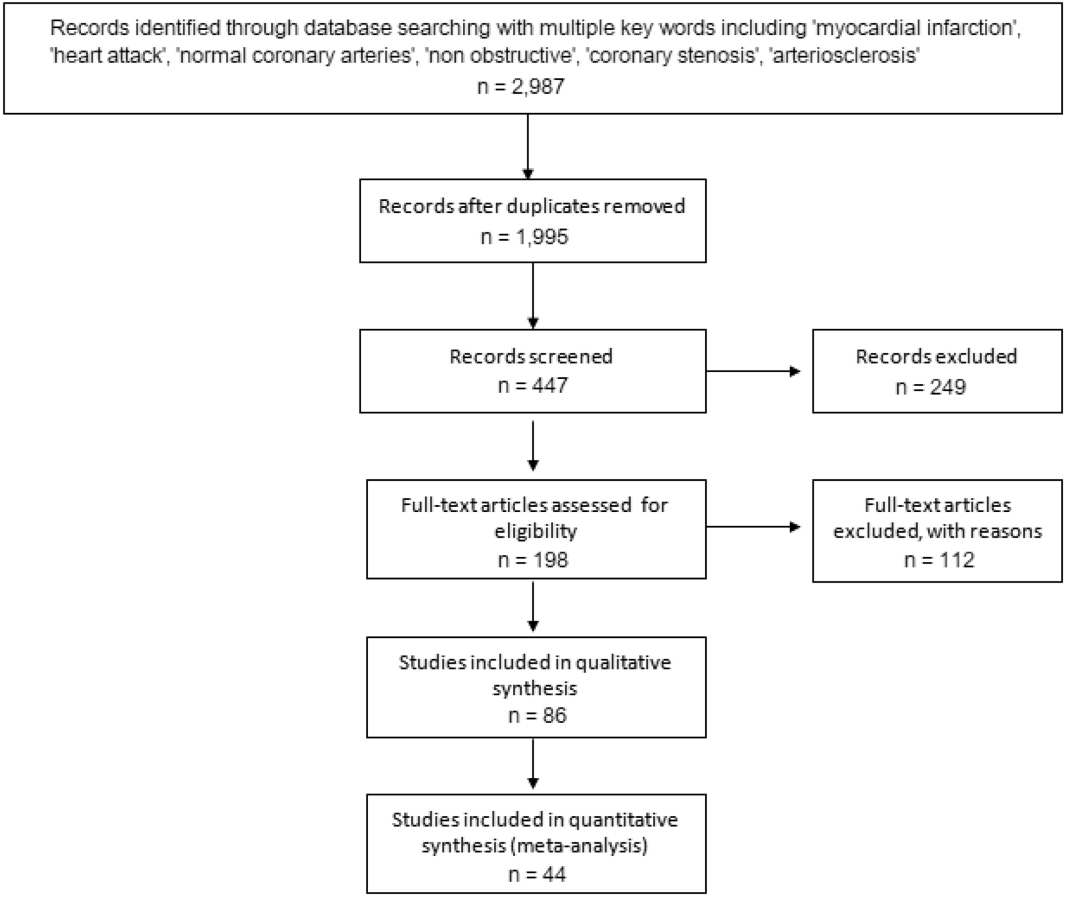

Records identified through database searching with multiple key words including 'myocardial infarction', 'heart attack', 'normal coronary arteries', 'non obstructive', 'coronary stenosis', 'arteriosclerosis'
n = 2,987
Records after duplicates removed
n = 1,995
Records screened
n = 447
Records excluded
n = 249
Full-text articles assessed for eligibility
n = 198
Full-text articles excluded, with reasons
n = 112
Studies included in qualitative synthesis
n = 86
Studies included in quantitative synthesis (meta-analysis)
n = 44

Figure 1

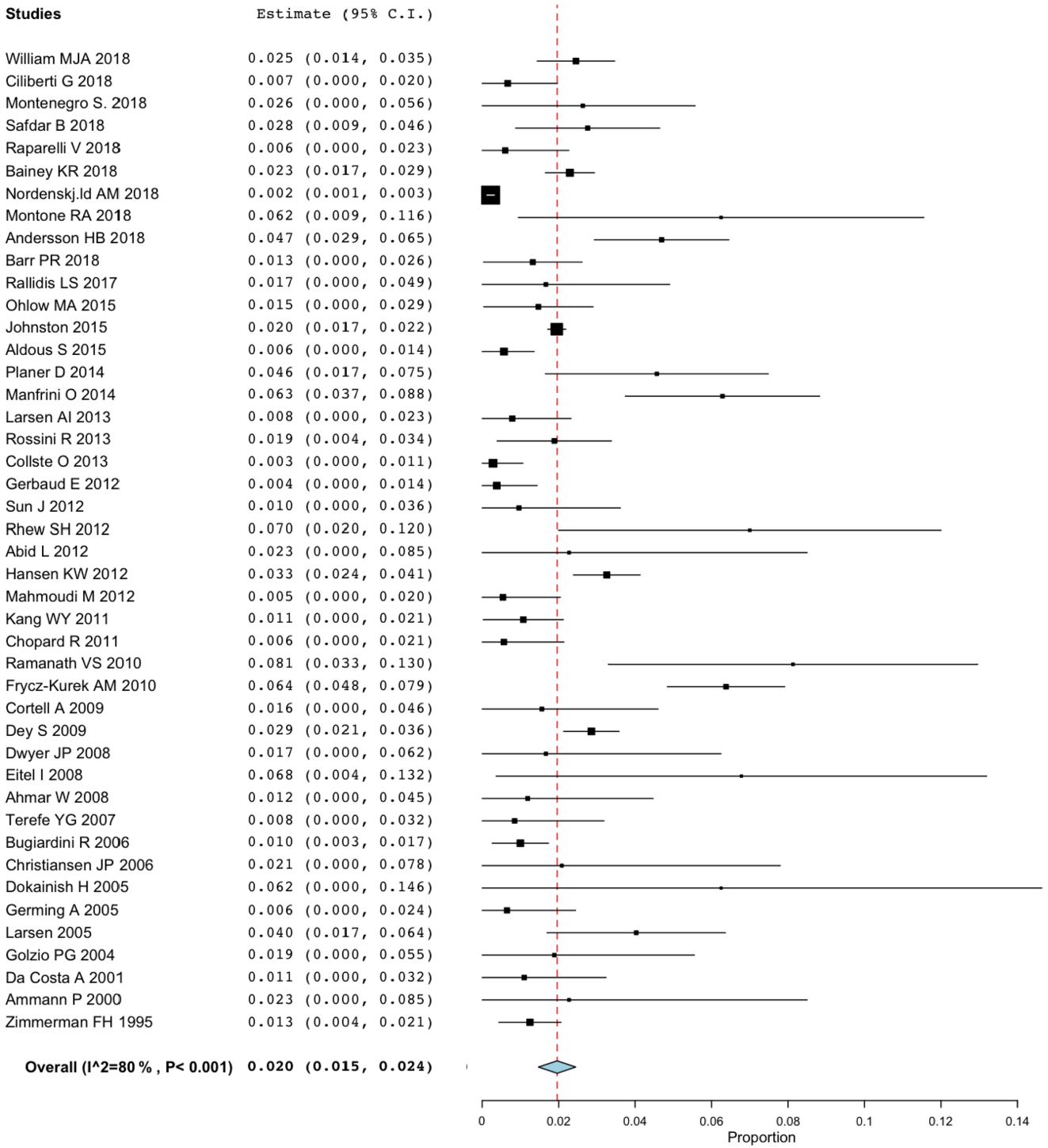

Studies
Estimate (95% C.I.)
William MJA 2018 0.025 (0.014, 0.035)
Ciliberti G 2018 0.007 (0.000, 0.020)
Montenegro S. 2018 0.026 (0.000, 0.056)
Safdar B 2018 0.028 (0.009, 0.046)
Raparelli V 2018 0.006 (0.000, 0.023)
Bainey KR 2018 0.023 (0.017, 0.029)
Nordenskj.ld AM 2018 0.002 (0.001, 0.003)
Montone RA 2018 0.062 (0.009, 0.116)
Andersson HB 2018 0.047 (0.029, 0.065)
Barr PR 2018 0.013 (0.000, 0.026)
Rallidis LS 2017 0.017 (0.000, 0.049)
Ohlow MA 2015 0.015 (0.000, 0.029)
Johnston 2015 0.020 (0.017, 0.022)
Aldous S 2015 0.006 (0.000, 0.014)
Planer D 2014 0.046 (0.017, 0.075)
Manfrini O 2014 0.063 (0.037, 0.088)
Larsen AI 2013 0.008 (0.000, 0.023)
Rossini R 2013 0.019 (0.004, 0.034)
Collste O 2013 0.003 (0.000, 0.011)
Gerbaud E 2012 0.004 (0.000, 0.014)
Sun J 2012 0.010 (0.000, 0.036)
Rhew SH 2012 0.070 (0.020, 0.120)
Abid L 2012 0.023 (0.000, 0.085)
Hansen KW 2012 0.033 (0.024, 0.041)
Mahmoudi M 2012 0.005 (0.000, 0.020)
Kang WY 2011 0.011 (0.000, 0.021)
Chopard R 2011 0.006 (0.000, 0.021)
Ramanath VS 2010 0.081 (0.033, 0.130)
Frycz-Kurek AM 2010 0.064 (0.048, 0.079)
Cortell A 2009 0.016 (0.000, 0.046)
Dey S 2009 0.029 (0.021, 0.036)
Dwyer JP 2008 0.017 (0.000, 0.062)
Eitel I 2008 0.068 (0.004, 0.132)
Ahmar W 2008 0.012 (0.000, 0.045)
Terefe YG 2007 0.008 (0.000, 0.032)
Bugiardini R 2006 0.010 (0.003, 0.017)
Christiansen JP 2006 0.021 (0.000, 0.078)
Dokainish H 2005 0.062 (0.000, 0.146)
Germing A 2005 0.006 (0.000, 0.024)
Larsen 2005 0.040 (0.017, 0.064)
Golzio PG 2004 0.019 (0.000, 0.055)
Da Costa A 2001 0.011 (0.000, 0.032)
Ammann P 2000 0.023 (0.000, 0.085)
Zimmerman FH 1995 0.013 (0.004, 0.021)
Overall (I^2=80 % , P< 0.001) 0.020 (0.015, 0.024)
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
Proportion

Figure 2

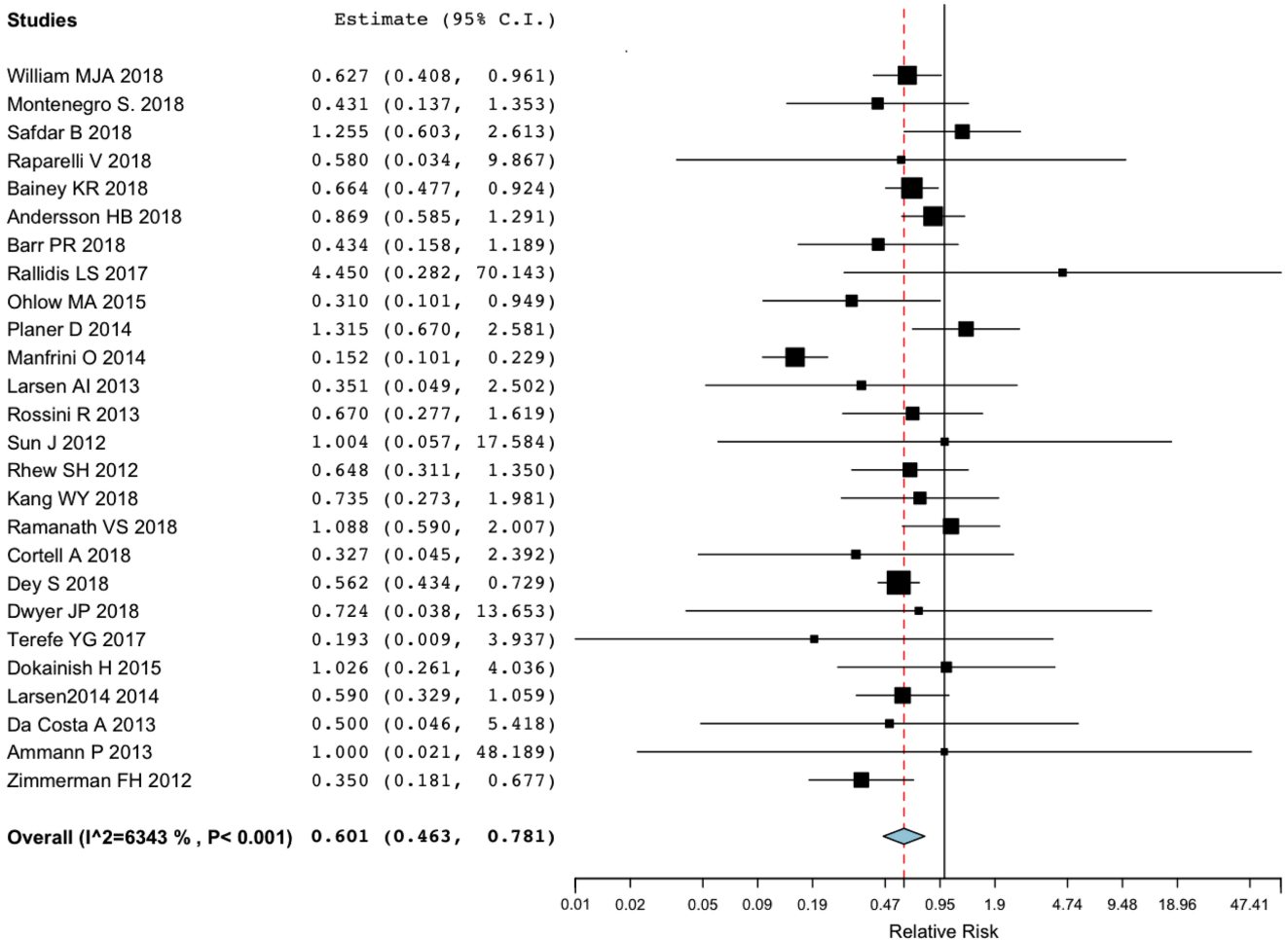
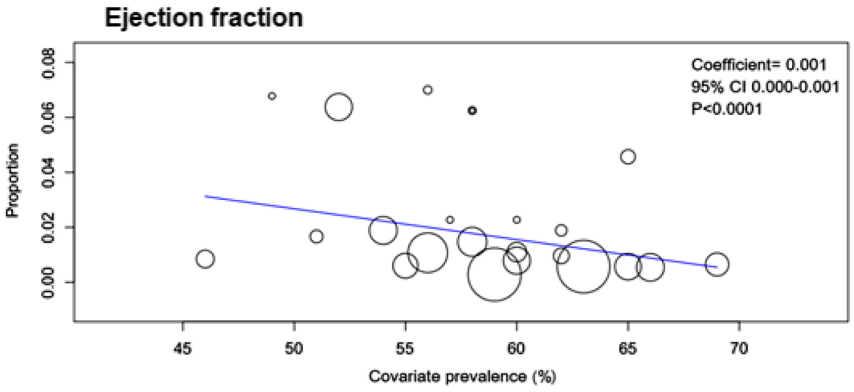
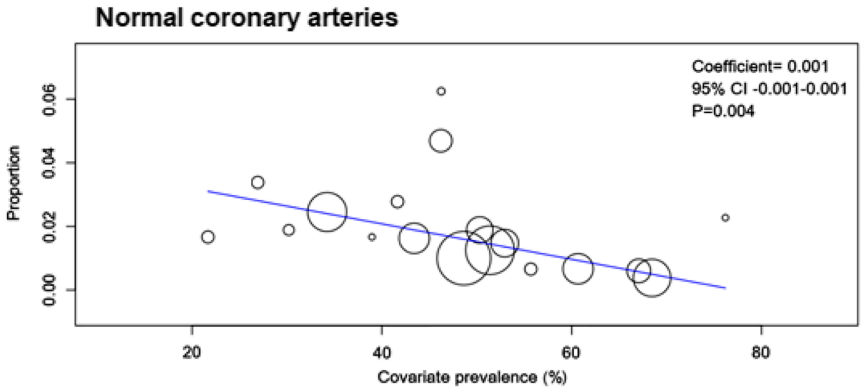
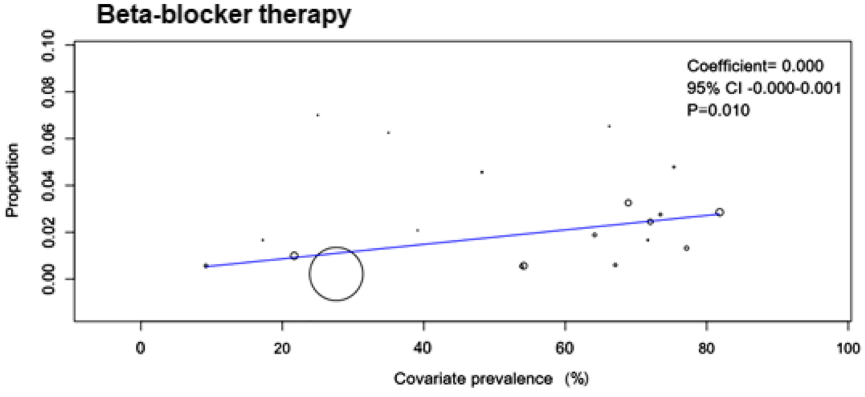

Studies
Estimate (95% C.I.)
William MJA 2018 0.627 (0.408, 0.961)
Montenegro S. 2018 0.431 (0.137, 1.353)
Safdar B 2018 1.255 (0.603, 2.613)
Raparelli V 2018 0.580 (0.034, 9.867)
Bainey KR 2018 0.664 (0.477, 0.924)
Andersson HB 2018 0.869 (0.585, 1.291)
Barr PR 2018 0.434 (0.158, 1.189)
Rallidis LS 2017 4.450 (0.282, 70.143)
Ohlow MA 2015 0.310 (0.101, 0.949)
Planer D 2014 1.315 (0.670, 2.581)
Manfrini O 2014 0.152 (0.101, 0.229)
Larsen AI 2013 0.351 (0.049, 2.502)
Rossini R 2013 0.670 (0.277, 1.619)
Sun J 2012 1.004 (0.057, 17.584)
Rhew SH 2012 0.648 (0.311, 1.350)
Kang WY 2018 0.735 (0.273, 1.981)
Ramanath VS 2018 1.088 (0.590, 2.007)
Cortell A 2018 0.327 (0.045, 2.392)
Dey S 2018 0.562 (0.434, 0.729)
Dwyer JP 2018 0.724 (0.038, 13.653)
Terefe YG 2017 0.193 (0.009, 3.937)
Dokainish H 2015 1.026 (0.261, 4.036)
Larsen2014 2014 0.590 (0.329, 1.059)
Da Costa A 2013 0.500 (0.046, 5.418)
Ammann P 2013 1.000 (0.021, 48.189)
Zimmerman FH 2012 0.350 (0.181, 0.677)
Overall (I^2=6343 % , P< 0.001) 0.601 (0.463, 0.781)
0.01 0.02 0.05 0.09 0.19 0.47 0.95 1.9 4.74 9.48 18.96 47.41
Relative Risk

Figure 3


Ejection fraction
Coefficient= 0.001
95% CI 0.000-0.001
P<0.0001
Proportion
0.00
0.02
0.04
0.06
0.08
45
50
55
60
65
70
Covariate prevalence (%)


Normal coronary arteries
Coefficient= 0.001
95% CI -0.001-0.001
P=0.004
Proportion
0.00
0.02
0.04
0.06
20
40
60
80
Covariate prevalence (%)


Beta-blocker therapy
Coefficient= 0.000
95% CI -0.000-0.001
P=0.010
Proportion
0.00
0.02
0.04
0.06
0.08
0.10
0
20
40
60
80
100
Covariate prevalence (%)

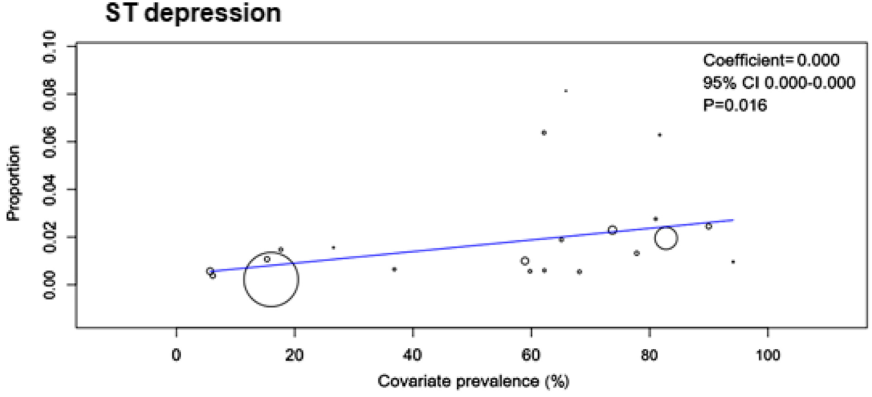

ST depression
Coefficient= 0.000
95% CI 0.000-0.000
P=0.016
Proportion
0.00
0.02
0.04
0.06
0.08
0.10
0
20
40
60
80
100
Covariate prevalence (%)

Figure 4

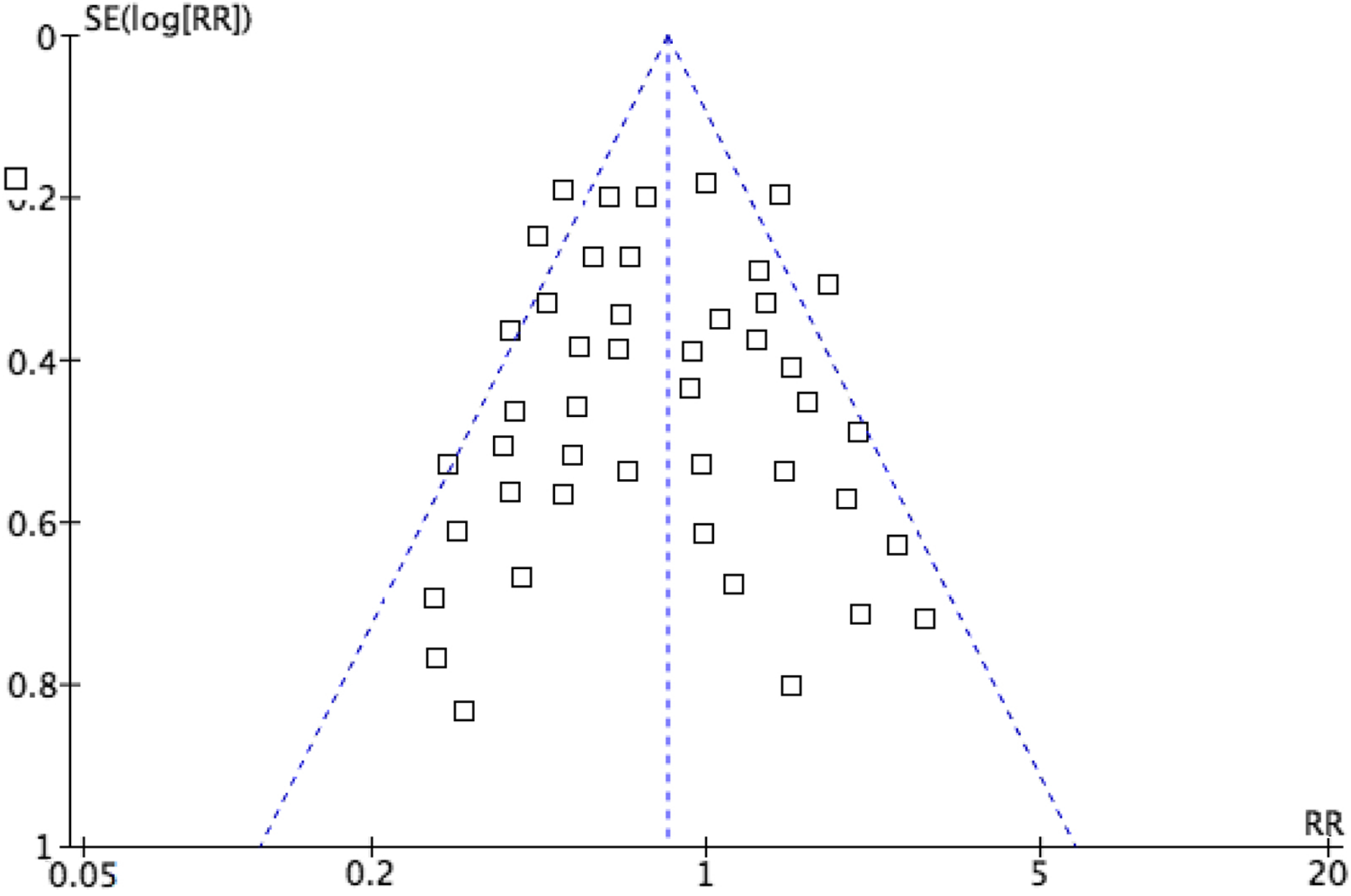


Figure 5