Comparing the adverse clinical outcomes in patients with non-insulin treated type 2 diabetes mellitus and patients without type 2 diabetes mellitus following percutaneous coronary intervention: a systematic review and meta-analysis

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Abstract

Background: Several studies showed Type 2 Diabetes Mellitus (T2DM) to be associated with worse adverse clinical outcomes compared to non-T2DM (NDM) following Percutaneous Coronary Intervention (PCI). In addition, patients with insulin-treated T2DM (ITDM) showed worse clinical outcomes compared to patients with non-insulin treated T2DM (NITDM). Since NITDM and NDM have seldom been systematically analyzed, this study aimed to compare the short and long term adverse clinical outcomes observed in patients with NITDM and patients without T2DM following PCI.

Methods: Medline/PubMed, EMBASE and the Cochrane library were searched for Randomized Controlled Trials (RCTs) and observational studies comparing patients with (including ITDM and NITDM) and without T2DM following PCI. Endpoints included adverse clinical outcomes reported during a short and a long term follow up period. Odd Ratios (OR) and 95% Confidence Intervals (CI) in accordance with either a fixed or a random effects model appropriately, were calculated and the pooled analyses were performed with RevMan 5.3.

Results: Twelve studies consisting of a total number of 52,451 patients (14,863 NITDM and 37,588 NDM) were included. Patients with NITDM were found to have significantly higher short-term Major Adverse Cardiac Events (MACEs) and mortality with OR: 1.63, 95% CI (1.17, 2.27); P = 0.004 and OR: 1.71, 95% CI (1.40, 2.10), P < 0.00001 respectively and higher long-term MACEs and mortality with OR: 1.25, 95% CI (1.12, 1.40), P = 0.0001 and OR: 1.32, 95% CI (1.19, 1.47), P < 0.000001 respectively compared to NDM following PCI. In addition, compared to NDM, long-term Target Vessel Revascularization (TVR) and Target Lesion Revascularization (TLR) were significantly higher in the NITDM group with OR: 1.36, 95% CI (1.18, 1.56), P < 0.0001 and OR: 1.32, 95% CI (1.10, 1.59), P = 0.003 respectively. However, even if an increased long-term stent thrombosis was observed in the NITDM group with OR: 1.13; 95% CI (0.91, 1.40), P = 0.28, the result was insignificant.

Conclusion: Short and long term MACEs and mortality were significantly higher in patients with NITDM compared to patients without diabetes following PCI. Revascularization also significantly favored patients without T2DM. However, stent thrombosis was not significantly different.

Keywords: Non-insulin treated diabetes mellitus, Percutaneous coronary intervention, Major adverse cardiac events, Stent thrombosis, Clinical outcomes

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**Background**

Patients with Type 2 Diabetes Mellitus (T2DM) have worse clinical outcomes compared to patients without T2DM (NDM) following Percutaneous Coronary Intervention (PCI). For example, the PRESTO trial showed that despite advances in interventional techniques, diabetes mellitus remained a significant predictor of adverse clinical events after PCI [1, 2]. Later on, it was shown that patients with insulin-treated T2DM (ITDM) had even worse adverse outcomes compared to patients with non-insulin treated T2DM (NITDM). To further illustrate this point, the FREEDOM trial showed a significantly higher rate of Major Adverse Cardiac Effects (MACEs) in those diabetic patients who were on insulin therapy following PCI compared to those patients without insulin therapy [2]. It is clear that patients without T2DM when compared to patients with T2DM and patients with NITDM compared to ITDM have lower adverse clinical events following PCI. Since NITDM and NDM have seldom been systematically analyzed, this study aimed to compare the short and long term adverse clinical outcomes observed in patients with NITDM and patients without T2DM following PCI.

**Methods**

**Data sources and search strategy**

Studies including Randomized Controlled Trials (RCTs) and observational studies were searched from Medline/PubMed, EMBASE and the Cochrane databases using the words 'diabetes mellitus and percutaneous coronary intervention/PCI' or 'insulin-treated and non-insulin treated diabetes mellitus and PCI'. The term 'angioplasty' and the abbreviations 'T2DM and DM' were also used. Reference lists of relevant publications obtained were also checked for suitable articles. Our search began on 2nd May 2015 and ended on 30th September 2015. This search was restricted only to articles which were published in English language.

**Inclusion and exclusion criteria**

Studies were included if:

(a) They were randomized trials and observational studies comparing the adverse outcomes between T2DM (including ITDM and NITDM) and NDM following PCI.
(b) They were published during or after the year 2006 (from the year 2006 to 2015).

Studies were excluded if:

(a) Data concerning patients with NITDM could not be retrieved from these diabetic patients.
(b) Patients without T2DM were not included as the control.

(c) Adverse clinical outcomes were not reported among their endpoints.
(d) They were meta-analyses, case studies or letter to editors.
(e) They were published before the year 2006.
(f) They were duplicates.

**Definitions, outcomes and follow up periods**

NITDM were defined as patients who were at an earlier stage of T2DM, or did not have any diabetic complications or patients with a good control of their blood glucose levels, therefore not requiring insulin therapy as treatment. These patients were either on a diet control or on oral hypoglycemic agents.

The adverse clinical outcomes were:

(a) Mortality: defined as all-cause mortality including cardiac and non-cardiac deaths.
(b) MACEs: were defined as death of cardiac or procedure-related origin, myocardial infarction, and/or, revascularization following coronary stents implantation. Due to limited outcomes reported, major adverse cardiac and cerebrovascular events (MACCEs) were considered in the same category as MACEs and analyzed in this study.
(c) Target lesion revascularization (TLR) and Target vessel revascularization (TVR)
(d) Myocardial infarction (MI): was defined as re-infarction which occurred in these patients after PCI. Any type of MI was relevant.
(e) Stent thrombosis (ST): Any type of ST was considered acceptable during this analysis.

**Short term follow-up period**: was defined as a follow-up period of less than 1 year.

**Long term follow-up period**: was defined as a follow up at or during one or more years (≥ one year).

**Data extraction and quality assessment**

Eligible studies were independently assessed by NL, YJY and MHC. The types of study and patients' baseline characteristics, the total number of patients with NITDM and without T2DM respectively, the year of publication, the clinical outcomes (MACEs, death, ST, TVR, TLR, MI) and the follow up duration were systematically extracted. Any disagreement which followed was resolved by consensus. Cochrane Collaboration was considered during bias risk assessment [3].

**Methodological quality and statistical analysis**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was followed in this type of research article [4]. The Cochrane Q-statistic test ($p$ value ≤ 0.05 was considered statistically significant)
and the $I^2$-statistic test ($I^2$ value of 0% indicated a very low heterogeneity) were used to assess heterogeneity. An $I^2$ value less than 50% indicated the use of a fixed effects model, whereas a random effects model was used if $I^2$ was greater than 50%. Funnel plots were used to assess publication bias.

We calculated Odd Ratios (OR) with 95% Confidence Intervals (CIs). The pooled analyses were performed with RevMan 5.3 software. All the authors had access to the data which were used in this study. Ethical approval was not necessary for this meta-analysis.

**Results**

**Study selection**

Two thousand four hundred and thirty-two articles were identified by titles and abstracts obtained from Medline/PubMed, EMBASE and the Cochrane library. An additional 16 articles were identified from the reference lists of suitable articles. After eliminating the duplicate studies, further articles were excluded since they were not relevant to the topic of this research. Forty-four full-text articles were assessed for eligibility. Another 32 articles were excluded for the following reasons: data for patients with NITDM could not be retrieved, data were not usable or the studies were published before the year 2006. Finally, 12 articles [5–16] were selected for this meta-analysis. The flow chart showing study selection has been illustrated in Fig. 1.

Table 1 shows the clinical outcomes reported in each of the 12 studies included.

**General features of the studies included in this analysis**

Table 2 represents the general features including the total number of patients in the NITDM and the NDM groups respectively, the type of study, and the follow-up periods of each of the studies included in this analysis.

As shown in Table 2, this meta-analysis included a total number of 52,451 patients among which, 14,863 were NITDM patients, whereas 37,588 patients were NDM.

**Baseline characteristics**

Data reporting the mean age of the patients in years, the percentage of patients with male gender, with comorbidities such as hypertension, dyslipidemia and the percentage of patients who were current smokers were listed in Table 3. According to Table 3, no significant

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**Fig. 1 Flow diagram representing the study selection**
differences were observed in the baseline characteristics between these two groups of patients (NITDM and NDM).

Results of the meta-analysis
A total number of 4163 patients were analyzed for MACEs and MI respectively and 17,015 patients were analyzed for mortality during the short-term follow-up period.

This analysis showed a significantly higher rate of MACEs and MI in the NITDM group with OR: 1.63, 95% CI (1.17, 2.27); \( P = 0.04 \) and OR: 1.82, 95% CI (1.08, 3.06); \( P = 0.02 \) when compared to NDM respectively during the short term follow up period following PCI. Compared to NDM, the mortality rate was also significantly higher in the NITDM group with OR: 1.71, 95% CI (1.40, 2.10), \( P < 0.00001 \). Results representing the short-term outcomes were illustrated in Fig. 2. Table 4 summarized the result for the short-term follow up period.

For the long-term follow up period, a total number of 21,465 patients were analyzed for MACEs, 37,756 patients were analyzed for mortality, 31,964 patients were analyzed for MI, 30,388 patients were analyzed for TLR, 14,320 patients were analyzed for TVR and 36,900 patients were analyzed for ST.

This current long-term analysis showed a significantly higher MACEs and mortality in the NITDM group with OR: 1.25, 95% CI (1.12, 1.40), \( P = 0.0001 \) and OR: 1.32, 95% CI (1.19, 1.47), \( P < 0.00001 \) respectively, and a significantly higher rate of TLR and TVR with OR: 1.32, 95% CI (1.10, 1.59), \( P = 0.003 \) and OR: 1.36, 95% CI (1.18, 1.56), \( P < 0.0001 \) respectively when compared to NDM. MI was similarly manifested with OR: 1.03, 95% CI (0.89, 1.21); \( P = 0.67 \). However, compared to NDM, even if the long-term ST was higher in the NITDM group, the result was not statistically significant with OR: 1.13, 95% CI (0.91, 1.40), \( P = 0.28 \). Results for the

| Table 1 | Outcomes reported in each study |
|---------|--------------------------------|
| Study   | Reported Outcomes               |
| Kappetein 2013 [5] | MACCE, Death, MI, Revascularization, Stent thrombosis |
| Kereiakes 2010 [6] | MACEs, MI, Stent thrombosis     |
| Kirtane 2008 [7]  | Death, MI, TLR, TVR, Stent thrombosis |
| Kirtane 2009 [8]  | MACEs, Death, MI, TLR, TVR, Stent thrombosis |
| Kumar 2007 [9]    | MACEs, Death, MI, TLR, Stent thrombosis |
| Stone 2011 [10]   | MACEs, Death, MI, TLR, Stent thrombosis |
| Tada 2011 [11]    | Death, MI, TLR, Stent thrombosis |
| Thukkani 2015 [12]| MACEs, MI, Death, TVR, Stent thrombosis |
| Witzenbichler 2011 [13] | Death               |
| Massalha 2015 [14]| MACEs, MI, Death, TVR, Stent thrombosis |
| Jain 2010 [15]    | Death, MACEs, TLR, TVR, Stent thrombosis |
| Silber 2013 [16]  | Death, MACEs, TLR, TVR, Stent thrombosis |

Abbreviations: MACEs major adverse cardiac events, MI myocardial infarction, TVR target vessel revascularization, TLR target lesion revascularization

| Table 2 | General features of the included studies |
|---------|----------------------------------------|
| Study   | No of NITDM | No of NDM | Type of study | Follow up |
| Kappetein 2013 [5] | 142 | 672 | RCT | 5 years |
| Kereiakes 2010 [6] | 826 | 2467 | RCT | 1 year |
| Kirtane 2008 [7]  | 562 | 2686 | RCT | 4 years |
| Kirtane 2009 [8]  | 333 | 1071 | RCT | 1 year |
| Kumar 2007 [9]    | 182 | 541 | OS | 9 months |
| Stone 2011 [10]   | 1375 | 4911 | RCT | 2 years |
| Tada 2011 [11]    | 3404 | 6378 | OS | 3 years |
| Thukkani 2015 [12]| 4862 | 7990 | OS | ≤12 months >12 |
| Witzenbichler 2011 [13] | 434 | 3006 | RCT | 30 days, 1 year |
| Massalha 2015 [14]| 196 | 694 | OS | 5 years |
| Jain 2010 [15]    | 1919 | 5269 | OS | 1 year |
| Silber 2013 [16]  | 628 | 1903 | RCT | 2 years |

Abbreviations: NITDM non-insulin treated diabetes mellitus, NDM non-diabetes mellitus, RCT randomized controlled trials, OS observational studies
long-term follow up period were illustrated in Figs. 3, 4 and 5. Table 5 summarized the results for this long-term follow up period.

A separate analysis was conducted (excluding observational studies) involving only randomized trials. The results showed long term MACEs and TVR to be significantly higher in the NITDM group with OR: 1.19, 95% CI (1.03, 1.36); \( P = 0.02 \) and OR: 1.47, 95% CI (1.23, 1.74); \( P < 0.0001 \) respectively when compared to NDM. However, even if mortality was higher in the NITDM group with OR: 1.20, 95% CI (0.96–1.50); \( P = 0.10 \), the result was not statistically significant. These results have been shown in Fig. 6. In addition, long term MI and ST were also not significantly different between these 2 groups with OR: 1.04, 95% CI (0.85, 1.28); \( P = 0.68 \) and OR: 1.05, 95% CI (0.77, 1.43); \( P = 0.75 \) respectively. These results have been shown in Fig. 7.

Discussion

Many studies have shown T2DM to be independently associated with increased adverse clinical outcomes following PCI compared to patients without T2DM. Other studies have shown the adverse complications to be significantly higher in patients with ITDM compared

### Table 3 Baseline features of the included studies

| Study            | Age (years) | Males (%) | HT (%) | Ds (%) | Cs (%) |
|------------------|-------------|-----------|--------|--------|--------|
| Kappetein 2013 [5] | 65.4/65.0  | 71.0/79.9 | 70.0/65.0 | 82.0/77.0 | 16.0/22.0 |
| Kereiakes 2010 [6] | 63.3/63.4  | 63.3/70.0 | 87.0/71.9 | 82.5/72.6 | 18.3/24.0 |
| Kirtane 2008 [7]   | 63.0/62.1  | 64.7/75.0 | 82.1/64.5 | 74.0/69.6 | 18.4/24.9 |
| Kirtane 2009 [8]   | 64.0/63.3  | 60.4/71.0 | 90.6/76.7 | 87.1/81.4 | 54.1/64.8 |
| Kumar 2007 [9]     | 67.0/66.0  | 67.0/73.0 | 93.0/77.0 | 92.0/80.0 | 8.0/14.0 |
| Stone 2011 [10]    | 63.8/63.0  | 63.2/71.3 | 83.1/62.5 | 79.4/64.0 | 19.6/27.1 |
| Tada 2011 [11]     | 67.9/68.8  | 76.0/76.0 | 78.0/73.0 | –       | 21.0/20.0 |
| Thukkani 2015 [12] | 64.3/64.2  | 98.5/98.3 | 96.4/88.5 | 82.9/80.0 | 36.7/48.7 |
| Witzenbichler 2011 [13] | 64.5/59.6 | 73.4/77.2 | 72.3/49.8 | 60.3/39.7 | 56.8/64.9 |
| Massalha 2015 [14] | 63.0/58.0  | 71.0/84.0 | 65.0/41.0 | –       | 22.0/23.0 |
| Jain 2010 [15]      | 64.9/62.3  | 71.8/80.2 | 77.5/63.7 | –       | 18.0/25.4 |
| Silber 2013 [16]    | 65.5/63.5  | 70.4/74.4 | 86.0/73.1 | 86.0/76.0 | 18.6/22.1 |

Abbreviations: HT hypertension, Ds dyslipidemia, Cs current smoker, NI: non-insulin treated diabetics, NDM non-diabetics
to patients with NITDM. We aimed to compare the clinical outcomes between NITDM and NDM in order to know whether they have similar outcomes or not following PCI.

Results of this analysis showed significantly higher long and short term mortality and MACEs in the NITDM group compared to the NDM group. MI was similarly manifested whereas revascularization was significantly higher in patients with T2DM. Moreover, even if ST was higher in patients with NITDM compared to patients without T2DM, the result was not statistically significant in this current study.

Similar to this current analysis, the study published by Kappetein et al. also showed significantly higher MACEs and repeated revascularization (TLR and TVR) in patients with NITDM compared to those without T2DM following PCI [5]. Moreover, the PRESTO Trial which included 75% of patients with T2DM not on insulin therapy, also showed T2DM to be a significant predictor of adverse outcomes after PCI compared to NDM. Death

| Analyzed Outcomes | No of studies analyzed | Total no of patients (n) | OR (Odd ratio with 95% CI) | P value | I² (%) |
|-------------------|------------------------|--------------------------|---------------------------|---------|--------|
| MACEs             | 2                      | 4163                     | 1.63 (1.17, 2.27)         | 0.004   | 0      |
| Death             | 3                      | 17,015                   | 1.17 (1.40, 2.10)         | <0.0001 | 5      |
| MI                | 2                      | 4163                     | 1.82 (1.08, 3.06)         | 0.02    | 0      |

Abbreviations: MACEs major adverse cardiac effects, MI myocardial infarction
in these patients with T2DM was reported as 2.1\% compared to those patients without T2DM with only 0.9\%. TVR was also higher in the T2DM group compared to the NDM group (17.9\% versus 12.8\%). This PRESTO Trial showed that compared to NDM, patients with T2DM had an advanced age, were mostly female patients and the majority had a history of heart failure and lower ejection fraction. These patients with T2DM were mainly overweight and obese, and had a high rate of comorbidities [1].

The SORT OUT IV Trial also showed T2DM to be associated with a significantly higher rate of MACEs following PCI (13\% in DM versus 6.4\% in NDM). However, this result included patients with both ITDM and...
NITDM [17]. This current analysis showed long term ST to favor the NDM group without any statistical significance. However, the study published by Jensen et al. in 2010 showed T2DM to be associated with an increased risk of definite ST compared to NDM after PCI. But their result included patients with both ITDM and NITDM [18] whereas this current analysis only involved diabetic patients without insulin therapy.

This current study only analyzed patients with NITDM. However, several other studies compared patients with ITDM and NITDM have shown the former to be associated with even worse adverse outcomes after PCI. For example, results from the FREEDOM Trial showed that in patients with diabetes and multi-vessel coronary artery disease, MACEs were higher in patients treated with insulin compared to patients without insulin therapy [2]. The study published by Jain et al. also showed patients with ITDM to have significantly higher MACEs, all-cause mortality, cardiac death as well as a significantly greater rate of target vessel failure.

### Table 5

Results for the long-term analysis

| Analyzed Outcomes | No of studies analyzed | Total no of patients (n) | OR (Odd ratio with 95% CI) | P value | I² (%) |
|-------------------|------------------------|--------------------------|---------------------------|---------|-------|
| MACEs             | 6                      | 21,465                   | 1.25 (1.12, 1.40)         | 0.0001  | 0     |
| Death             | 8                      | 37,756                   | 1.32 (1.19, 1.47)         | <0.0001 | 33    |
| MI                | 7                      | 31,964                   | 1.03 (0.89, 1.21)         | 0.67    | 17    |
| TLR               | 6                      | 30,388                   | 1.32 (1.10, 1.59)         | 0.003   | 62    |
| TVR               | 4                      | 14,320                   | 1.36 (1.18, 1.56)         | <0.0001 | 32    |
| ST                | 9                      | 36,900                   | 1.13 (0.91, 1.40)         | 0.28    | 17    |

Abbreviations: MACEs major adverse cardiac effects, MI myocardial infarction, TLR target lesion revascularization, TVR target vessel revascularization, ST stent thrombosis

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**Fig. 6** Long term adverse clinical outcomes observed between non-insulin treated T2DM and non-T2DM using only randomized patients (part 1)
compared to those diabetic patients not on insulin therapy after PCI [15]. Their study also showed no significant difference in definite and probable ST between ITDM and NITDM. Moreover, Bundhun et al. recently confirmed that insulin therapy was associated with significantly higher adverse clinical outcomes compared to NITDM whether during a short or long term follow up period [19]. Their analysis showed results with very low heterogeneity whereby mortality, MACEs, and revascularization were significantly higher in the ITDM group compared to the NITDM group. However, other studies suggested factors such as female gender, insulin resistance, coronary plaque vulnerability and post challenge hyperglycemia to be responsible for these adverse clinical outcomes following PCI [20–23]. However, this current study mainly focused on NITDM and NDM.

No significant difference in ST was observed between NITDM and NDM even if the percentage of ST among NITDM was higher. It should be noted that NITDM could be at an earlier stage of disease without severely being affected by diabetic complications. However, Ford et al. also showed a significantly improved trend in cardiovascular diseases among a population of United States between the years 1999 to 2000 and the years 2009 to 2010 respectively [24]. 7,751 patients from the National Health and Nutrition Examination Survey were used whereby a mean 10-year prediction of coronary heart disease was 7.2 and 6.5% during the years 1999 to 2000 and 2009 to 2010 respectively, and 9.2 and 8.7% for cardiovascular diseases during the same time period respectively. In addition, Gregg et al. [25] also showed a decline in the rate of complications due to T2DM between the years 1990 to 2010 which could be another reason due to which, ST did not differ significantly between NITDM and NDM in this current analysis.

This study is new in several ways. First of all, it is the first meta-analysis systematically comparing the adverse clinical outcomes between NITDM and NDM patients following PCI. Several studies compared T2DM with NDM, ITDM with NITDM, but this is the first meta-analysis comparing NITDM with NDM following PCI. The short-term and long-term follow up periods analyzed in this particular study have also added novelty to this research. Moreover, a larger number of patients obtained from randomized trials and observational studies were included in this analysis further contributing to its novelty.

**Limitations**

This study also has limitations. First of all, due to the smaller number of patients analyzed, a robust result might not be expected. Moreover, in one study, all cause-death was not reported. However, data for cardiac death was considered and included in the subgroup analyzing all-cause mortality. This might have an effect
on the result of this analysis. In addition, several types of ST were considered and analyzed altogether without relying a particular definition. To be more clear, ST defined according to protocol and ST defined according to academic research consortium (ARC) were combined and analyzed. This could have contributed to another main limitation of this study. Furthermore, PCI and anti-platelet therapy have evolved significantly during the last 5 years with new technologies, and new platelet inhibitors preventing ST and resulting in a lower level of complications among patients with T2DM. Ignoring this major consideration could have had a major effect on the result of this study further contributing to its limitations.

**Conclusion**

According to this analysis, short and long term MACEs and mortality were significantly higher in patients with NITDM compared to patients without diabetes following PCI. Revascularization also significantly favored patients without T2DM. However, stent thrombosis was not significantly different.

**Abbreviations**

ITDM: Insulin-treated diabetes mellitus; MACEs: Major adverse cardiac events; NDM: Non-diabetes mellitus; NITDM: Non-insulin treated diabetes mellitus; PCI: Percutaneous coronary intervention; ST: Stent thrombosis

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**Availability of data and materials**

All data and materials used in this research are freely available. References have been provided.

**Authors’ contributions**

NL was responsible for the conception and design, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it critically for important intellectual content. YGY was responsible for the conception and design, acquisition of data, interpretation of data, and for revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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