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Stent thrombosis is not increased following percutaneous coronary intervention in patients with non-insulin dependent diabetes mellitus taking metformin

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ABSTRACT

Objective: Recent studies have suggested that metformin may inhibit endothelialization following limus-eluting stent (LES) placement and may increase the risk of stent thrombosis. Therefore, we assessed the impact of metformin on stent thrombosis and major adverse cardiovascular events (MACE) in non-insulin-dependent diabetes mellitus (NIDDM) patients who receive drug-eluting stents (DES).
Methods: We assessed the impact of metformin and stent type on stent thrombosis, MACE, and death in NIDDM patients following DES placement. Of the 1201 patients included, 74.8% received LES, 25.2% received paclitaxel-eluting stents (PES), and 55% were taking metformin.
Results: There was no difference in stent thrombosis, regardless of stent type or metformin use. While Kaplan–Meier curves demonstrated reduced MACE ($p = 0.007$) and death ($p = 0.006$) with metformin use, multivariate analysis demonstrated that stent type and metformin use were not associated with outcome.
Conclusion: In NIDDM patients, metformin use or stent type following DES placement did not increase stent thrombosis and MACE rates.

1. Introduction

Diabetes mellitus (DM) continues to be a major contributing risk factor in the development and progression of coronary artery disease (CAD). Not only does DM hasten the development of atherosclerosis, but these patients have worse outcomes following treatment with percutaneous coronary intervention (PCI) and stent placement compared with non-diabetic individuals [1]. Interestingly, while the rates of restenosis are significantly higher in diabetics, the rate of in-stent thrombosis is also increased compared with non-diabetics [2]. Drug-eluting stents (DES) have reduced target lesion revascularization (TLR) and have not increased stent thrombosis in diabetic patients undergoing primary PCI when compared to bare metal stents [3].

Metformin, a biguanide insulin sensitizer, has significantly reduced major adverse cardiovascular events (MACE) in patients with non-insulin-dependent diabetes mellitus (NIDDM) [4]. The outcome benefits seen with metformin are thought to be linked to anti-inflammatory effects [5] and regulation of lipogenesis [6], both of which are critical mediators of atherosclerosis. Recent studies, however, suggest that metformin could increase the risk of stent thrombosis in diabetics following placement of either sirolimus-eluting stents (SES) [7] or everolimus-eluting stents (EES) [8] since metformin impairs endothelialization by activation of 5′-adenosine monophosphate-activated protein kinase (AMPK) with convergent signaling at the mammalian target of rapamycin (mTOR) pathway. Given these concerns, we compared clinical outcomes, including stent thrombosis rates, following percutaneous coronary intervention (PCI) in NIDDM patients who received either a limus-eluting stent (LES, [SES or EES]) or paclitaxel-eluting stents (PES) to determine whether metformin increased risk. We hypothesized that use of metformin will not increase the risk of stent thrombosis or MACE following PCI with LES placement in patients with NIDDM.

2. Methods

Consecutive NIDDM patients undergoing PCI with EES, SES, or PES placement, and were discharged with oral diabetic medications

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from April 2003 to August 2012 were included in this retrospective study. Patients discharged on insulin therapy or those who received two different DES types were excluded. This was conducted in compliance with our local institutional ethics committee. The procedures were performed according to standard clinical guidelines and interventional strategy, medications, and stent selection was left to the operators' discretion. Clinical and demographic data were collected and patients underwent clinical follow-up for 12 months. Outcomes included all-cause mortality, myocardial infarction (MI), TLR, and cumulative stent thrombosis. MACE was defined as all-cause mortality, *Q*-wave MI, or TLR during follow-up. We do not have data regarding medical therapy during follow-up.

All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina). Continuous variables are presented as mean ± SD and categorical variables are presented as numbers and percentages. Continuous variables were compared using an unpaired Student's *T*-test or ANOVA and categorical variables using chi-square or Fisher's exact test, as appropriate. Univariate Cox proportional hazard regression analysis was performed to determine which clinically relevant variables were associated with outcomes. We then performed multivariate Cox proportional hazard regression analysis with the variables of clinical interest showing the greatest association in univariate analysis along with stent type and metformin use to determine which variables are independently associated with the outcome of interest. We performed Kaplan–Meier analysis to assess the impact of stent-type and metformin use on outcome and comparison between groups was performed via long-rank test. Statistical significance was defined as a p-value <0.05 using a two-tailed hypothesis.

3. Results

We included 1201 NIDDM patients with a mean age of 66 ± 10 years; 64.1% were male; 62.8% were Caucasian; 33.2% underwent PCI for stable angina, 46.3% for unstable angina, and 17.2% for acute MI. Patients received a SES (44.5%), EES (30.4%), or PES (25.2%). Metformin was used alone in 43.5% of patients; while 11.5% of patients were taking metformin together with ≥1 other antihyperglycemic agent. Patients taking metformin were significantly younger, had a lower baseline creatinine, less peripheral arterial disease, less congestive heart failure, a higher left ventricular ejection fraction, fewer vessels diseased, less procedural acute renal failure, and were less likely to undergo PCI for acute MI (Table 1). There were no significant differences in medications at discharge (Table 1).

There were no significant differences in stent thrombosis, MACE, TLR, MI, and all-cause mortality at 1-year follow-up based on the type of stent received (Table 2). Patients on metformin who

Table 1
Patient characteristics based on whether the patient was discharged on metformin and whether the patient received a Limus-eluting stent (LES) or paclitaxel-eluting stent (PES).

Variable	Metformin		No metformin		p-Value
	LES (n = 513)	PES (n = 147)	LES (n = 386)	PES (n = 155)	
Age	64 ± 10	64 ± 10	68 ± 11	68 ± 11	<0.001
Male gender	65.0%	72.1%	59.6%	65.2%	0.06
BMI (kg/m^2)	32.6 ± 6.5	30.4 ± 5.5	31.1 ± 6.7	30.7 ± 6.5	<0.001
Race					
Caucasian	64.7%	59.9%	63.2%	58.7%	0.48
African American	27.7%	29.3%	30.3%	34.8%	0.39
Prior MI	20.9%	14.1%	25.8%	24.6%	0.03
Prior CAD	46.6%	43.5%	49.7%	54.2%	0.22
Prior CABG	21.1%	22.6%	25.1%	27.7%	0.30
Prior PCI	31.6%	29.3%	33.8%	36.1%	0.58
Hypertension	94.2%	91.8%	93.8%	90.3%	0.33
Hypercholesterolemia	92.2%	91.2%	94.3%	93.5%	0.52
Baseline creatinine	1.01 ± 0.53	1.02 ± 0.31	1.40 ± 1.35	1.35 ± 0.99	<0.001
Baseline hemoglobin A1c	8.0 ± 6.2	9.3 ± 10.7	7.1 ± 1.3	7.2 ± 1.1	0.15
PAD	12.2%	13.7%	21.0%	24.5%	<0.001
History of HF	11.4%	5.7%	19.7%	22.8%	<0.001
Current smoker	18.5%	17.0%	18.7%	12.9%	0.40
Prior smoker	37.4%	40.1%	29.5%	34.2%	0.043
PCI for stable angina	36.3%	36.1%	29.9%	29.2%	0.14
PCI for unstable angina	48.7%	49.7%	45.1%	39.0%	0.15
PCI for AMI	13.6%	15.8%	19.3%	26.0%	0.003
LVEF (%)	50 ± 14	51 ± 14	45 ± 16	44 ± 17	<0.001
Vessels diseased	1.71 ± 0.80	1.89 ± 0.91	1.95 ± 0.87	1.93 ± 0.92	0.005
Stents implanted	1.56 ± 0.85	1.58 ± 0.76	1.61 ± 0.92	1.48 ± 0.69	0.48
Stent diameter	3.04 ± 0.60	2.99 ± 0.37	3.01 ± 0.45	3.01 ± 0.33	0.69
Stent length (mm)	19.6 ± 7.0	19.7 ± 6.5	20.0 ± 6.2	20.0 ± 6.3	0.81
Angiographic success	99.3%	99.5%	99.0%	98.6%	0.68
Procedural acute renal failure	0.4%	0.0%	2.1%	3.2%	0.006
Medications					
Aspirin	97.5%	98.6%	97.4%	99.4%	0.48
Pre-loaded clopidogrel	33.2%	26.1%	31.5%	23.6%	0.10
Post-loaded clopidogrel	60.6%	69.0%	64.3%	69.9%	0.11
Beta-blocker	81.2%	77.4%	79.6%	79.4%	0.77
ACE inhibitor	61.5%	63.9%	54.3%	60.4%	0.10
ARB	27.2%	20.4%	22.3%	21.9%	0.20
Statins	82.4%	77.6%	83.3%	78.1%	0.29
Gylcoprotein IIb/IIIa use	5.9%	6.8%	7.6%	3.9%	0.42
Warfarin	7.9%	4.5%	7.6%	5.1%	0.84

ACE: angiotensin converting enzyme, AMI: acute myocardial infarction, ARB: angiotensin receptor blocker, BMI: body mass index, CABG: coronary artery bypass graft surgery, CAD: coronary artery disease, HF: heart failure, LES: limus-eluting stents, LVEF: left ventricular ejection fraction, MI: myocardial infarction, PAD: peripheral arterial disease, PCI: percutaneous coronary intervention, PES: paclitaxel-eluting stents.