Original Article

Long-term Outcomes of Medical Therapy Versus Coronary Revascularisation in Patients with Intermediate Stenoses Guided by Pressure Wire

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Abstract

Introduction: This study aimed to examine the long-term clinical outcomes of coronary fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) in a real-world population in an Asian tertiary centre. Materials and Methods: All patients who underwent FFR measurement for intermediate coronary lesions in our centre from June 2002 to December 2009 were enrolled. A threshold of FFR ≤0.75 was used for revascularisation. All the patients were prospectively followed-up for major adverse cardiac events (MACE) of death, myocardial infarction (MI), target vessel revascularisation (TVR) and stent thrombosis. Results: Based on FFR measurement, 368 (57%) patients were treated medically while 278 (43%) underwent revascularisation. At a mean follow-up duration of 29.7 ± 16 months, 53 (14.4%) patients in the medical therapy group and 32 (11.5%) patients in the revascularised group experienced MACE (*P* = 0.282). There were no statistical differences in all the clinical endpoints between the 2 groups. Conclusion: Medical therapy based on FFR measurement is associated with low incidences of MACE at long-term follow-up.

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Key words: Fractional flow reserve, Major adverse cardiac events, Percutaneous coronary intervention

Introduction

Although coronary angiography has been used as the "gold standard" imaging technique for the diagnosis of coronary artery disease, it is essentially a lumenogram that offers no information on the functional significance of a coronary lesion. It is difficult to define the haemodynamic significance of a stenosis from the angiogram, especially in intermediate lesions (diameter stenosis of 50% to 70%).[1]

Fractional flow reserve (FFR), defined as the ratio of pressure in the stenotic artery to the pressure in the same artery in the theoretical absence of stenosis, is a specific index for epicardial stenosis. A FFR value of 0.75 means that the stenotic vessel provides only 75% of the normal expected flow in the theoretical absence of stenosis. A FFR value of <0.75 is taken as a cutoff for ischaemia in many studies.[2] It is the only functional index that has been validated against gold standard non-invasive functional tests such as stress echocardiography and single-photon emission computed tomography (SPECT).[3-7]

Several clinical randomised control trials, such as DEFER trial and FAME trial, have demonstrated significant superiority in percutaneous coronary intervention (PCI) guided by FFR when compared with angiography.[8,9] However, the role of FFR measurement in the real world is not clear. Therefore, we decided to perform a retrospective analysis based on data extracted from National University Hospital (NUH) cardiovascular database to evaluate the long-term clinical outcomes of medical therapy versus revascularisation in patients with intermediate lesions guided by pressure wire.

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Materials and Methods

Study Patients

Patients who underwent coronary angiography and FFR measurement for intermediate coronary artery stenoses (defined visually as between 50% to 75%) at NUH, Singapore, between 2002 and 2009 were enrolled in this retrospective study. Patients with ST segment elevation myocardial infarction (MI) within 1 week after the coronary angiography were excluded.

Procedure and Antiplatelet Regimen

Percutaneous coronary angiogram was performed in accordance with standard techniques, and the intermediate lesion was determined visually by the operator. FFR was measured with Radi wire and PressureWire™ Certus FFR Measurement System (St Jude Medical, USA) positioned distally across the stenosis. Following initial pressure wire calibration and equalisation, intracoronary glyceryl trinitrate was administered to eliminate vasospasm. Maximal hyperaemia was achieved through intracoronary administration of papeverine or adenosine. Intracoronary papeverine has a duration effect of 45 seconds.[10] Patients with FFR measurement of >0.75 were treated medically while those with FFR ≤0.75 were revascularised. All patients receiving PCI were pretreated with clopidogrel and aspirin. A loading dose of 300 mg of clopidogrel was administered if the patient had not been pretreated. After the procedure, dual antiplatelet therapy for at least 1 year for drug eluting stent and 1 month for bare metal stent (BMS), followed by aspirin (100 mg/d to 300 mg/d) indefinitely were administered. Cardiac enzymes and 12-lead electrocardiogram (ECG) were determined routinely after the interventions.

Definitions and Follow-up

A major adverse cardiac event (MACE) was defined as the occurrence of death, MI, or need for a new revascularisation procedure. MI was defined by an increase in creatine kinase-MB fraction of more than 3 times the upper limit of normal. Stent thrombosis was defined as angiographic documentation of thrombotic stent occlusion associated with a clinical event, an unexplained sudden cardiac death, or MI not clearly attributable to another coronary lesion.

Clinical follow-up was obtained through hospital records, clinic visits and telephone phone calls.

Statistical Analysis

Categorical variables were presented as frequencies (percentages) and were compared with chi-square statistics or, when appropriate, Fischer's exact test. Continuous variables were presented as mean ± standard deviation and compared with Student's t-test. Survival of MACE and each component were estimated using the Kaplan-Meier method, and the difference between the 2 survival curves were compared with the log rank test. Cox proportional hazards multiple regression models were used to estimate association between medical therapy versus revascularisation on long-term outcomes, after adjusting for other patient characteristics that were significantly different between groups. A *P* value of less than 0.05 was considered statistically significant, and all statistical tests were 2-tailed. Statistical analyses were performed with SPSS 13.0 (SPSS, Inc, Chicago, Illinois).

Results

Baseline Clinical Characteristics

A total of 646 patients with 812 intermediate lesions were included in this study. All of them received FFR measurement during cardiac catheterisation. In the group with FFR of more than 0.75 (n = 360), 347 patients (96.3%) were treated with medical therapy. Among those with an FFR ≤0.75 (n = 386), 249 patients (87.1 %) were treated with revascularisation. There was a crossover of subjects in the 2 groups that did not go with the conventional algorithm because of the operators' decision. These included 21 patients with lesions of FFR more than 0.75 who crossed over to revascularisation, among which 9 patients had intravascular ultrasound (IVUS) examination which showed minimum lumen area (MLA) of less than 3 mm^2, and 12 patients had documented ischaemia on stress echocardiogram or myocardial SPECT imaging. Twenty-nine patients who had lesions with FFR ≤0.75 were treated medically due to unsuitability for PCI and patients' wishes. PCI was performed in 255 patients (91.7%) with the details shown in Figure 1.

The baseline characteristics for the 2 groups were largely similar, except that the revascularised group had higher prevalence of hypertension and previous history of MI. Most patients presented with stable angina (Table 1).

Angiographic and Procedural Characteristics

Multivessel coronary artery disease accounted for two-thirds of revascularised patients, which was significantly higher than that in the medical therapy group. There was no significant difference in the lesion location between the 2 groups. More than half of the lesions were located in the left anterior descending artery. Left main artery and graft disease made up only a small percentage of the cohort (Table 2).

There was similar use of IVUS in both groups. Quantitative coronary analysis (QCA) showed higher diameter stenosis

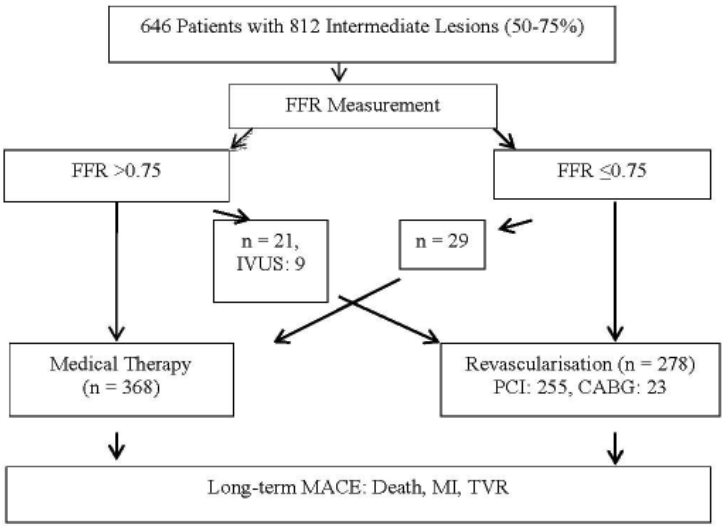

Fig. 1. Flow chart of the study. FFR: Fractional flow reserve; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; IVUS: Intravascular ultrasound; MACE: Major adverse cardiac event; MI: Myocardial infarction; TVR: Target vessel revascularisation

Table 1. Baseline Clinical Characteristics of the Study Patients

	Medical Therapy (n = 368)	**Revascularisation (n = 278)**	***P* Value**
Age (years)	59.2 ± 10.4	57 ± 10.5†	0.008
Male (%)	273 (74.2)	234 (84.2)†	0.003
Ethnic group			0.454
Chinese, n (%)	238 (64.7)	192 (69.1)	
Indian, n (%)	60 (16.3)	42 (15.1)	
Malay, n (%)	53 (14.4)	37 (13.9)	
Others, n (%)	17 (4.6)	7 (2.5)	
Current smoker, n (%)	98 (26.6)	79 (28.4)	0.656
Hypertension, n (%)	255 (69.3)	169 (60.8)*	0.03
Diabetes, n (%)	144 (39.1)	104 (37.4)	0.683
Hyperlipidaemia, n (%)	271 (73.6)	211 (75.9)	0.524
Family history, n (%)	28 (7.6)	26 (9.4)	0.474
Previous MI, n (%)	46 (12.5)	58 (20.9)†	0.005
Previous PCI, n (%)	113 (30.7)	105 (37.7)	0.06
Indication of angiogram			0.94
Stable angina, n (%)	289 (78.6)	219 (78.7)	
NSTE-ACS, n (%)	79 (21.4)	59 (21.3)	
LVEF <50%, n (%)	68 (18.5)	54 (19.4)	0.762
Medicines			
Aspirin, n (%)	324 (88)	264 (95)†	0.002
Clopidogrel, n (%)	203 (55.2)	272 (97.8)†	0.000
Statins, n (%)	310 (84.2)	263 (94.6)†	0.000
ACEI or ARB, n (%)	196 (53.3)	167 (60.1)	0.093
Beta blockers, n (%)	269 (73.1)	221 (79.5)	0.064

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; LVEF: Left ventricle ejection fraction; MI: Myocardial infarction; NSTE-ACS: Non-ST segment elevated acute coronary syndrome; PCI: Percutaneous coronary intervention

*P <0.05

†P <0.01

Table 2. Angiographic and Procedural Characteristics of Study Patients

	Medical Therapy (n = 368)	Revascularisation (n = 278)	*P* Value
Number of diseased vessel, n (%)			0.015
1	165 (44.8)	94 (33.8)*	
2	133 (36.1)	115 (41.4)	
3	70 (19)	69 (24.8)	
Location			0.067
LM, n (%)	20 (4.7)	11 (2.8)	
LAD, n (%)	254 (59.8)	262 (67.7)	
LCX, n (%)	66 (15.5)	39 (10.1)	
RCA, n (%)	79 (18.6)	71 (18.3)	
Grafts, n (%)	6 (1.4)	4 (1)	
IVUS use, n (%)	34 (9.2)	25 (9)	1.000
QCA measurement			
Diameter stenosis (%)	51.8 ± 11.4	70.5 ± 11.8†	0.000
Reference diameter (mm)	3.09 ± 2.67	2.72 ± 0.56	0.091
Lesion length (mm)	14.7 ± 9.3	21.4 ± 10.7†	0.000
Percentage of BMS (%)	NA	91 (32.7)	

BMS: Bare metal stent; IVUS: Intravascular ultrasound; LAD: Left anterior descending artery; LCX: Left circumflex artery; LM: Left main; QCA: Quantitative coronary angiography; RCA: Right coronary artery
*P <0.05
†P <0.01

and longer lesion length in the revascularised group. BMS was used in one-third of this patient cohort.

In-hospital and Long-term Results

One in-hospital cardiac death occurred in the medical therapy group and another in the revascularised group. There were no non-cardiac death, MI and repeat revascularisation before the patients were discharged from the hospital.

At a mean follow-up duration of 29.7 ± 16 months, there were no observed differences in the incidence of death, target vessel revascularisation (TVR), MI, and overall MACE rate (Table 3). The overall MACE rate was 14.4% in the medical therapy group and 11.5% in the revascularisation patients. The Kaplan-Meier analysis showed a similar MACE-free survival and survival rates between the 2 groups (Fig. 2). Likewise, there were no significant differences in the rates of TVR and MI between the 2 groups.

After adjustment for baseline characteristics in a Cox multivariable model, there were no significant differences in long-term outcomes between medical therapy and revascularisation guided by FFR measurement (Table 4).

Discussion

This retrospective study showed that patients treated with medical therapy based on FFR measurement of intermediate coronary lesions resulted in acceptable long-term outcomes with a low incidence of TVR and MACE events.

Our study had a MACE event of 14.4% in the medical therapy group and 11.5% in the revascularised group, which was comparable with published studies.[8,9,10-14] Notably, there were more complex lesions in the revascularised group than in the medical therapy group, with a higher proportion of multivessel disease, higher diameter stenosis, smaller reference vessel diameter and more diffuse lesions, which might have presented higher risk in this patient group to some extent. The results indicated that aggressive intervention with revascularisation is reasonable in intermediate lesions with haemodynamic significance.

For those patients with FFR more than 0.75, which indicated the presence of a functionally insignificant stenosis, the residual cardiac risks were still a challenge. The PROSPECT study showed that the cardiac event risk caused by non-culprit lesions with mean diameter stenosis of 32.3% ± 20.6% is high at 11.4%, after 3.4 years of follow-up.[15] More aggressive medical therapy is still recommended in this patient group.

In our study, the medical therapy group had reasonable long-term outcomes when compared with the revascularisation group. Although recent studies had used a new threshold of FFR <0.8 as the level for recommendation for revascularisation, our work was done during the early

Table 3. Long-term Outcomes of Study Patients

	Medical Therapy (n = 368)	Revascularisation (n = 278)	*P* Value
Death (%)	7 (1.9)	9 (3.2)	0.314
Cardiac death	4 (1.1)	4 (1.4)	0.731
Target vessel revascularisation (%)	35 (9.5)	21 (7.6)	0.232
MI (%)	30 (8.1)	22 (8)	0.891
Thrombosis (%)	2 (0.5)	6 (2.2)*	0.021
MACE (%)	53 (14.4)	32 (11.5)	0.282

MACE: Major adverse cardiac event; MI: Myocardial infarction
*P <0.05

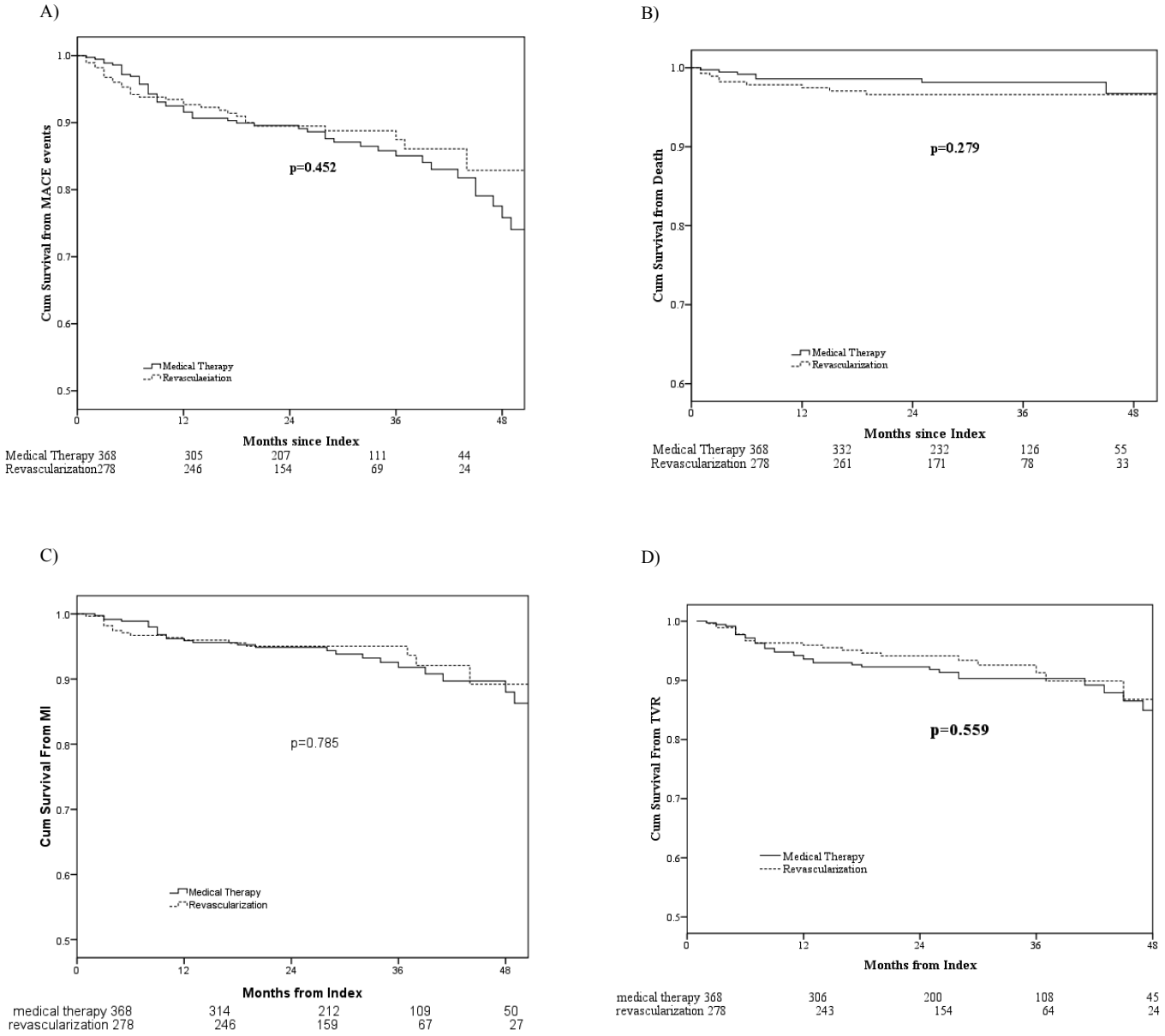

Fig. 2. Kaplan-Meier estimates of the time to cardiac events related to the target vessel during an average follow-up of 29 months for the medical therapy group and the revascularisation group (A, B, C, D).

Table 4. Cox Multivariable Models for Determinants of Outcome Events

Events	Adjusted HR*	95% CI	*P* Value
FFR-guided PCI vs medical therapy			
Death	2.162	0.794 – 5.891	0.132
Cardiac death	1.689	0.412 – 6.917	0.466
Target vessel revascularisation	0.76	0.431 – 1.34	0.343
MI	0.897	0.47 – 1.71	0.741
Thrombosis	2.801	0.443 – 17.709	0.274
MACE	0.861	0.544 – 1.362	0.522

CI: Confidential interval; FFR: Fractional flow reserve; HR: Hazard ratio; MACE: Major adverse cardiac events; MI: Myocardial infarction
*Adjusted for age, sex, smoker, diabetes, hypertension, hyperlipidaemia, family history, prior myocardial infarction, prior PCI indication.

period of 2002 to 2009 when FFR ≤0.75 was still used as the cutoff for haemodynamic significance. Our results indicated that the deferral of revascularisation in patients with FFR more than 0.75 was safe. More than 85% patients were free of MACE events at follow-up at 29 months, which implied potential cost saving from the obviation of initial PCI procedures.

In our study, IVUS was used in about 10% of the patients, and 9 patients with FFR more than 0.75 were revascularised according to IVUS findings. IVUS can provide more information about the coronary plaque than angiography alone, although several studies have revealed only a moderate correlation between minimal lesion diameter on IVUS and FFR. The correlation was dependent on the lesion location, reference vessel diameter and lesion length.[16-18] A recent study suggested that both FFR-guided and IVUS-guided PCI strategies were associated with favourable outcomes for intermediate coronary lesions, and no significant difference was noted between both strategies.[19] However, FFR-guided PCI reduced the need for revascularisation in many situations, with potential reduction of MACE event and cost of therapy. Li et al from the Mayo Clinic reported a comparative study using coronary angiography alone versus FFR for decision-making on PCI in daily practice. His results suggested that a FFR-guided strategy was associated with a favourable long-term outcome,[20] in corroboration with our findings. However in that study, the follow-up MACE event rate was high at 50%, compared with our medically treated MACE rate of 15%. There are several potential explanations. Firstly, our study had a shorter follow up duration of 29.7 months compared with theirs at 50.9 month. Secondly, the mortality rate in Li's study was especially high at 21% in the FFR-guided group and 32% in the angiography guided group, which counted for about half of the MACE events. This may be explained by the higher inherent risk among the patient cohort studied, which included 25% patients with previous MI history and prior PCI in 40%.

There are several limitations to our study. This is a single centre study with a limited sample size. However, the study population comprised several Asian ethnic groups and is still one of the largest clinical studies focusing on the use of FFR in intermediate coronary lesions in an Asian setting.

Secondly, some patients were treated with BMS in this study. Whether a more widespread use of drug eluting stents will give better clinical results in intermediate coronary lesions is unknown. Moreover, there was a crossover rate of about 10% in the study groups, based on the operators' discretion following clinical assessment, consideration of anatomic feasibility for intervention, and after IVUS interrogation.

Conclusion

This retrospective study indicated that FFR-guided medical treatment of intermediate coronary lesions is feasible and associated with low incidences of TVR and MACE at long-term follow-up. Our findings corroborate with published data that FFR-guided strategy in treatment of patients with intermediate coronary artery disease reduces the need for intervention and has significant cost-saving implication in real world practice.

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