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Five-year outcomes following PCI with DES versus CABG for unprotected LM coronary lesions: meta-analysis and meta-regression of 2914 patients

Desfechos de 5 anos do tratamento de lesões de TCE por stents farmacológicos versus CRM: meta-análise e meta-regressão de 2914 pacientes

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Abstract

Objective: To compare the safety and efficacy at long-term follow-up of coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) using drug-eluting stents (DES) in patients with unprotected left main coronary artery (ULMCA) disease.

Methods: MEDLINE, EMBASE, CENTRAL/CCTR, SciELO, LILACS, Google Scholar and reference lists of relevant articles were searched for clinical studies that reported outcomes at 5-year follow-up after PCI with DES and CABG for the treatment of ULMCA stenosis. Five studies (1 randomized controlled trial and 4 observational studies) were identified and included a total of 2914 patients (1300 for CABG and 1614 for PCI with DES).

Results: At 5-year follow-up, there was no significant difference between the CABG and PCI-DES groups in the risk for death (odds ratio [OR] 1.159, $P=0.168$ for random effect) or the composite endpoint of death, myocardial infarction, or stroke (OR 1.214, $P=0.083$). The risk for target vessel revascularization (TVR) was significantly lower in the CABG group compared to the PCI-DES group (OR

0.212, $P<0.001$). The risk of major adverse cardiac and cerebrovascular events (MACCE) was significantly lower in the CABG group compared to the PCI-DES group (OR 0.526, $P<0.001$). It was observed no publication bias about outcomes and considerably heterogeneity effect about MACCE.

Conclusion: CABG surgery remains the best option of treatment for patients with ULMCA disease, with less need of TVR and MACCE rates at long-term follow-up.

Descriptors: Meta-analysis. Myocardial revascularization. Drug-eluting stents.

Resumo

Objetivo: Comparar segurança e eficácia do seguimento a longo prazo da cirurgia de revascularização miocárdica (CRM) com intervenção coronária percutânea (ICP), utilizando stents farmacológicos (SF) em pacientes com lesão de tronco de coronária esquerda não-protetida (TCE).

Métodos: MEDLINE, EMBASE, CENTRAL/CCTR, SciELO, LILACS, Google Scholar e listas de referências de

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Abbreviations, Acronyms & Symbols	
CABG	Coronary artery bypass graft
CENTRAL/CCCTR	Cochrane Central Register of Controlled Trials
CI	Confidence interval
DES	Drug-eluting stents
EuroSCORE	European System for Cardiac Operative Risk Evaluation
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MACCE	Major adverse cardiac and cerebrovascular events
MeSH	Medical subject heading
OR	Odds ratio
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SciELO	Scientific Electronic Library Online
TVR	Target vessel revascularization
ULMCA	Unprotected left main coronary artery

artigos relevantes foram escaneados para estudos clínicos que relataram resultados em 5 anos de seguimento após ICP-SF e CRM para o tratamento de lesão de TCE. Cinco estudos (um

ensaio clínico randomizado e quatro estudos observacionais) foram identificados e incluíram um total de 2914 pacientes (1300 para CRM e 1614 para ICP-SF).

Resultados: Aos 5 anos de seguimento, não houve diferença significativa entre os grupos CRM e ICP-SF no risco de morte (odds ratio [OR] 1,159, $P=0,168$) ou desfecho composto de morte, infarto do miocárdio, ou AVC (OR 1,214, $P=0,083$). O risco de necessidade de nova revascularização foi significativamente menor no grupo CRM em comparação com o grupo de ICP-SF (OR 0,212, $P<0,001$). O risco de eventos adversos cardíacos maiores e cerebrovasculares (EACMC) foi significativamente menor no grupo CRM em comparação com o grupo de ICP-SF (OR 0,526, $P<0,001$). Não foi observado viés de publicação sobre os resultados e considerável heterogeneidade dos efeitos sobre EACMC.

Conclusão: CRM continua sendo a melhor opção de tratamento para pacientes com lesão de TCE, com menos necessidade de novas revascularizações e EACMC no seguimento a longo prazo.

Descritores: Metanálise. Revascularização miocárdica. Stents farmacológicos.

INTRODUCTION

Rationale

Current guidelines recommend percutaneous coronary intervention (PCI) of unprotected left main coronary artery (ULMCA) with stents as a Class IIa or IIb alternative to coronary artery bypass graft (CABG) in patients with conditions that are associated with a low risk of PCI procedural complications and/or increased risk of adverse surgical outcomes [1]. Capodanno et al. [2] recently published a meta-analysis of 4 randomized controlled trials and suggested, boldly, that “based on that study, revision of the guidelines regarding left main PCI is warranted, raising the level of evidence of current recommendations from B to A”. Although recent randomized controlled trials have suggested that PCI with drug-eluting stents (DES) could be a non-inferior strategy that might be used safely [3,4], sample sizes are small (and some conclusions may be affected by this aspect) and observational studies (“real-world” studies) should not be ignored in meta-analyses.

Recently, Sá et al. [5] published a new meta-analysis with 16 studies (three randomized and 13 observational) with 1-year follow up results. This one argued against the “non-inferiority” of PCI with DES in comparison

to CABG surgery and against the idea that PCI could be considered a reasonable choice in elective cases (not mentioning prohibitive risk patients, acute patients and those who reject surgery), given that, although the rates of death between both strategies were not statistically different, the need of new procedures and major adverse cardiac and cerebrovascular events rates were clearly lower in patients treated with CABG surgery. Sá et al. [5] emphasized that the length of follow-up considered for their study may have been too short (1-year) to truly detect differences between the treatment groups, and so was the study of published by Capodanno et al. [2].

Performing a quick search on medical literature, we found no meta-analyses that evaluated the long-term results regarding this topic (PCI with DES versus CABG in ULMCA disease). Taking into considerations all these aspects, it is necessary to evaluate the long-term results of CABG surgery versus PCI with DES in scenario of ULMCA disease, using the highest level of existing evidence.

Objective

We performed a meta-analysis of randomized controlled trials and observational studies to compare

CABG to PCI with DES for the treatment of patients with ULMCA disease, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6].

METHODS

Eligibility Criteria

Using PICOS studies were considered if: (1) population comprised patients with ULMCA disease; (2) compared efficacy or effectiveness between CABG and PCI with DES; (3) outcomes studied included myocardial infarction, cerebrovascular events, death, target vessel revascularization (TVR) or combined outcomes (MACCE – major adverse cardiac and cerebrovascular events); (4) presented follow-up of at least 5 years.

Information Sources

The following databases were used (until July 2012): MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), ClinicalTrials.gov, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde – The Latin American and Caribbean Health Sciences), Google Scholar and reference lists of relevant articles.

Search

We conducted the search using Medical Subject Heading (MeSH) terms “coronary artery bypass graft” OR “coronary artery bypass grafting” OR “coronary artery bypass surgery” OR “coronary bypass surgery” OR “coronary artery bypass graft surgery” OR “coronary artery bypass” OR “coronary bypass” AND “drug-eluting stent” OR “sirolimus-eluting stent” OR “paclitaxel-eluting stent” AND “unprotected left main” OR “left main stenting” OR “left main coronary artery disease” OR “left main PCI” OR “unprotected left main coronary artery” OR “left main stenosis” OR “left main coronary artery stenting” OR “unprotected left main stenting”.

Study Selection

The following steps were done: (1) identification of titles of records through databases searching; (2) removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text articles; (5) final inclusion in study.

One reviewer followed the steps 1 to 3. Two independent reviewers followed step 4 and selected studies. Inclusion

or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer took the final decision.

Data Items

The primary endpoint was the Odds Ratio (OR) for mortality after PCI or CABG, up to 5 years. Secondary end points were the OR for composite endpoint of death, myocardial infarction or stroke; TVR (target vessel revascularization – repeat revascularization of the treated vessel) after the procedure; and MACCE (major adverse cardiac and cerebrovascular events – composite endpoint of death, myocardial infarction, stroke or TVR).

Data Collection Process

Two independent reviewers extracted the data. When there was disagreement about data, a third reviewer (the first author) checked the data and took the final decision about it. From each study, we extracted patient characteristics, study design, and outcomes at 5-year after treatment of ULMCA stenosis. When possible, actual probabilities of mortality and death after 5-year following PCI or CABG were used to calculate odds ratios. Alternatively, probabilities of mortality or MACCE were estimated from published Kaplan-Meier survival curves. We also extracted TVR from the total MACCE events and reported this outcome as a separate measure. When MACCE was not reported, we calculated it using the events of death, myocardial infarction, stroke and TVR and reported this outcome as a separate measure.

Risk of Bias in Individual Studies

Included studies were assessed for the following characteristics: design (prospective or retrospective), randomization (yes or no), multicenter enrollment (yes or no), characteristics of participants and personnel (performance bias), outcome assessment (detection bias), incomplete outcome data addressed (attrition bias) and adequation of multivariate adjustment for possible confounders.

Two independent reviewers assessed risk of bias. Agreement between the two reviewers was assessed using kappa statistics for full text screening, and rating of relevance and risk of bias. When there was disagreement about risk of bias, a third reviewer (the first author) checked the data and took the final decision about it.

Summary Measures

The principal summary measures were OR's with

95% Confidence Interval (CI) and *P* values (that will be considered statistically significant when <0.05). The meta-analysis was completed using the software Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, New Jersey, USA).

Synthesis of Results

Forest plots were generated for graphical presentations for clinical outcomes and we performed the I^2 test and χ^2 statistics for assessment of heterogeneity across the studies [7]. Each study was summarized by the OR for PCI compared to CABG. The OR's were combined across studies using DerSimonian-Laird random effects model [8] and with the fixed effects model using the Mantel-Haenszel model [9]. Both models were weighted by number of events in each study.

Risk of Bias Across Studies

To assess publication bias, a funnel plot was generated (for each outcome), being statistically assessed by Begg and Mazumdar's test [10] and Egger's test [11].

Meta-regression Analysis

Meta-regression analyses were performed to determine whether the effects of CABG were modulated by pre-specified factors. Meta-regression graphs describe the effect of CABG on the outcome (plotted as a log OR on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis). Meta-regression coefficients show the estimated increase in log OR per unit increase in the covariate. Since $\log OR > 0$ corresponds to $OR > 1$ and $\log OR < 0$ corresponds to $OR < 1$, a negative coefficient would indicate that as a given factor increases, the OR decreases.

The pre-determined modulating factors for all outcomes to be examined were: sex, age, diabetes and prior PCI. Sex was represented as the proportion of females in the studies. Age was represented as the mean age of the patients participating in the studies. Diabetes was represented as the proportion of diabetics in the studies. Prior PCI was represented as the proportion of patients who underwent PCI before any interventions in the studies.

RESULTS

Study Selection

A total of 14,705 citations were identified, of which 31 studies were potentially relevant and retrieved as full-text. Five publications fulfilled our eligibility criteria [12-16]. Interobserver reliability of study relevance was excellent

(Kappa=0.84). Agreement for decisions related to study validity was very good (Kappa=0.81). The search strategy can be seen in Figure 1.

Study Characteristics

Characteristics of each study are shown in Table 1. A total of 2914 patients were studied with 1300 receiving CABG and 1614 receiving PCI with DES. Of the 5 studies, one was randomized controlled trial [14], one matched the treatment cohorts using European System for Cardiac Operative Risk Evaluation (EuroSCORE) [16], two used other propensity scores to guarantee like-to-like comparisons [12,15], Four studies mostly used Cypher stent (sirolimus) or Taxus stent (paclitaxel) and one study did not report which DES was used. The overall internal validity was moderate risk of bias and is illustrated in Table 2.

Synthesis of Results

The OR of the risk of death in the CABG group compared with the PCI-DES group in each study, at the 5-year time point, is reported in Figure 2. There was no evidence for heterogeneity of treatment effect among the studies for death. The overall OR (95% confidence interval) of mortality showed no difference between CABG and PCI-DES at 5-year (fixed effect model: $OR\ 1.159$, $P=0.168$; random effect model: $OR\ 1.159$, $P=0.168$).

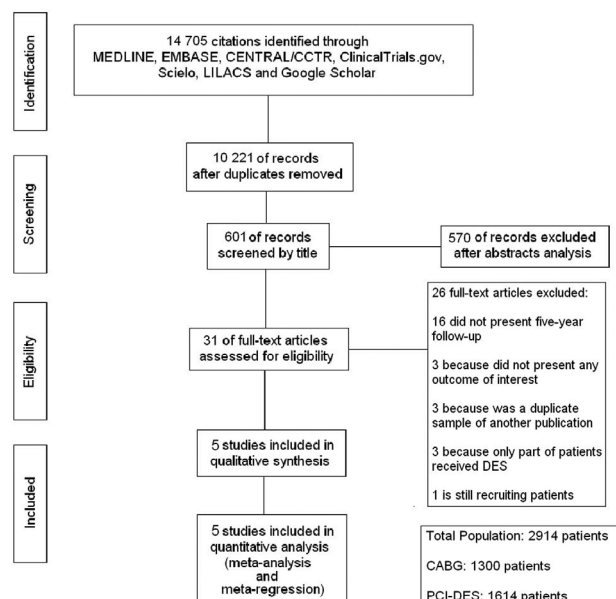


Fig. 1 – Flow diagram of studies included in data search

Table 1. Study characteristics.

Study	PCI (n)	DES	Complete revascularization with PCI (%)	CABG (n)	LIMA to LAD (%)	Off-pump (%)	Complete revascularization with CABG (%)	Unadjusted risk	Method of Adjustment
Chang et al. 2012 [12]	556	NR	NR	309	NR	NR	NR	CABG higher risk clinical profile; EuroSCORE higher risk profile; SYNTAX score higher risk profile	Propensity matched
Terazawa et al. 2012 [13]	68	Cypher (88%) Taxus (12%)	NR	57	93	51	NR	CABG higher risk clinical profile; EuroSCORE higher risk profile	Multivariate logistic regression and multivariable Cox regression
Boudriot et al. 2011 [14]	100	Cypher (98%) Taxus (2%)	98	101	99	46	97	Randomized, same risk	Unneeded
MAIN-COMPARE registry 2010 [15]	396	Cypher (79%) Taxus (21%)	NR	396	98	42	NR	Propensity score matched	Unneeded
Chieffo et al. 2010 [16]	107	Cypher (51.4%) Taxus (48.2%)	NR	142	NR	NR	NR	CABG higher risk clinical profile	Propensity score adjusted (EuroSCORE)

CABG: coronary artery bypass grafting; DES: drug-eluting stent; LAD: left anterior descending; LIMA: left internal mammary artery; PCI: percutaneous coronary intervention; NR: non-reported

Table 2. Analysis of risk of bias – internal validity.

Study	Study design	Selection bias	Performance bias	Attrition bias	Detection bias	Multivariate adjustment for possible confounders
Chang et al. 2012 [12]	NP, NR, M	B	B	C	B	Probably adequate
Terazawa et al. 2012 [13]	NP, NR, NM	B	B	B	B	Probably adequate
Boudriot et al. 2011 [14]	P, R, M	A	B	A	B	Probably adequate
MAIN-COMPARE registry 2010 [15]	P, NR, M	B	B	B	B	Probably adequate
Chieffo et al. 2010 [16]	NP, NR, NM	B	B	C	B	Probably adequate

This was performed by 2 independent reviewers. The overall bias of the combined studies was considered moderate. A: risk of bias is low; B: risk of bias is moderate; C: risk of bias is high; D: incomplete reporting

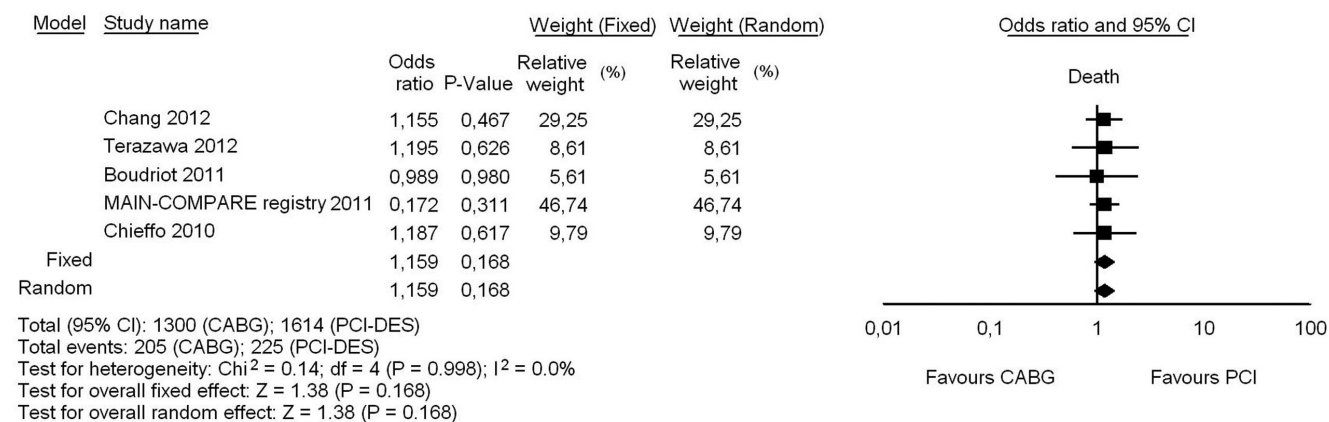


Fig. 2 – Odds ratio and conclusions plot of mortality associated with CABG versus DES

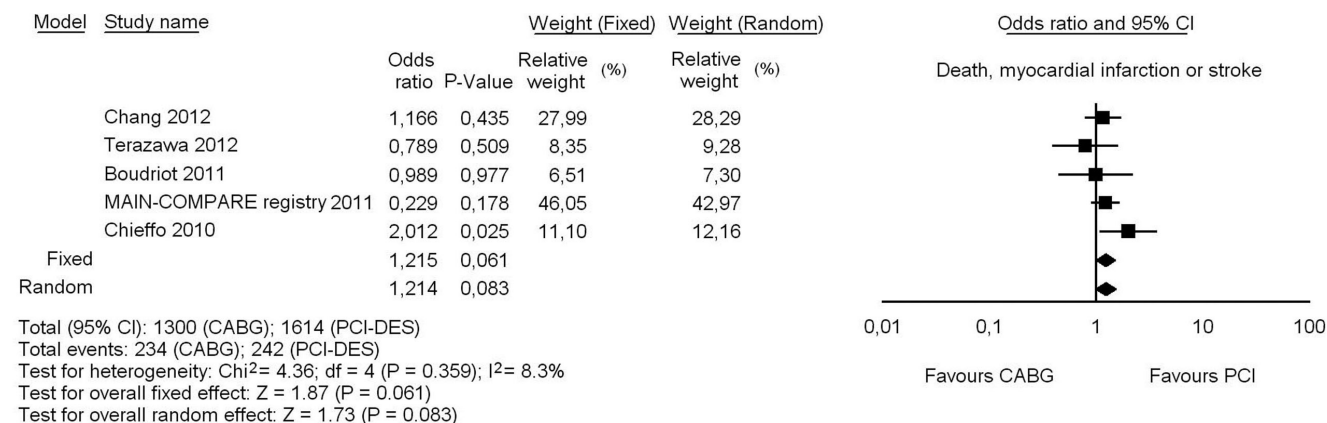


Fig. 3 – Odds ratio and conclusions plot of composite endpoint (death, myocardial infarction or stroke) associated with CABG versus DES

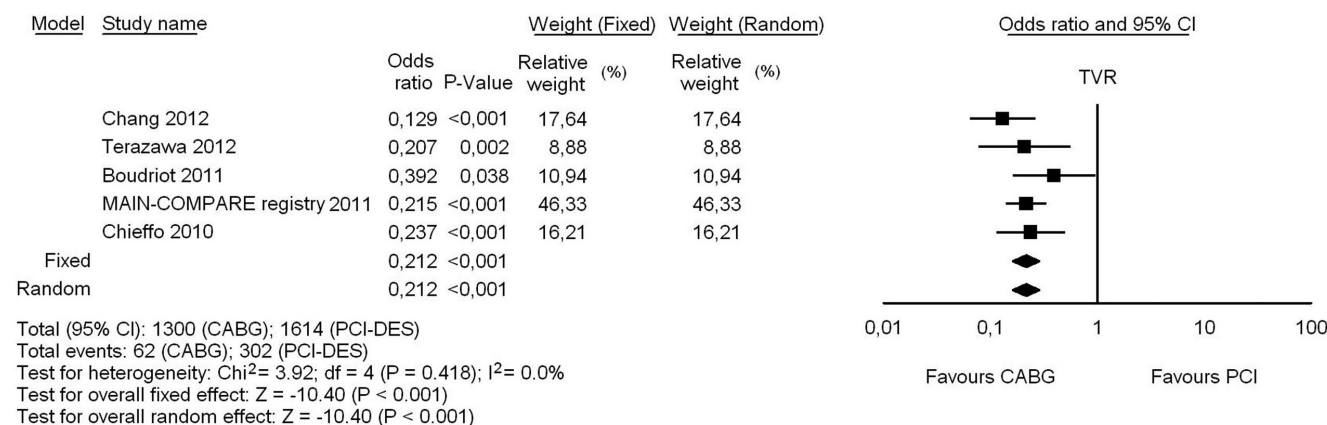


Fig. 4 – Odds ratio and conclusions plot of target vessel revascularization (TVR) associated with CABG versus DES

The OR of the risk of composite endpoint of death, myocardial infarction or stroke in the CABG group compared with the PCI-DES group in each study, at the 5-year time point, is reported in Figure 3. There was evidence of low heterogeneity of treatment effect among the studies for this composite endpoint. The overall OR (95% confidence interval) of composite end point showed no difference between PCI-DES and CABG at 5-year (fixed effect model: OR 1.215, $P=0.061$; random effect model: OR 1.214, $P=0.083$).

The OR of the risk of TVR in the CABG group compared with the PCI-DES group in each study, at the 5-year time point, is reported in Figure 4. There was no evidence for heterogeneity of treatment effect among the studies for TVR. The overall OR (95% confidence interval) of TVR showed an important difference between CABG and PCI-DES at 5-year (fixed effect model: OR 0.212, $P<0.001$;

random effect model: OR 0.212, $P<0.001$), which favors the CABG strategy.

The OR of the risk of MACCE in the CABG group compared with the PCI-DES group in each study, at the 5-year time point, is reported in Figure 5. There was a considerably evidence for heterogeneity of treatment effect among the studies for MACCE. The overall OR (95% confidence interval) of MACCE showed an important difference between CABG and PCI-DES at 5-year (fixed effect model: OR 0.543, $P<0.001$; random effect model: OR 0.526, $P<0.001$), which favors the CABG strategy.

Risk of Bias Across Studies

Funnel plot analysis (Figure 6) disclosed symmetry around the axis for the treatment effect in all outcomes, which means we probably do not have publication bias related to these end points.

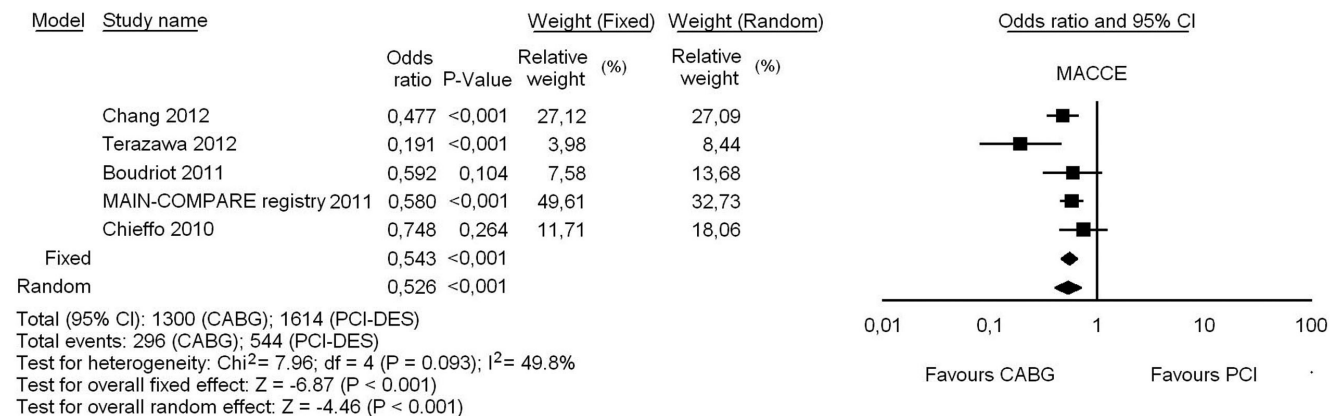


Fig. 5 – Odds ratio and conclusions plot of major adverse cardiac and cerebrovascular events (MACCE) associated with CABG versus DES

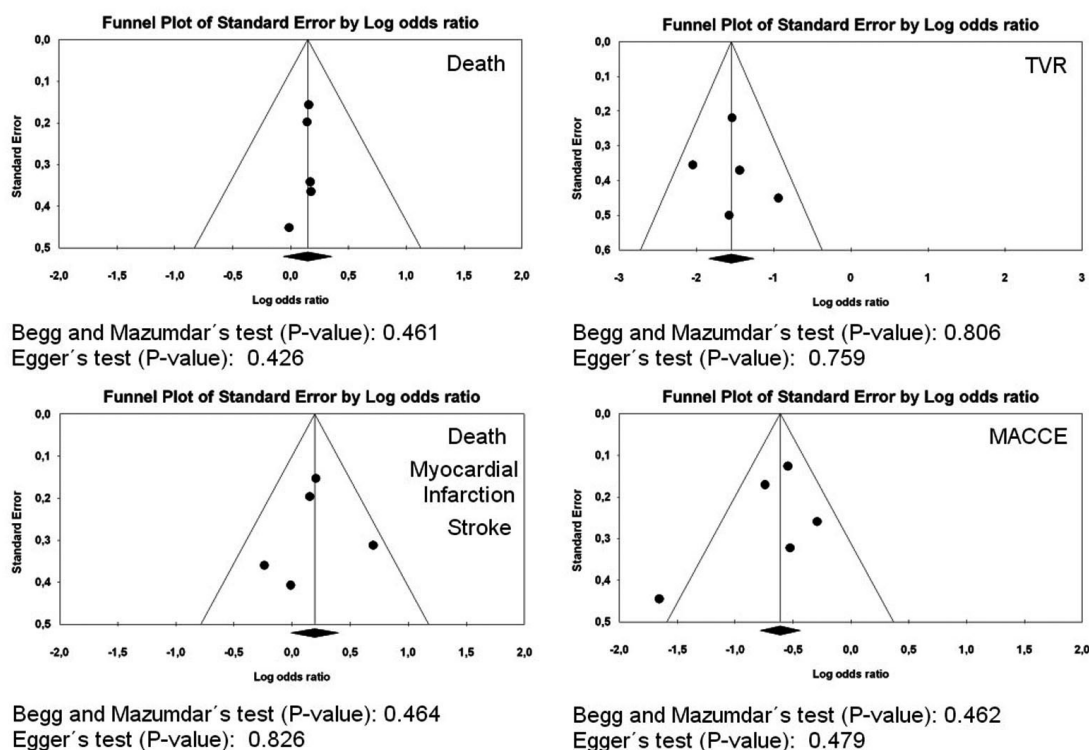


Fig. 6 – Publication bias analysis by funnel plot graphic

Meta-regression Analysis

We observed a statistically significant coefficient for 2 situations: (1) MACCE and proportion of diabetic patients (coefficient -0.04, 95% CI -0.07 to -0.01, $P=0.016$); (2) MACCE and proportion of prior PCI (coefficient -0.03, 95% CI -0.05 to -0.01, $P=0.010$). It

means that the greater the proportion of diabetic patients and prior PCI in a population undergoing CABG, the lower the OR for MACCE in CABG group, i.e., the greater the protective effect of CABG for diabetic patients and/or submitted to prior PCI in relation to the incidence of MACCE (Figure 7).

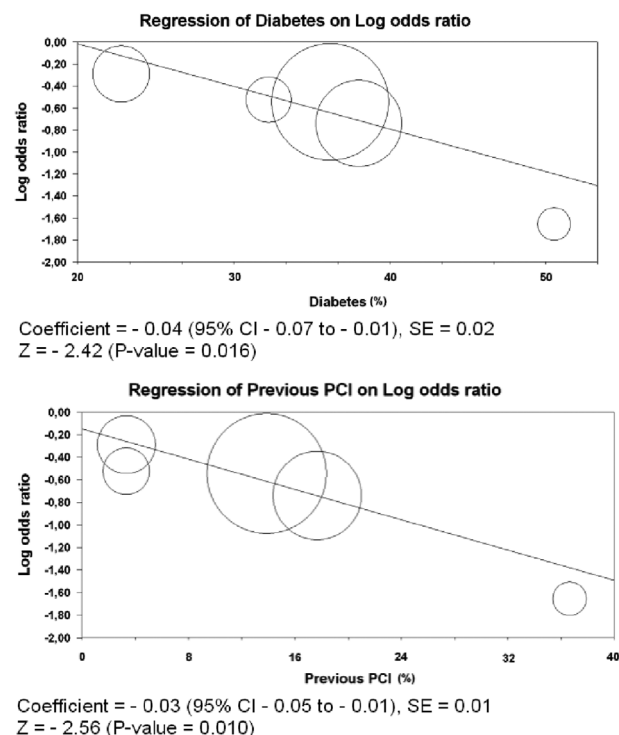


Fig. 7 – Meta-regression analysis by representative plots

DISCUSSION

Summary of Evidence

The results of this meta-analysis demonstrate that CABG remains the best option for ULMCA disease. At 5-year follow-up, although there was no difference in the risk for death and composite endpoint of death, myocardial infarction and stroke, there was a significantly higher risk for TVR and MACCE (this last one under the influence of heterogeneity of the effects) associated with PCI with DES, with no publication bias of the summary measures of all outcomes.

Considerations About this Meta-Analysis

To our knowledge, this is the first meta-analysis of studies with 5-years follow-up performed to date about PCI-DES versus CABG in ULMCA disease, providing incremental value by demonstrating that CABG reduces the incidence of TVR and MACCE compared with PCI-DES. Furthermore, this analysis suggests that PCI-DES does not significantly reduce the incidence of long-term all-cause mortality and composite endpoint of death, myocardial infarction and stroke in comparison with

CABG. The potential benefits of CABG on these outcomes appear to be influenced by diabetes and previous PCI.

Diabetes mellitus is a powerful independent predictor of cardiovascular events. It is associated with extensive coronary artery disease, increased mortality regardless of revascularization mode and unfavorable prognosis if treated medically [17]. The SYNTAX trial [18] has shown in the diabetic subset of patients at 1 year, similar death/infarction/stroke rates between the two revascularization groups, increased risk across all SYNTAX terciles and higher mortality and MACCE in diabetic patients with SYNTAX score ≥ 33 with PCI over surgery. As we can see by meta-analysis and meta-regression, the total population of patients with ULMCA disease benefit from surgery (in comparison with PCI-DES) and the population of diabetics benefit more, since the presence of diabetes modulate the effect toward the protective effect (lesser odds ratio).

In case of prior PCI, the severity of the progression of coronary atherosclerotic disease may justify the greater MACCE in PCI-DES group previously submitted to PCI, making CABG appears to be more protective. Currently, patients undergoing initial PCI with a stent have severe atherosclerotic disease, but not as severe as those undergoing initial surgical treatment; when treatment with stents fails, these patients are referred for surgical revascularization, however the atherosclerotic disease is then more severe and diffuse [19]. At present, the totality of evidence suggests that CABG appears better for the “sicker” patients, i.e., those with multivessel disease or ULMCA disease and characteristics indicative of extensive atheroma burden with or without depressed left ventricle ejection fraction [20]. We should not forget that SYNTAX trial showed the undoubted benefits of surgery (in comparison with PCI-DES) in the group with higher SYNTAX score, i.e., more extensive and complex lesions [4].

Risk of Bias and Limitations

Another limitation is the heterogeneity of the strategies across the studies. Among PCI strategies, studies used many combinations of sirolimus-stent and paclitaxel-stents (one did not report). Among CABG strategies, there is variability in rates of use of internal thoracic artery (two did not report), use of cardiopulmonary bypass (on-pump versus off-pump CABG; two did not report), etc. And among both studies, an important aspect to consider is the rate of complete revascularization (not reported in four studies), which reflects in outcomes.

There are inherent limitations with meta-analyses, including the use of cumulative data from summary

estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups. This meta-analysis included data from nonrandomized observational studies, which reflects the “real world” but are limited by treatment bias, confounders, and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes nonrandomized studies less robust.

We tried to analyze the influence of surgical risk profile and profile of lesion complexity; however, it was not possible because studies did not report these issues more systematically and broadly; it would be interesting, for example, that studies always evaluate SYNTAX score of groups, as this would allow further analysis of outcomes with respect to this variable, including meta-analyses on this topic.

A final limitation is the absence of adequate published comparative data for the third therapeutic option, medical therapy. PCI with DES has not been compared with medical therapy alone when we consider ULMCA disease, but CABG has been shown to be superior to medical therapy in this set.

Perspectives

Ongoing and planned trials (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease - PRECOMBAT 1 and 2; Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization - EXCEL) will further facilitate evidence-based clinical decisions for ULMCA disease. Furthermore, the 5-year SYNTAX results (not published yet) will provide us a valuable extension of the 3-year information and possibly elucidate whether PCI should be further performed even in high-risk, very complex coronary disease by experienced teams in large volume centers. Others important registries (as CUSTOMIZE registry [11]) did not report their 5-year results yet. We hope that with the publication of all these studies, we will have more evidence about the long-term results, which will enable new meta-analyses with larger samples and other meta-regression analyses, in search of other factors that modulate the results.

CONCLUSIONS

We found evidence that argues against the “non-inferiority” of PCI with DES in comparison to CABG

surgery and against the idea that PCI can be considered a reasonable choice in elective cases (not mentioning prohibitive risk patients, acute patients and those who reject surgery), given that, although the rates of death and composite endpoint (death, myocardial infarction or stroke) between both strategies were not statistically different, the need of new procedures and MACCE rates were clearly lower in patients treated with CABG surgery. However, careful analysis of the data shows that no definite conclusion can be drawn from the evidence available due to the heterogeneity of studies with respect to some outcomes, heterogeneity of strategies (different drug-eluting stents, different ways to perform surgery, etc) and heterogeneity of coronary lesions complexity. Rigorous studies are necessary to define the best way to treat each subset of ULMCA disease.

Based on our findings, we conclude that there is not clear evidence that left main PCI presents non-inferiority to CABG surgery and revision of the guidelines regarding left main PCI must be viewed with caution, and we still do not have enough evidences that make the level of evidence of current recommendations raises from B to A”.

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