

Clinical outcomes after percutaneous coronary intervention in patients with and without history of diabetes mellitus with different stent size

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Research

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Abstract

Background

There are different reports on the occurrence of post-revascularization outcomes of diabetic patients in previous studies. Lesion complexity, which is reflected in stent size, influences the occurrence of outcomes. The aim of the present study was to investigate the occurrence of clinical outcomes in patients with history of diabetes (hDM) after percutaneous coronary intervention (PCI) with emphasis on stent length and diameter.

Methods

In a retrospective single-center cohort approach, among patients with stable coronary artery disease who underwent PCI with first- and second-generation DES, subjects were included from 2003 until 2019. Outcomes including revascularization, myocardial infarction, and death, totally defined as major adverse cardiac events (MACE), were sought in follow-up phase. All the patients whether with and without hDM received aspirin and clopidogrel as DAPT for at least two years and one year, respectively.

Results

About 29% out of 1630 participants had hDM and 37.8% of patients who experienced MACE had hDM. Unlike age and time-to-event, there was significant difference in gender between hDM and non-hDM groups. However, no difference was seen in type of MACE between these two groups. Also, after adjusting confounder variables, there was no significant difference in MACE incidence between hDM and non-hDM groups with different stent length and diameter (different lesion length and diameter).

Conclusions

hDM did not affect MACE incidence significantly in different stent length and diameter. We think that using of DES supplemented by long term DAPT and tight control of glycemic status after PCI are the underlying reasons.

Background

Undoubtedly diabetes mellitus (DM) has been become one of the global health emergencies. The current 451 million people with DM will project 693 million by 2045 (1). It is known as one of the major risk factors for coronary artery disease (CAD). The prevalence of coronary involvement in diabetic patients was reported to be 10 times higher than in general population. Accordingly, CAD has been known as the leading cause of death in diabetics (2, 3). Subsequently, DM was shown to be a better predictor of cardiac death even compared to increased age and decreased left ventricular ejection fraction (4).

Percutaneous and surgical angioplasties are the options ahead of CAD patients. However, some considerations exist about using the former in diabetics with respect to long-term mortality and repeated

revascularization. Albeit, medications such as glycoprotein IIb/IIIa inhibitors improved the outcome of stenting in CAD patients with DM. Bare metal stent (BMS) was used in percutaneous coronary intervention (PCI) for years. It was replaced by drug eluting stent (DES) with additional capability to reduce restenosis rate. Indeed, it was reported that DES delivers its advantageous in terms of reducing restenosis more than BMS both in DM and non-DM patients.

Coronary lesions in diabetic patients typically appear to be long and diffuse more likely in small diameter arteries. Stent size (stent length and diameter) is representative of lesion complexity. Thereby, stent size could possibly be as a prognostic marker for upcoming cardiovascular events. Deployment of long stents increases the risk of post-PCI outcomes. In contrary, another report claimed no inferiority of long stents than shorter ones (3, 5, 6). This study aimed to compare the incidence of post-PCI clinical outcomes between CAD patients with and without history of diabetes (hDM) with emphasis on stent length and diameter which is representatives of lesion length and diameter.

Materials And Methods

The present study is in conformity with the Helsinki declaration and has approved by the regional Research Ethics Committee. Participants were among patients with hDM and stable CAD who underwent PCI (index PCI) in hospitals affiliated with Shiraz University of Medical Sciences from March 2003 till January 2019. CAD patients with multivessel disease, syntax score of more than 32, acute coronary syndrome, and primary PCI were excluded

DM was defined as fasting plasma glucose of ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test or A1C of $\geq 6.5\%$ (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) (7) or those who were under antidiabetic medications. Patients who had systolic blood pressure of ≥ 130 mmHg or diastolic blood pressure of ≥ 80 mmHg or both or receiving antihypertensive medications before index PCI were considered with history of hypertension (hHTN) (8). Patients who had hyperlipidemia (HLP) or used antihyperlipidemic medications were regarded as those with history of HLP (hHLP) (9). hSmoking was defined as being smoker of any amount of any type (cigarette, water pipe, cigar, and pipe) before index PCI.

PCI was performed as standard technique if coronary anatomy was suitable. The criteria of doing angioplasty were based on $\geq 75\%$ narrowing in left anterior descending artery, Diagonal, left circumflex artery, obtuse marginal branches, right coronary artery, posterior descending artery, and posterior left ventricular branch branch (10). Based on availability, DES of first-generations (Sirolimus Eluting Stent, SES; Paclitaxel Eluting Stent, PES) and second-generations (Zotarolimus Eluting Stent, ZES; Everolimus Eluting Stent, EES) were applied in the patients.

Clopidogrel (600 mg) and aspirin (ASA, 325 mg) were given before the procedure and continued by 150 mg clopidogrel and 325 mg ASA for three weeks followed by 75 mg/day of clopidogrel and 80 mg (160 mg in case of hDM) of ASA in diabetic patients for at least two years and in non-diabetic patients

for at least one year. Also, atorvastatin at 40–80 mg was administered to all participants. Heparin (80–100 mg/kg) was given at the time of index PCI.

All the study subjects were followed up for a composite of coronary death, MI, and repeat revascularization (PCI or coronary artery bypass grafting, CABG) totally defined as MACE. During follow-up phase, an endocrinologist supervised hDM patients in order to control glycemic status. Time from index PCI to the earliest MACE was considered as time-to-event. Age was considered as the age of participants at the time of index PCI. It is noteworthy that lesion size is reflected in stent size.

All of data were recorded in dedicated online database. In case of participants' absence in the clinic, phone calls were made to their spouse or first-degree relatives. Miss-to-follow up is defined as missing just after PCI. Death was considered as the end-point of the study.

Data were presented as mean \pm standard deviation (SD) for continues and n (%) for categorical variables. T test and Chi-square tests were used for continues and categorical variables, respectively. Cox proportional-hazards regression with two sided tests at the 5% level of significance was done. All the analyses were performed using the statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA).

Results

Overall, 1630 patients were found to be eligible for entering the study. Minimum and maximum follow-up duration was 15 days and 201.4 months, respectively. Also, minimum and maximum time-to-event was 16 days and 105.6 month, respectively with a median of 34.63 month. hDM was found in 485 CAD patients (29.8%). According to table 1, no statistical difference was seen in age of hDM versus non- hDM at the time of enrollment PCI. Females were significantly higher in hDM compared to non- hDM. Also, those with history of hypertension (hHTN) and history of hyperlipidemia (hHLP) were significantly higher in hDM patients compared to non- hDM while no difference was seen between these two groups with regard to hSmoking. MACE was occurred in 126 (7.7%) of the study subjects. Among them, revascularization, MI, and death were 69%, 5.6%, and 25.4%, respectively. Occurrence of a MACE at 0.10% per person month was confirmed. Lesion length and diameter were not statistically different between hDM and not-hDM patients. Also, the rate of MACE incidence as well as time-to-event was not statistically different between these two groups. There was no difference in number of stents, type of DES, and number of diseased vessels in hDM compared to non- hDM.

Table 2 shows incidence of MACE stratified by hDM status. MACE incidence was not statistically different between different lesion length (stent length) and different stent diameter (lesion diameter) both in hDM and non-hDM groups, even by adjusting confounder variables (Fig. 1).

Discussion

This present study designed to reflect the real-world practice in Shiraz (11). Data were collected through trained individuals with standard case-report forms in one of the longest follow-up period in literature (about 190 months). Important messages that resonate from this paper are as follows. The lesion length and diameter were not statistically different between hDM and non-hDM. We used dual-antiplatelet therapy (DAPT) at least 2 years for diabetics (one year for non-diabetics) and first- and second-generation DES in both diabetics and non-diabetics. MACE incidence was not different between hDM and non-hDM with different stent length and different stent diameter. Females were higher in hDM group compared to non-hDM peers while MACE incidence was statistically equal in these two groups. Although number of patients with hHTN and hHLP were higher in hDM, this did not result in significant difference in MACE incidence.

DM distributes drastic effects through several adverse functions including reduction in fibrinolytic capacity, increasing concentrations of hemostatic proteins, and endothelial dysfunction such as intimal hyperplasia and vascular inflammation (12, 13). Accordingly, early onset and progression of multifocal atherosclerotic plaques is facilitated in diabetic patients especially in small-caliber coronary arteries (14). Diabetic patients are in higher risk for coronary atherosclerosis, plaque burden, and development of multivessel CAD in comparison to non-diabetic counterparts (15).

Other than atherosclerosis, diabetes mellitus is known as an established risk factor for restenosis after PCI (16, 17). Restenosis is one of the major long-term complications of PCI in diabetic patients (18–20). It is an expected observation in the case of involvement of small vessels by long lesions as this condition favor poor prognosis such as coronary restenosis especially in diabetic patients (21, 22). Moreover, number of diseased vessels, stent length, and duration of involvement with diabetes were categorized as the most important angiographic and clinical factors for restenosis (23). However, diabetes status was reported to be in poor correlation with restenosis in some studies (24, 25).

CAD patients with diabetes are among one of the high risk groups for doing PCI. Introduction of DES into interventional cardiology brings new hope in order to reduce BMS-related complications. DES showed promising results such as no MACE, no late lumen loss, and no binary restenosis than invasive surgery (26). New-generation stents brings pronounced impact in terms of safety and efficacy compared to balloon angioplasty, bare-metal stents, and early-generation DES, especially in diabetic patients (16).

However, there are conflicting findings regarding contribution of diabetic status and CAD complexity to clinical outcomes after PCI with DES (16). The correlation of diabetes mellitus with repeat revascularization was reported only in case of complex lesions. It seems that DES mitigate DM-related vasculoproliferation in simple lesions (27). In consistent with our findings, a study showed that different stent length had no impact on 30-day mortality, all-cause mortality, MACEs, target lesion revascularization (TLR), and target vessel revascularization (TVR) (28). Another report declared that increase in the length of the stents even 1 mm translates into the restenosis odds ratio of 1.065 (21). However, MACE, TLR, and TVR were seen more in patients with implanted small stent (< 3 mm) than large stent (\geq 3 mm) in another study (29, 30). Also, it was reported that longer stents were associated to thrombosis (31, 32). Similar to

our study, some studies declared that no relationship was found between DM and MACE development. In a cohort study on patients with chronic total occlusion, the authors claimed that complication rate after PCI were similar in diabetics versus non-diabetics (33).

It should be noted that peri-procedural control of plasma glucose significantly reduces restenosis rate in a 6-months follow up mainly due to downregulation of inflammatory cytokines and oxidative stress. Such a meticulous control probably had beneficial effects on endothelial function, even more than DES (20).

In patients with diabetes, hyperglycemia may increase platelet reactivity. The mechanism include decrease in membrane fluidity and increase in platelet adhesion, osmotic effect of glucose and activation of protein kinase C, a mediator of platelet activation (34, 35). DAPT with aspirin and P₂Y₁₂ inhibitor has used for many years as the main treatment after PCI. This treatment has shown to be associated with great reduction in MACE outcome especially in diabetic patients (36).

Trials on duration of dual antiplatelet therapy (DAPT) after PCI has discussed in literature in certain patients such as diabetics. These trials mostly include early- and second-generations stents. They showed that extended DAPT duration (more than 24 months) has been associated with reduction in MACE rate. Although DAPT reduces the risk of MACE, first generations DES had late and very late stent thrombosis leading to the development of second-generations DES with improved efficacy and safety (37).

The most recent guidelines on duration of DAPT in stable ischemic heart disease recommend at least 12 months after an acute coronary syndrome and at least 6 months after revascularization. In case of no concerns about bleeding events, this duration could be lengthened beyond 6 and 12 months, respectively. There is no recommendation about continuation of DAPT after these times and leave the decision to clinicians to individualize therapy for each patient based on risks and benefits assessment (10).

Of strengths of this study are long and close follow up and acceptable mass of sample population which facilitated demonstration of differences in post-PCI clinical outcomes.

Limitations of this study include inherent restrictions imposed on non-randomized retrospective studies. In the present study, only patients with hDM were considered and those with newly diagnosed diabetes or those who become diabetic after PCI were ignored. Also, it was not feasible to measure the blood glycemetic status of the patients at the follow-up phase. Appropriate expansion of the stents is another important determinant (38). The degree of expansion is a subject of eminent importance that plays substantial role in a successful PCI. As in every real-world practice, some data lost during follow up phase. In order to make the results of this study generalizable, it is better to evaluate it with similar ones from other regions of the world.

Conclusion

In the present study, we concluded that similar rate of MACE occurrence in hDM compared to non-hDM patients originates probably from using DES as well as dual antiplatelet therapy (ASA and clopidogrel) for at least two years along with tight control of plasma glucose under supervision of an endocrinologist.

Declarations

Ethics approval and consent to participate: The present study is in conformity with the Helsinki declaration and has approved by the Research Ethics Committee of Shiraz University of Medical Sciences.

Consent for publication: Not applicable

Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: MJZ and EH contributed substantially to the design of the study. EH, SSM and SK acquired data. MS, AM and IRJ had roles in data interpretation. IRJ wrote the initial draft. All the authors reviewed the manuscript critically.

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Tables

Due to technical limitations, Tables 1-2 are provided in the Supplementary Files section.

Figures

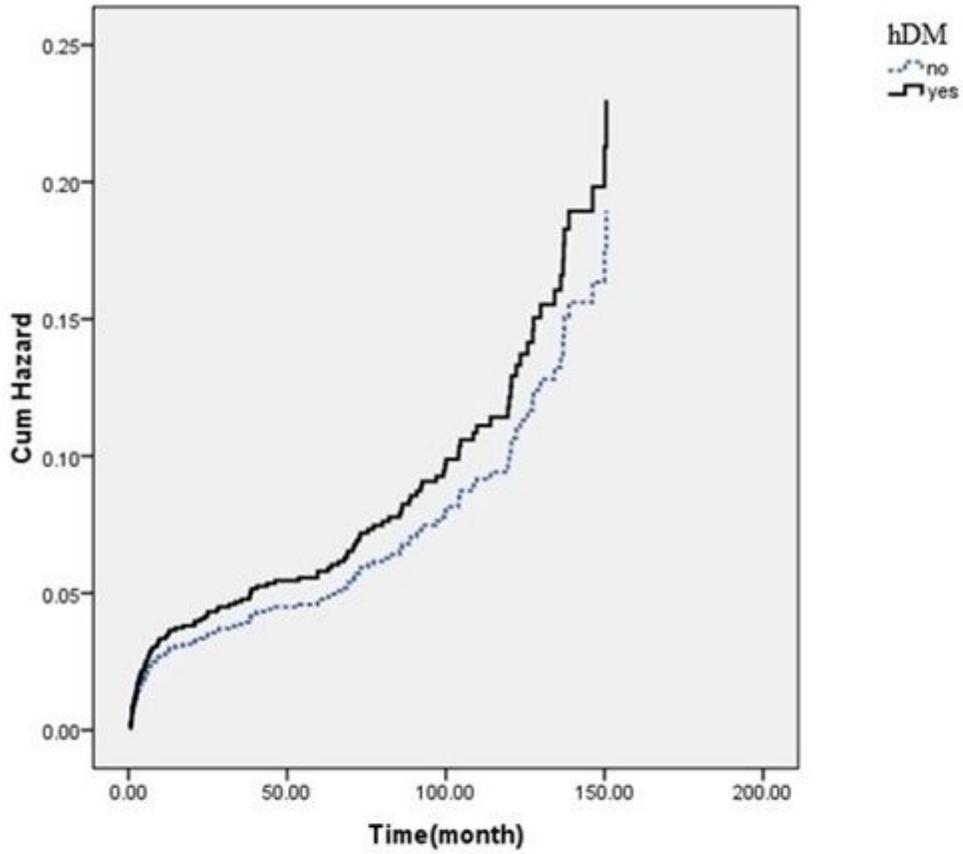


Figure 1

Cumulative hazard function for hDM and non-hDM patients according to stent length