

Minimally Invasive Direct Coronary Artery Bypass Versus Percutaneous Coronary Intervention for Isolated Left Anterior Descending Artery Stenosis: An Updated Meta-Analysis

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ABSTRACT

Background: The optimal revascularization strategy for isolated left anterior descending (LAD) coronary artery lesion between minimally invasive direct coronary artery bypass (MIDCAB) and percutaneous coronary intervention (PCI) remains controversial. This updated meta-analysis aims to compare the long- and short-term outcomes of MIDCAB versus PCI for patients with isolated LAD coronary artery lesions.

Methods: The Pubmed, Web of Science, and Cochrane databases were searched for retrieving potential publications from 2002 to 2022. The primary outcome was long-term survival. Secondary outcomes were long-term target vessel revascularization (TVR), long-term major adverse cardiovascular events (MACEs), and short-term outcomes, including postoperative mortality, myocardial infarction (MI), TVR, and MACEs of any cause in-hospital or 30 days after the revascularization.

Results: Six randomized controlled trials (RCTs) and eight observational studies were included in this updated meta-analysis. In total, 1757 patients underwent MIDCAB and 15245 patients underwent PCI. No statistically significant difference was found between the two groups in the rates of long-term survival. MIDCAB had a lower long-term MACE rate compared with PCI. Besides, PCI resulted in an augmented risk of TVR. Postoperative mortality, MI, TVR, and MACEs were similar between the two groups.

Conclusions: The updated meta-analysis presents the evidence that MIDCAB has a reduced risk of long-term TVR

and MACEs, with no benefit in terms of long-term mortality and short-term results, in comparison with PCI. Large multicenter RCTs, including patients treated with newer techniques, are warranted in the future.

INTRODUCTION

Coronary artery disease (CAD) remains one of the most prevalent causes of mortality worldwide, despite recent advancements in coronary revascularization techniques and pharmacotherapeutics [Kandaswamy 2018]. Minimally invasive direct coronary artery bypass (MIDCAB) and percutaneous coronary intervention (PCI) are feasible alternative procedures for patients with isolated left anterior descending (LAD) coronary artery lesions [Wang 2016]. MIDCAB has been recognized as a standard-of-care surgical procedure for isolated LAD lesions in most cardiovascular centers worldwide for low postoperative morbidity and mortality and favorable major adverse cardiovascular events (MACEs)-free survival [Mastroiacovo 2021; Mehran 2000; Seo 2018]. Recently, robotically assisted coronary artery bypass grafting (CABG) has been reported with additional benefits, such as reduced postoperative morbidity and shortened hospital stays, due to this procedure's more minimally invasive nature [Fitchett 2014]. PCI has evolved for decades from bare-metal stent (BMS) to new-generation drug-eluting stent (DES), and the postprocedural restenosis rates and need for repeated revascularization have recently markedly decreased [Bhatt 2018]. However, the optimal revascularization strategy for isolated LAD lesions remains controversial. Several recent randomized controlled trials (RCTs), observational studies, and meta-analyses revealed no additional benefit in survival and MACEs from MIDCAB compared with PCI [Blazek 2013; Blazek 2015; Li 2021]. Nevertheless, other reports have demonstrated that MIDCAB offered superior freedom from MACEs in comparison with PCI [Etienne 2013; Iakovou 2002]. However, it is not clear whether the long-term survival

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benefit that has been demonstrated with conventional CABG also applies to MIDCAB.

This updated meta-analysis aims to compare the long- and short-term outcomes of MIDCAB versus PCI for isolated LAD coronary artery lesions.

METHODS

We performed a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [Page 2021] Statement and registered with PROSPERO (CRD42022333850).

Search strategy: A literature search was conducted independently by two authors on the Pubmed, Web of Science, Cochrane library from 2002 to 2022 for retrieval of eligible studies reported on the revascularization of patients with isolated LAD stenosis. The search terms used included: (((left anterior descending) OR (single vessel)) AND (((((((((((("Percutaneous Coronary Intervention"[Mesh]) OR (Coronary Intervention, Percutaneous)) OR (Coronary Interventions, Percutaneous)) OR (Coronary Interventions, Percutaneous)) OR (Interventions, Percutaneous Coronary)) OR (Percutaneous Coronary Interventions)) OR (Percutaneous Coronary Revascularization)) OR (Coronary Revascularization, Percutaneous)) OR (Coronary Revascularizations, Percutaneous)) OR (Percutaneous Coronary Revascularizations)) OR (Revascularization, Percutaneous Coronary)) OR (Revascularizations, Percutaneous Coronary)) OR (PCI) OR (stent))) AND (((((((((((Coronary Artery Bypass[MeSH Terms]) OR (Artery Bypass, Coronary)) OR (Artery Bypasses, Coronary)) OR (Bypasses, Coronary Artery)) OR (Coronary Artery Bypasses)) OR (Coronary Artery Bypass Surgery)) OR (Bypass, Coronary Artery)) OR (Aortocoronary Bypass)) OR (Aortocoronary Bypasses)) OR (Bypass, Aortocoronary)) OR (Bypasses, Aortocoronary)) OR (Bypass Surgery, Coronary Artery)) OR (Coronary Artery Bypass Grafting))) AND (((minimally invasive) OR (MIDCAB)) OR (robotic)) OR (endoscopic)). Authors screened the retrieved articles based on their titles and abstracts. Next, the full-text articles of all potentially eligible studies were obtained for detailed evaluation. We also sought additional studies by checking the reference lists of included articles. Disagreements were resolved by consensus among all authors.

Inclusion and exclusion criteria: Inclusion criteria: (I) full-text, English-language, and peer-reviewed articles; (II) Adult patients with isolated LAD stenosis; (III) Studies compared MIDCAB versus PCI; (IV) interesting outcomes including long- and short-term survival, target vessel revascularization (TVR), and MACEs of MIDCAB versus PCI; (V) study-level data available for statistical analysis.

Exclusion criteria: (I) Case reports, editorials, reviews, and meta-analysis articles; (II) studies unpublished or with insufficient data; (III) patients with multi-vessel coronary artery disease, including those who underwent MIDCAB as part of a hybrid coronary revascularization strategy; (IV) surgical procedures concomitant with other intra-cardiac interventions.

If there was overlap in the patient populations in different studies from the same center, we included only the study with the longest follow up or largest patient cohort.

Data extraction: Data extraction was performed separately by two authors. The data extraction items included authorship, year of publication, study design and quality, length of follow up, baseline characteristics, and outcomes of interest. The primary outcome was long-term survival. Secondary outcomes were long-term TVR, long-term MACEs, and short-term outcomes. Short-term outcomes included postoperative mortality, myocardial infarction (MI), TVR, and MACEs of any cause in-hospital or 30 days after the revascularization. MACE is defined as all-cause mortality, MI, TVR, or stroke. The minimum long-term follow up reported was four years and the maximum was 10 years.

Quality assessment: The quality assessment independently was conducted by two authors. The Newcastle-Ottawa Quality Assessment Scale (NOS) [Lo 2014] was used to assess the risk of bias of all observational studies. The quality of randomized controlled trials (RCTs) was assessed using the RoB2 (Revised Cochrane risk of bias tool for randomized trials) [Sterne 2019].

Statistical analysis: Continuous variables are shown as mean \pm SD or median (1st to 3rd quartile). Categorical variables are shown as frequencies and percentages. For the analysis of time-to-event data, the estimated treatment effect and relative standard error were calculated from the estimated hazard ratio (HR) and the log-rank variance [Tierney 2007]. If reported, HRs directly were extracted from original articles or indirectly calculated from the Kaplan Meier curves using Engauge Digitizer. Short-term outcomes were expressed in the form of risk ratio (RR) along with 95% confidence intervals (CIs). A random-effects model was selected for pooling the data from included studies. Funnel plots were used to assess the potential biases. Statistical significance was considered as *P*-value less than 0.05. Heterogeneity amongst the studies was determined by the Chi-square test, and *P*-value less than 0.10 was regarded as significant. *I*² statistics were calculated to test for heterogeneity between included studies, and *I*² more than 50% indicated significant heterogeneity. Subgroup analysis based on stent types was carried out to explore the heterogeneity between groups. Statistical analysis was performed using Review Manager software Version 5.4.

RESULTS

Study selection and inclusion: Our search yielded 392 articles after discarding duplicates. Then, 365 studies categorized as irrelevant after titles and abstracts review were excluded, leaving 27 studies pending re-examination. After carefully checking the full texts, 13 studies were omitted for reasons explained in Figure 1. (Figure 1) Consensus was reached among all authors regarding the final inclusion of studies.

Study characteristics and quality assessment: Ultimately, 14 studies were included, of which six studies were randomized controlled trials and eight studies were observational (two prospective and six retrospective). In total, 1757

Table 1. Study characteristics

Source	Design	Patient inclusion	Patients (n) MID-CAB	Patients (n) PCI	Age (years) MIDCAB	Age (years) PCI	Male (%) MIDCAB	Male (%) PCI	Hypertension (%) MIDCAB	Hypertension (%) PCI
Cisowski 2002	RCT	2000-2001	50	50	54.1±9.1	53.3±10.2	41 (82)	42 (84)	28 (56)	26 (52)
Iakovou 2002	Retrospective	1996-1999	119	441	62±12	63 ±12	84 (71)	300 (68)	65 (55)	238 (54)
Drenth 2004	RCT	1997-1999	51	51	60 ±1.6	60 ±1.3	40 (78)	38 (75)	8 (16)	17 (33)
Reeves 2004	RCT	1999-2001	50	50	58.8 (53.2-66.6)†	54.5 (48.9-61.4)†	35 (70)	43 (86)	-	-
Shirai 2004	Prospective	1990-1999	152	429	61±12	63±11	111 (73)	279 (65)	90 (59)	227 (53)
Hong 2005	RCT	2003-2003	70	119	61.4±9.9	60.5±9.6	45 (64.3)	76 (63.9)	39 (55.7)	60 (50.4)
Kim 2005	Prospective	2000-2001	50	50	63±12	61±12	35 (70)	30 (60)	28 (56)	27 (54)
Blazek 2013	RCT	1997-2001	110	110	61.6±10.0	62.5±10.2	85 (77)	79 (72)	78 (71)	79 (72)
Etienne 2013	Retrospective	1997-2011	260	196	63.4 ±12	62.4 ±12	194 (74.6)	144 (73.5)	155 (57)	131 (67)
Benedetto 2014	Retrospective	2001-2013	303	303	-	-	251 (82.8)	250 (82.5)	209 (69.0)	191 (63.0)
Blazek 2015	RCT	2003-2007	65	65	66 (59–71)†	66 (59–72)†	46 (71)	45 (69)	55 (85)	54 (83)
Hannan 2021	Retrospective	2010-2016	211	13,115	65.29±11.75	64.78±11.78	147 (69.7)	8558 (65.3)	-	-
Li 2021	Retrospective	2007-2014	108	108	58.07 ± 10.44	58.56 ± 11.42	81 (75.0)	81 (75.0)	71 (65.7)	74 (68.5)
Patel 2022	Retrospective	2008-2016	158	158	62.6±10.3	61.9±12.0	113 (71.5)	105 (66.5)	-	-

†Median (with interquartile range) was reported. RCT, randomized controlled trial; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass grafting; PCI, percutaneous coronary intervention; BMS, bare-metal stent; DES, drug-eluting stent

Supplementary Table 1. Assessment of the quality of observational studies according to the Newcastle-Ottawa Quality Assessment Scale (NOS) tool

Study	Benedetto 2014	Etienne 2013	Hannan 2021	Iakovou 2002	Kim 2005	Li 2021	Patel 2022	Shirai 2004
Representativeness of exposed cohort	1	1	1	1	1	1	1	1
Selection of nonexposed cohort	1	1	1	1	1	1	1	0
Ascertainment of exposure	1	1	1	1	1	1	1	1
Outcome of interest absent at start of study	1	1	1	1	1	1	1	1
On the basis of the design or analysis	2	1	2	2	2	2	2	2
Assessment of outcome	1	1	1	1	1	0	1	1
Follow up long enough for outcomes to occur	1	1	1	1	1	1	1	0
Adequacy of follow up	0	1	0	0	0	1	1	0
Total score	8	8	8	8	8	8	9	6

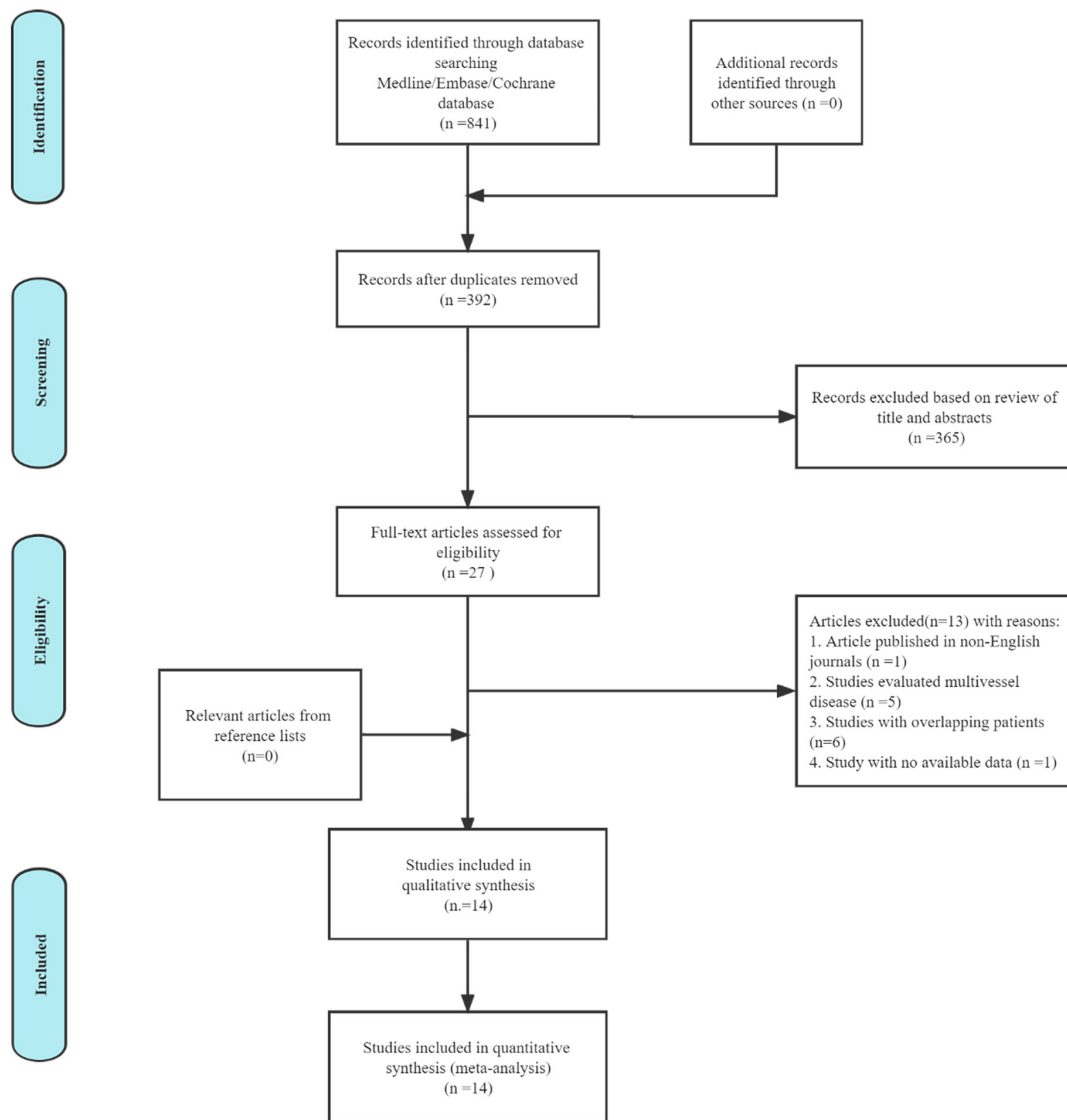


Figure 1. The PRISMA recommended flow-diagram depicting the methodology of article selection for this meta-analysis.

Supplementary Table 2. Assessment of the quality of randomized controlled trials according to Cochrane Risk of Bias Tool for randomized controlled trials

Authors	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Score (quality)
Blazek 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blazek 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cisowski 2002	Some concern	Some concern	Some concern	Low risk	Low risk	Some concern
Drenth 2004	Some concern	High risk	Low risk	Low risk	Low risk	High risk
Hong 2005	Some concern	Some concern	Low risk	Low risk	Low risk	Some concern
Reeves 2004	Low risk	Some concern	Low risk	Low risk	Low risk	Some concern

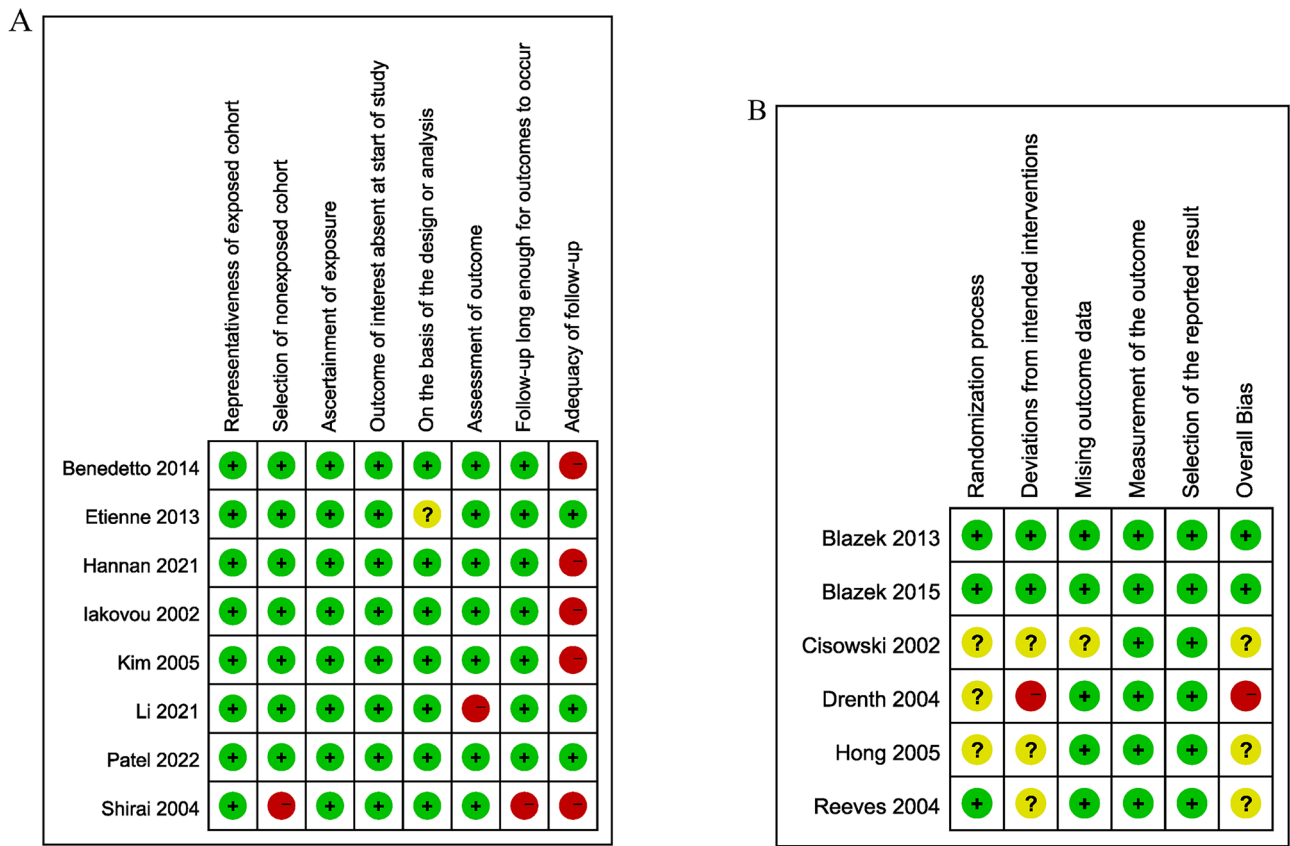


Figure 2. A) Risk of bias in each study assessed using the NOS tool. B) Risk of bias in each study assessed using the RoB 2.0 tool.

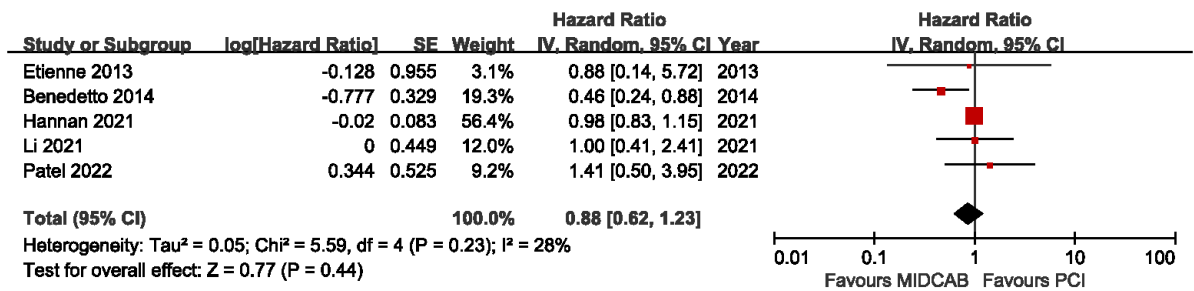


Figure 3. Long-term survival with MIDCAB versus PCI for isolated LAD disease.

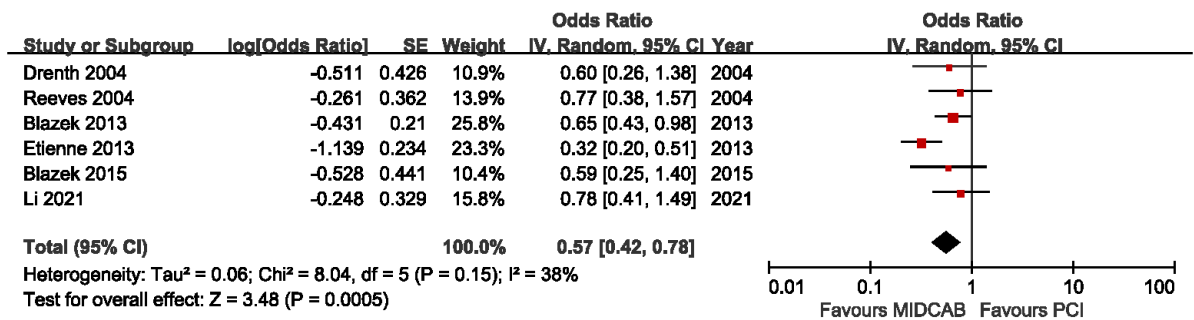


Figure 4. Forest plots for long-term MACES comparing MIDCAB with PCI.

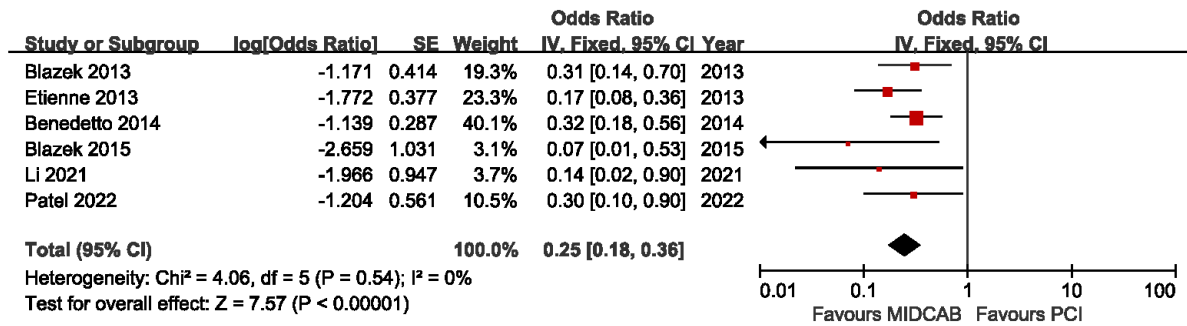


Figure 5. Forest plots depicting long-term TVR of MIDCAB versus PCI.

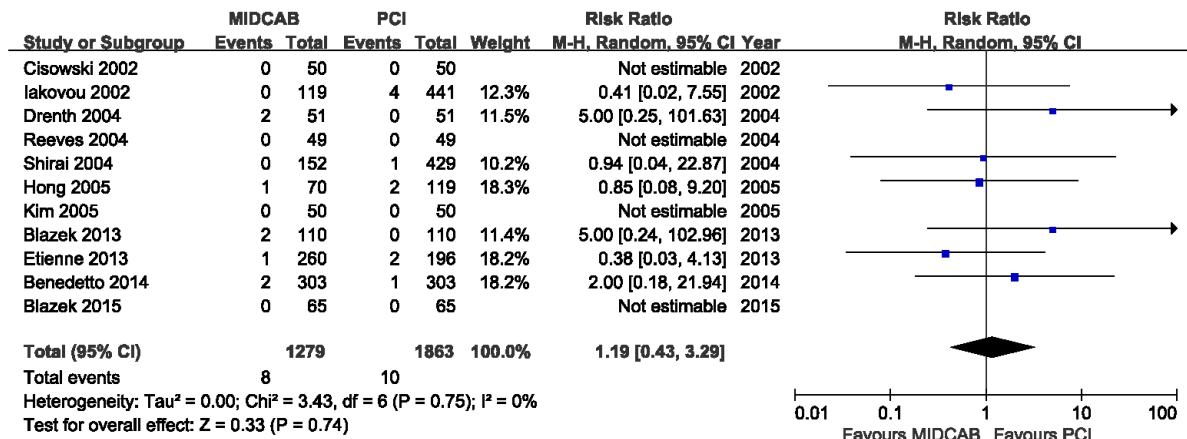


Figure 6. Short-term survival with MIDCAB versus PCI for isolated LAD disease.

patients underwent MIDCAB and 15245 patients underwent PCI. Characteristics of included studies are detailed in Table 1 [Blazek 2013; Blazek 2015; Li 2021; Etienne 2013; Iakovou 2002; Cisowski 2002; Drenth 2004; Reeves 2004; Shirai 2004; Hong 2005; Kim 2005; Benedetto 2014; Hannan 2021; Patel 2022]. (Table 1) The operative details of the MIDCAB and PCI procedure were reported in 11 studies. In all MIDCAB procedures, the left internal mammary artery (LIMA) was harvested and then anastomosed to the LAD. Eight studies used a thoracotomy approach, one study used the ministernotomy procedure, and two studies used robotic techniques. For PCI procedures, seven studies included patients who received DESs, among which six were first-generation and one was second-generation. The remaining seven studies used BMSs.

The methodological qualities of eight observational studies were assessed by the NOS tool. Based on grading standards, quality was assessed as high for seven studies and moderate for one study (Figure 2A, Table S1). (Figure 2) (Supplementary Table 1) The quality of six RCTs evaluated by the RoB 2 tool is shown in Figure 2B and Table S2. (Supplementary Table 2)

Long-term outcomes: Long-term survival was reported in five studies comparing MIDCAB and DES. Our analysis showed that there was no significant difference in long-term survival between MIDCAB and PCI (HR=0.88, 95% CI =

[0.62,1.23], P = 0.44, phetero=0.23, I²=28%) (Figure 3)

Long-term MACEs were reported in six studies. The pooled results revealed that MIDCAB correlated with a lower MACE rate (HR=0.57, 95% CI = [0.42,0.78], P = 0.0005, phetero=0.15, I²=38%), when compared to PCI. (Figure 4) Subgroup analysis, according to stent type, yielded a consistent result comparing MIDCAB and DES (HR=0.50, 95% CI = [0.28,0.92], P = 0.03, phetero=0.07, I² = 62% or comparing MIDCAB and BMS (HR=0.67, 95% CI = [0.48,0.92], P = 0.01, phetero=0.89, I²=0%). (Supplementary Figure 1)

Long-term TVR rates were reported in six studies. The meta-analysis demonstrated that MIDCAB had an extremely lower risk of TVR compared with PCI (HR=0.25, 95% CI = [0.18,0.36], P < 0.00001, phetero=0.54, I²=0%). (Figure 5) The pooled analysis showed a similar result (HR=0.24, 95% CI = [0.16,0.36], P < 0.00001, phetero=0.44, I²= 0%) after omitting the only one study reporting PCI with BMS by Blazek et al. (Supplementary Figure 2)

Short-term outcomes: There were 11 studies that examined the short-term survival in hospital or within 30 days after the revascularization, with a total of 3142 patients (1279 undergoing MIDCAB versus 1863 undergoing PCI). The analysis showed a similar incidence of short-term mortality between two groups (RR=1.19, 95% CI = [0.43, 3.29], P = 0.74, phetero=0.75, I²=0%). (Figure 6) Mortality was similar when comparing DES with MIDCAB (RR=0.86, 95%

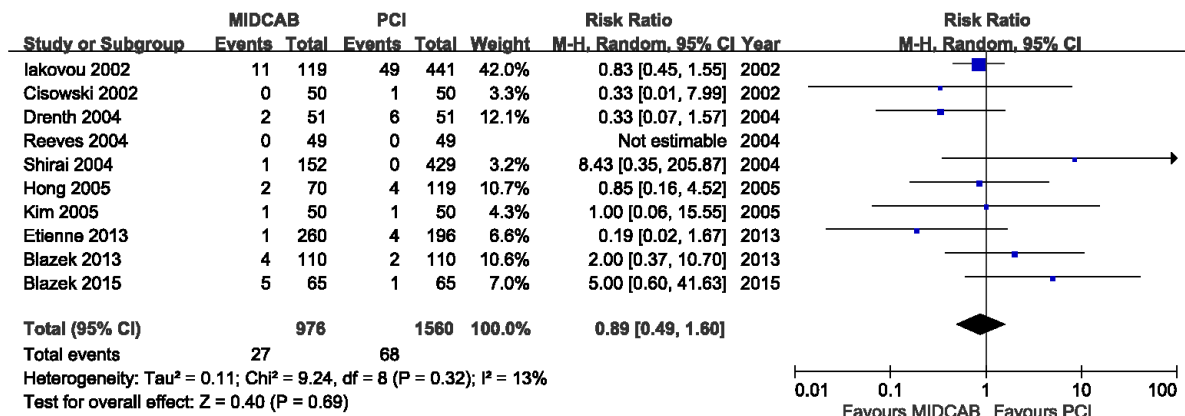


Figure 7. Forest plots for short-term MI comparing MIDCAB with PCI.

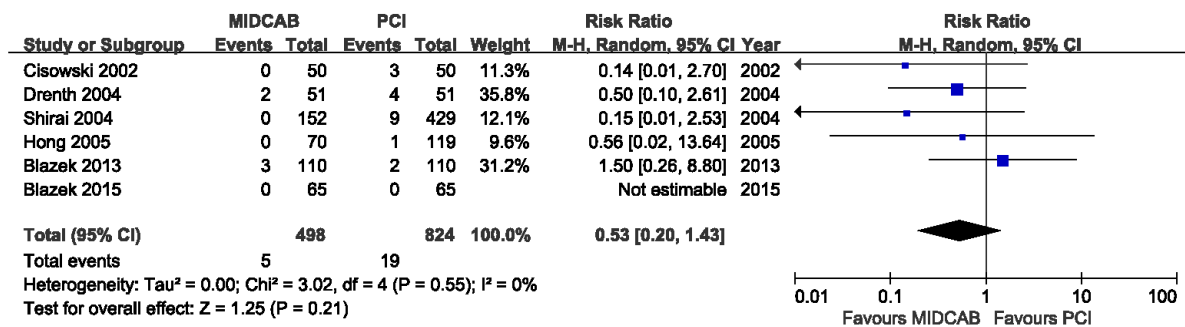


Figure 8. Forest plots depicting short-term TVR of MIDCAB versus PCI.

CI = [0.22, 3.43], $P = 0.83$, phetero=0.63, $I^2=0\%$) or BMS with MIDCAB (RR=1.74, 95% CI = [0.38, 7.94], $P = 0.47$, phetero=0.57, $I^2=0\%$). (Supplementary Figure 3)

Ten studies with 2536 patients (976 undergoing MIDCAB versus 1560 undergoing PCI) reported the short-term MI. The meta-analysis demonstrated a similar risk of MI between MIDCAB and PCI groups (RR=0.89, 95% CI= [0.49, 1.60], $P = 0.69$, phetero=0.32, $I^2=13\%$). (Figure 7) Similar results were obtained when DES (RR=0.94, 95% CI = [0.17, 5.20], $P = 0.94$, phetero=0.11, $I^2=55\%$) or BMS (RR=0.85, 95% CI = [0.51, 1.44], $P = 0.55$, Phetero=0.45, $I^2=0\%$) were compared with MIDCAB separately. (Supplementary Figure 4)

Short-term TVR was assessed in six studies recruiting 1322 patients (498 with MIDCAB versus 824 with PCI). There was no difference observed, in terms of short-term TVR between two procedures (RR=0.53, 95% CI = [0.20, 1.43], $P = 0.21$, phetero=0.55, $I^2=0\%$). (Figure 8) Similar findings were noted when DES comparing MIDCAB or BMS comparing MIDCAB were pooled separately (DES: RR=0.56, 95% CI = [0.02, 13.64], $P = 0.72$; BMS: RR=0.53, 95% CI = [0.19, 1.50], $P = 0.23$, phetero=0.39, $I^2=1\%$). (Supplementary Figure 5)

Short-term MACEs were assessed in nine studies with 2080 patients (716 MIDCAB versus 1364 PCI). The pooled results showed no significant difference between the two groups (RR=0.76, 95% CI= [0.46, 1.26], $P = 0.29$, phetero=0.48, $I^2=0\%$). (Figure 9) Similarly, MACEs were comparable

between the two groups when DES or BMS were compared separately with MIDCAB (DES: RR=0.79, 95% CI = [0.33, 1.86], $P = 0.59$, phetero=0.88, $I^2=0\%$); BMS: RR=0.70, 95% CI= [0.33, 1.50], $P = 0.36$, phetero=0.26, $I^2=23\%$). (Supplementary Figure 6)

DISCUSSION

In the present study, we performed an updated meta-analysis of six randomized trials and eight cohort studies enrolling 17,002 participants to compare long- and short-term survival and MACEs of MIDCAB versus PCI for isolated LAD stenosis. The main findings of this meta-analysis were that MIDCAB had a lower risk of long-term TVR and MACEs compared with PCI. Nevertheless, MIDCAB was comparable with PCI, in terms of long-term survival and short-term survival, MI, TVR, and MACEs. Besides, similar results were observed when subgroup analysis based on stent types was performed.

Several meta-analyses including randomized and observational studies comparing MIDCAB versus PCI previously have been performed. One study (12 studies, 7,710 patients) [Raja 2018] concluded that the MIDCAB cohort had better TVR with similar mortality, MI, and MACEs compared with PCI with DES for revascularization in patients with isolated proximal LAD stenosis. Another meta-analysis [Deppe 2015] including a total of 2885 patients from 12 studies, found an increased incidence

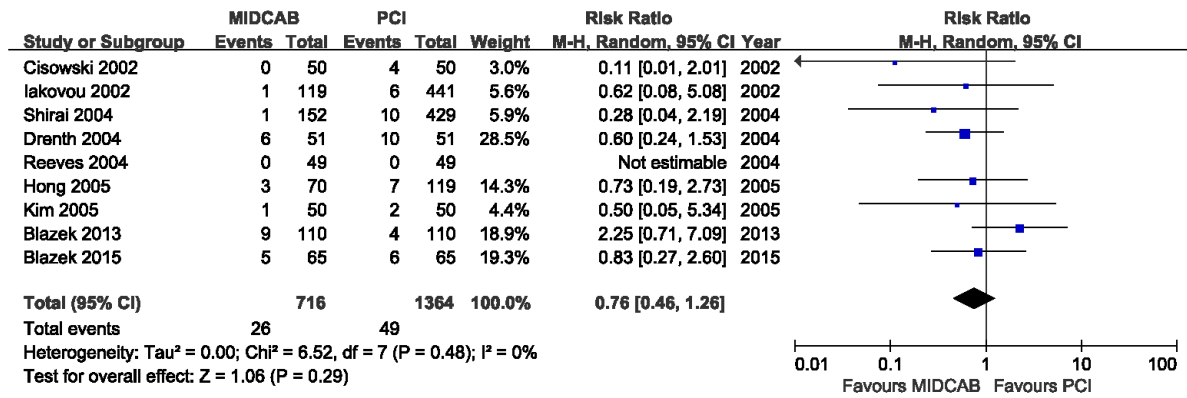
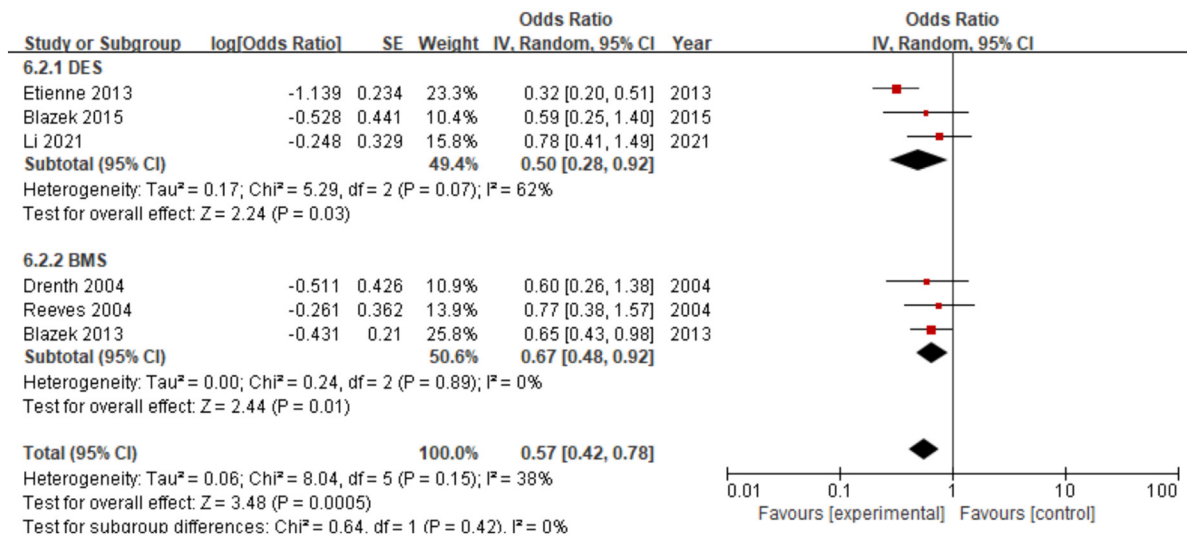


Figure 9. Forest plots for short-term MACEs comparing MIDCAB with PCI.



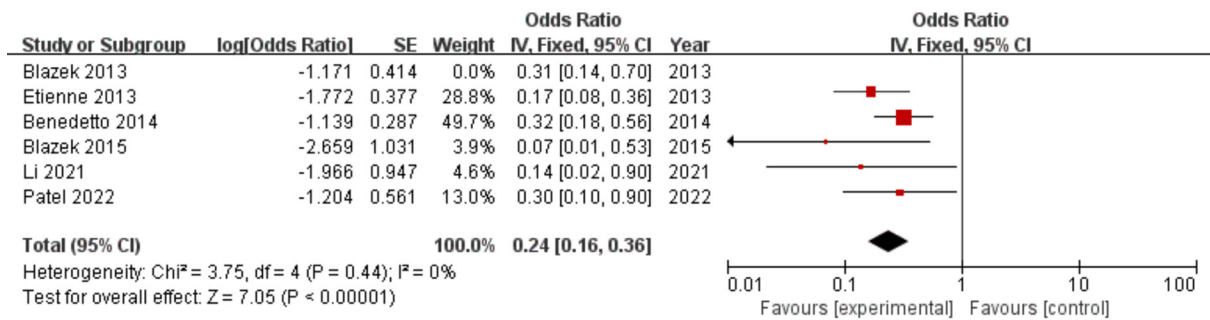
Supplemental Figure 1.

of MACEs 6 months following PCI compared with MIDCAB. Particularly, PCI was associated with an increased odds of target vessel revascularization. For comparison of PCI with DES with MIDCAB, PCI seemed to be associated with more frequent TVR without reaching statistical significance. And no difference concerning stroke, MI, and all-cause mortality was observed between both groups. The third meta-analysis [Wang 2016] recruiting 941 patients from 14 studies reported no significant difference in the safety outcomes between MIDCAB and PCI in patients with LAD. However, MIDCAB was superior to PCI for TVR and MACEs at 6 months and beyond 1-year follow up.

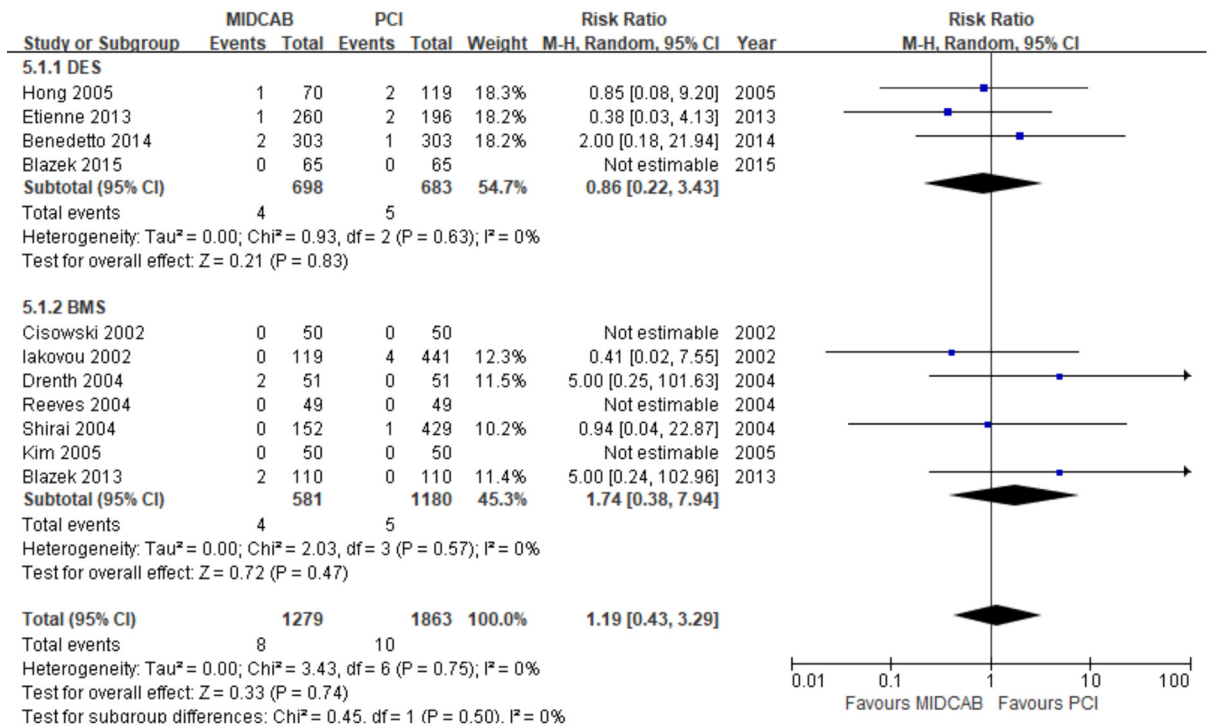
The present updated meta-analysis having more rigorous inclusion criteria and including more studies and patients, showed consistent short-term results compared with previous studies. Moreover, to the best of our knowledge, our analysis was the first thus far using HR as the effect measure comparing the follow-up outcomes of both techniques. The pooled results of time-to-event data showed that TVR and MACEs were higher at long-term follow up in the PCI group, though no long-term survival difference was found between MIDCABG and PCI.

Although MIDCAB is more invasive and prolongs the time of ICU and hospital stay [Deppe 2015], several studies demonstrated no higher periprocedural complication rates [Cisowski 2002; Reeves 2004; Hong 2005; Benedetto 2014]. Present data from this meta-analysis revealed similar rates of postoperative mortality and MI between the two procedures. Additionally, a cost analysis documented by Patel et al. [Patel 2022] showed that the aggregate cost of the MIDCAB cases over the study duration was 17.3% lower than DES-PCI after accounting for the frequency of reintervention.

There are several limitations in the current study. First, as studies with different designs were included, the results of our meta-analysis might have potential heterogeneity. Second, inclusion of small RCTs, non-matched cohort studies and the lack of availability of all relevant data were a source of inherent bias. Third, the extent and location of isolated LAD lesions and other significant variables were not consistent across studies. Finally, the stents used for PCI were BMS or first-generation DES in most studies, and only two studies reported the robot-assisted technique. Thus, the present



Supplemental Figure 2.



Supplemental Figure 3.

study might not reflect contemporary practice. Herein, large multicenter RCTs including patients treated with newer techniques are warranted in the future.

In conclusion, our updated meta-analysis demonstrated that MIDCAB had a reduced risk of long-term TVR and MACEs compared with PCI. MIDCAB and PCI were not significantly different, in terms of long-term mortality and short-term results.

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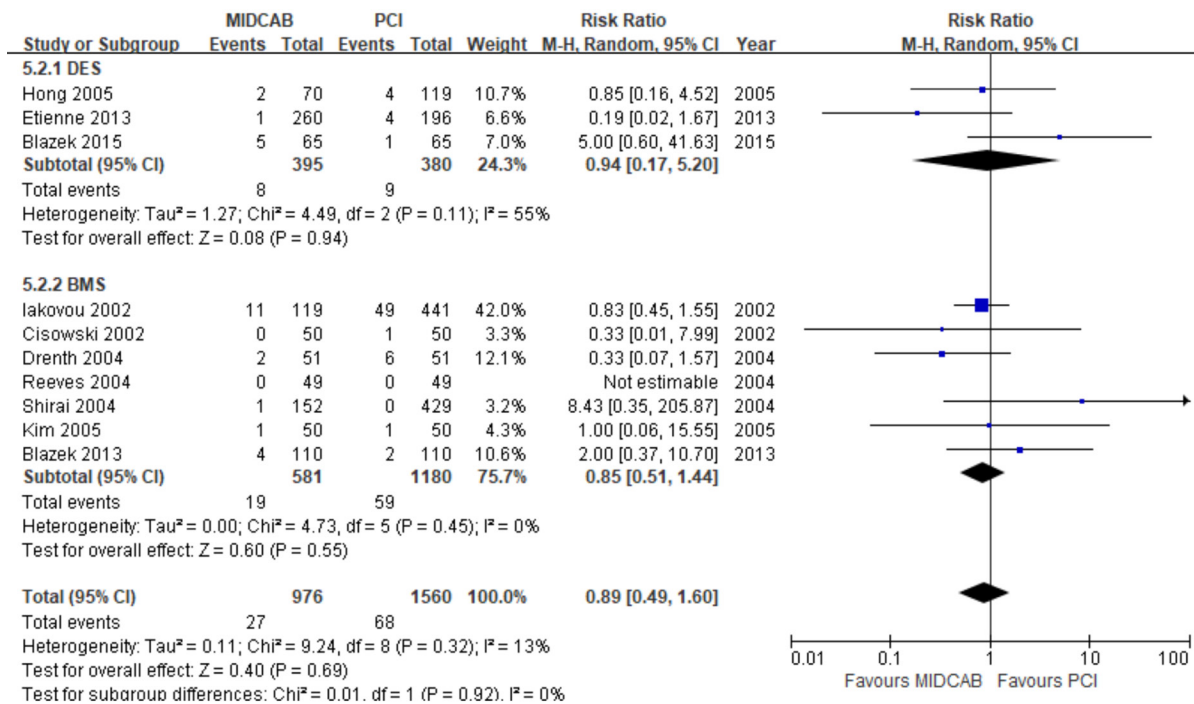
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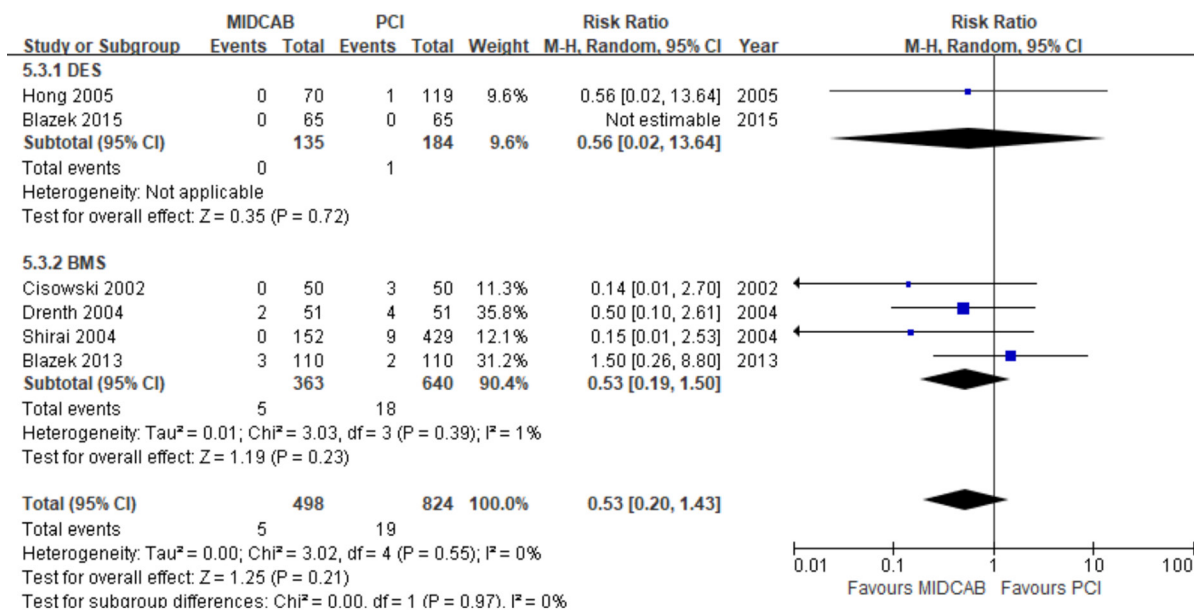
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Supplemental Figure 4.



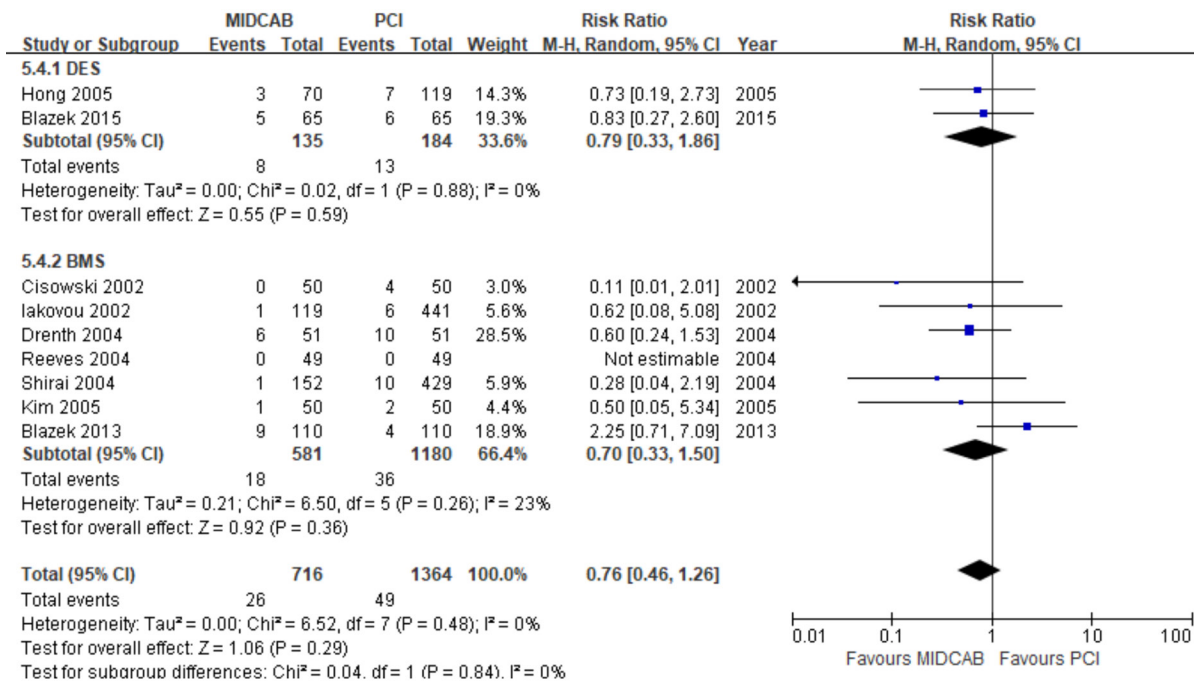
Supplemental Figure 5.

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Supplemental Figure 6.

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