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Metanalysis comparing Outcomes of Drug Eluting Stents versus Single and Multi-Arterial Coronary Artery Bypass Grafting

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Abstract

Relative benefits of coronary artery bypass (CABG) using single and multiple arterial grafting (SAG, MAG) and drug eluting stent (DES) in multivessel coronary disease remain uncertain. We compared SAG, MAG and DES in a pairwise and network meta-analysis. Randomized trials and adjusted observational studies comparing CABG versus DES were included (primary endpoint: long-term mortality; secondary endpoints: operative mortality, perioperative stroke and follow-up repeated revascularization [RR]). Studies with ≥1.7arterial grafts/patient were classified as MAG. Bayesian network meta-analyses (NMAs) and random-model pairwise meta-analyses were performed. 53,239 patients (8 randomized, 17 observational studies) were included (26,306 DES;26,933 CABG). In pairwise comparison (mean follow-up:5.42 years), CABG (MAG+SAG) was associated with lower long-term mortality (incident rate ratio[IRR]0.77, 95%CI 0.66-0.90), lower RR (IRR 0.37, 95%CI 0.27-0.51), increased perioperative stroke (odds ratio[OR]3.18, 95%CI 1.70-5.97) and similar operative mortality (OR 1.04, 95%CI 0.64-1.70) compared to DES. There was a non-significant trend toward lower long-term mortality for studies with higher mean number of arterial grafts. In NMA, compared to DES, MAG was associated with lower long-term mortality (IRR 0.72, 95%CrI 0.57-0.92) and late RR (IRR 0.32, 95%CrI 0.21-0.49), SAG was associated with lower long-term mortality and RR (IRR 0.80, 95%CrI 0.66-0.97 and IRR 0.42, 95%CrI 0.29-0.61 respectively). In conclusion, CABG was associated with reduced 5-year mortality and need for RR compared to DES. MAG was ranked as the best treatment for the primary and all secondary outcomes.

Key words: CABG, DES, multi arterial grafting

Introduction

If percutaneous interventions (PCI) or coronary artery bypass surgery (CABG) is the best treatment for patients with multivessel coronary artery disease is still debated. However, the outcomes of both procedures are influenced by procedural variations. For PCI, the use of drug eluting stents (DES) significantly reduce the restenosis rate and improve survival.[1] For CABG, the use of multiple instead of single arterial grafts (MAG vs SAG respectively) lead to better patency rate and possibly improved clinical outcome.[2] In this meta-analysis, we compare the contemporary therapeutic options for the treatment of patients with multiple vessel disease: PCI with DES, vs MAG CABG and SAG CABG.

Methods

This systematic review and network meta-analysis (NMA), follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (**Supplementary Figure 1**).[3,4]

Ovid's version of MEDLINE and EMBASE were searched from inception to June 2017 (full search strategy attached in **Appendix**). Inclusion criteria were: English language publications, adjusted or matched observational studies or randomized clinical trials (RCTs) comparing CABG to PCI with DES. In addition, we hand-searched recent meta-analyses and reviews on this topic for potential additional studies. All citations were reviewed by three investigators independently and any disagreements were resolved by consensus. In case of overlapping studies, the largest series were included. Studies reporting different outcomes from the same trial were classified together.

We classified the study as using MAG or SAG in the CABG group based on the mean number of arterial grafts per patient in the CABG arm. Studies with a mean number ≥1.7 of arterial grafts per patient in the CABG arm were included in the MAG group, studies with a mean number <1.7 of arterial grafts per patient in the CABG arm were included in the SAG group. Studies where the mean number of arterial grafts was not reported were excluded unless the authors provided a detailed explanation of their surgical strategy that allowed classification of the study in the MAG or SAG group. The arbitrary 1.7 cut-off was established after exploratory analyses using both more liberal (1.5) and more restrictive (2.0) cut-off in order to have a comparable amount of trials in the two groups and in the meantime keep a rational distinction between MAG and SAG (results of the exploratory analyses are given in the **Supplementary Figure 2**). To date no study has strictly compared MAG vs DES and, as in the current practice both in the US and In Europe only a minority of CABG patients receive more than one arterial graft, it is the authors' opinion that studies where a second artery was used in at least 70% of the patients could be defined as MAG. For the PCI group, we included only studies that exclusively used DES and did not allow for any mixing of bare metal stents (BMS) in the analysis.

Two investigators (M.R and A.A) performed data extraction independently. The following variables were included: study demographics (sample size, number of centers, institutions involved, publication year, study period, design and country), patient demographics (age, sex, comorbidities (hypertension, diabetes, ejection fraction, dyslipidemia, cerebrovascular accident, myocardial infarction, peripheral vascular disease) and procedural and postoperative factors (procedure performed and stents used). The quality of the included studies was assessed by the Newcastle-Ottawa Scale (NOS).[5]

Only RCTs and observational studies of high quality (NOS score >6) were included in the final analysis.

The primary outcome was all-cause 5-year mortality. The secondary outcomes were operative (30 days or in-hospital) mortality, perioperative stroke, and repeat revascularization. Two levels of analyses were conducted for all outcomes: A) Pairwise meta-analysis between CABG (with either MAG or SAG) and DES, and B) NMAs between SAG only, MAG only, and DES.

Late outcomes were pooled as the natural logarithm of the incident rate ratio (IRR) to account for potentially different follow-up durations between the groups. We estimated the IRR through several means depending on the available study data. When hazard ratios (HRs) for matched (preferentially) /adjusted cohorts were provided, we took the natural logarithm of the HR; the standard error (SE) was derived from the 95% CI or log rank p-value.[6] When Kaplan Meier (K-M) curves were present, we estimated the event rates from the curves using GetData Graph Digitizer software 2.26 (http://getdata-graph-digitizer.com/). In case of absence of K-M curves, we used the reported event rates in order to calculate the IRR, as previously described.[7,8] Short-term binary outcomes were pooled using odds ratio (OR) with 95% confidence interval (CI) using the generic inverse variance method.[9] Random effect meta-analysis was performed using meta and metafor packages in R (version 3.3.3 R Project for Statistical Computing).

Heterogeneity was reported as: low (I^2=0-25%), moderate (I^2 =26-50%), high (I^2>50%).[10] Sensitivity analysis using leave-one-out analysis and publication bias assessment by funnel plot and Egger's test were conducted for the primary outcome. Subgroup analysis was used to compare the relative results of MAG and SAG vs. DES. Meta-regression was used to explore the effect of the mean number of arterial grafts per patient on the IRR for the primary outcome.

NMA was conducted in R (version 3.3.3 R Project for Statistical Computing) using "netmeta" statistical package based on the method described by Rucker.[11–13] It uses a frequentist method based on electrical networks and graph theory that performs as well as the classical Bayesian network analysis.[14] Inconsistency was evaluated with Cochran's Q.[15] Similar to our direct comparison, we used pooled log IRR with 95% credible intervals (CrIs) to determine the relative effect estimates of late outcomes from the NMA. For the binary outcomes, we pooled ORs with 95% CrIs. We preferentially used a random effects model to improve the model fit but results using fixed model were also reported. Regarding consistency, an assumption of NMA models is that "direct and indirect sources of evidence estimate the same true treatment effect". To test this assumption, we measured consistency by comparing the direct and indirect evidence results to identify any statistically significant differences. The difference between direct and indirect estimate was considered as an estimate of inconsistency with the null hypothesis that consistency between the direct and indirect evidence exists and rejection of the null hypothesis will be done in case of presence of a statistically significant difference between the direct and indirect evidence comparison ($p<0.05$). Statistical significance was considered when the CrIs did not cross the line of no effect.

Results

A total of 2616 studies were retrieved; 25 met inclusion criteria and were included in the final analyses (**Supplementary Figure 1; references of included studies reported in Appendix**). A total of 53,239 patients were included (26,933 CABG [11,155 MAG and 15,778 SAG] and 26,306 DES) from 8 RCTs (n=17,554) and 17 observational studies (n=35,685). The evidence network is shown in **Figure 1**. Demographics and a summary of the characteristics of the included studies are shown in **Supplementary Tables 1 and 2**. Baseline characteristics were comparable in all studies. Details of the type of DES used was not reported in 14 studies. The remaining studies used: Everolimus eluting stents (EES) (n=3), Sirolimus eluting stents (SES) (n=3), SES and Paclitaxel eluting stents (PES) (n= 2), EES and Zotarolimus eluting stents (ZES) (n=1), SES, PES and ZES (n=1), and SES, PES and other DES (n=1).

All 17 observational studies had a NOS score of 8 or more (**Supplementary Table 3**).

When CABG was compared to DES independently of the number of arterial grafts in the CABG arm, the long-term mortality at median follow-up time of 5.42 years and the need for RR at a mean follow-up of 6.06 years were lower in the surgical group (15% vs 18.19%, IRR 0.77, 95%CI 0.66-0.90 and 10.3% vs. 15.5%, IRR 0.37, 95%CI 0.27-0.51 respectively). Operative mortality was similar (1.17 vs. 1.11%, OR 1.04, 95%CI 0.64-1.70) and perioperative stroke rate was higher in the CABG arm (1.18% vs 0.31%, OR 3.18, 95%CI 1.70-5.97) (**Figure 2**).

When comparing MAG and DES, long-term mortality and need for RR were lower in the MAG se ries at 6.37 years mean follow-up (11.7% vs. 18.3% and 7.2% vs. 16.6%, IRR 0.73, 95%CI 0.55-0. 96 and 0.34, 95%CI 0.26-0.45 respectively). There was no difference in operative mortality (0.7 7% vs 1.46%, OR 0.53, 95%CI 0.17-1.67) and perioperative stroke rate between the two arms (1 .03 vs 0%, OR 6.85, 95%CI 0.83-56.56) (**Table 1**).

When comparing SAG and DES, long-term mortality and need for RR at 4.4 year mean follow-up were also lower in the surgical arm (16.8% vs. 17.8% and 11.1% vs 14.9%, IRR 0.80, 95%CI 0.66-0.97 and 0.42, 95%CI 0.28-0.63 respectively). Operative mortality was similar and perioperative stroke rate was higher in the SAG group (1.24% vs 1.05% and 1.21% vs 0.37%, OR 1.18, 95%CI 0.67-2.07 and OR 2.95, 95%CI 1.53-5.71 respectively) (**Table 1**).

At subgroup analysis based on the number of arterial grafts the IRR for long-term mortality compared to DES was lower in the MAG group, but this difference was not statistically significant (P=0.58; **Figure 3**). At meta-regression there was a clear although non-statistically significant trend toward a negative correlation between the mean number of arterial grafts per patient and the IRR for long term mortality compared to DES (**Figure 4**)

Leave-one-out analysis was robust for the primary outcome (**Supplementary Figure 3A**). In the funnel plot, Egger's test intercept for the primary outcome was -0.55±0.60, P=0.366) (**Supplementary Figure 3B**).

Compared to DES, MAG was associated with lower 5-year mortality (IRR 0.72, 95%CrI 0.57-0.92) and need for follow-up RR (IRR 0.32, 95%CrI 0.21-0.49). There was no difference in operative mortality (OR =0.53, 95%CrI 0.16-1.77) and in perioperative stroke rate (OR 6.85, 95%CrI 0.83-56.56) between the two groups. Compared to DES, SAG was associated with lower 5-year mortality (IRR 0.80, 95%CrI 0.66-0.97) and reduced need for follow-up RR (IRR 0.42, 95%CrI 0.29-0.61). Operative mortality was similar for DES and SAG (OR 1.40, 95%CrI 0.95-2.06), whereas the perioperative stroke rate was higher in the SAG group (OR 2.95, 95%CrI 1.53-5.71). Compared to SAG, MAG was associated with similar 5-year mortality (IRR=0.90, 95%CrI 0.67-1.22) and need for RR (IRR 0.76, 95%CrI 0.45-1.31). There was no difference in operative mortality (OR 0.38, 95%CrI 0.11-1.34) and perioperative stroke rate (OR 2.32, 95%CrI 0.25-21.18) between the two groups. Results of the NMA are summarized in **Figure 5**. MAG was ranked as the best treatment for the primary and all secondary outcomes.

Inconsistency estimate among long term outcomes and ranking of different treatment modalities are shown in **Figures 6 and 7**.

Discussion

This is the first NMA to compare the results of the contemporary strategies for the treatment of patients with multivessel CAD. We decided to include only RCTs and adjusted observational studies to provide a summary of the best possible evidence and to minimize confounders.

The main finding is that CABG was associated with reduced 5-year mortality and need for RR compared to DES. This was not significantly influenced by the number of arterial grafts used. However, at meta-regression we found a trend toward increased survival advantage for studies using MAG. As mean follow-up of the included studies was limited to 6 years and there is an exponential increase in the attrition rate of vein grafts after the 4th postoperative year,[2] it is to be seen if the observed difference in favor of MAG will become significant at ten years.

The second most important finding is that MAG resulted in a similar risk of perioperative stroke versus DES, whereas in studies that used SAG the incidence of perioperative neurologic complications was significantly higher in the surgical arm. A possible mechanistic explanation is the lower degree of aortic manipulation when performing MAG using in-situ conduits. A recent meta-analysis has reported how the adoption of a no-touch aorta technique can reduce by almost 80% the risk of intraoperative stroke during CABG.[16] Stroke has traditionally been the Achilles' heel of CABG compared to PCI and one of the main reasons advocated to justify widespread adoption of percutaneous interventions in patients with multiple vessel disease.[17] In this regard, the finding of similar neurological risk for MAG and DES has particular relevance.

A meaningful comparison of CABG and PCI must be considered in the context of the procedural characteristics of both these interventions. Studies have shown that DES provide better clinical outcomes compared to BMS.[1] Thus, an analysis that compares CABG to PCI with studies that include BMS would bias against the potential benefits of PCI. In a similar way, conduit selection can impact CABG outcomes. The mid-term and late patency of arterial grafts are significantly superior to venous grafts.[2] There is also a growing body of evidence to suggest that arterial grafts can protect the downstream coronary circulation from the progression of atherosclerosis, most likely through the production of anti-inflammatory and anti-thrombotic vascular mediators.[18] Furthermore the use of in-situ arterial grafts minimizes intraoperative aortic manipulation and also has the potential to significantly reduce the incidence of perioperative stroke.[16]

The above considerations provided the basis for our hypothesis why a meta-analysis comparing CABG stratified by MAG or SAG to DES can produce different results than a meta-analysis that compared all CABG to DES. Our analyses support at least in part this hypothesis. The finding of reduced neurological risk and potentially larger survival benefit for studies using MAG and not SAG in the surgical arm is an important finding that requires further investigation.

This study must be interpreted in the context of some limitations. While we included only adjusted observational studies, treatment allocation bias of patients to SAG or MAG exist. Surgeons may be more likely to perform MAG in patients with a potential longer life expectancy and thus select a healthier population compared to SAG.[19] Also, differences in drug composition within a stent and generational differences within the same stent class may have an impact on outcome. However, given the number of categories and the small number of studies per category, a subgroup analysis based on specific DES type was not possible. In terms of CABG, we did not account for factors such as off- versus on-pump surgery, minimally invasive, or anaortic techniques. We hypothesize that those undergoing MAG may have less manipulation of the aorta compared to SAG through the higher utilization of bilateral internal thoracic arteries and that this might explain the difference in perioperative stroke between the two groups. Finally, some comparisons are based on a limited number of studies.

In conclusion, CABG is associated with reduced 5-year mortality and need for RR compared to DES. The use of MAG in the surgical arm may be associated with increased benefits both perioperatively and at long-term follow-up.

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Figure Legends

Figure 1. Network plot based on revascularization strategy. Circles represent each revascularization strategy as a node and lines represent the direct comparisons. The extent of circle indicates the number of patients receiving each revascularization strategy and the line thickness indicates the number of studies included in each comparison.
MAG, Multi-Arterial Coronary Artery Bypass Grafts; DES, Drug eluting stent; SAG, Single Arterial Coronary Artery Bypass Grafts.

Figure 2. Pairwise meta-analysis comparing CABG vs DES: A) Long term mortality (expressed as IRR), B) Repeated revascularization (expressed as IRR), C) Stroke (expressed as odds ratio), D) Operative mortality (expressed as OR).
Coronary artery bypass, CABG; drug eluting stent, DES; Incidence rate ratio, IRR; odds ratio, OR.

Figure 3. Subgroup analysis according to the mean number of arterial grafts in the CABG arm.
CABG, coronary artery bypass; CI, confidence intervals; DES, drug eluting stent; IRR, incidence rate ratio

Figure 4. Meta-regression according to the mean number of arterial grafts in the CABG arm.
CABG, coronary artery bypass grafting.

Figure 5. Network meta-analysis estimates for long-term outcomes expressed as IRR with relative 95% CrI for long term outcomes using random effects model: A) Long term mortality, B) Repeated revascularization, C) Perioperative mortality and D) Perioperative stroke.
CrI, credible interval; DES, drug eluting stent; IRR, incidence rate ratio; OR, odds ratio; MAG, Multi-Arterial Coronary Artery Bypass Grafts; SAG, Single Arterial Coronary Artery Bypass Grafts.

Figure 6. League tables for our network meta-analysis estimates for different outcomes expressed as IRR for long term outcomes and OR for short term outcomes with relative 95%CrI using fixed and random effects model (MAG as comparator): A) Long term mortality (tau^2 = 0.1037; I^2 = 74.8%), B) Repeated revascularization (tau^2 = 0.4062; I^2 = 94.6%), C) Perioperative mortality (tau^2 = 0.0387; I^2 = 10.6%) and D) Perioperative stroke (tau^2 = 0; I^2 = 0%).
CI, confidence interval; DES, drug eluting stent; MAG, Multi-Arterial Coronary Artery Bypass Grafts; OR, odds ratio; SAG, Single Arterial Coronary Artery Bypass Grafts.

Figure 7. Ranking of different treatment modalities in different outcomes (the higher P-score value, the better rank).