Factors Associated With Deferred Lesion Failure Following Fractional Flow Reserve Assessment in Patients With Diabetes Mellitus

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Objective: To explore the predictors of deferred lesion failure (DLF) in patients with diabetes mellitus (DM) and lesions with a fractional flow reserve (FFR) >0.80 and to examine whether a predictive relationship between negative FFR values (>0.80–1.00) and DLF exists. **Background:** DM is associated with rapidly progressive atherosclerosis and predictors of DLF in FFR negative lesions in this high-risk group are unknown. **Methods:** All DM patients who underwent FFR-assessment between 1/01/2010 and 31/12/2013 were included, and followed until 1/7/2015. Patients carrying ≥1 FFR negative lesion(s) were assessed for DLF, and multivariate models used to identify independent factors associated with DLF. **Results:** A total of 205 patients with 252 FFR >0.80 lesions were identified. At a mean follow-up of 3.1 ± 1.4 years, DLF occurred in 29/205 (14.1%) patients, 31/252 (12.3%) lesions. Using marginal Cox regression multivariate analysis, insulin requiring DM [HR 2.24 (95%CI; 1.01–4.95), $P = 0.046$] and prior revascularization [HR 2.70 (95%CI 1.21–6.01), $P = 0.015$] were identified as being associated with a higher incidence of DLF. Absolute FFR values in FFR negative lesions in DM patients are not predictive of DLF (receiver operating characteristics curve analysis: area under the curve: 0.57 ± 0.06, 95%CI 0.46–0.69). **Conclusions:** In DM patients with FFR negative lesions, insulin requiring DM and prior revascularization are predictors for DLF. In contrast to non-DM patients, no predictive relationship between absolute negative FFR values (ranging >0.80–1.00) and the risk of DLF exists in DM patients.

Key words: diabetes mellitus; fractional flow reserve; deferred lesion failure

INTRODUCTION

The global incidence and prevalence of Diabetes Mellitus (DM) is rapidly increasing, with the number of patients with DM expected to exceed 592 million worldwide by 2035 [1]. DM is an established independent risk factor for cardiovascular disease, associated with a poorer prognosis in both acute and stable coronary artery disease (CAD) [2,3]. Additionally, DM is associated with more extensive atherosclerosis, a greater number of significant stenoses, longer lesions and more diffuse disease [4–6]. As such, DM represents a high-risk condition, and diabetic patients with CAD have higher rates of death, non-fatal myocardial infarction (MI) and repeat revascularization than non-diabetic patients [7]. Whilst fractional flow reserve (FFR) has an extensive evidence base, a low proportion of patients with DM were included in the landmark studies [8–10]. Recent evidence has suggested that deferred revascularization based upon FFR in DM patients may not be associated with a similar low risk of MI or target lesion revascularization as seen in non-DM patients [11–14]. Whilst risk prediction models have been developed to better predict the risk of FFR-guided deferred lesion failure (DLF), such models may

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not be as applicable in DM patients, given the significantly different nature of atherosclerosis seen in this condition [15–17]. This study sought to identify the factors associated with an increased risk of DLF and in particular to evaluate the predictive value of absolute FFR values in FFR negative lesions (ranging from 0.81 to 1.00) in a large real-world cohort of DM patients in which revascularization was deferred based upon FFR.

METHODS

Patient Population

From a total of 3,379 patients who underwent FFR-guided revascularization from January 2010 until December 2013, we identified all DM patients. After excluding those patients who had complete FFR-guided revascularization, 205 DM patients who had deferred revascularization of $\geq$1 lesion based upon a FFR $>$0.80 formed the final study population. All patients were followed until July 1, 2015. Baseline demographics were obtained using electronic medical records, as was data relating to the FFR measurement and baseline angiography. Follow up events were obtained primarily from the electronic patient record and by telephone contact with primary care physicians or direct contact with patients where required. Follow up was complete in all patients. DM was defined by patient history and classified by treatment with diet, exercise, oral antidiabetic medication, or insulin.

FFR Measurement and Lesion Assessment

FFR was performed using a standard coronary pressure wire (PressureWire Certus; St. Jude Medical, St Paul, Minnesota; or Combowire; Volcano Corporation, Rancho Cordova, CA), which was advanced just outside the tip of the guiding catheter, and the pressure measured by the sensor equalized to that of the guiding catheter. The wire was then placed distal to the stenosis under investigation. Special attention was paid to avoid pressure damping of the guide catheter pressure and variation of the FFR wire position. Adenosine (140 μg/kg/min) was administered through the brachial or femoral vein for at least 2 min or until steady-state hyperemia was achieved. FFR was calculated as the ratio of mean distal intracoronary pressure measured by the pressure wire and the mean arterial pressure measured through the coronary guiding catheter. A lesion with an FFR value $>$0.80 was considered functionally non-significant leading to deferred revascularization and further medical treatment. FFR assessment was systematically performed in patients with intermediate native coronary lesions ranging from 40 to 80% diameter stenosis (DS), where no prior non-invasive test of ischemia was performed or when these were inconclusive. FFR was not performed for culprit lesions in MI, lesions with TIMI flow $<$3, or when the operator deemed a lesion to be clearly of hemodynamic significance. Visual assessment of reference vessel diameter, DS, American Heart Association/American Cardiology College (AHA/ACC) lesion type and the presence of calcification and diffuse disease were noted for all lesions by two independent interventional cardiologists. Both reviewers were blinded to the clinical outcomes. A third interventional cardiologist was used in cases where discordance arose. In addition, the Syntax Score (SS) was calculated, based upon the index (time of FFR-measurement) coronary angiogram, by scoring all lesions $>$1.5 mm with at least 50% DS [18]. For those patients with a prior coronary artery bypass graft (CABG), no SS was calculated.

Endpoints

The primary outcome was DLF, defined as any deferred lesion revascularization (DLR) or deferred vessel myocardial infarction (DVMI). Owing to the retrospective nature of the study, and thus the inability to definitively attribute death to a deferred lesion, cardiac death was not included in the primary outcome.

Statistical Methods

Patient and lesion level characteristics at the time of index FFR assessment were included in the univariate Cox proportional hazards multiple regression model and a marginal Cox model used to account for correlated data in patients having multiple deferred lesions. The model was reduced using a stepwise backward variable selection technique employing a threshold $P > 0.15$ for removal. Variables entered in the model included: age (per year increment), male gender, index revascularization, renal insufficiency, family history of CAD, FFR result, recent MI, multivessel CAD, current smoker, prior revascularization, HbA1c and insulin requiring DM. Results are expressed as hazard ratio's (HR) with 95% confidence intervals. Receiver-operating characteristics (ROC) curve analysis was used to evaluate the diagnostic performance of FFR in identifying DLF. ROC curves were generated and the area under the curve (AUC) calculated. AUC summarizes the diagnostic accuracy of a test; a perfect test is represented by an area of 1, whilst a poor test has an area of 0.5. A P value of $<$0.05 was considered significant. All analyses were conducted using SAS 9.3 (Cary, NC).

TABLE I. Baseline Clinical, Angiographic, and Lesion Characteristics in Patients with and without DLF

	Total	With DLF	Without DLF
	***n* = 205**	***n* = 29**	***n* = 176**
Age (years; mean ± SD)	69.7 ± 9.6	68.0 ± 8.8	70.0 ± 9.7
Men	125 (61%)	18 (62%)	107 (61%)
DM	205 (100%)	29 (100%)	176 (100%)
Insulin requiring DM	87 (42.4%)	18 (62.1%)	69 (39.2%)
Left ventricle ejection fraction	51.8 ± 10.2	53.1 ± 6.6	51.6 ± 10.6
Multivessel CAD	115 (56.1%)	15 (51.7%)	100 (56.8%)
Family history of CAD	61 (29.8%)	12 (41.4%)	49 (27.8%)
Hypertension	197 (96.1%)	29 (100.0%)	168 (95.5%)
Hypercholesterolemia	198 (96.6%)	29 (100.0%)	169 (96.0%)
Current smoker	41 (20%)	7 (24.1%)	34 (19.3%)
Renal insufficiency	30 (14.6%)	4 (13.8%)	26 (14.8%)
HbA1c (mean ± SD)	53.7 ± 10.5	58.0 ± 13.7	53.0 ± 9.7
Prior MI	93 (45.4%)	13 (44.8%)	80 (45.5%)
Remote MI	47 (22.9%)	6 (20.7%)	41 (23.3%)
Recent MI	46 (22.4%)	7 (24.1%)	39 (22.2%)
Prior percutaneous coronary intervention	82 (40%)	16 (55.2%)	66 (37.5%)
Prior CABG	29 (14.1%)	7 (24.1%)	22 (12.5%)
Clinical syndrome at time of FFR performance:			
ACS	73 (35.6%)	9 (31.0%)	64 (36.4%)
Non-ACS	132 (64.4%)	20 (69.0%)	112 (63.6%)
SS (mean ± SD)	10.95 ± 7.00	10.95 ± 5.51	10.95 ± 7.20
Low scores (0–22)	165 (80.5%)	21 (72.4%)	144 (81.8%)
Intermediate scores (23–32)	7 (3.4%)	1 (3.4%)	6 (3.4%)
High scores (≥33)	4 (2.0%)	0 (0.0%)	4 (2.3%)
Unclassified, prior CABG	29 (14.1%)	7 (24.1%)	22 (12.5%)
FFR result (mean ± SD)	0.88 ± 0.05	0.87± 0.05	0.88 ± 0.05
Lesion characteristics: lesion level			
Number of lesions:	252	31	221
AHA/ACC lesion type classification:			
Type A	33 (13.1%)	2 (6.5%)	31 (14.0%)
Type B1	136 (54%)	19 (61.3%)	117 (52.9%)
Type B2	66 (26.2%)	8 (25.8%)	58 (26.2%)
Type C	17 (6.7%)	2 (6.5%)	15 (6.8%)
Calcified lesion	51 (20.2%)	5 (16.1%)	46 (20.8%)
Diffuse disease	65 (25.8%)	8 (25.8%)	57 (25.8%)
Reference vessel diameter (mm)[a]	2.93 ± 0.44	3.01 ± 0.34	2.92 ± 0.45
DS (%)[a]	59.56 ± 8.15	59.68 ± 6.05	59.55 ± 8.41

Renal Insufficiency was defined as an estimated glomerular filtration rate, eGFR<60mL/min.
[a]Visual assessment.

RESULTS

Baseline Patient and Lesions Characteristics

Baseline clinical, angiographic and lesion characteristics are noted in Table I. The average age of patients was 69.7 ± 9.6 years, with 42% insulin-requiring. Patients had a high prevalence of cardiovascular risk factors; 46% had a history of MI and 54% had prior revascularisation. The mean HbA1c level was 53.7 ± 10.5. In total there were 252 lesions, which underwent deferred revascularisation, with a mean FFR value 0.88 ± 0.05.

DLF-Incidence and Setting

During a mean follow-up of 3.1 ±1.4 years (range 3–66 months), DLF occurred in 29/205 patients (14.2%) and 31/252 (12.3%) deferred lesions (Fig. 1). Of the 31 lesions with DLF, DLR occurred in 30 lesions (11.9%) and 8 lesions (3.2%) resulted in subsequent DVMI. All DVMI were non-ST segment elevation MI (NSTEMI). In addition, 14 lesions resulted in unstable angina pectoris and so the majority of lesions (22/31, 8.7% of all deferred lesions), resulted in subsequent acute coronary syndrome (ACS). For those patients with stable or unstable angina, 52.2% (12/23) underwent repeat ischemic detection prior to revascularization, whilst clear angiographic progression was noted in the remainder (Table AI appendix).

DLF Risk Model

The univariate predictors for DLF are shown in Table II. Following backward selection marginal Cox

proportional modeling techniques, insulin-requiring DM [HR 2.24 (95%CI; 1.01–4.95), $P = 0.046$] and prior revascularization [HR 2.70 (95%CI 1.21–6.01), $P = 0.015$] were identified as independent predictors for DLF (Table II). In addition, a trend for DLF with increasing HbA1c levels (per unit increase) was observed, HR 1.03 (95%CI; 1.00–1.07), although this fell short of statistical significance ($P = 0.066$).

Correlation between FFR Value and the Risk of DLF

Interestingly, rates of DLF did not show any gradient association with FFR values and ROC curve analysis, with an AUC 0.57 ± 0.06 (95%CI; 0.46–0.69), showed that absolute FFR values are an unreliable predictor for future DLF in DM patients with a negative FFR (Figs. 2 and 3).

DISCUSSION

This study is the first to examine those clinical factors which are associated with a higher incidence of DLF in a population of only DM patients. As seen from the results, DLF in this high-risk group is common and more often results in subsequent ACS. The most important finding of this study is that in DM patients, insulin-requiring DM and prior revascularization are associated with an increased risk of DLF. Interestingly in DM patients with a negative FFR, in contrast to what has been previously shown in non-DM patients, higher FFR values (closer to 1.0) are not associated with less risk than lower FFR values (closer to 0.80) [15].

FFR is the guideline recommended reference standard invasive assessment of ischemia in intermediate coronary lesions. Based upon the results of landmark trials, deferred revascularization in those lesions with a FFR >0.80 is associated with a low risk of future adverse cardiac outcomes [8–10]. However, more recently, several studies have shown that deferred revascularization based on FFR assessment of intermediate lesions in high risk patients and specifically in DM patients may not be as safe and is associated with worse outcomes than in non-DM patients [11,12].

DM coronary disease is associated with a greater atherosclerosis burden and unique and unremitting

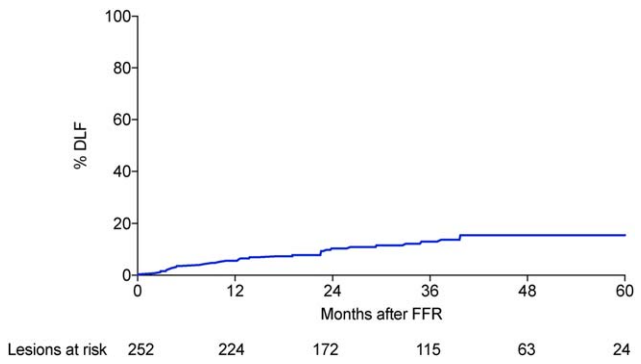

Fig. 1. Time-to-event estimates for DLF (lesion level analysis). FFR, fractional flow reserve; DLF, deferred lesion failure. [Color figure can be viewed at wileyonlinelibrary.com]

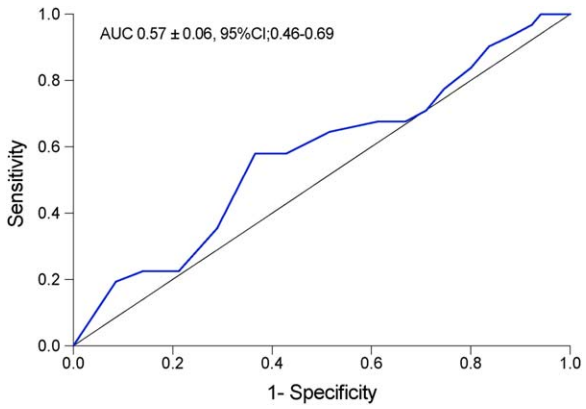

Fig. 2. ROC curve FFR value and risk of DLF. FFR, fractional flow reserve; AUC, area under the curve; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Univariate and Multivariate Predictors of DLF

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
FFR (per 0.05 decrease)	1.36	0.89–2.06	0.15			
Male	1.07	0.50–2.30	0.86			
Age (per year increase)	0.98	0.95–1.02	0.28			
HbA1c (per unit increase)	1.04	1.00–1.08	0.03	1.03	1.00–1.07	0.067
Insulin requiring DM	2.38	1.10–5.13	0.03	2.24	1.01–4.95	0.046
Renal Insufficiency	1.02	0.34–3.10	0.97			
Recent MI	1.13	0.48–2.64	0.79			
Family history CAD	1.81	0.84–3.89	0.13			
Smoker	1.55	0.65–3.72	0.32			
Multivessel CAD	0.68	0.32–1.43	0.31			
Index revascularization	0.74	0.25–2.19	0.60			
Prior revascularization	2.48	1.14–5.39	0.02	2.70	1.21–6.01	0.015

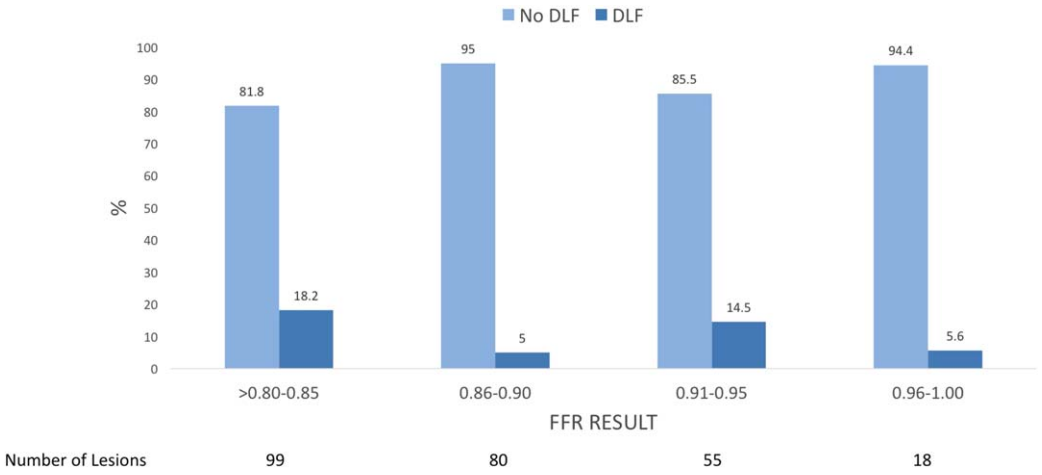

Fig. 3. DLF rates per FFR quartiles >0.80–0.85, 0.86–90, 0.91–0.95, and 0.96–1.00. DLF, deferred lesion failure; FFR, fractional flow reserve. [Color figure can be viewed at wileyonlinelibrary.com]

progression [5]. In the PRESTO trial, diabetic patients had a 33% increase over non-diabetic patients in new lesion formation over a nine month follow-up [19]. Similarly, in the DIABETES study, at 2-year follow-up, 50% of repeat revascularizations were as a result of progression in a vessel or segment remote from the one previously treated [20]. Thus, whilst FFR is often seen as a binary assessment of ischemia, the absence of FFR detected ischemia in the setting of such rapid progression may not necessarily be reassuring. In the multivariate analysis in this study, insulin requiring DM and prior revascularization were identified as predictors of increased risk for DLF, both characteristics associated with increased burden, faster atherosclerosis progression, and worse outcomes [21,22].

Furthermore, atherosclerotic disease in DM patients is associated with more vulnerable plaque, which may result in future clinical events irrespective of stenosis severity and progression in such lesions is often unpredictable. This may explain the differences in outcomes with deferred revascularization and the lack of predictive effect of FFR values in DM patients as seen in our study, compared with previous reports [23]. Indeed, Marso et al., have shown that significant differences in the composition of plaque exists in DM patients; with lesion length, plaque burden, necrotic core, and calcium content significantly greater in such patients [17]. Additionally, the prevalence of thin cap fibroatheroma, a predictor of adverse outcomes, is more abundant in DM patients, especially amongst those patients with poorer glycemic control [24]. Whether the trend observed in our study of a greater risk of DLF with increasing HbA1c levels, reflects such an increased prevalence of higher-risk atheroma is unknown. Finally, in the PROSPECT study, as in our study, insulin requiring DM was identified as an independent predictor (HR 3.32) of future non-culprit MACE, in lesions which were angiographically milder (DS; median 36.2%) than even those non-ischemic lesions included here [25]. Together the findings from these studies extend to non-culprit/non-hemodynamically significant lesions in DM patients, the knowledge from multiple prior studies, that insulin treatment is associated with worse outcomes, either due to more aggressive disease or an adverse effect of insulin itself [22,26,27].

Based upon several studies, it appears that there exists a linear relationship between FFR values and the risk of major adverse cardiac events (MACE), with lesions which are close to FFR 1.0 being associated with a lesser risk than those lesions closer to 0.80 [15,16,23,28]. However, Liu et al. have recently examined this relationship in a group of diabetic and non-diabetic patients with stable angina pectoris [12]. This study confirmed that amongst non-diabetic patients, higher FFR values are associated with a lower risk of MACE, defined as a composite of all cause death, non-fatal MI and any revascularization. However, in DM patients the risk of MACE was independent of the FFR value. Our study, in which we studied a more lesion specific outcome (DLF), confirms this lack of predictive effect of FFR values (range 0.81–1.00) in DM patients.

Whether this lack of predictive effect of FFR values is due to a higher prevalence of microvascular dysfunction in DM patients is a possibility. Recently Lee et al, have shown in patients with FFR values >0.80 that an elevated index of microvascular resistance and a low coronary flow reserve is associated with the worst clinical outcomes [13]. Furthermore, within this group, DM was identified as an independent predictor of poor outcomes. These findings are in keeping with those

previously mentioned studies showing that deferred revascularization based upon FFR is not as safe in DM patients as compared with non-DM patients [11]. In this study, based upon the ROC curve analysis, we show that further efforts to define an alternative cut-off value to improve outcomes with a FFR guided-revascularization strategy in DM patients appears to be of little value. Whether the addition of prospective microvascular assessments may improve outcomes in DM patients with FFR negative lesions remains to be answered.

STUDY LIMITATIONS

This study is a single-center, non-randomized, observational study and thus the results should be considered as hypothesis generating. Cox proportional hazards multiple regression models were limited by the sample size and number of events to three factors to avoid over-fit models. Prior studies have shown that the duration of DM is associated with more abundant plaque burden and more rapid disease progression, as such we cannot exclude the possibility that patients with subsequent DLF may have had a longer duration of DM. Additionally, although insulin status was known for all patients, whether patients had type 1 versus type 2 DM was unknown. Nonetheless, our study confirms the findings of multiple other studies, which have indicated that DM patients treated with insulin have significantly worse outcomes than DM patients who are not insulin requiring. Whether the poorer outcomes in patients treated with insulin reflects more advanced vascular disease in these patients, a longer duration of DM or an effect of insulin itself, cannot be answered from this study. As was the case in the FAME II study, neither patients nor clinicians were blinded to the FFR result, therefore, in those patients with ongoing symptoms, knowledge of a prior borderline FFR measurement may have influenced the subsequent rates of TLR or rehospitalization for ACS, however considering the retrospective nature of the study this was unavoidable, nevertheless such a bias was not reflected in the ROC analysis [29]. In addition, the majority of subsequent revascularizations were driven by ACS or repeat ischemic evaluation and as such we believe our practice is a close to guideline recommended practice as is achievable in a real-world setting (Table AI appendix).

CONCLUSION

Lesion failure in FFR guided deferred revascularization in DM patients is considerable and is unpredictable based upon FFR absolute values and efforts to define a more accurate FFR cut-off appear futile. Clinical characteristics such as insulin requiring DM and prior revascularization provide greater predictive accuracy for DLF. These findings should be considered in DM patients undergoing deferred revascularization based upon FFR assessment for better risk stratification.

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