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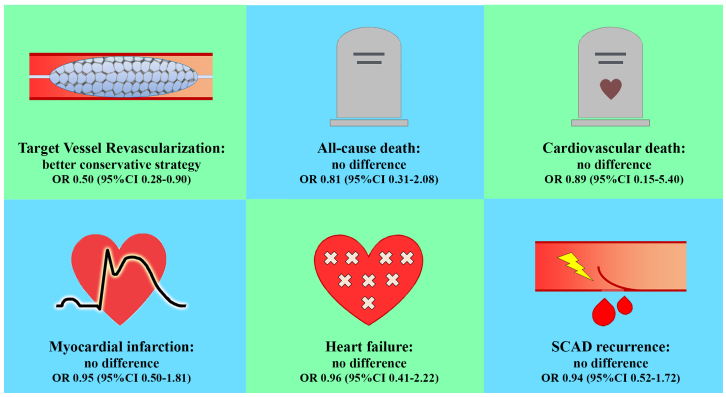

Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study

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ABSTRACT

Background. Data regarding the best treatment for spontaneous coronary artery dissection (SCAD) are scarce. **The** aim of the present study was to compare the **clinical outcomes** of conservative *versus* invasive treatment in SCAD patients.

Methods. We systematically searched the literature for studies evaluating the comparative efficacy and safety of invasive revascularization *versus* medical therapy for the treatment of SCAD from 1990 to 2020. The study endpoints were all-cause death, cardiovascular death, myocardial infarction, heart failure, SCAD recurrence and target vessel revascularization (TVR) rates. Random-effect meta-analysis was performed comparing the clinical outcomes between the two groups. A univariate meta-regression analysis was also performed.

Results. 24 observational studies with 1720 patients were included. After 28±14 months, a conservative approach was associated with **lower** TVR rate compared with invasive treatment (OR=0.50; 95%CI 0.28-0.90; P=0.02). No statistical difference was found regarding all-cause death (OR=0.81; 95%CI 0.31–2.08; P=0.66), cardiovascular death (OR=0.89; 95%CI 0.15–5.40; P=0.89), myocardial infarction (OR=0.95; 95%CI 0.50-1.81; P=0.87), heart failure (OR 0.96; 95%CI 0.41–2.22; P=0.92) and SCAD recurrence (OR=0.94; 95%CI 0.52-1.72; P=0.85). The meta-regression analysis suggested that male gender, diabetes mellitus, smoking habit, prior coronary artery disease, left main coronary artery involvement, lower ejection fraction and low TIMI flow at admission are related with higher overall mortality, whereas SCAD recurrence was higher among patients with fibromuscular dysplasia.

Conclusions. A conservative approach was associated with similar clinical outcomes and lower TVR rates compared ~~to~~ **with** an invasive strategy in SCAD patients; future prospective studies are needed to **confirm these results**.

Keywords: spontaneous coronary artery dissection; SCAD; percutaneous coronary intervention; revascularization; medical therapy.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is defined as the acute development of a false lumen within the coronary artery wall which is not secondary to iatrogenic nor traumatic insults.[1-2] Despite the true incidence of SCAD is unknown due its frequent underdiagnosis, recent reports state that it may represent up to 4% of angiographic studies performed for non-atherosclerotic acute coronary syndromes.[1-4] About 90% of SCAD patients are women, with a high SCAD prevalence of 23% to 36% among young female patients presenting with acute coronary syndromes.[1-7] Risk factors for SCAD include pregnancy and peri-partum periods, multiparity (i.e. more than 3 births), fibromuscular dysplasia, connective tissue disorders, hormonal therapy and strong mechanical and emotional stressors;[8-15] the correlation between SCAD and typical ischemic heart disease risk factors remains to be elucidated.[12-16]

SCAD treatment is debated with case series and observational and retrospective studies reporting heterogeneous outcomes.[3,4,7,11-18] The European Society of Cardiology position paper and the American Heart Association Scientific Statement on SCAD favor a conservative strategy when revascularization is not mandatory due to hemodynamic instability or ongoing ischemia;[1,2] this is mostly due to the suboptimal percutaneous coronary intervention (PCI) success and the high risk of peri- and post-procedural complications in the setting of SCAD.[12,16-18] Nevertheless, the best medical therapy and the role of invasive management are still a matter of debate. Accordingly, the aim of the present study was to compare the **clinical outcomes** of conservative versus invasive treatment in patients with SCAD.

METHODS

Study identification

We systematically searched MEDLINE/PubMed, Embase, the Cochrane database, Google Scholar, www.tctmd.com, www.clinicaltrials.gov and www.clinicaltrialresults.org for randomized controlled trials (RCTs) and observational studies that evaluated the comparative efficacy and safety of invasive revascularization *versus* medical therapy for the treatment of SCAD from database inception to September 30, 2020. We excluded studies that investigated only iatrogenic or traumatic coronary artery dissections; studies not providing differentiate sub-analyses for such types of dissections and SCAD were excluded as well.

To be eligible for inclusion, studies had to report on baseline characteristics of patients, procedural features and at least one of the outcomes of interest.

Keywords used were “spontaneous coronary artery dissection” or “SCAD”. MeSH terms used were: “coronary artery dissection, spontaneous”. Searches were limited to English language articles. Reference letters, reviews, meta-analyses and editorials were also checked to identify potentially eligible studies. The process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement.[19-20] The original study protocol was registered on the PROSPERO platform (ID CRD42020166977).

Study selection

Three independent investigators (PPB, FA and LF) reviewed all titles and abstracts and selected the potentially eligible ones. For each eligible study, full texts, supplementary materials and online appendices were examined for inclusion/exclusion criteria, whereas their reference list was scanned to find other studies of potential interest; discrepancies were resolved by consensus. When studies including a large population did not report sufficient data of interest, the original dataset was requested to the respective authors for further specific sub-analysis. Studies with fewer than 10 cases were excluded.

Data extraction

Data regarding study design, sample size, patients’ characteristics, clinical presentation, coronary angiography findings, length of follow-up and outcomes of interest were extracted from the selected studies. SCAD was categorized as type 1, 2 or 3 as described by Saw *et al.*,[12] when such data were available. The initial management strategy (conservative *versus* invasive) was defined as the treatment decided at the time of coronary angiography or within the next 24 hours when individual patient data were available. Discrepancies were resolved by discussion and consensus among the authors.

Endpoints

The outcomes of interest were all-cause death, cardiovascular death, non-fatal myocardial infarction (MI), heart failure (HF), target vessel revascularization (TVR) and SCAD recurrence. MI was defined as reported by each included study. MI and HF events were considered eligible as efficacy outcomes only when occurring throughout the follow-up period after the index-event at presentation according to the individual studies. TVR

was defined as PCI or coronary artery bypass grafting to the index SCAD-involved vessel at follow-up; the initial attempted PCI procedure on the SCAD-involved vessel was thus excluded from the TVR definition. SCAD recurrence was defined as new spontaneous dissection not involving extension of dissection of the original SCAD lesion, unless otherwise specified in each article.[21]

Statistical analysis

Odds ratio (OR), mean difference and 95% confidence interval (CI) were obtained for each endpoint with a random effect model. Heterogeneity between studies was assessed by measuring inconsistency using the I^2 index, which describes the percentage of total variation across the studies that is due to heterogeneity rather than chance.[22] I^2 values of 25%, 50%, and 75% represented small, moderate and large amounts of heterogeneity, respectively.

For the endpoints that were found out to be significantly different between the two groups, absolute risk reduction and number needed to treat were calculated.

A leave-one-out sensitivity analysis was performed on the efficacy endpoints to evaluate if the results were largely affected by single studies. The minimum number of subjects needed for a power of 80% with an alpha error of 0.05 was assessed for each study outcome by comparing the incidence of individual events in each treatment group. A sensitivity analysis on the study outcomes was also performed addressing studies published before and after the Societies' position papers on SCAD in a separate fashion (i.e. prior to 2018 and after 2018).[1,2] The incidences of conservative *versus* invasive treatment strategies according to the clinical presentation (ST-segment elevation MI vs non ST-segment elevation MI) and Thrombolysis in Myocardial Infarction (TIMI) flow (grades 0-1 vs grades 2-3) were also compared, by means of Chi-square test.

A univariate meta-regression analysis for unadjusted log OR was also performed. The potential moderator effect of age, sex, body mass index, arterial hypertension, diabetes mellitus (DM), prior or current smoking habit, dyslipidemia, peripartum condition, fibromuscular dysplasia, prior coronary artery disease, ST-segment elevation MI at presentation, left ventricular ejection fraction (LVEF) at presentation, left main coronary artery involvement, multivessel disease, use of intracoronary imaging and TIMI flow grade 0 or 1 was explored.

The presence of eventual publication bias was assessed by funnel plot and Egger's regression test. Quality of study assessment was performed by two independent investigators by means of the ROBINS-I tool;[23] conflicts were resolved by consensus. The analyses were performed with Review Manager version 5.3

(Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), OpenMeta-Analyst version beta 1.0 and Meta-Essentials.[24]

RESULTS

Study and patient characteristics

Overall, 1458 titles and abstracts were identified through database searching from database inception to September 30, 2020; after exclusion according to pre-specified criteria, 24 studies were included in the present analysis (Figure 1, Supplemental Table 1).[4,12,13,15,17,18,21,25-41] All the included studies were observational. The work by Conrotto *et al.* did not report data on the overall study population, but patients' clinical characteristics and outcomes were furnished by the author upon request and analyzed with the author's permission.[35] SCAD was defined by angiography in all the selected studies with the optional use of additional imaging techniques by some groups.

A total of 1720 patients were included: 1041 (61%) patients received medical therapy, whereas the remaining 679 (39%) patients underwent revascularization, be it either PCI (599 patients, 88%) or coronary artery bypass grafting (81 patients, 12%). Mean follow-up time was 28 ± 14 months. 7 studies reported data regarding fibromuscular dysplasia (FMD), which was present in 56% of the included patients;[12,13,15,18,21,31,39] FMD had been actively screened for in 6 out of 7 studies but this piece of information is not specified in the study by Tweet *et al.*.[31] Supplemental Table 2 shows the main baseline characteristics for each study. Mean age was 49 ± 5 years. 23% of patients were male and common cardiovascular risk factors were present in less than half of the study population (arterial hypertension 39%, DM 8%, smoking habit 34%, dyslipidemia 31%). Patients presented more frequently with acute coronary syndromes (ST-segment elevation MI 40%, non-ST-segment elevation MI 48%, unstable angina 3%) and cardiac arrest was the clinical presentation in 6% of cases. Mean LVEF at presentation was 53±5%. Type 2 SCAD was the main coronary angiography finding (63%), left anterior descending (LAD) was the most affected coronary artery (51%) and a multivessel involvement was present in 13% of patients. 35% of patients had lesions with TIMI flow grade 0 or 1 at presentation, while lesions with flow grade 2 or 3 were present in 74% of patients (Supplemental Table 3).

Endpoints

After a mean follow-up of 28±14 months all-cause death occurred in 15 (2.9%) patients in the medical treatment group and in 24 (4.8%) patients in the revascularization group (OR 0.81; 95% CI 0.31–2.08; P=0.66) with a moderate heterogeneity among the 20 studies (1048 patients) reporting this outcome (I^2=33%) (Figure 2A). Likewise, no statistical difference was found between conservative and invasive treatments regarding cardiovascular death (OR 0.89; 95% CI 0.15–5.40; P=0.89), MI (OR 0.95; 95% CI 0.50-1.81; P=0.87), HF (OR 0.96; 95% CI 0.41–2.22; P=0.92) and SCAD recurrence (OR 0.94; 95% CI 0.52-1.72; P=0.85) (Figure 2B-E).

A total of 59 TVR events were recorded across the 11 studies (635 patients overall) assessing this outcome; 20 TVR events occurred in the medical therapy group and 39 in the invasive revascularization group. Medical therapy was associated with a **significantly lower** ~~**reduction of the**~~ risk of TVR compared with invasive revascularization (OR 0.50; 95% CI 0.28-0.90; P=0.02)~~**, with an absolute risk reduction of 7.2% and a number needed to treat of 14**~~ (Figure 2F).

Heterogeneity was unimportant among the studies as for the analyses on cardiovascular death, MI, HF, SCAD recurrence and TVR (I^2=0%).

Risk of bias assessment

The overall risk of bias was low in 12 (50%) studies, moderate in 11 (46%) studies and serious in 1 (4%) study. The bias assessment for each study is shown in Supplemental Table 4. Visual assessment of the funnel plots and Egger's regression test for TVR (t-test=0.06; P=0.956) did not show the presence of any publication bias (Supplementary appendix, Figures S1 and S2).

Sensitivity analyses

The ORs remained stable in the leave-one-out analyses on cardiovascular death, MI, HF and SCAD recurrence. The results on TVR became non-significant when the study by Tweet *et al.* was removed (OR 0.48; 95% CI 0.18-1.23; P=0.13) and marginally non-significant after excluding the study by Lettieri *et al.* (OR 0.56; 95% CI 0.30-1.01; P=0.06) (Supplemental Figure 3 and Supplemental Figure 4).[17,31]

The sensitivity analysis addressing studies published before and after the Societies' position statements on SCAD separately showed that medical therapy was associated with a marginally significant lower all-cause mortality compared to an invasive treatment before 2018 (OR 0.41; 95% CI 0.16-1.01, P=0.05), but a borderline significant higher all-cause mortality from 2018 onward (OR 3.24; 95% CI 1.00-10.49; P=0.05); medical therapy was associated with lower TVR rate before 2018 (OR 0.51; 95% CI 0.28-0.92; P=0.02), but only the

study by Kim et al. was available after 2018 assessing this endpoint;[40] no differences regarding the other study outcomes were found (Supplemental Figure 5).

The number of patients treated conservatively or invasively according to the clinical presentation, namely ST-segment elevation MI and non ST-segment elevation MI, was reported by twelve studies including 525 patients overall;[4,13,17,26,27,30-32,34,36-38] an invasive strategy was pursued in 110 STEMI patients (62.2%) compared to 82 (35.0%) NSTEMI patients (P<0.001). Eight studies reported the number of individual treatment strategies according to TIMI flow rate for a total of 485 patients;[4,17,30-32,37,38,40] 126 (67.7%) patients with TIMI flow grades 0 to 1 underwent revascularization as compared to 115 (38.5%) patients with TIMI flow grades 2 to 3 (P<0.001) (Supplemental Table 5).

Meta-regression analysis

At meta-regression analysis male gender (β-coefficient: 0.001; P<0.001), DM (β-coefficient: 0.002; P=0.002), smoking habit (β-coefficient: 0.001; P<0.001), history of coronary artery disease (β-coefficient: 0.003; P<0.001), left main coronary artery involvement (β-coefficient: 0.003; P<0.001), lower LVEF at admission (β-coefficient: -0.002; P=0.014) and low TIMI flow (β-coefficient: 0.001; P=0.018) were associated with a higher rate of all-cause death (Figure 3). Smoking habit was related to a lower TVR rate (β-coefficient: -0.002; P=0.032) and to a lower incidence of SCAD recurrence (β-coefficient: -0.002; P<0.001) (Supplemental Figure 6 and Supplemental Figure 7). On the contrary, FMD was associated with a higher recurrence of SCAD (β-coefficient: 0.001; P=0.019), whereas DM was related with a lower SCAD recurrence rate (β-coefficient: -0.006; P=0.008) (Supplemental Figure 6). Complete data regarding meta-regression analysis are reported in Supplemental Table 6.

DISCUSSION

This study was conducted to compare the efficacy and safety of conservative and invasive strategies in patients presenting with SCAD. This is the largest meta-analysis facing this issue to date and the first providing meta-regression analysis. Our work suggests that invasive revascularization is associated with higher rates of TVR than medical therapy with no significant difference in all-cause death, cardiovascular death, MI, HF and SCAD recurrence rates after a mean follow-up of 28±14 months.

SCAD management is challenging and treatment decisions are often taken by caring physicians based on patients' clinical and angiographic characteristics on a case-by-case basis.[13,25-27,30,32] The European Society of Cardiology position paper and the American Heart Association Scientific Statement on SCAD recommend an initial conservative approach with medical therapy in hemodynamically stable patients without ongoing signs or symptoms of ischemia;[1,2] this recommendation is based on data from previous observational studies suggesting an increased risk of complications in the revascularization treatment group compared to medically managed patients.[12,15,18,28,31,42] Nevertheless, no RCTs facing this issue exist to date. A previous meta-analysis conducted by Martins *et al.* on a total population of 631 patients from 11 observational studies showed that revascularization as the initial approach was associated with a marginally significant increased risk of TVR compared to medical therapy (risk difference 0.06; 95% CI 0.01-0.11).[42] A most recent meta-analysis by Jamil assessing the same issue and including 22 studies and 1435 patients did not find any difference in one or other treatment strategy.[43] In line with previous studies,[42,43] we found no statistical difference between conservative and invasive treatment strategies as for all-cause death, cardiovascular death, MI, HF and SCAD recurrence; however, as the present analysis further extended to include 1720 patients, a significant difference was found as for TVR, showing higher rates of TVR in the invasive treatment group as compared to the conservative strategy.

An initial conservative strategy is supported by the high rates of spontaneous angiographic healing over few months and by the fact that SCAD recurs mostly on vessels different from the original culprit coronary artery.[11] PCI in the setting of SCAD is often laborious and its success rates are unsatisfactory. As a matter of fact, in 8 out of the 17 studies from our analysis that reported on PCI success its rate was lower than 80% and the overall mean PCI success rate was only 48%.[4,12,17,21,29,31-33] Moreover, literature data suggest that only 30% of the PCI procedures performed in SCAD have long-lasting results at follow-up.[7] The procedural and technical difficulties in this scenario should not be underestimated. In fact, there are several PCI-associated risks such as entering the false vessel lumen with the guidewire, causing iatrogenic dissections and the unpredictability of intramural hematoma shifting during angioplasty which can worsen the outcome.[1,2] This latter issue is often underappreciated by angiography and it could be the very main driver of PCI failure.[31] Intravascular imaging by means of intravascular ultrasound or optical coherence tomography might optimize PCI and stent implantation in the setting of SCAD but its adoption for the diagnosis of SCAD in the setting of acute coronary syndromes is fairly low, with only 65% of the studies included in the present analysis reporting its use;[15,17,27-33,35-39] besides, intravascular imaging might be difficult to achieve in a dissected vessel due

to the high risk of misplacing the guidewire in the false lumen and subsequent iatrogenic dissection extension. Therefore, when feasible, a conservative strategy seems the best initial approach whereas revascularization therapy should be considered for patients presenting with incessant symptoms, arrhythmias and ongoing signs of ischemia.

On the other hand, it must be acknowledged that the final reason for initial revascularization *versus* conservative management remains difficult to capture in the original studies and this may represent a major bias (more severe, aggressive, presentation in patients requiring revascularization) which, in turn, may partially explain the results; as a matter of fact, if revascularization can provide similar clinical outcomes to those seen in patients selected for conservative management, but in much more challenging patients, this would remain the strategy of choice for this population. This might also explain the relatively high percentage (49%) of patients who had undergone an invasive treatment, which might be due to the high prevalence of MI presentation with unreported hemodynamic instability or ongoing signs of ischemia. The incidence of conservative *versus* invasive treatment strategies according to clinical presentation and TIMI flow rate reported more frequent revascularizations in patients admitted with ST-segment elevation MI compared to non ST-segment elevation MI and in patients with low compared to high TIMI flow, suggesting that the initial patient's conditions might indeed play a role in the operator's decision to pursue an invasive *versus* a conservative treatment strategy. Moreover, revascularization might have been performed selectively in patients with extensive SCAD involvement of the coronary arteries (e.g., left main SCAD extending into left anterior descending and circumflex coronary arteries) requiring high total stent length, and revascularization may protect against severe adverse outcomes at the cost of increased TVR in these ominous scenarios.

The best conservative management remains unclear in the setting of SCAD as no studies have compared different pharmacological strategies to date. Our study shows that acetylsalicylic acid is most commonly used in this scenario and clopidogrel is mostly favored over potent P2Y12 inhibitors when a dual antiplatelet regimen is commenced.[13,15,17,21,26,28-30,34-37] Dual antiplatelet therapy with acetylsalicylic acid and clopidogrel seems appropriate in the acute phase independently from the treatment strategy due to the frequent presence of a luminal thrombus in the dissected coronary artery demonstrated by optical coherence tomography studies.[1,11,21,29]

Meta-regression data suggest that male gender, DM, prior or current smoking habit, coronary artery disease history, left main coronary artery involvement, lower LVEF and low TIMI flow at admission are related with

higher risk of overall death; this may be due to the higher mortality related with these concomitant conditions as well as to the greater prevalence of cardiovascular risk factors in men compared to women at the same young age. SCAD recurrence was higher among FMD patients, as previous studies already suggested.[10,11] Interestingly, smoking habit was associated with lower TVR rate and SCAD recurrence seems to be lower in smokers and DM patients. These results resemble the paradoxical apparent protective roles of smoking in acute coronary syndromes or DM in Takotsubo syndrome;[45,46] nevertheless, study biases need to be considered when exploring these results, which must be viewed as hypothesis-generating rather than definitive.

Limitations

There are some limitations to this study. First, only observational studies could be included in the analysis and most of them were retrospective. Each study carries intrinsic selection biases invariably associated with patients' own characteristics, operators' preferences at the time of revascularization and different SCAD treatment approaches in individual centers; the wide variability in sample sizes and follow-up times across the studies implies another limitation of the present work, as suggested by the results of the leave-one-out analyses. Since this research encompasses works published since 1994, another study bias comes from changes in treatment decisions over time due to advances both in invasive procedures and in pharmacological science. The study results were derived from univariate analyses and the potential biases coming from this approach must be considered as well. Moreover, only the TVR analysis was sufficiently powered to detect differences between conservative and invasive treatment strategies. Overall event rate was low and the absence of significant difference between the two strategies regarding the other efficacy outcomes might be due to the relatively small sample size of the study population rather than a real lack of statistical difference between treatments. The number of patients undergoing coronary artery bypass grafting was low and no definite conclusion could be drawn on this specific population. Peripartum period definition was not clearly reported in the component studies and different "peripartum" time intervals might have been considered. Patients' screening for FMD varied in individual studies and results on FMD patients might have affected by such heterogeneity. A potential selection bias should also be considered, as patients selected for PCI might have been sicker than patients being offered medical therapy, as previously discussed; unfortunately, the included studies did not provide separate data on **the study outcomes** in conservative vs invasive groups according to the initial presentation or TIMI flow **and the impact of these variables on the relative benefit of invasive versus conservative approach**

could not be assessed. Lastly, the results of the sensitivity analyses and the meta-regression results might have been affected by the small number of the included studies and unmeasured confounding factors and they must be interpreted with caution.

Conclusions

This meta-analysis corroborates previous data on SCAD management suggesting that a conservative first-line approach is associated with similar results to invasive treatment in terms of long-term survival, MI, HF and SCAD recurrence, but is associated with a significantly lower incidence of TVR. Larger prospective studies and RCTs are needed to confirm these results and better clarify the best initial approach in SCAD patients.

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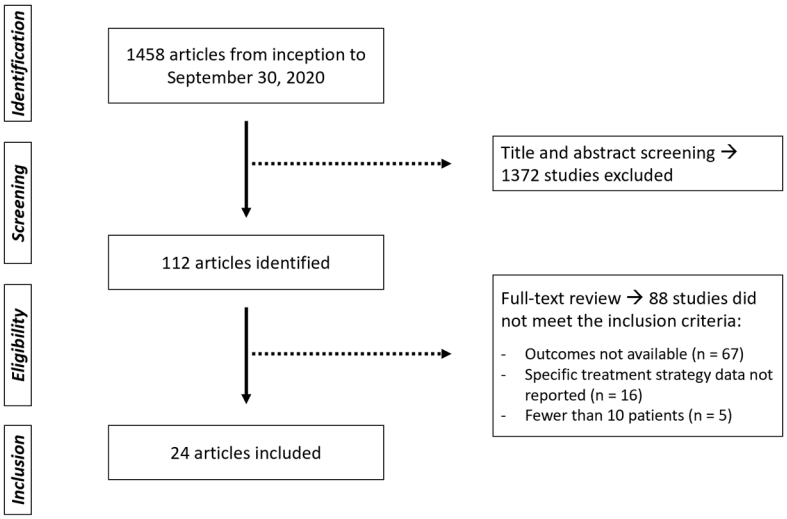
FIGURE LEGENDS

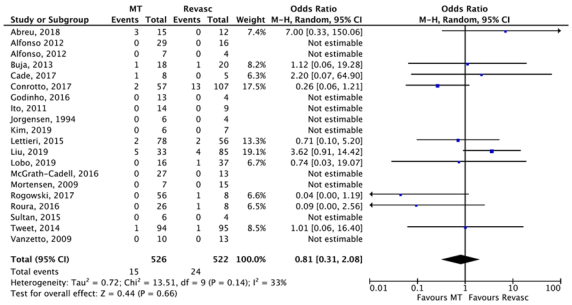
Figure 1: Flow-chart describing the screening and selection of the included studies.

Figure 2: Forest plot event-rates of all-cause death (A), cardiovascular death (B), myocardial infarction (C), heart failure (D), recurrent spontaneous coronary artery dissection (E) and target vessel revascularization (F). CI, confidence interval; MT, medical therapy; Revasc, revascularization; SCAD, spontaneous coronary artery dissection.

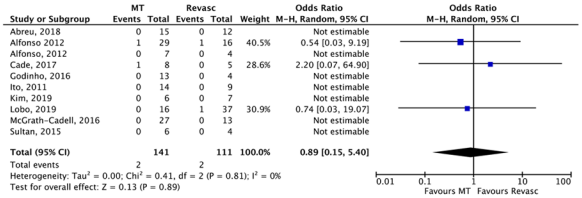
Figure 3: Meta-regression analysis graphs describing the effects of male gender (A), diabetes mellitus (B), prior or current smoking habit (C), prior coronary artery disease (D), initial ejection fraction (E), left main coronary artery territory involvement (F) and TIMI flow (G) on the proportion of all-cause mortality. CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; EF, ejection fraction; SE, standard error; TIMI, Thrombolysis In Myocardial Infarction.



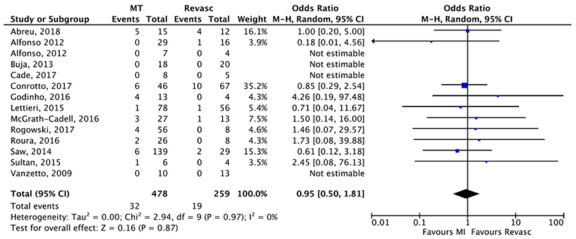
A. All-cause death



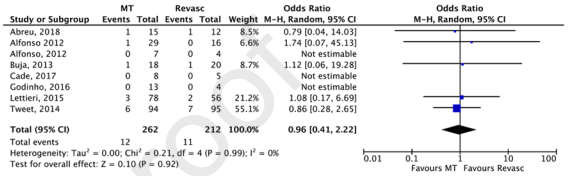
B. Cardiovascular death



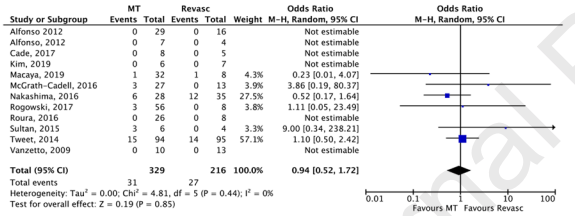
C. Myocardial infarction



D. Heart failure



E. Recurrent SCAD



F. Target vessel revascularization