Short- and long-term cardiovascular outcomes in insulin-treated versus non-insulin-treated diabetes mellitus patients after percutaneous coronary intervention: A systematic review and meta-analysis☆

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ABSTRACT

Aims: This study aims to assess differences in severity of short-term (<1 year) and long-term (≥1 year) adverse CV outcomes after PCI in insulin-treated vs. non-insulin-treated diabetes mellitus (DM) patients.
Methods: A systematic search on Pubmed and Embase led to the incorporation of 29 studies that compared post-percutaneous coronary interventional outcomes in insulin-treated and non-insulin-treated diabetes mellitus. Diabetes mellitus (type 2) was defined as fasting blood glucose (FBG) level of >7.0 mmol/L or with an oral glucose tolerance test (OGTT) level of >11.1 mmol/L at least on two separate occasions. Adverse CV outcomes were assessed in insulin-treated and non-insulin-treated DM after the PCI procedure considered for the analyses were mortality, MACE, TLR, TVR, MI, stent thrombosis, target lesion failure (TLF), and need for-post PCI CABG. Data were pooled and analyzed using Review Manager 5.3, and risk ratios (RR) with respective 95% confidence intervals (CI) were calculated.The statistical analyses were carried out by Review Manager v.5.3, and the data were pooled using a random-effects model. Risk ratios (RRs) with 95% confidence intervals (CI) were reported along with forest plots. The chi-square test was performed to assess for differences between the subgroups. Heterogeneity across studies was evaluated using Higgins I^2 statistics. Visual inspection of the funnel plot and Begg's regression test were used to assess publication bias.
Results: A total of 40,527 patients (11742 in the Insulin-treated diabetes mellitus group and 28785 in the non-insulin-treated DM group) who underwent PCI were included. The pooled analysis of short-term follow up outcomes preceding PCI demonstrated a significantly higher risk of mortality (RR = 1.75 [1.24,2.47]; *p* = 0.002), MI (RR = 1.81[1.14,2.87]; *p* = 0.01], stent thrombosis (RR = 1.63[1.13, 2.35]; *p* = 0.009) and target lesion revascularization (TLR) (RR = 1.29[1.02,1.63]; *p* = 0.03) in insulin-treated DM patients. Similarly, analysis of long-term follow-up studies depicted a significantly higher risk mortality (RR = 1.55 [1.22, 1.97]; *p* = 0.0003), MI (RR = 1.63 [1.35, 1.97]; *p*=<0.00001), MACE (R = 1.47 [1.31, 1.65]; *p*=<0.00001), stent thrombosis (RR = 1.54 [1.19,1.99]; *p* = 0.001), TLR (RR = 1.40 [1.18, 1.66]; *p* = 0.0001), target vessel revascularization (TVR) (RR = 1.35 [1.11, 1.64]; *p* = 0.003) in insulin-treated DM group after PCI versus non-insulin-treated DM patients.
Conclusion: Despite a tremendous technical success rate of multi-vessel stenting, people living with diabetes who were being treated with insulin had higher long-term, and short-term mortality rates, MI, TLR, TVR, and stroke compared to people living with diabetes who were being treated with means other than insulin and are more prone to detrimental cardiovascular outcomes.

Abbreviations

TLR	Target lesion revascularization
TVR	Target vessel revascularization
TLF	Target lesion failure
CABG	Coronary artery bypass graft
PCI	Percutaneous intervention
DM	Diabetes mellitus
CV	Cardiovascular outcomes

1. Introduction

As the current consumer lifestyle is becoming increasingly sedentary, the world faces an epidemic of 'diabetes mellitus (DM)' with more than 171 million people affected worldwide.[1] It is one of the most common chronic medical conditions known for its progressive nature; DM poses a severe public health challenge in the twenty-first century. Initially, DM is managed through dietary modification and oral hypoglycemic drugs; an intensification of therapy is generally required as the disease progresses over the years rendering insulin addition to the regimen a necessity.[2] It is well-established that cardiovascular (CV) complications are the leading cause of morbidity and mortality in people living with diabetes; hence standard practice involves aggressive risk factor control, yet approximately 20−30% of patients require percutaneous coronary interventions (PCI) at some point during the disease.[3]

There is currently conflicting evidence about the severity of adverse CV outcomes following PCI in diabetic populations treated with insulin compared to those with diabetes who have not received insulin therapy.[4–6] Several studies have shown that the risk of adverse outcomes like target lesion failure (TLF) and target lesion revascularization (TLR) after PCI is higher in insulin-treated people living with diabetes than in non-insulin-treated people living with diabetes.[3,6] However, other studies have concluded that the increased risk of adverse cardiovascular (CV) outcomes is only present until propensity score has been adjusted. Moreover, the frequency of stent thrombosis and mortality rates after stent placement were also found to be comparable in both groups i.e. insulin-treated patients living with diabetes and non-insulin-treated patients living with diabetes.[7,8]

Therefore, with the aim to standardize the issue, conclude the current debate and, further evaluate the risk of wide range of CV events in insulin-treated versus non-insulin-treated patients living with diabetes, we assessed short-term (<1 year) and long-term (≥1 year) adverse CV outcomes after PCI in both the aforementioned groups. We also aimed at analyzing the protective effects of insulin in DM population undergoing PCI.The primary adverse CV outcomes were death, major adverse cardiac effects (MACE), TLR, TVR, myocardial infarction (MI), and stent thrombosis, while the secondary outcome was stroke.

2. Methods

2.1. Data sources and search strategy

The preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines were followed in this meta-analysis. All study types, including randomized controlled trials (RCTs), comparative studies, registries, cohort studies, and observational studies were searched electronically (without any language and time restrictions) on Pubmed and Embase, using the search string: 'diabetes OR 'insulin-treated diabetes mellitus OR non-insulin treated diabetes mellitus AND percutaneous coronary intervention/PCI OR PCI coronary stent AND clinical outcomes' OR results'.

The term 'angioplasty' has also been used to enhance this search further. In addition, the reference list of retrieved trials, previous meta-analysis, and review articles was manually screened to identify any relevant studies.

2.2. Study selection

Inclusion criteria: Randomized controlled trials (RCTs), comparative studies, registries, cohort studies, and observational studies that reported occurrences of any adverse CV outcomes (including but not limited to death) for insulin-treated and non-insulin-treated DM patients after PCI, irrespective of the types of stents implanted, were eligible for inclusion in the studies (observational and RCTs). The studies reporting either a short-term follow-up (<1 year) or a long-term follow-up (≥1 year) after PCI were eligible for our analyses. Case reports, literature reviews, and studies not reporting comparable data for both groups were excluded.

Exclusion criteria: Studies in which adverse clinical outcomes were not among the clinical endpoints, were meta analysis, case studies, or letter to editors, were excluded. Studies in which the control group/non-insulin-treated DM patients were absent were not included. Studies that did not incorporate data with discontinuous variables or data which could easily be converted to discontinuous variables were not eligible. Duplicate studies were also removed.

2.3. Outcomes and definitions

Patients living with diabetes (Type 2 DM) were defined as patients with a fasting blood glucose (FBG) level of >7.0 mmol/L or with an oral glucose tolerance test (OGTT) level of >11.1 mmol/L at least on two separate occasions. DM patients were divided into insulin-treated (requiring insulin) and non-insulin-treated (not on insulin but may or may not be taking oral hypoglycemics) DM patients in this study.

Outcomes considered for the analyses were mortality, MACE, TLR, TVR, MI, stent thrombosis, target lesion failure (TLF), and need for-post PCI CABG. The primary study investigators' definition was accepted for all outcomes. Ambiguous outcome terms have been elaborated.

Major adverse cardiac effects (MACEs) were a composite of death of cardiac or procedure-related origin, MI, and/or, revascularization after stents implantation. Target lesion revascularization (TLR) was defined as clinically indicated percutaneous or surgical revascularization of the index lesion, and target vessel revascularization (TVR) concerned the vessel affected. Target lesion failure (TLF) was a composite of clinically driven TLR, MI, or cardiac death related to the target vessel. If it could not be determined with certainty whether an MI or death is related to the target vessel, and at the same time if no other specific reasons can be given, it was considered as a case of TLF. Revascularization was clinically indicated if there was >70% diameter stenosis on angiography or >50% stenosis together with a positive stress test or ischemic symptoms.

2.4. Data extraction and assessment of study quality

All identified articles were exported to Endnote Reference Library X8.1 (Clarivate Analytics, Philadelphia, Pennsylvania) to remove duplicates. The articles were carefully assessed by two independent reviewers, and only those studies that met the eligibility were selected. Studies were narrowed down based on titles and abstracts, and full-texts were read for final inclusion. In case of any

discrepancy, a consultation was carried out by a third party. Data related to baselines and outcomes were extracted in a predesigned form. The modified Cochrane Collaboration's risk of bias tool was used to assess the quality of published RCTs,[9] observational studies were assessed using New Castle Ottawa scale.[10]

2.5. Statistical analysis

All statistical analyses were carried out by Review Manager v.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The data were pooled using a random-effects model, and risk ratios (RRs) with 95% confidence intervals (CI) were reported along with forest plots. The chi-square test was performed to assess for differences between the subgroups. Heterogeneity across studies was evaluated using Higgins I2 statistics, and a value of 25%–50% was considered mild, 50%–75% as moderate, and >75% as severe heterogeneity. Potential causes of heterogeneity were explored by carrying out subgroup analysis. Visual inspection of the funnel plot and Begg's regression test were used to assess publication bias. A p-value <0.05 was considered significant in all cases.

2.6. Ethical approval

No approval was required from the ethical review board as this was an analysis of publicly available data.

3. Results

A total of 2695 articles were identified from the initial literature search. After the exclusion of duplicated articles and based on title and abstract, a total of 29 studies (18 observational and 11 RCTs) were included in this meta-analysis(Fig. 1).

3.1. Baseline characteristics

The 29 studies included a total of 40,527 patients (11,742 in the Insulin-treated diabetes mellitus group and 28,785 in the non-insulin-treated DM group) who underwent PCI. Details about baseline characteristics, comorbidities, and previous surgeries according to types of study are given in Tables, 1, 2, 3, 4.

3.2. Assessment of baseline characteristics

When baseline characteristics were pooled, we found a significant probability of non-insulin treated DM patients being males (RR = 0.89[0.87, 0.92]; $p=<0.00001$) and smokers (RR = 0.89 [0.83.0.97]; $p = 0.006$). However, for insulin-treated DM patients we found a significant probability of comorbidities like chronic kidney disease (RR = 1.17[1.09, 1.27]; $p=<0.00001$), previous MI (RR = 1.11[1.03, 1.20]; $p = 0.008$) and previous PCI (RR = 1.17[1.06, 1.30]; $p = 0.003$. All the remaining characteristics were insignificant between both groups. Differences in key baseline between insulin-treated DM patients and non-insulin-treated DM patients undergoing PCI are represented in (Table 5).

3.3. Quality assessment and publication bias

The quality assessment of studies using the New Castle Ottawa scale depicted a significantly low risk of bias in all the included observational studies (Supplementary Table S1). Assessment of RCTs by Cochrane tool showed fair to good quality results (Supplementary Table S2). The funnel plots showed no publication bias for both short and long-term follow-up outcomes (Supplementary Figure S1 and S2), which was confirmed by Begg's test. The details of Begg's test for all outcomes is given in (Table 6).

3.4. Cardiovascular outcomes of PCI

The results of all meta-analyses have been summarized in Fig. 2.

3.4.1. Short-term (<1 year)

Short-term outcomes were reported in 12 studies. The pooled analysis of short term follow up outcomes (<1 year) preceding PCI demonstrated a significantly higher risk of mortality (RR = 1.75 [1.24,2.47]; $p = 0.002$), MI (RR = 1.81[1.14,2.87]; $p = 0.01$), MACE (RR = 1.37[1.17,1.60]; $p = 0.001$), stent thrombosis (RR = 1.63 [1.13,2.35]; $p = 0.009$) and TLR (RR = 1.29[1.02,1.63]; $p = 0.03$) in insulin-treated DM patients as compared to non-insulin-treated DM group. Conversely, no significant differences were observed between both the groups in the risk of CABG (RR = 1.06 [0.58, 1.94]; $p = 0.84$) and TVR (RR = 1.06 [0.74, 1.52]; $p = 0.75$) following PCI. The results of short term outcomes are illustrated in Fig. 2. Supplementary Table S3 and supplementary Figure S3 contain individual outcome results for short-term.

3.4.2. Long-term (≥1 year)

Similarly, the pooled analysis of long-term follow-up (≥1 year) studies depicted a significantly higher risk of cardiovascular events in the insulin-treated DM group versus the non-insulin-treated DM group except post-PCI need for CABG. The risk for mortality (RR = 1.55 [1.22, 1.97]; $p = 0.0003$), MI (RR = 1.63 [1.35, 1.97]; $p=<0.00001$), MACE (R = 1.47 [1.31, 1.65]; $p=<0.00001$), stent thrombosis (RR = 1.54 [1.19,1.99]; $p = 0.001$), TLR (RR = 1.40 [1.18, 1.66]; $p = 0.0001$), TVR (RR = 1.35 [1.11, 1.64]; $p = 0.003$), TLF (RR = 2.02 [1.48, 2.76]; $p=<0.00001$) and stroke (RR = 1.94 [1.13, 3.33]; $p = 0.02$) were significantly higher in insulin-treated DM group after PCI as compared to non-insulin-treated DM patients. However, no significant distinction was discerned in both the groups in the risk of post-PCI CABG (RR = 0.82 [0.24, 2.80]; $p = 0.74$). The results for the long term outcomes have been illustrated in Fig. 2. Supplementary Table S4 and Supplementary Figure S4 contain individual outcome results for long-term.

3.5. Subgroup analysis

Subgroup analysis was performed to check whether Bifurcation lesion and American Heart Association (ACC/AHA) class B2/C lesion influence the results produced. The individual angiographic characteristics for each study are given in Supplementary Table S5. It was noted that no significant difference was observed in any CV outcomes among the subgroups (with and without bifurcation lesion; with and without class B2/C lesion) except that risk of TVR was significantly higher in patients having ACC/AHA class B2/C lesion (RR = 1.28[1.08, 1.51]; $p = 0.02$). The details of other subgroup analyses are given in Table 7.

3.6. Propensity matched/adjusted data analysis

Adjusted short-term mortality and MACE were reported by two studies only. However, a significant difference in mortality was observed between insulin-treated DM group and non-insulin-treated DM group (aOR = 1.78 [1.28, 2.49]; $p = 0.0007$). Whereas, for short-term MACE, no significant difference was observed between both the groups (aOR = 1.84 [0.93, 3.64]; $p = 0.08$). The forest plots of these outcomes are illustrated in Supplementary Figure S5.

Three studies reported adjusted long-term mortality, and a significant difference in mortality was observed between insulin-treated DM group and non-insulin-treated DM group (aHR = 1.46 [1.15, 1.86]; $p = 0.002$). However no significant differences were observed between both the groups in adjusted long-term MI
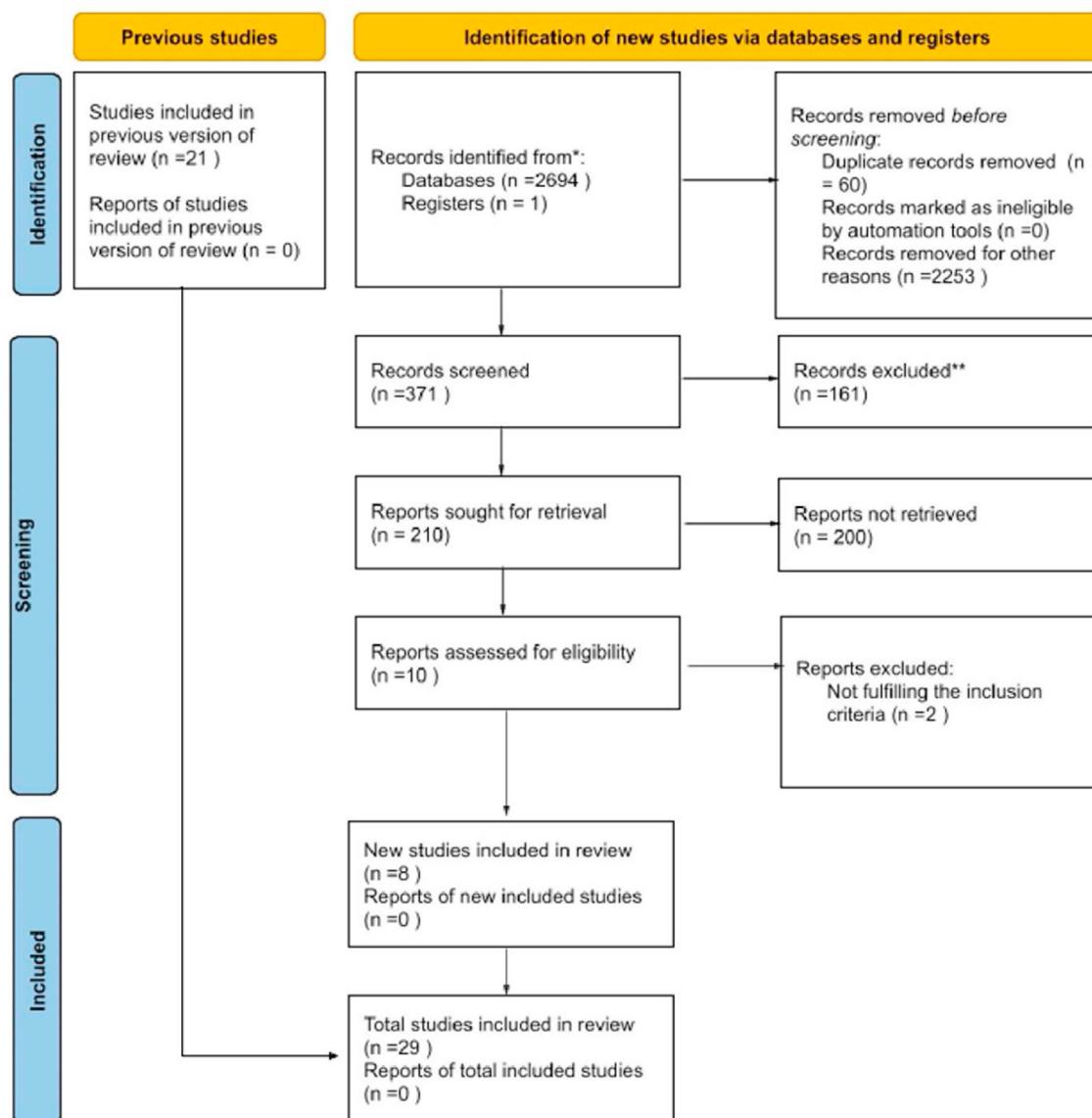
Fig. 1. Prisma Flow chart.

(aHR = 1.13 [0.75, 1.71]; *P* = 0.58), adjusted long-term MACE (aHR = 1.02 [0.96, 1.09]; *p* = 0.45) and adjusted long-term stent thrombosis (aHR = 1.56 [0.87.2.80]; *p* = 0.14). Moreover, adjusted long-term TLR was reported in three studies which demonstrated a significant difference between the insulin-treated DM group and non-insulin-treated DM group (aHR = 1.46 [1.15,1.86]; *p* = 0.002). The forest plots of these outcomes are shown in Supplementary Figure S6.

4. Discussion

Our meta-analysis consisting of 29 comparative studies, in essence, demonstrated the following main findings: (i) Treatment with insulin was associated with higher rates of mortality, MI, MACE, stent thrombosis, TLR, TVR, and stroke on both short-term and long-term basis; (ii) There was no significant difference in the need for post-PI CABG between the two groups; and (iii) The presence of bifurcation lesions or class B2/C lesions had no significant effect on the cardiovascular outcomes post-PCI. These findings are consistent with the previous meta-analyses.[4]

Considerable efforts have been made to understand the reasons behind this significantly higher rate of adverse CV outcomes in insulin-treated DM patients after PCI. Firstly, insulin-treated DM patients have worse clinical outcomes regardless of the treatment regimen, either due to more advancing disease in these patients or an adverse effect of this insulin therapy.[31] This impression is backed by our analysis which shows patients with insulin-treated DM had a significantly higher rate of comorbidities like MI, hypertension, dyslipidemia, chronic kidney disease, and previous PCI history. Typically, insulin therapy is implemented in a more advanced stage of diabetes.[36] Therefore, a higher rate of detrimental outcomes should be foreseen in these complicated patients after PCI. By the same token, it has been seen that although insulin controls diabetes-induced hyperglycemia, it can also boost pro-inflammatory response by macrophages and stimulate hormonal activation of signal transduction pathways, thus accelerating the progression of atherogenesis by disturbing the balance between the synthesis and release of endothelial mediators.[37,38] Apart from this, studies show that treatment with insulin has been associated with increased platelet aggregation,[19] thus contributing to the

Table 1
Baseline demographics of observational studies.

Study and year	Study type	Study center	Follow up period	Total No. of patients (n)		Mean Age (year)		Male n (%)	
				ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM
Biswas, S., 2021[6]	Pros.obs	Australia	1 year	1111	3468	65.2 ± 11.3	67.1 ± 11.2	741 (66.7)	2531 (73.0)
Pepe, M., 2019[11]	Pros.obs	Italy	1 year	83	248	73.01 ± 9.7	69.2 ± 10.0	61 (73.5)	188 (75.8)
Pi, S. H., 2018[12]	Pros.obs	Korea	1 year	617	1169	65.2 ± 9.6	65.2 ± 9.6	346 (56.1)	848 (72.5)
Schofer, J., 2000[13]	Retr.obs	Germany	6 months	48	177	60 ± 9	62 ± 9	34 (71)	136 (77)
Stien, B., 1995[14]	Retr.obs	USA	In-Hospital	352	781	58 ± 11	60 ± 10	187 (53.1)	516 (66.1)
Chandrasekhar, J., 2018[15]	Retr.obs	USA	1 year	2313	5737	64.86 ± 10.59	65.76 ± 10.62	1360 (58.7)	3886 (67.7)
Tada, T., 2011[16]	Pros.obs	Japan	3 years	996	3404	66.7	67.9	667 (67)	2587 (76)
Nakamura, M., 2010[17]	Pros.obs	Japan	3 years	200	647	66.2	67.2	13240 (66.2)	488 (75.4)
Mulukutla, S. R., 2009[18]	Pros.obs	Pennsylvania	1 year	817	1749	63.5	64	414 (50.7)	1076 (61.5)
Kumar, R., 2007[19]	Pros.obs	USA	9 months	115	182	62	67	71 (62)	122 (67)
Mehran, R., 2004[20]	Pros.obs	USA	in hospital	63	66	63 ± 11	66 ± 10	49 (77)	51 (77)
Abizaid, A., 1998[21]	Retr.obs	Washington	For 1 year	97	151	63 ± 12	63 ± 11	48 (49.5)	96 (63.6)
Akin, I., 2010[22]	Pros.obs	Germany	1 year	581	1078	66.9 ± 9.4	66.6 ± 9.4	380 (65.4)	809 (75)
Antoniucci, D., 2004[23]	Pros.obs	Italy	6months	84	82	69 ± 12	68 ± 11	55 (65)	60 (73)
Jain, A. K., 2010[24]	Retr.obs	Multicenter	12 months	682	2039	66.57 ± 9.85	64.90 ± 1 0.23	424 (62.2)	1463 (71.8)
Kuchukulanti, P. K., 2010[25]	Pros.obs	USA	6 months	265	586	65.1	65.1	160 (60.5)	355 (60.5)
Konishi, Y., 2016[26]	Pros. obs	Tokyo	At 1 year	199	575	68.3 ± 8.9	69.7 ± 9.4	121 (60.8)	442 (76.9)

Pros.obs: Prospective observational; Retr.obs: Retrospective observational.

Table 2
Comorbidities of patients in observational studies.

Study and year	Hypertension n (%)		Dyslipidemia n (%)		Chronic Kidney Disease n (%)		Prior MI n (%)		Prior PCI n (%)		Smoker n (%)	
	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM
Biswas, S., 2021	947 (85.3)	2875 (83)	930 (83.8)	2833 (81.8)	595 (54.7)	2404 (71.1)	485 (43.7)	1161 (33.5)			179 (16.6)	578 (16.9)
Pepe, M., 2019	70 (84.3)	216 (87.1)	49 (59.0)	157 (63.3)	28 (33.7)	41 (16.5)	29 (34.9)	60 (24.2)	29 (34.9)	68 (27.4)	27 (32.5)	97 (39.1)
Pi, S. H., 2018	475 (77.4)	855 (73.3)	298 (49.3)	449 (38.6)	330 (53.5)	296 (25.6)	64 (10.4)	148 (12.7)	124 (20.1)	169 (14.5)	110 (18.2)	299 (25.8)
Schofer, J., 2000	35 (73)	132 (75)	31 (65)	128 (72)			24 (50)	67 (38)			6 (13)	35 (20)
Stien, B., 1995	200 (56.8)	492 (63.0)					145 (41.2)	276 (35.3)				
Chandrasekhar, J., 2018	2260 (97.7)	5573 (97.1)	2238 (96.8)	5577 (97.2)	1060 (48.1)	1648 (29.8)					258 (11.2)	720 (12.6)
Tada, T., 2011	757 (76)	2655 (78)					285 (28.6)	1026 (30.1)	513 (51.5)	1704 (50.1)	159 (16)	715 (21)
Nakamura, M., 2010	136 (68)	466 (72)	116 (58)	414 (64)	87 (43.5)	272 (42.0)					24 (12.0)	126 (19.5)
Mulukutla S. R., 2009	693 (84.8)	1452 (83)	654 (80.0)	1352 (77.3)	368 (45.0)	311 (17.80)	572 (70.1)	1062 (60.7)			138 (16.9)	339 (19.4)
Kumar, R., 2007	108 (94.0)	169 (93.0)	102 (89.0)	167 (92.0)	30 (26)	30 (16)	65 (57)	72 (40)			13 (11)	15 (8)
Mehran, R., 2004	45 (71)	44 (67)	13 (20)	9 (13)	30 (48)	36 (54)	28 (45)	20 (31)	7 (11)	5 (8)		
Abizaid, A., 1998	71 (73)	103 (68)	58 (60)	97 (64)			53 (54.5)	82 (54.5)	60 (61.4)	86 (57)	48 (49.0)	73.4 (48.6)
Akin, I., 2010	537 (92.4)	1003 (93)	471 (81.0)	900 (83.50)	145 (24.9)	323 (30.0)	198 (34.1)	326 (30.2)	280 (48.2)	467 (43.3)	87 (14.9)	208 (19.3)
Antoniucci, D., 2004	34 (40)	35 (43)	25 (30)	25 (30)			14 (17)	13 (15.9)			17 (20)	21 (26)
Jain, A. K., 2010	560 (82.1)	1580 (77.5)	463 (67.9)	1380 (67.7)	44 (6.5)	47 (2.3)	244 (35.8)	652 (32)	200 (29.3)	479 (23.5)	95 (13.9)	367 (18)
Kuchukulanti, P. K., 2010	236 (89)	522 (89)	235 (88.5)	519 (88.5)							42 (16)	94 (16)
Konishi, Y., 2016	152 (76.4)	446 (77.6)	159 (79.9)	487 (84.7)	99 (49.8)	139 (24.2)	75 (37.7)	172 (29.9)	94 (47.2)	217 (37.7)	37 (18.6)	108 (18.8)

Table 3
Baseline demographics of randomized controlled trials.

Study and year	Study type	Study center	Follow up period	Total No. of patients (n)		Mean Age (year)		Male n (%)	
				ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM
Bangalore, S., 2016[7]	RCT	Not specified	1 year	747	1083	58.52 ± 8.63	58.27 ± 9.52	530 (71.0)	847 (78.2)
Witzenbichler, B., 2011[27]	RCT	Multicenter	At 1 year	159	434	64.5	64.5	117 (73.4)	319 (73.4)
Kappetein, A. P., 2013[28]	RCT	USA	5 years	89	142	65.4	65.4	63 (71)	101 (71)
Beneduce, A., 2019[3]	RCT	Italy	1 year	113	372	68 ± 9	69 ± 9	82 (72.5)	307 (82.5)
Kalkman, D. N., 2017[29]	RCT	Netherlands	1 year	64	117	64.8 ± 9.4	68.6 ± 9.4	43 (67.2)	86 (72.9)
Stone, G. W., 2011[30]	RCT	USA	2 years	494	1375	63.8	63.8	312 (63.2)	869 (63.2)
Dangas, G. D. 2014[31]	RCT	Not specified	5 years and 1 month	602	1248	62.55 ± 9.2	63.25 ± 9	368 (61.1)	954 (76.4)
Hermiller, J. B, 2004[32]	RCT	Not specified	1 year	105	213	62.2	62.2	67 (63.5)	135 (63.5)
Kereiakes, D. J, 2010[33]	RCT	Not specified	12 months	314	826	63.3	63.3	199 (63.3)	523 (63.3)
Kirtane, A. J., 2009[34]	RCT	USA	1 year	137	319	64	64	83 (60.4)	193 (60.4)
Kirtane, A. J. 2008[8]	RCT	Not specified	4 years	265	562	63	63	171 (64.7)	364 (64.7)
Moussa, I., 2004[35]	RCT	USA	During 1 year	—	—	—	—	—	—

RCT: Randomized controlled trial.

Table 4
Comorbidities of patients in randomized controlled trials.

Study and year	Hypertension n (%)		Dyslipidemia n (%)		Chronic Kidney Disease n (%)		Prior MI n (%)		Prior PCI n (%)		Smoker n (%)	
	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM	ITDM	Non-ITDM
Bangalore,S.,2016	490 (65.6)	727 (67.1)	569 (76.2)	843 (77.8)			277 (37.1)	465 (42.9)	82 (11.0)	63 (5.8)	92 (12.3)	181 (16.7)
Witzenbichler, B., 2011	115 (72.3)	314 (72.3)	96 (60.3)	262 (60.3)			27 (16.7)	72 (16.7)	26 (16.5)	72 (16.5)	90 (56.8)	247 (56.8)
Kappetein, A. P., 2013	62 (70)	99 (70)	73 (82)	116 (82)			29 (32)	45 (32)			14 (16)	22.7 (16)
Beneduce, A., 2019	100 (88)	301(81)	90 (24)	258 (69)	38 (34)	78 (21)	35 (31)	97 (26)	60 (53)	186 (50)	19 (17)	108 (29)
Kalkman, D. N., 2017	51 (79.7)	94 (79.7)	51 (79.7)	80 (67.8)	10 (15.6)	15 (12.7)	23 (35.9)	38 (32.2)	26 (40.6)	42 (35.6)	12 (18.8)	20 (16.9)
Stone, G. W., 2011	411 (83.1)	1143 (83.1)	392 (79.4)	1092 (79.4)							97 (19.6)	270 (19.6)
Dangas, G. D. 2014	175 (29.0)	166 (13.3)					308 (51.1)	644 (51.6)			217 (36)	362 (29)
Hermiller, J. B, 2004	85 (81.1)	173 (81.1)	75 (71)	151 (71)								
Kereiakes, D. J, 2010	273 (87)	719 (87)	259 (82.5)	681 (82.5)							57 (18.3)	151 (18.3)
Kirtane, A. J., 2009	240 (90.6)	509 (90.6)	231 (87.1)	490 (87.1)							143 (54.1)	304 (54.1)
Kirtane, A. J. 2008	112 (82.1)	262 (82.1)	101 (74)	236 (74)							25 (18.4)	59 (18.4)
Moussa, I., 2004	–	–	–	–	–	–	–	–	–	–	–	–

Table 5
Pooled baseline demographics comparing insulin-treated DM group versus non-insulin-treated DM group.

Baseline Characteristics	Insulin-treated	Non-insulin-treated	Insulin-treated DM vs non-insulin-treated DM (95% CI)	p-value
Age (mean ± SD)	62.3 ± 26.5	62.8 ± 51.2	WMD = −0.59 [-1.22, 0.030]	0.06
Male	11742	28785	RR = 0.89 [0.87, 0.92]	<0.00001
Hypertension	11559	28785	RR = 1.01 [0.98, 1.04]	0.65
Dyslipidemia	9791	23352	RR = 1.00 [0.98, 1.02]	0.91
Chronic Kidney disease	4028	10541	RR = 1.17 [1.09, 1.27]	<0.0001
Prior Myocardial Infarction	7619	18520	RR = 1.11 [1.03, 1.20]	0.008
Prior PCI	4407	10645	RR = 1.17 [1.06, 1.30]	0.003
Smoker	11222	5422	RR = 0.89 [0.83, 0.97]	0.006

DM, Diabetes millets; RR, relative risks; WMD, weighted mean difference; CI, confidence interval.

Table 6
Results of Begg's test of publication bias for short and long term outcomes.

Outcomes	Begg's p- value for short term	Begg's p-value for short term
Mortality	0.458	0.547
MI	0.404	0.054
MACE	0.573	0.411
TLR	0.091	0.951
TVR	0.089	0.788
TVF	–	0.174
Stent thrombosis	0.142	0.681
CABG	0.117	0.602
Stroke	–	0.117

MI: Myocardial infarction; MACE: Major adverse cardiac effects; TLR: Target lesion revascularization, TVR: Target vessel revascularization, TLF: Target lesion failure, CABG: coronary artery bypass grafting.

higher rates of stent re-thrombosis in patients treated with insulin. Another reason that can be linked to the increased risk of adverse outcomes in insulin-treated DM patients is obesity leading to treatment-resistant diabetes and the greater prevalence of family history of coronary as well as peripheral arterial disease in these patients.[34]

Similar to this meta-analysis, previously, several meta-analyses of large-scale trials have shown that patients with insulin-treated DMare associated with worse adverse cardiovascular outcomes than patients with non-insulin-treated T2DM following PCI.[39,4] A meta-analysis of 21 studies published by Bundhun et al comparing the adverse outcomes in patients with insulin-treated DM and non-insulin-treated T2DM showed that both short-term and long-term adverse outcomes were significantly more likely ininsulin-treated DM subgroup following PCI.[4] In concordance to that, another study showed that adverse outcomes after PCI were significantly higher in the long-term follow-up period compared to short-term follow-up in patients with ITDM.[38]

Nevertheless, a few studies have published results that were different from this meta-analysis. A study conducted by Zhuo et al showed that although the risk of stent thrombosis was higher in short-term follow-up, it was not significantly higher in long-term follow-up period in patients with insulin-treated DM.[1] Another study concluded that the risk of stent thrombosis did not differ significantly across the groups.[40]

A study published by Beneduce et al showed that the rate of TLR and TLF in patients with insulin-treated DM and non-insulin-treated T2DM were comparable. However, ITDM patients showed higher rates of cardiac deaths.[3] Similarly, a meta-analysis conducted in patients with insulin-treated DM found that mortality associated with cardiac causes was significantly higher than non-cardiac related mortality following PCI procedure.[39]

Moreover, a study that followed participants over an 11-year follow-up found that the rate of worse outcomes of PCI was higher in diabetic women than in diabetic men. Thus, treatment with insulin might not be the only reason for the worse outcomes seen in patients living with diabetes following PCI.[41]

Compared to the earlier studies, the strength of this study is the performance of subgroup analysis and the increment in the number of the outcomes as well a larger sample size, making results more
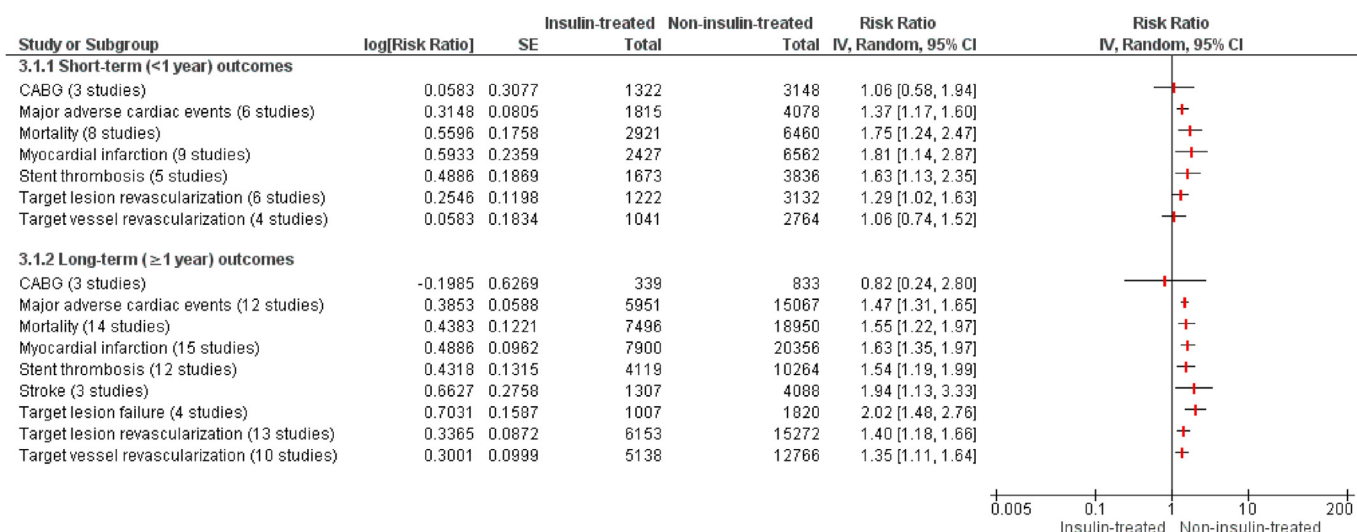
Study or Subgroup	log[Risk Ratio]	SE	Insulin-treated Total	Non-insulin-treated Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
3.1.1 Short-term (<1 year) outcomes						
CABG (3 studies)	0.0583	0.3077	1322	3148	1.06 [0.58, 1.94]	
Major adverse cardiac events (6 studies)	0.3148	0.0805	1815	4078	1.37 [1.17, 1.60]	
Mortality (8 studies)	0.5596	0.1758	2921	6460	1.75 [1.24, 2.47]	
Myocardial infarction (9 studies)	0.5933	0.2359	2427	6562	1.81 [1.14, 2.87]	
Stent thrombosis (5 studies)	0.4886	0.1869	1673	3836	1.63 [1.13, 2.35]	
Target lesion revascularization (6 studies)	0.2546	0.1198	1222	3132	1.29 [1.02, 1.63]	
Target vessel revascularization (4 studies)	0.0583	0.1834	1041	2764	1.06 [0.74, 1.52]	
3.1.2 Long-term (≥1 year) outcomes						
CABG (3 studies)	-0.1985	0.6269	339	833	0.82 [0.24, 2.80]	
Major adverse cardiac events (12 studies)	0.3853	0.0588	5951	15067	1.47 [1.31, 1.65]	
Mortality (14 studies)	0.4383	0.1221	7496	18950	1.55 [1.22, 1.97]	
Myocardial infarction (15 studies)	0.4886	0.0962	7900	20356	1.63 [1.35, 1.97]	
Stent thrombosis (12 studies)	0.4318	0.1315	4119	10264	1.54 [1.19, 1.99]	
Stroke (3 studies)	0.6627	0.2758	1307	4088	1.94 [1.13, 3.33]	
Target lesion failure (4 studies)	0.7031	0.1587	1007	1820	2.02 [1.48, 2.76]	
Target lesion revascularization (13 studies)	0.3365	0.0872	6153	15272	1.40 [1.18, 1.66]	
Target vessel revascularization (10 studies)	0.3001	0.0999	5138	12766	1.35 [1.11, 1.64]	

0.005   0.1   1   10   200
Insulin-treated   Non-insulin-treated

Fig. 2. Short and long term follow-up cardiovascular outcomes of insulin-treated DM group versus non-insulin-treated DM group undergoing percutaneous intervention (PCI).

Table 7
Subgroup analysis by the presence of Bifurcation lesion for cardiovascular outcomes after PCI.

Outcomes	Bifurcation lesion		p value subgroups	I^2 (%)	ACC/AHA lesion B2/BC		p value subgroups	I^2 (%)
	With Bifurcation lesion	Without Bifurcation lesion			With ACC/AHA lesion B2/BC	Without ACC/AHA lesion B2/BC		
	RR (95% CI)	RR (95% CI)			RR (95% CI)	RR (95% CI)		
All-cause mortality	1.69 [1.37, 2.08]	1.65 [1.40, 1.94]	0.85	0	1.80 [1.46, 2.21]	1.64 [1.38, 1.96]	0.52	0
Myocardial Infarction (MI)	1.76 [1.33, 2.33]	1.44 [1.17, 1.78]	0.26	19.9	1.78 [1.31, 2.42]	1.42 [1.21, 1.66]	0.20	37.9
Major adverse cardiac effects (MACEs)	1.45 [1.14, 1.84]	1.46 [1.32, 1.61]	0.97	0	1.44 [1.23, 1.69]	1.41 [1.24, 1.61]	0.83	0
Stent thrombosis	1.66 [1.29, 2.13]	1.35 [0.90, 2.02]	0.39	0	1.57 [1.09, 2.26]	1.57 [1.21, 2.03]	0.98	0
Target lesion failure (TLF)	2.25 [1.33, 3.80]	2.00 [1.21, 3.31]	0.75	0	2.44 [1.57, 3.79]	1.69 [1.09, 2.61]	0.25	25.0
Target vessel revascularization (TVR)	1.46 [1.05, 2.02]	1.20 [0.97, 1.49]	0.33	0	1.46 [1.23, 1.75]	1.03 [0.81, 1.31]	0.02	81.4
Target lesion revascularization (TLR)	1.53 [1.35, 1.74]	1.23 [0.93, 1.63]	0.16	49.6	1.63 [1.38, 1.93]	1.28 [1.03, 1.59]	0.09	66.1
Coronary Artery Bypass Graft (CABG)	1.30 [0.71, 2.38]	0.72 [0.27, 1.92]	0.31	1.3	0.71 [0.31, 1.60]	1.04 [0.43, 2.51]	0.53	0

robust. Nevertheless, there are a few limitations to this study. Firstly, the size of the population of the diabetic group was small in all individual studies. Secondly, like the previous meta-analysis[3] non-insulin-treated T2DM patients had patients on different oral medications; the difference in the dose and medication class could have contributed to some undesirable heterogeneity. In addition to these limitations, we found great variability in the definition of MACE in the studies included in our analysis as well as other similar studies. This disparity in definition may have led to inaccurate determination of the concerned outcome. Finally, our study may have been affected by the factor that different stents were used on patients who were observed during the study.

As insulin-treated DM patients showed a significant increase in both short-term and long-term adverse outcomes following PCI, it is imperative for cardiothoracic surgeons to be vigilant. This necessitates an introduction of a pre-procedure protocol to rule out high-risk insulin-treated DM patients and minimize any risk factor that could precipitate an adverse outcome after the procedure. Alternatively, the increment in adverse outcomes faced by insulin-treated DM patients also warrants the need to devise secondary treatment strategies to replace PCI. Additionally, to increase the validity of the current findings, further studies are required to be done with similar kinds of stents being used in the study population and an equal number of patients across study groups i.e.,

insulin-treated DM patients and non-insulin-treated T2DM patients.

5. Conclusion

Insulin-treated DM patients showed a significant rise in short-term as well as long-term adverse outcomes following PCI, compared to non-insulin-treated DM patients indicating that PCI, otherwise a highly successful procedure, entails a poor prognosis in the diabetic population treated with insulin. Careful pre and post-PCI assessments are warranted for insulin-treated DM patients to reduce the risk of adverse CV outcomes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.12.004.

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