Percutaneous Coronary Intervention with Drug-Eluting Stent versus Coronary Artery Bypass Grafting: A Meta-Analysis of Patients with Left Main Coronary Artery Disease

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Abstract

Background: The relative efficacy and safety of percutaneous coronary intervention (PCI) with drug-eluting stents (DES), in comparison to coronary artery bypass grafting (CABG) for left main coronary artery disease (LMCAD) remains controversial.

Methods: We performed a meta-analysis of randomised studies comparing patients with LMCAD treated with PCI with DES versus those treated with CABG, with respect to clinical outcomes at 1, 3 and 5 years. A secondary meta-analysis was performed according to low (<32), or high (≥33) SYNTAX score.

Results: Five studies comprising 4595 patients were included. There was no significant difference in all-cause death at all time points or when stratified with respect to SYNTAX score. The need for repeat revascularization was significantly higher with PCI at all time-points, and regardless of SYNTAX score. There was significant association between need for repeat revascularization with PCI and diabetics (p=0.04). At 5 years, non-fatal MI was higher with PCI owing to increased non-procedural events (OR 3.00; CI 1.45-6.21; p=0.003). CABG showed higher rate of stroke at 1 year (OR 0.21; CI 0.07-0.63; p=0.005). There was no difference in non-fatal MI or stroke at other time points, nor according to SYNTAX score.

Conclusions: PCI with DES or CABG are equivalent strategies for LMCAD up to 5 years with respect to death, regardless of SYNTAX score. PCI increases the rate of non-procedural MI at 5 years. CABG avoids the need for repeat revascularization, especially in diabetics, but this benefit is offset by higher rate of stroke in the first year of follow up.

Key Words: left main stem, coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting

Abbreviations

CABG = coronary artery bypass grafting

DAPT = dual antiplatelet therapy

DES = drug-eluting metal stents

LMCAD = left main coronary artery disease

MACCE = major adverse cardiovascular and cerebrovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

Introduction

Coronary artery bypass grafting (CABG) is considered the gold standard for the vast majority of patients with left main coronary artery disease (LMCAD) [1, 2]. However, over the past decade, there have been a number of studies reporting comparable results between percutaneous coronary intervention (PCI) with drug-eluting stents (DES) and surgical revascularization for the treatment of LMCAD [3-5]. This has been attributed to advances in stent technology, intra-procedural imaging allowing stent optimization, as well as advances in pharmacotherapy to reduce peri-procedural and long term thrombosis risk and restenosis. Consequently, there has been uncertainty regarding the optimal revascularization strategy, especially in light of the recent publication of two additional dedicated multi-centre randomised trials of LMCAD [6, 7].

Although previous meta-analyses comparing PCI with DES and CABG have demonstrated equipoise between the two strategies, the analyses included observational data [3-5]. A recent meta-analysis of randomised trial data from the longest available follow-up has demonstrated no difference in clinical outcomes between PCI with DES and CABG in patients with LMCAD [8]. Our aim was to perform a comprehensive systematic review and meta-analysis of randomised clinical trials in order to evaluate clinical outcomes at short (1 year), medium (3 years) and long (5 years) follow-up duration, and stratify according to coronary disease complexity using the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score.

Methods

Study objectives and design

The outcomes of interest were all-cause death, non-fatal myocardial infarction (MI), repeat revascularization, stroke, defined according to the original study protocols, at 1, 3 and 5 years. We also performed a secondary meta-analysis according to SYNTAX score, bimodally classified as low (<32) or high SYNTAX score (≥33) at maximum follow-up duration. A SYNTAX score cut-off of more than 33 was found to be useful in distinguishing high risk patients after PCI [9, 10]. Inclusion criteria were randomised controlled trials comparing PCI with DES versus CABG for LMCAD, and reporting clinical outcomes. The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [11] and Cochrane methodology [12]. A complete PRISMA 2009 checklist has been followed to guide reporting of our meta-analysis.

Study search strategy

Using Medline, Embase, Scopus, and the Cochrane Library, we performed searches of articles published until December 2016, without language restrictions. Eligible studies were identified using various combinations of the terms: left main, drug-eluting stent, percutaneous, coronary, myocardial infarction, angina, angioplasty, bypass, grafting, and intervention in the abstract or title. Reference lists of the retrieved articles were reviewed to identify further eligible studies. When two similar studies were reported from the same institution, the most recent publication was included in the analysis. Two reviewers independently reviewed all titles, or titles and abstracts from the search results to identify articles according to fulfillment of inclusion criteria. Selected trials were compared, and

disagreement was resolved by team discussion and consensus. Studies were excluded from the meta-analysis if they were duplicates, single-arm studies or included the use of bare-metal stent.

Data extraction

Data extraction was carried out independently and in duplicate by the study investigators. Results of data extraction were then compared, and discrepancies resolved by consensus. If results were incomplete or unclear, the study authors were contacted. Articles selected for the final review were checked to avoid inclusion of data published in duplicate. Data were collated from each study regarding baseline characteristics, including sample characteristics, dual antiplatelet duration, stent type, EuroSCORE, SYNTAX score, and clinical outcomes at 1, 3 and 5 years. All outcomes were defined according to the original study's protocol definition [Supplemental Table 1]. If target vessel revascularization was not reported, we used all repeat revascularizations instead. All-cause death data were used in the analysis, as cardiovascular death data were incomplete at our chosen time points of interest. Of note, peri-procedural MI was included in 4 trials [7, 9, 13, 14], whereas 1 trial only assessed non-procedural MI [6].

Statistical analysis

Pooled odds ratio (OR) with 95% confidence interval (CI) were estimated for binary variables using a random-effects model by the method of DerSimonian and Laird [15]. A pooled analysis of the hazard ratio with 95% CI was also reported [Supplemental Table 2]. Heterogeneity between individual studies was explored by X^2 statistic and characterized with I^2 statistic. In sensitivity analysis, we included only studies that included patients who had non-procedural MI at 5 years. We examined the following relationships; (1) the log-transformed OR of the

effect of PCI with DES on repeat revascularization risk and the log-transformed OR of the effect of PCI with DES on non-fatal MI risk at maximum follow-up duration, (2) the log-transformed OR of the effect of PCI with DES on repeat revascularization risk at maximum follow-up duration and the trial reported percentage of distal bifurcation or trifurcation involvement, and (3) the log-transformed OR of the effect of PCI with DES on repeat revascularization risk at maximum follow-up duration and the trial reported percentage of patients with diabetes mellitus.

The results from meta-analysis were shown using forest-plot. Publication bias was minimised by a comprehensive and inclusive literature search. In addition, funnel plot was used to investigate publication bias. All tests were two-sided, and statistical significance was fixed at 0.05 level. Analysis was carried out using Review Manager Software (RevMan V. 5.3) and Stata V. 11.2 (StataCorp, College Station, Texas, USA).

Results

Five randomised trials involving a total of 4595 patients were identified [6, 7, 9, 13, 14], which directly compared the clinical outcomes of PCI with DES, and CABG in patients with LMCAD [Supplemental Figure 1]. The methodological quality of included studies is described in Supplemental Table 3. The primary outcomes of included studies are listed in Supplemental Table 4. There was no evidence of publication bias having a significant effect on the results [Supplemental Figure 2].

The characteristics of randomised trials are listed in Supplemental Table 5. Greater than three-quarters of patients were male with a mean age of 65±2 years, 25.4% were diabetics, and 34.8% received first generation DES. Of the 2297 patients randomised to receive PCI with DES, stent types were: first generation paclitaxel-eluting stents (n=359), first generation sirolimous eluting stents (n=440), second generation biolimus-eluting stents (n=550), and second generation everolimus-eluting stent (n=948). The maximum follow-up duration for all studies was a median of 5 years.

There was no significant difference in all-cause mortality between PCI and CABG at 1 year (OR 0.70; CI 0.44-1.12; p=0.14) [Figure 1 A], 3 years (OR 1.14; CI 0.73-1.80; p=0.56) [Figure 1 B], or 5 years (OR 0.92; CI 0.69-1.24; p=0.60) [Figure 1 C], and with low (OR 0.89; CI 0.47-1.71; p=0.74), or high (OR 0.88; CI 0.19-3.95; p=0.86) SYNTAX score [Supplemental Figure 3].

There was no difference in the incidence of non-fatal MI between PCI and CABG at 1 year (OR 1.17; CI 0.70-1.95; p=0.55) [Figure 2 A], or 3 years (OR 1.21; CI 0.65-2.26; p=0.54) [Figure 2 B]. However, at 5 years, non-fatal MI was higher with PCI (OR 2.04; CI 1.30-3.19; p=0.002) [Figure 2 C], owing to an increased rate of non-procedural MI (OR 3.00; CI 1.45-6.21; p=0.003) [Supplemental Figure 4]. There

was no difference in the incidence of non-fatal MI between PCI and CABG with low (OR 1.24; CI 0.67-2.29; p=0.49), or high (OR 1.86; CI 0.82-4.24; p=0.14) SYNTAX score [Supplemental Figure 3].

The need for repeat revascularization was significantly higher with PCI with DES compared to CABG, consistent across each follow up time point; at 1 year (OR 2.51; CI 1.57-4.02; p<0.001) [Figure 3 A], 3 years (OR 1.84; CI 1.43-2.37; p<0.001) [Figure 3 B], 5 years (OR 1.86; CI 1.45-2.38; p<0.001) [Figure 3 C], and with low (OR 1.69; CI 1.31-2.17; p<0.001), or high (OR 3.75; CI 2.14-6.57; p<0.001) SYNTAX score [Supplemental Figure 3].

CABG significantly increased the rate of stroke at 1 year (OR 0.21; CI 0.07-0.63; p=0.005) [Figure 4 A], but not at 3 years (OR 0.51; CI 0.19-1.40; p=0.19) [Figure 4 B], 5 years (OR 0.93; CI 0.24-3.64; p=0.92) [Figure 4 C], or with low (OR 0.72; CI 0.42-1.22; p=0.22), or high (OR 0.32; CI 0.08-1.33; p=0.12) SYNTAX score [Supplemental Figure 3].

At maximum follow-up duration, there was significant association between repeat revascularization risk with PCI with DES and the trial reported percentage of patients with diabetes (p=0.04) [Supplemental Figure 5], but not with non-fatal MI risk (p=0.23) [Supplemental Figure 6], nor the trial reported percentage of distal bifurcation or trifurcation involvement (p=0.40) [Supplemental Figure 7].

Discussion

The major findings of our review suggest that, in selected patients, PCI is a safe and durable alternative to CABG at short-term follow-up in patients with LMCAD.

PCI increased the incidence of non-procedural MI at 5 years, a result that merits further investigation, as it is driven by a single study. The absence of benefit of CABG over PCI in terms of mortality or stroke, at all time points and even at 5 years from the index procedure, suggests that the increased rate of repeat revascularization in the PCI arm does not translate into clinical harm, compared with CABG. In our analysis, CABG was associated with an increased risk of stroke at one year follow-up, yet this risk was abated at longer follow-up period. This result is in line with previous analyses of LMCAD patients undergoing CABG [4, 16]. This is an important issue because patients, and many cardiologists, may be willing to accept the trade-off between the need for repeat revascularization with PCI in order to avoid the potential early risk of stroke with CABG. The early increased risk of stroke peri-operatively with CABG is likely multifactorial, related to cerebral embolism, hypoperfusion injury, surgical manipulation of the great vessels, or perioperative atrial fibrillation [17]. Furthermore, PCI is also more attractive to patients with its minimally invasive approach and shorter length of hospital stay.

In the era of bare-metal stent, the LE MANS randomised trial of 105 patients with LMCAD and low SYNTAX score showed that PCI was associated with favourable outcomes up to 10 years compared to CABG [18]. The results of two landmark studies were recently published. The NOBLE trial suggests that CABG might be better than PCI with DES for the treatment of LMCAD at 5 years follow-up (6). However, the EXCEL trial shows that PCI with DES was non-inferior to CABG at 3 years follow-up (7).

Equipoise in short to medium term outcomes between the two strategies in our analysis was independent of coronary disease complexity, as assessed with the SYNTAX score. In other words, PCI with DES in LMCAD patients may be suitable for low- as well as select high-risk PCI patients. However, this conclusion must be moderated by the fact that the trials included only a small number of patients with a high SYNTAX score. First-generation DES were used in about 35% of patients, and have been associated with an increased risk of very late stent thrombosis (>1 year) [19]. This may have contributed to the increased risk of non-procedural MI with PCI at 5 years. Despite this increased risk, our analysis shows an equivalence of PCI with DES and CABG strategies for up to 5 years with respect to mortality.

As might be expected, our analysis shows that PCI is associated with increased rate of repeat revascularization when compared to CABG at all follow-up durations, independent of SYNTAX score. This seems to be consistent amongst all included trials, and regardless of first or second generation DES [Figure 3]. However, counter-intuitively, this need for increased revascularization was not related to more complex coronary anatomy (such as distal bifurcation or trifurcation), nor was it associated with an increase risk of MI. What drives the difference in our analysis seems to be the beneficial effect of CABG on reducing the need for repeat revascularization. Of note, although graft failure is common, occurring in up to 43% of patients post-CABG during the first 4 years from surgery [20], this does not always lead to revascularization probably because it is clinically silent in many patients; in part due to the preservation of collateral flow through the native vessel, in stark contrast to the typical ST-elevation MI presentation of acute stent occlusion. Moreover, the routine use of the internal mammary artery in CABG can provide very long-term patency rates.

The need for repeat revascularization was found to be associated with PCI with DES for LMCAD in patients with diabetes. This is not surprising since these patients generally have a great burden of atherogenic risk factors, and disease burden [21]. This is supported by previous studies showing that CABG achieved more favorable outcomes compared with PCI in diabetic patients [22]. Thus, with few exceptions, CABG should therefore remain the preferred treatment option in diabetics with LMCAD.

The utility of the SYNTAX score for selecting PCI versus CABG in LMCAD is uncertain and may not be important [23]. As with most coronary angiographic disease complexity scores, it does not incorporate clinical factors or the functional significance of the stenosis. Available data suggests a SYNTAX score threshold of 34 to identify patients who benefit most from CABG [9, 10]. Our meta-analysis of randomised trial data, however, is hypothesis generating, and suggests that clinical safety outcomes, including mortality, may not differ between percutaneous or surgical revascularization strategies based on the SYNTAX score.

There are several reasons why the trials included in this analysis are not directly comparable. The use of intravascular ultrasound in PCI patients varied significantly between trials [Supplemental Table 5], with about a third of patients not receiving this optimization modality. There is abundant evidence that intravascular ultrasound decreases stent thrombosis, restenosis, and revascularization rates [24, 25]. We believe that intravascular ultrasound guidance during PCI of LMCAD is necessary to optimize stent expansion and ensure full lesion coverage and achieve optimal long-term outcomes. The duration of dual antiplatelet therapy (DAPT), the mainstay treatment post PCI to minimise

stent thrombosis and MI risk [26], varied between 6 and 12 months in included trials. Recently, there has been much controversy concerning the optimal duration of DAPT with many supporting long-term (>1 year) therapy, especially following left main angioplasty or complex PCI to reduce ischemic outcomes [27, 28]. Further studies are needed to evaluate the clinical outcome of PCI with DES with longer DAPT duration.

Our study has several limitations. Firstly, we did not have access to patient-level data. Availability of individual patient data could improve the reliability of the findings and permit more flexible analyses. Secondly, variable definitions of clinical outcomes by the primary studies may have introduced detection bias. The definition of repeat revascularization slightly differed between trials. Target vessel revascularization rates and cardiovascular death rates were not reported in all trials. The definition of MI also differed between trials and non-procedural MI events were unavailable. Thirdly, only few studies were available for analyses and this resulted in small sample size with non-significant overall effect size. Additionally, incomplete reporting resulted in underpowered SYNTAX analyses and may have introduced reporting bias. Finally, the randomised trials included were open-label with a potential for high performance bias.

In conclusion, PCI with DES or CABG appear equivalent management strategies for LMCAD for up to 5 years with respect to death, regardless of SYNTAX score. PCI increases the rate of non-procedural MI at 5 years. CABG avoids the need for repeat revascularization, especially in diabetics, but this benefit is offset by a higher rate of stroke in the first year of follow up, that is likely procedure-driven.

Longer-term follow-up is required to examine whether additional differences between PCI and CABG emerge over time.

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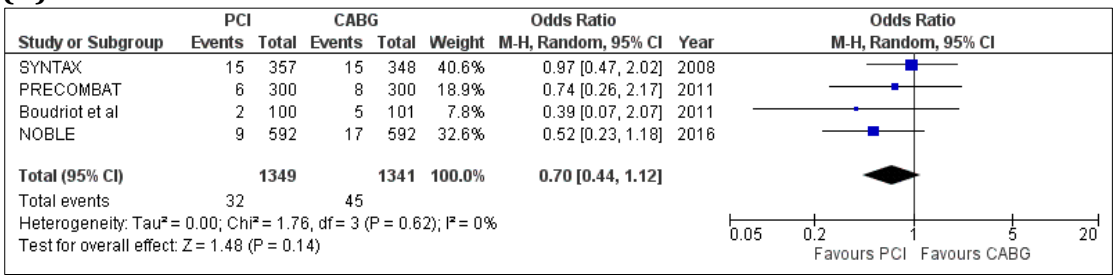
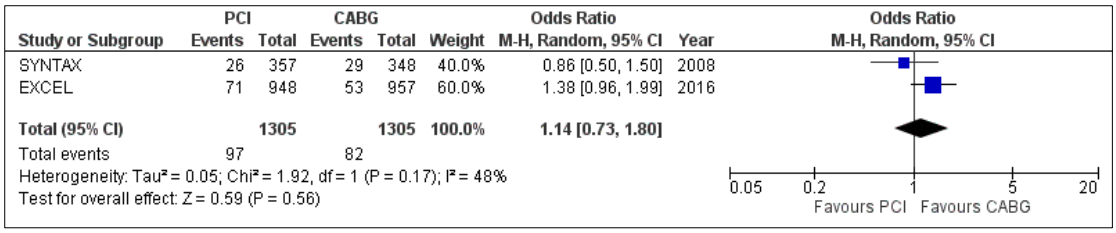
Figure 1: Death with PCI with DES versus CABG in randomised studies in LMCAD
(A) 1 year, (B) 3 years and (C) 5 years

(A)



(B)



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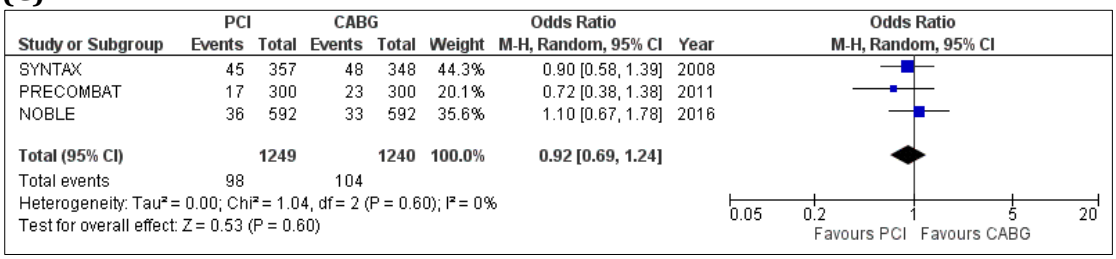
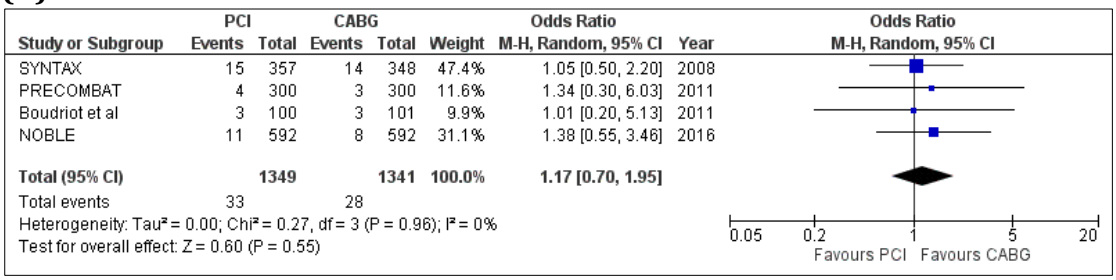


Figure 2: Myocardial infarction with PCI with DES versus CABG in randomised studies in LMCAD
(A) 1 year, (B) 3 years and (C) 5 years

(A)



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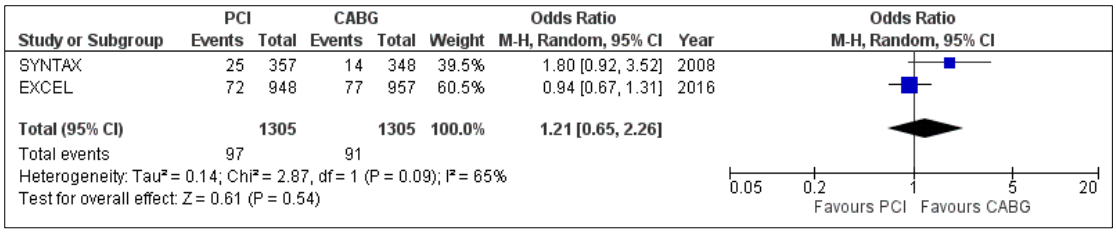

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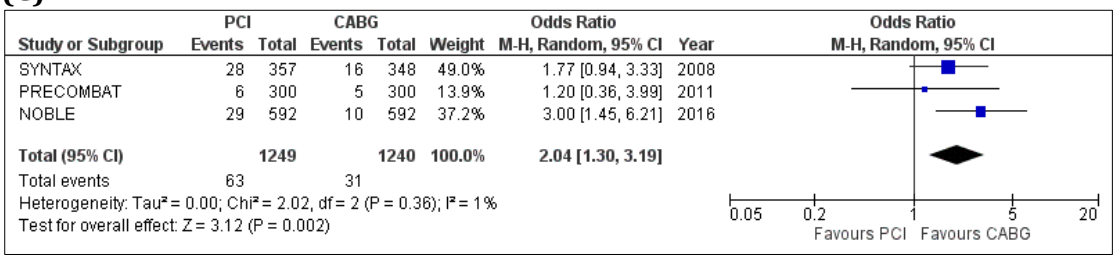
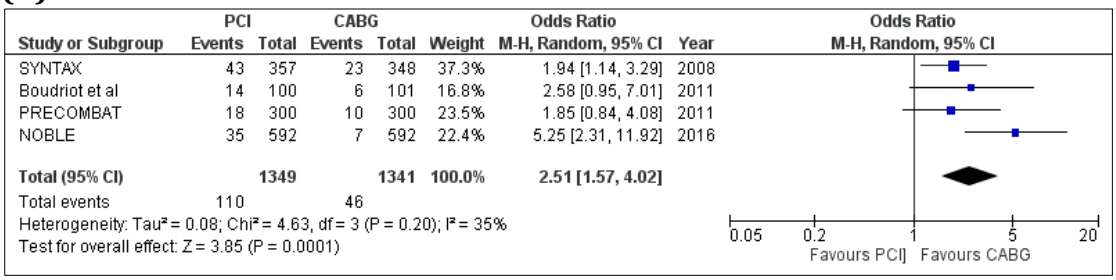
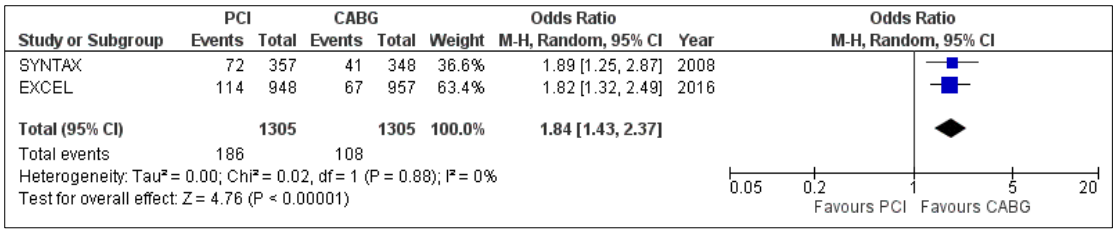


Figure 3: Repeat revascularization with PCI with DES versus CABG in randomised studies in LMCAD
(A) 1 year, (B) 3 years and (C) 5 years

(A)



(B)



(C)

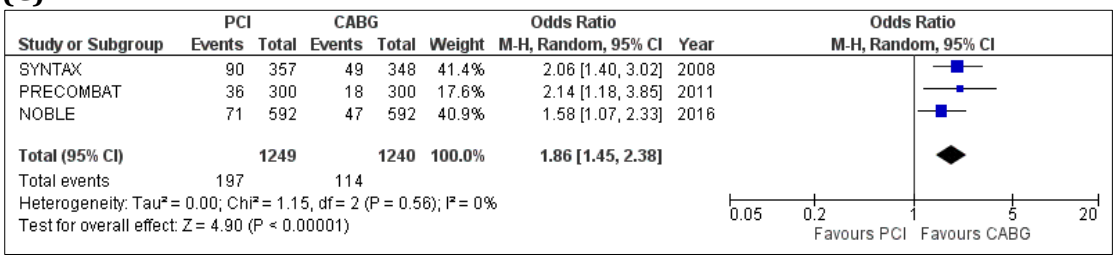
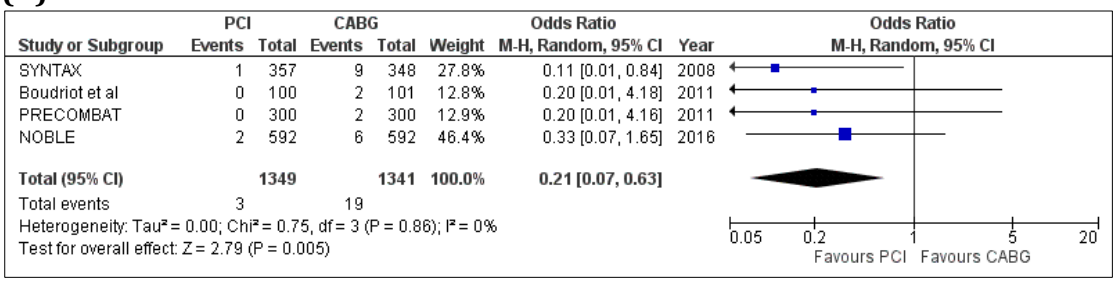
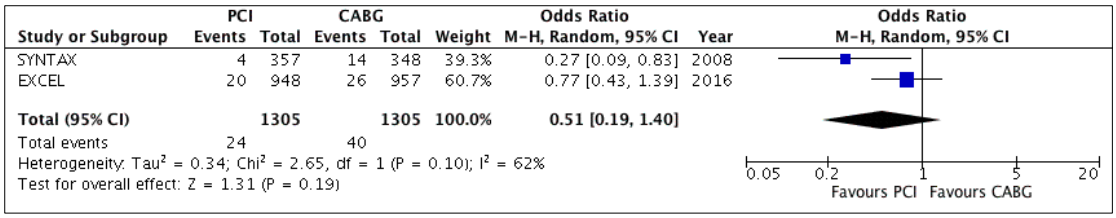


Figure 4: Stroke with PCI with DES versus CABG in randomised studies in LMCAD
(A) 1 year, (B) 3 years and (C) 5 years

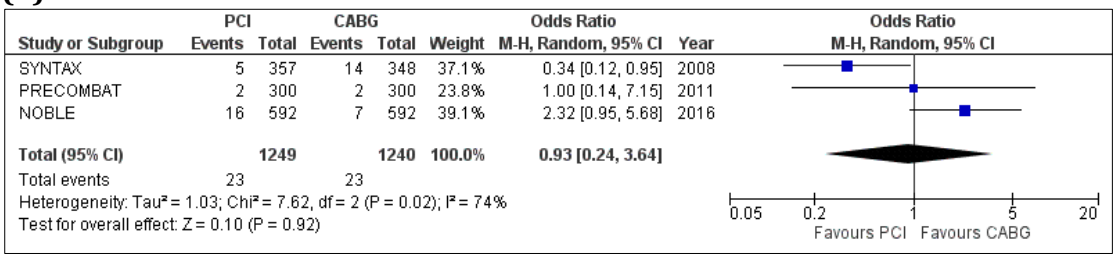
(A)



(B)


PCI
CABG
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
SYNTAX 4 357 14 348 39.3% 0.27 [0.09, 0.83] 2008
EXCEL 20 948 26 957 60.7% 0.77 [0.43, 1.39] 2016
Total (95% CI) 1305 1305 100.0% 0.51 [0.19, 1.40]
Total events 24 40
Heterogeneity: Tau² = 0.34; Chi² = 2.65, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 1.31 (P = 0.19)
0.05 0.2 1 5 20
Favours PCI Favours CABG

(C)


PCI
CABG
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
SYNTAX 5 357 14 348 37.1% 0.34 [0.12, 0.95] 2008
PRECOMBAT 2 300 2 300 23.8% 1.00 [0.14, 7.15] 2011
NOBLE 16 592 7 592 39.1% 2.32 [0.95, 5.68] 2016
Total (95% CI) 1249 1240 100.0% 0.93 [0.24, 3.64]
Total events 23 23
Heterogeneity: Tau² = 1.03; Chi² = 7.62, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 0.10 (P = 0.92)
0.05 0.2 1 5 20
Favours PCI Favours CABG