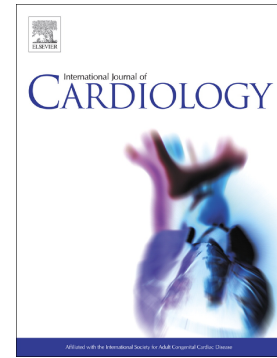


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Impact of Coronary Bypass or Stenting on Mortality and Myocardial Infarction in Stable Coronary Artery Disease

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ABSTRACT

Background: To assess whether coronary bypass (CABG) or stenting reduce the risk of mortality and myocardial infarction (MI) compared with optimal medical therapy (OMT) in stable coronary artery disease (CAD)

Methods: We performed a systematic review and network meta-analysis of contemporary randomized controlled trials comparing OMT, CABG and different stent types in stable CAD. All-comer trials were included if the rate of patients with acute myocardial infarction (AMI) was $\leq 20\%$. Endpoints were all-cause mortality and MI.

Results: Ninety-seven trials including 75754 patients were analyzed at a weighted mean follow up of 42.5 months. Compared to OMT, CABG was associated with a lower risk of death (OR=0.84; 95%CI:0.71-0.97). After exclusion of trials in left main and/or multivessel disease(LM/MVD) this benefit was not statistically significant (OR=0.89; 95%CI:0.74-1.06). CABG was associated with a lower risk of MI (OR=0.67;95%CI: 0.49-0.91) showing, however, a certain degree of inconsistency ($p=0.10$). None of the stent types included was associated with a lower risk of death. However, durable-polymer-CoCr-everolimus-eluting stent, by mixed evidence, after exclusion of either LM/MVD (OR=0.73;95%CI: 0.54-0.98) or all-comer/post-MI trials (OR=0.62;95%CI:0.39-0.98) was associated with a lower risk of MI than OMT. Similar findings, by indirect evidence, were confirmed for bio-absorbable-polymer-CoCr-sirolimus eluting stent (LMV/MVD trials excluded OR=0.46; 95%CI=0.29-0.74, all-comer/post-MI trials excluded:OR=0.41;95%CI:0.22-0.79).

Conclusions: In stable CAD, CABG reduces the risk of mortality and MI compared to OMT, especially in patients with higher extent of CAD. Our study suggests that some of second and latest-generation drug-eluting stents may reduce the risk of MI. Future research should confirm these latter findings.

Key words: stable coronary artery disease, coronary bypass, stent implantation

1. Introduction

The prognostic role of coronary revascularization associated with optimal medical therapy (OMT) in patients with stable coronary artery disease (CAD) is still a matter of debate [1-3]. Early trials showed that coronary artery bypass grafting (CABG) reduces the risk of death or myocardial infarction (MI) as compared to OMT, especially in patients with left main or multivessel disease [4]. However, those trials are outdated because they were conducted before the adoption of most of currently recommended lifesaving medications, and when use of arterial bypass grafts was marginal. Further, recent CABG trials are not powered to detect between-group differences in individual hard clinical endpoints [2, 5].

On the other hand, recent randomized clinical trials [1-3] and meta-analyses [6-8] have consistently shown that percutaneous coronary intervention (PCI) in patients with stable CAD does not reduce the risk of death and MI compared to OMT, although it is associated with a better and faster symptoms' relief.

Most recent advances and improvements of revascularization techniques have contributed to ameliorate the benefit/risk ratio of PCI. Indeed, compared to bare metal stents (BMS) and first-generation drug eluting stents (DES), second-generation DES have shown to reduce the risk of stent thrombosis [9]. In a comprehensive network meta-analysis [10] of revascularization versus OMT in patients with stable CAD, both CABG and second generation DES with everolimus but no other PCIs showed to improve survival compared to OMT alone. However, the main analyses of this study comprised CABG trials conducted in the era without preventative medications and PCI trials with plain old balloon angioplasty without stent implantation. Indeed, after restriction of the analysis to contemporary trials (after 1999) both CABG and everolimus eluting stent showed an inconclusive survival benefit with the upper bound of the 95% credibility intervals beyond unity.

Recently, longer follow up of many trials, included in the previous meta-analysis, and new randomized clinical trials investigating third-generation DES have been published. Therefore, we undertook an updated, contemporary and comprehensive network meta-analysis to investigate whether there are major differences in terms of all-cause death and MI between CABG, PCI with different stent types and OMT in patients with stable CAD.

2. Materials and Methods

We carried out a systematic review of the available publications according to the current PRISMA guidelines to perform meta-analyses of randomized clinical trials [11]. We searched for relevant articles as of 14th March 2019, published in the MEDLINE and the Cochrane Library, and for abstracts and presentations from major cardiovascular meetings using the following key words: stable angina pectoris, stable coronary disease, percutaneous coronary intervention, bare-metal stent, drug-eluting stent, coronary artery bypass grafting and coronary artery bypass filtered by randomized clinical trials. We also checked the reference lists of reviews and relevant articles. No language restriction was used.

Inclusion criteria were as follows: 1) patients with stable CAD (low risk unstable angina, stable angina, asymptomatic coronary obstruction) had to be randomized to OMT, CABG or different types of stent, 2) all-comer trials were included if either the portion of any acute MI patients was $\leq 20\%$ or data from stable cohort could be extracted, 3) Data on clinical outcome available 4) Stent implantation in more than 50% of PCI patients. Exclusion criteria were: 1) trials antedating the use of either aspirin or statins for the treatment of coronary artery disease, 2) sample size < 100 patients, 3) follow up duration < 12 months, 4) trials that compared OMT with revascularization as a whole (PCI and CABG pooled together), 5) limited comparisons (< 3 trials) between available devices.

Stents of interest were grouped as follows: 1) **BMS**, 2) durable polymer (DP) paclitaxel eluting stent (**DP-PES**) (*Taxus*, Boston Scientific, Natick, Massachusetts); 3) DP sirolimus-eluting stent (**DP-SES**) (*Cypher*, Cordis, Warren, New Jersey); 4) DP Endeavor zotarolimus-eluting stent (**DP-E-ZES**) (*Endeavor*, Medtronic, Santa Rosa, California); 5) DP Resolute zotarolimus-eluting stents (**DP-R-ZES**) (*Resolute*, Medtronic, Santa Clara, California) 6) DP cobaltum chromium everolimus eluting stent (**DP-CoCr-EES**) (*Promus*, Boston Scientific Corp., Natick, Massachusetts, or *Xience*, Abbott Vascular Devices, Santa Clara, California) 7) DP platinum chromium everolimus-eluting stent (**DP-PtCr-EES**) (*Promus Element*, Boston Scientific); 8) bio-absorbable (BP) biolimus A9 eluting stent (**BP-BES**) (*Nobori*, Terumo, Tokyo, Japan or *Biomatrix* Biosensors, Newport Beach, California) 9) **BP-CoCr-SES** (including: *Orsiro*, Biotronik, Berlin, Germany; *Mistent*, Micell Tech., Durham, NC; *Biomime*, Meril Life Sciences, Gujarat, India, *Firehawk*, MicroPot Medical, Shanghai, China, *Tivoli*, EssenTech, Beijing, China) and 10) Polymer free SES (**PF-SES**), (*Yukon Choice*, Translumina GmbH, Hechingen, Germany). Some of the currently available devices

(supplemental table 1) were not included in this study, because in patients with stable CAD they had limited comparisons with other devices.

Two investigators (N.T, E.C.D.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus. The study endpoints were the rate of all-cause death and MI. We used definitions applied in each study. Data were extracted on the basis of the intention-to-treat populations and at the longest follow up available with a maximum of seven years. Risk of bias assessment was conducted according to the Cochrane criteria[12]. The reporting of the study was in compliance with the PRISMA extension statement for network-meta-analysis [13]

We compared dichotomous outcome variables with mean odd ratios (OR) and 95% confidence intervals (95% CI) by means of frequentist network meta-analysis[14].

The specification of nodes in the network were based on the randomized intervention or, in case of strategy trials, on the intervention received by the majority of patients in a trial arm[10].

Along with primary analyses including all trials we performed the following sensitivity analyses excluding:

- 1) all-comer and post MI trials
- 2) trials on left main disease
- 3) trials on left main and/or multivessel disease,
- 4) trials on diabetic patients.

Statistical disagreement of direct and indirect evidence, known as inconsistency, was evaluated by means of both a global approach, via the Wald test, and a local node-splitting approach[15]. The possibility of publication bias was assessed by visual inspection of funnel plots.

Statistical analyses were performed using Stata/SE 14.2 (StataCorp LP, College Station, TX).

3. Results

Figure 1 shows the flow chart for the study analysis. Of 7755 potentially relevant articles initially screened, 97 RCTs (references are reported in page 75 of the supplemental material) met the inclusion criteria and were included in the meta-analysis with 75754 patients enrolled. List of excluded trials is reported in Supplemental Table 1.

Supplemental table 2 shows the main characteristics of included trials. Overall, the number of AMI patients included in our study was 2343 (3% of study population). Supplemental table 3 shows main inclusion and exclusion criteria for each trial.

Baseline characteristics and medications were fairly comparable between trials (supplemental table 4-6). Supplemental figure 1 shows the distribution of the risk of bias of the included trials according to the Cochrane collaboration's tool.

Figure 2 shows the network of evidence. Ninety four trials with 72692 patients available at a weighted mean follow up of 42.5 months contributed to the analysis of all-cause death. Figure 3A shows the relative risk of all-cause mortality for each intervention compared to OMT. Only CABG was associated with a lower risk of all-cause mortality (OR=0.83;95%CI:0.72-0.96). There was no inconsistency between direct and indirect treatment comparisons in both global and local test ($p=0.99$; $p=0.48$, respectively). On sensitivities analyses CABG was still associated with a lower risk of death as compared to OMT with no signs of inconsistency. This survival benefit was mitigated only after exclusion of trials focusing on left main/multivessel disease with loss of statistical significance (Table). The relative risk of all-cause mortality for each pair of comparisons and all inconsistency tests between direct and indirect treatment comparisons are depicted in supplemental tables 7-16. Visual inspection of funnel plots did not suggest any small studies effect or publication bias (Supplemental Figure 2).

Ninety-four trials with 71280 patients available contributed to the analysis of occurrence of MI. Compared to medical therapy, CABG (OR = 0.67; 95%CI 0.49-0.91) and BP-CoCr-SES (OR = 0.49, 95%CI 0.28-0.86) were associated with a lower risk of MI (Figure 3B). These findings were confirmed also on sensitivity analyses (Table). Comparisons between BP-CoCr-SES and OMT were all indirect. On main and sensitivity analyses there were signs of inconsistency between direct and indirect treatment comparisons at the global approach. After a local node-splitting approach inconsistency was observed for comparisons involving OMT, BMS, CABG, first and early second generation (DP-CoCr-EES, BP-BES) of DES (Supplemental tables 17-26).

Noteworthy, after exclusion of all-comer and post-MI trials (OR=0.62;95%CI:0.39-0.98) or trials focusing on left main/multivessel disease (OR=0.73;95%CI:0.54-0.98) DP-CoCr-EES compared to OMT was associated with a lower risk of MI (table), with no signs of local inconsistency. In the latter sensitivity

analysis, BP-CoCr-EES showed a lower risk of MI than DP-CoCr-EES with a certain degree of inconsistency between direct and indirect treatment comparisons (Supplemental Figure 3). Visual inspection of funnel plots did not suggest any small studies effect or publication bias (Supplemental Figure 4).

4. Discussion

We report the most comprehensive and updated network meta-analysis of 97 contemporary trials and 75754 patients with stable CAD comparing OMT vs. CABG and PCI with different stent types. The main results of the present study may be summarized as follows: 1) Compared to OMT, CABG was associated with a lower risk of all-cause mortality and MI; 2) None of the study stent was associated with a lower risk of death, 3) DP-CoCr-EES and BP-CoCr-SES could be associated with a lower risk of MI than OMT, in patients at a lower extent of CAD.

Benchmark studies demonstrating a survival benefit of CABG with OMT were conducted with outdated standards for both study's arms. In the present analysis, we confirmed that in patients with stable CAD, CABG offers a survival benefit compared to OMT alone. This mortality reduction was mitigated, with loss of statistical significance, only excluding both left main and multivessel disease trials. We extended previous results since we included only studies with a large use of arterial conduits, ranging from 73% to 100% of the patients, and excluded trials that antedated the use of preventative medications, making our results more generalizable to a contemporary clinical practice [16]. The strength of these findings relies on the satisfaction of assumption for network meta-analysis [17] in terms of *risk of bias* (supplemental figure 1: effect of performance biases are mitigated on all-cause mortality), *indirectness* (Supplemental table 4-6 show similar distribution of important effect modifiers across the network comparisons. Yet, the main results were confirmed even after exclusion of left main disease patients, not enrolled in trials comparing revascularization and OMT), *inconsistency* (Table: there were no signs of inconsistency between direct and indirect comparisons) and *publication bias* (supplemental figure 3). Accordingly, the evidence from our study showing a survival benefit associated with CABG compared to OMT could be rated as high and significantly contribute to the clinical decision making in patients with stable CAD.

Our study also shows that CABG reduces the risk of MI compared to OMT. However, a certain degree of inconsistency was found on both main and sensitivity analyses. After the local node splitting

approach we showed that loop of inconsistencies involved OMT, CABG, BMS, first generation and early second generation of DES. This result, shared with previous investigations[10], is likely related to different definitions of re-infarction applied in each study (as shown in Supplemental Table 27). Yet, there was a high inter-study and intra-study arm (PCI vs. CABG) variability in the definition of peri-procedural MI that are clearly reported only in a very minority of cases. Further, unlike endpoints as all-cause mortality, the risk of performance bias (lack of blinding of patients and personnel) on evaluation of endpoints such as MI may be higher. However, in the great majority of the studies included in the network, MI adjudication was blind (supplemental figure 1). Nonetheless, it is worth noting that results in terms of all cause death and MI are all in the same direction. Taken together, findings of our study suggest that the survival benefit of CABG over OMT alone may be related to a lower risk of MI, especially in patients with a greater extent of CAD.

Among other findings of our study we found that CABG was associated with a lower risk of death and MI (supplemental table 7, 17) compared to BMS, DP-PES and DP-SES. These results are in line with findings of a recent individual patient level meta-analysis [18] showing a survival benefit of CABG over stenting in patients with multivessel disease.

Unlike coronary bypass, recent randomized clinical trials[1-3] and meta-analyses[6-8] comparing stent implantation with OMT in patients with stable CAD have not shown a prognostic benefit. Latest generation DES have been ameliorated on many aspects, including the polymer (more bio-compatible, bio-resorbable or absent) and reduced strut thickness, that overall improved safety and efficacy of the devices [9]. Accordingly, in a comprehensive network meta-analysis[10] of revascularization versus OMT in stable CAD, DP-CoCr-EES but no other percutaneous interventions showed to improve survival compared to OMT. These findings are consistent with a previous meta-analysis that included only first-generation DES and did not show a reduction in mortality with PCI as compared with OMT.

Compared to previous studies[8, 10] our analysis was significantly extended to include current third-generation DESs, providing the following updated results.

1) In the setting of stable CAD none of the included stent types was associated with a mortality reduction compared to OMT. Therefore, our analysis does not confirm that DP-CoCr-EES was associated with a lower risk of all-cause mortality as suggested by the previous network meta-analysis by Windecker et al.[10] We cannot rule out the play of chance for this finding. However, in the analysis restricted only to contemporary

trials Windecker et al. also did not show any significant survival advantage with the DP-CoCr-EES. In addition, after that publication, more trials and longer follow ups became available and were included in our study, making our data somewhat more robust. Finally, comparing the main analyses of both studies, a major difference resides in the inclusion in the previous meta-analysis of all-comer trials with a high portion of AMI patients, that overall was about 29%. On the contrary, our choice to exclude trials with AMI patients $\geq 20\%$ restricted to a trivial 3% the percentage of AMI patients included. This is noteworthy, because the benefit of stent implantation over OMT in AMI patients is well established and it might have influenced the slightly different results of the previous network meta-analysis.

2) After exclusion of all-comer and post-MI trials or trials focusing on left main and multivessel disease, we showed a MI reduction with DP-CoCr-EES compared to OMT. This evidence stemmed from both direct and indirect comparison with no signs of inconsistency. However it should be noted that the direct comparison is represented only by the FAME II study [3] that is the only study endorsing an FFR-guided strategy for PCI. Both sensitivities analysis excluded the BEST trial [19] where DP-CoCr-EES was associated with a higher rate of MI than CABG (4.8% vs. 2.7%, $p=0.11$) in multivessel disease. These observations may support the hypothesis that in patients with stable CAD and limited extent of CAD, treatment of coronary lesions associated with signs of myocardial ischemia, with stents with a good efficacy/safety profile such as the DP-CoCr-EES [9], may reduce the risk of MI as compared to OMT.

3) BP-CoCr-SESs were associated with a lower risk of MI than OMT. These findings stemmed only from indirect evidence and should be interpreted with caution. Although indirect comparisons are [20]integral to the network meta-analysis, their reliability are built on an assumption of transitivity. Transitivity is satisfied when population, treatment and outcome are sufficiently similar among studies making different direct comparisons [21]. In the present study we substantially included trials that enrolled patients with stable CAD whose baseline characteristics and medications are overall comparable (supplemental table 4). Nonetheless, it should be underlined that among the 7 BP-CoCr-SES trials, all excluded patients with left main disease and 4 those with 3-vessel disease (supplemental table 3), yet detailed information on the number of vessel diseased lacked in most of cases (supplemental table 5). Accordingly, concerns over intransitivity should be arisen. However, this issue appears less relevant in the analysis excluding left main/multivessel disease trials.

In this latter analysis, as indirect evidence, BP-CoCr-SESs were associated with a lower risk of MI compared to OMT. This finding relies on the results derived from the network meta-analysis showing a lower risk of MI with BP-CoCr-SES than DP-CoCr-EES with a type of evidence mixed. This finding is consistent with the results of a recent meta-analysis[22] showing a better performance of this technology compared to second generation DES. Indeed, the BP-CoCr-SES group comprises mostly ultra-thin (60-65µm, supplemental table 28) strut DES that have been associated with a low thrombogenicity[23], lower stent-induced arterial wall inflammation, lower turbulence, lower shear stress and a lower risk of side branch coverage in case of bifurcation treatment [24]. However, our study shows a certain degree of inconsistency between direct and indirect comparisons of BP-CoCr-EES vs. DP-CoCr-EES (supplemental figure 3) suggesting caution in interpreting this data. Differences in outcome definition may still explain these results. However, trials comparing directly BP-CoCr-SES vs. DP-CoCr-SES included mostly patients at low degree of anatomical complexity (maximum 2 vessel, no bifurcation involving a side branch > 2.00 mm, no long lesions) compared to other DP-CoCr-EES trials. Accordingly, a realistic appraisal of the BP-CoCr-SES performance should be evaluated in more unselected settings.

Data on the role of revascularization in stable coronary artery disease are conflicting and underpowered. In this setting, meta-analyses are often relied upon to provide a consensus direction. However, their results are difficult to interpret since limitations may not be that obvious. Besides, network meta-analyses present specific assumptions to be met. One of the strengths of our work relies on the fact that we thoroughly discussed where these assumptions may be met and where concerns may be arisen, for the reader to make an informed judgement about how to evaluate our findings. For instance, in the present network meta-analysis of 97 contemporary trials in stable CAD, we extended our analysis to stents that had few or none direct comparison with OMT. Accordingly, based on the limitations described in the discussion the lower risk of MI associated with both DP-CoCr-EES and BP-CoCr-SESs should be considered as hypothesis-generating and confirmed in future investigations.

We cannot rule out a possible positive effect of other latest generation DES that were not included in the present study. For example, the DP-R-Onyx-ZES was recently shown in the all comer BYONIX trial [25] to be non-inferior to the BP-CoCr-SES for the combined safety/efficacy endpoint at 1 year, with a lower incidence of definite or probable stent thrombosis (0.7 % vs. 0.1%; $p = 0.01$).

We included trials performed over almost two decades and different definitions of MI have occurred. We were prevented from discriminating between peri-procedural and spontaneous MI. This would have been of great interest since the latter has been strongly associated with mortality whilst most peri-procedural MI are not clinically relevant [26]. We observed that life-saving medications were quite comparable between trials. However it should be noted that those treated with PCI and stenting must receive a course of dual antiplatelet therapy, unlike patients treated either conservatively or with CABG. Nonetheless, it is unlikely that this could have affected the study results given the fact that dual antiplatelet therapy has not been shown superior to single antiplatelet therapy in patients with stable coronary artery disease [27].

Finally, it would have been desirable to investigate whether the burden of myocardial ischemia might modulate the clinical effect of either stenting or coronary bypass. Unfortunately, among the studies included in the present network meta-analysis the evidence of ischemia as inclusion criteria was mandatory only in a very minority of cases (8 trials including 3380 patients as shown in supplemental table 3). Since we used aggregate data we were prevented from evaluating the prognostic role of the myocardial ischemic burden. The prognostic role of myocardial ischemia in patients with stable CAD has been intensively debated. Early nuclear sub-study from the COURAGE trial [28] suggested that patients undergoing PCI had a higher reduction of myocardial ischemia compared to OMT and those with ischemia reduction had a lower risk of death and MI, especially if they disclosed a moderate-to-severe ischemia at baseline. However, these findings have not been confirmed by a meta-analysis (including also the COURAGE trial), enrolling 5286 patients with documented myocardial ischemia, showing no benefit of PCI over OMT [7]. Most importantly, in the recent International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) randomized controlled trial (Hochman JS, oral presentation at AHA 2019) revascularization as a whole in patients with stable ischemic heart disease and moderate to severe ischemia was not associated with the reduction of the composite primary endpoint of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure up to 3.3 years as compared with optimal medical therapy.

Unlike myocardial ischemia, another sub-study [29] from the COURAGE trial showed that the anatomic burden of CAD represents a strong and consistent predictor of death and myocardial infarction. This latter

finding is in line with the results of our network meta-analysis showing a reduction of mortality and re-infarction especially in patients with left main/multivessel disease targeted by coronary bypass.

In conclusion, in patients with stable CAD bypass reduces the risk of all-cause mortality and MI, especially in patients with left main/multivessel disease. For PCI, none of the included stent types was associated with a reduced risk of all-cause mortality. However, our analysis suggests a lower risk of MI with DP-CoCr-EES and BP-CoCr-SES in patients at a lower extent of CAD. These findings should be confirmed in future investigations, possibly targeting only coronary lesions clearly associated with myocardial ischemia.

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6. Figure legend

Figure 1. Study flow chart. Abbreviations: AMI = acute myocardial infarction

Figure 2. Network map. Each node represents 1 intervention. The size of the node is proportional to the number of studies randomizing that intervention. The edges represent direct comparisons between two interventions and the width of the edge is proportional to the number of direct comparisons. Numbers denote the total of patients randomized to each intervention.

Abbreviations: BMS = bare metal stent; BP-BES = bio-absorbable biolimus A9 eluting stent, BP-CoCr-SES = bio-absorbable-CoCr-sirolimus eluting stent, CABG = coronary artery bypass grafting; DP-CoCr-EES = durable polymer-CoCr-everolimus eluting stent; DP-E-ZES = durable polymer Endeavor zotarolimus eluting stent; DP-PES = durable polymer paclitaxel eluting stent; DP-PtCr-EES = durable polymer-PtCr-everolimus eluting stent; DP-R-ZES = durable polymer Resolute zotarolimus eluting stent; DP-SES = durable polymer sirolimus eluting stent; OMT = optimal medical therapy

Figure 3. Estimated mean Odds Ratio (95% confidence intervals) for all cause mortality and recurrence of MI from network meta-analysis for different interventions compared to OMT.

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References

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Table 1. Relative risk of all cause mortality and myocardial infarction for CABG vs. OMT. Main and sensitivities analyses

Treatment	Odds Ratio (95%CI)	Type of evidence	p value for global inconsistency	p value for local inconsistency
All cause mortality				
All trials n = 72692 pts				
CABG	0.83 (0.72-0.96)	mixed*	0.99	0.48
All-comer and post-MI trials excluded n = 46699 pts				
CABG	0.83 (0.71-0.97)	mixed	0.99	0.47
LM trials excluded n = 67013				
CABG	0.84 (0.72-0.97)	mixed	0.99	0.41
LM/MVD trials excluded n = 60581				
CABG	0.89 (0.74-1.06)	mixed	0.99	0.47
Diabetes trials excluded n = 66402				
CABG	0.83 (0.71-0.97)	mixed	0.94	0.56
Myocardial infarction				
All trials n = 71280 pts				
CABG vs. OMT	0.67 (0.49-0.91)	mixed*	0.10	0.12
BP-CoCr-SES vs. OMT	0.49 (0.28-0.86)	indirect		-
All-comer and post-MI trials excluded n = 45287 pts				
CABG	0.64 (0.44-0.93)	mixed	0.03	0.18
DP-CoCr-EES vs. OMT	0.62 (0.39-0.98)	mixed		0.89
BP-CoCr-SES vs. OMT	0.41 (0.22-0.79)	indirect		-
LM trials excluded n = 65501				
CABG vs. OMT	0.72 (0.52-0.99)	mixed	<0.001	0.052
BP-CoCr-SES vs. OMT	0.46 (0.26-0.82)	indirect		-
LM/MVD trials excluded n = 59169				
CABG vs. OMT	0.64 (0.42-0.97)	mixed	0.04	0.065
DP-CoCr-EES vs. OMT	0.73 (0.54-0.98)	mixed		0.559
BP-CoCr-SES vs. OMT	0.46 (0.29-0.74)	indirect		-
BP-CoCr-SES vs. DP-CoCr-EES	0.63 (0.43-0.93)	mixed		0.094
Diabetes trials excluded n = 66402				
CABG	0.73 (0.51-1.03)	mixed	0.04	0.27
BP-CoCr-SES vs. OMT	0.51 (0.30-0.89)	indirect		-

* = stemming from both direct and indirect comparisons

BP-CoCr-SES = bio-absorbable polymer cobaltum chromium sirolimus eluting stent ; CABG = coronary artery bypass grafting; DP-CoCr-EES = durable polymer cobaltum chromium everolimus eluting stent; OMT = optimal medical therapy

Journal Pre-proof

Sample CRediT author statement

Re: Impact of Coronary Bypass or Stenting on Mortality and Myocardial Infarction in Stable Coronary Artery Disease

Nevio Taglieri: conceptualization, methodology, investigation, writing-original draft preparation

Antonio Giulio Bruno: Visualization

Maria Letizia Bacchi Reggiani: Visualization, formal analysis, Data curation

Emanuela Concetta D'Angelo: investigation

Gabriele Ghetti: resources

Matteo Bruno: resources

Tullio Palmerini: Writing - Review & Editing

Claudio Rapezzi: Writing - Review & Editing

Nazzareno Galiè: Writing - Review & Editing

Francesco Saia: Writing - Review & Editing, supervision

Highlights

- 1) In patients with stable CAD coronary bypass reduces the risk of death and MI
- 2) None of the stent type were associated with mortality reduction
- 3) DP-CoCr-EES and BP-CoCr-SES reduce the risk of MI in patient at lower extent of CAD

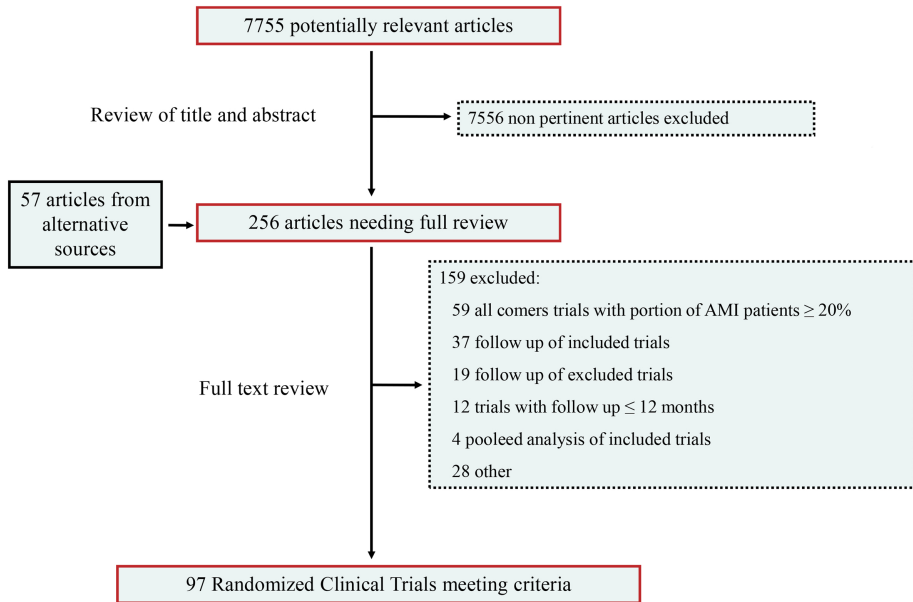


Figure 1

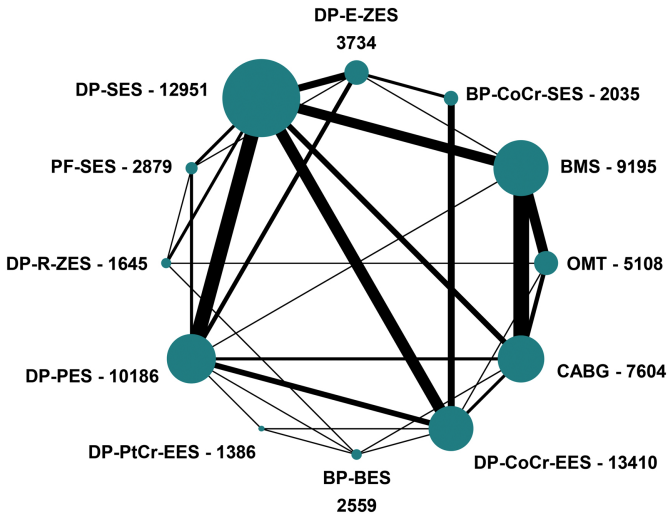


Figure 2

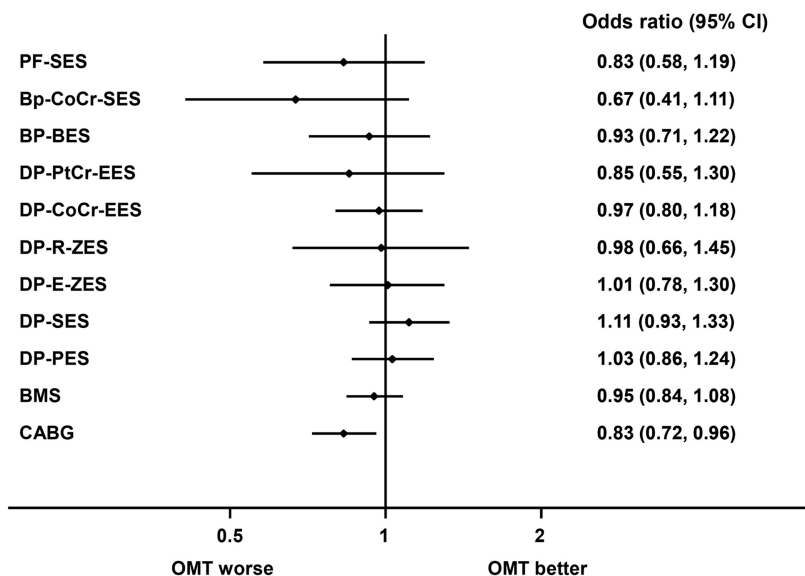
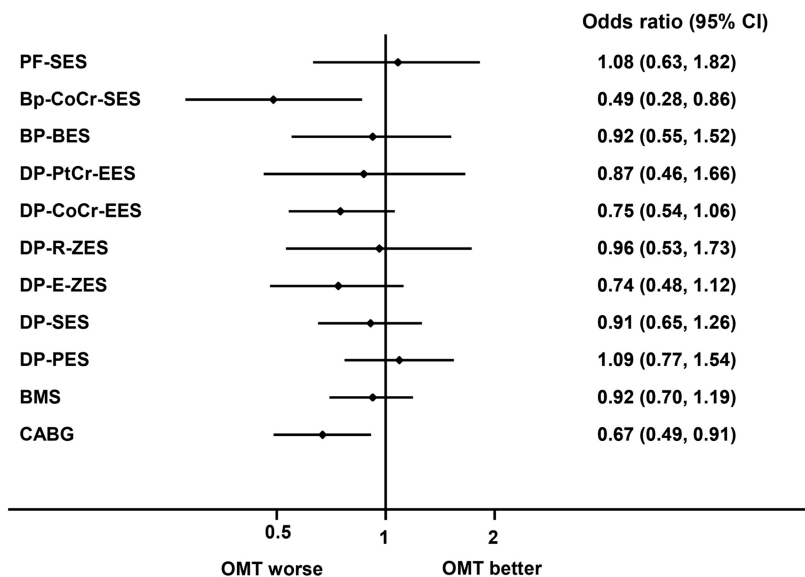
A
All cause mortality (94 trials, 72692 pts)

B
Myocardial Infarction (94 trials, 71280 pts)


Figure 3