European Heart Journal (2015) **36**, 3182–3188
doi:10.1093/eurheartj/ehv452

Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial

Frederik M. Zimmermann[1], Angela Ferrara[2], Nils P. Johnson[3], Lokien X. van Nunen[1,4], Javier Escaned[5], Per Albertsson[6], Raimund Erbel[7], Victor Legrand[8], Hyeong-Cheol Gwon[9], Wouter S. Remkes[10], Pieter R. Stella[11], Pepijn van Schaardenburgh[12], G. Jan Willem Bech[13,14], Bernard De Bruyne[2], and Nico H.J. Pijls[1,4]*

[1]Department of Cardiology, Catharina Hospital Eindhoven, Michelangelolaan 2, Eindhoven 5623 EJ, The Netherlands; [2]Cardiovascular Center, Aalst, Belgium; [3]Weatherhead PET Center For Preventing and Reversing Atherosclerosis, Division of Cardiology, Department of Medicine, University of Texas Medical School and Memorial Hermann Hospital, Houston, TX, USA; [4]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands; [5]Hospital Clínico San Carlos/Faculty of Medicine, Complutense University of Madrid, and Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; [6]Department of Cardiology, Sahlgrenska University Hospital Gothenburg, Sweden; [7]Department of Cardiology, West-German Heart and Vascular Centre, University Hospital of Essen, Essen, Germany; [8]Department of Cardiology, University Hospital of Liège, Liège, Belgium; [9]Division of Cardiology, Cardiac and Vascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [10]Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands; [11]Department of Interventional Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; [12]Department of Cardiology, VieCuri, Venlo, The Netherlands; [13]Department of Cardiology, HagaZiekenhuis, The Hague, The Netherlands; and [14]Reinier de Graaf Groep, Delft, The Netherlands

Received 1 June 2015; revised 22 July 2015; accepted 14 August 2015; online publish-ahead-of-print 24 September 2015

Aims Stenting an angiographically intermediate but functionally non-significant stenosis is controversial. Nevertheless, it has been questioned if deferral of a functionally non-significant lesion on the basis of fractional flow reserve (FFR) measurement, is safe, especially on the long term. Five-year follow-up of the DEFER trial showed that outcome after deferral of percutaneous coronary intervention (PCI) of an intermediate coronary stenosis based on FFR $\geq$ 0.75 is excellent and was not improved by stenting. The aim of this study was to investigate the validity of this position on the very long term.

Methods and results In 325 patients scheduled for PCI of an intermediate stenosis, FFR was measured just before the planned intervention. If FFR was $\geq$0.75, patients were randomly assigned to deferral (Defer group; $n = 91$) or performance (Perform group; $n = 90$) of PCI. If FFR was $<$0.75, PCI was performed as planned (Reference group; $n = 144$). Clinical follow-up was 15 years. There were no differences in baseline clinical characteristics between the randomized groups. Complete 15-year follow-up was obtained in 92% of patients. After 15 years of follow-up, the rate of death was not different between the three groups: 33.0% in the Defer group, 31.1% in the Perform group, and 36.1% in the Reference group (Defer vs. Perform, RR 1.06, 95% CI: 0.69–1.62, $P = 0.79$). The rate of myocardial infarction was significantly lower in the Defer group (2.2%) compared with the Perform group (10.0%), RR 0.22, 95% CI: 0.05–0.99, $P = 0.03$.

Conclusion Deferral of PCI of a functionally non-significant stenosis is associated with a favourable very long-term follow-up without signs of late 'catch-up' phenomenon.

Keywords Fractional flow reserve • Percutaneous coronary intervention • Coronary artery disease • Long-term follow-up

* Corresponding author. Tel: +31 40 2397004, Fax: +31 40 2447885, Email: nico.pijls@inter.nl.net; carias@cze.nl

Introduction

It has been well documented that decisions with respect to revascularization of coronary stenoses should take into account not only angiographic criteria but also non-invasive or invasive evidence of reversible myocardial ischaemia.[1–7] Stenting an angiographically significant but functionally non-significant stenosis is controversial.[8,9] Nevertheless, it has been questioned if deferral of revascularization of a functionally non-significant lesion on the basis of fractional flow reserve (FFR) measurement is safe, especially over the long term. Concerns about future plaque rupture have played a major role in that discussion.[10–13] The DEFER study was the first randomized controlled trial investigating the suitability of FFR to guide coronary interventions.[14] The purpose of the DEFER study was to compare deferral vs. performance of percutaneous coronary intervention (PCI) of an anatomic intermediate but functionally non-significant stenosis as indicated by FFR $\geq$ 0.75. The 2- and 5-year follow-up showed that, both with respect to outcome and to symptoms, deferral was at least as good as mechanical revascularization of such stenoses. Up to 5 years, there was no difference with respect to mortality, myocardial infarction (MI), or revascularization related to the deferred lesions. No differences were present either with respect to functional class or use of medication.[15] The present report extends that follow-up to 15 years with respect to the outcome parameters: mortality, MI, and revascularization.

Methods

Design and participants

The design and methods of the DEFER study have been described previously and are summarized briefly below.[14] The DEFER study was a multicenter, international, randomized controlled trial performed in 12 European and 2 Asian centres between 1997 and 1998. Patients were enrolled if they met two inclusion criteria: (i) referral for elective PCI of a single angiographically significant *de novo* stenosis (>50% diameter reduction by visual assessment) in a native coronary artery with a reference diameter of >2.5 mm and (ii) no conclusive evidence of reversible ischaemia as documented by non-invasive testing within the last 2 months. Main exclusion criteria were total occlusion of the target artery, MI, or unstable angina. The institutional review boards of all centres approved the study protocol. All patients provided written consent before enrolment.

Randomization

In order to prevent bias, patients were randomized before measuring FFR (*Figure 1*). After inclusion in the study and before physiological measurement, patients were randomized to deferral or performance of PCI. Thereafter, FFR was measured. If the FFR value was <0.75 indicating reversible ischaemia, then randomization was ignored and PCI was performed anyway because it was felt unethical at that time to leave such a stenosis unrevascularized (Reference group). In contrast, if the FFR value was $\geq$0.75, then the stenosis was treated according to the randomization, resulting in one group of patients with FFR $\geq$ 0.75 in whom PCI was performed (Perform group) and a second group of patients with FFR $\geq$ 0.75 in whom PCI was deferred and the further treatment was medically (Defer group). All patients received optimal medical therapy for that era.

Quantitative angiography and fractional flow reserve measurement

Angiograms were performed in at least two orthogonal projections after administration of intracoronary nitroglycerin. All angiograms were analysed using QCA-CMS system (Medis, Leiden, the Netherlands). Fractional flow reserve was measured with a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) and adenosine-based hyperaemia given intravenously (140 μg per minute per kg of body weight) or intracoronary.[16,17] Percutaneous coronary intervention was performed according to the standards at that time, before the era of drug-eluting stents, by either bare metal stents (BMS) or balloon angioplasty.

Endpoints

The primary endpoint was freedom from major adverse cardiac events (death, MI, and repeat revascularization) after 2 years of follow-up, and 5-year follow-up was a secondary endpoint. It should be noted that the DEFER study was not powered for a 15-year follow-up and that no a priori hypothesis for such long-term follow-up was defined. The 15-year follow-up was added later due to the importance of understanding long-term clinical outcomes after FFR-guided revascularization. Because non-cardiac mortality will dominate cardiac mortality during such very long-term follow-up, we distinguished among cardiac, unknown, and non-cardiac mortality. Myocardial infarction was defined as a clinical episode of typical chest pain with development of new pathologic Q-waves on the electrocardiogram or an increase of serum creatinine kinase (CK) levels to more than twice the normal value, reflecting the practice pattern during the era of patient recruitment. Repeated angiography was only performed if clinically indicated or in case of an adverse event. While events were adjudicated by a clinical event committee up to 5 years, events thereafter were site determined and verified by source documentation (including related vessel, cardiac enzymes, and cause of death).

National database

In those patients for whom no complete follow-up could be acquired, applicable national databases were queried to obtain the survival status. These data were used only for comparing all-cause mortality.

Statistical analysis

All analyses used an intention-to-treat assignment. Continuous variables are expressed as mean $\pm$ 1 SD and were compared using Student's *t*-test. Dichotomous variables are expressed as absolute numbers and percentages (%) and were compared using the χ^2 test or Fisher's exact test as appropriate. Myocardial infarction rates were visualized with the use of Kaplan–Meier survival curves, using the log-rank test for the comparison between groups.

A *P*-value of <0.05 was considered significant, and applicable tests were always two sided. All analyses were conducted using SPSS 19.0.0.1 software (IBM Corporation, Armonk, NY, USA) or R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and procedural results

Of 325 patients, 167 were randomly assigned to deferral and 158 to performance of PCI (*Figure 1*). Baseline characteristics of patients in both randomization arms were similar, including angiographic characteristics and FFR (*Table 1*). Fractional flow reserve was $\geq$0.75 in

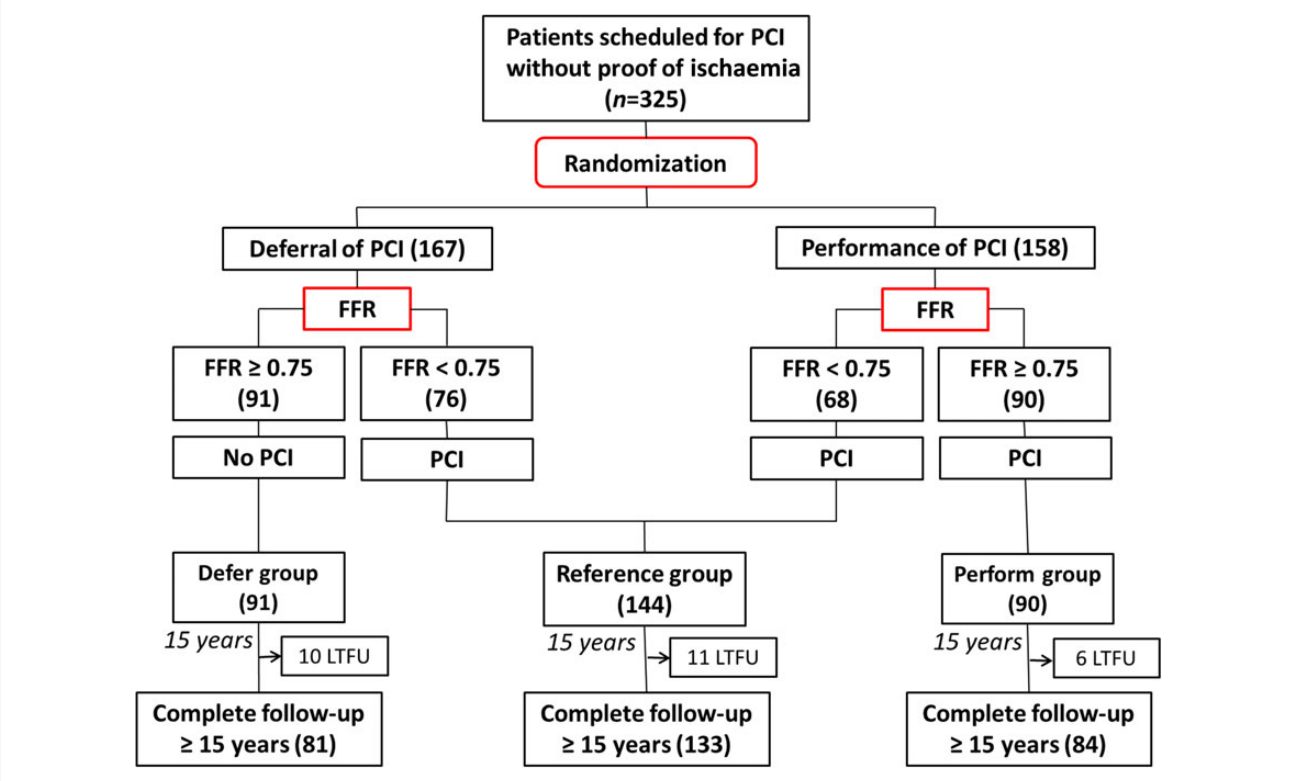


Figure 1 Flowchart of the study, randomization, definition of the three groups, and 15-year follow-up.

181 patients of whom 91 belonged to the group randomized to deferral of PCI (Defer group) and 90 to the group randomized to performance of PCI (Perform group). Fractional flow reserve was <0.75 in 144 patients. In the latter group (Reference group), randomization was ignored and PCI was performed anyway. Mean percent diameter stenosis was more severe in the Reference group (FFR < 0.75). However, overlap of data was so large that quantitative coronary angiography was absolutely not useful for predicting the true functional stenosis severity in individual patients. Fractional flow reserve was 0.86 ± 0.06 in the Defer group, 0.87 ± 0.07 in the Perform group, and 0.57 ± 0.16 in the Reference group. In the Performance group, 41 patients (46%) were treated by BMS and 85 patients (59%) in the Reference group. Finally, all angiographic parameters after PCI were similar in the Perform and Reference groups, indicating that no difference was present in the quality of stenting between the Perform and Reference groups.

15-year follow-up

Complete follow-up was obtained in 325 patients (100%) after 12 months, in 317 patients (98%) after 24 months, in 313 patients (97%) after 5 years, and in 298 patients (92%) after 15 years. Mean follow-up of patients alive was 16.9 years (interquartile range 16.0–17.5 years). Patients lost to follow-up were similarly distributed among Defer (10 of 91, 11%), Perform (6 of 90, 7%), and Reference (11 of 144, 8%) groups ($P = 0.62$). Follow-up with respect to all-cause mortality after 15 years was obtained in 311 patients (96%) by checking national databases.

Clinical outcome after 15 years

Mortality

Mean age of the patients at the start of the study was 61 years. Consequently, after a mean follow-up of 16.9 years, a considerable portion of patients had died from a predominance of non-cardiac causes. There was no difference in all-cause mortality after 15 years among the three groups: 33.0% in the Defer group, 31.1% in the Perform group, and 36.1% in the Reference group (Defer vs. Perform, RR 1.06, 95% CI: 0.69–1.62, $P = 0.79$) (*Table 2*). Also cardiac death was not different between 5.5% in the Defer group, 4.4% in de Perform group, and 10.4% in the Reference group (Defer vs. Perform $P = 1.00$).

Myocardial infarction

The rate of MI was significantly lower in the Defer group (2.2%) compared with the Perform group (10.0%), RR 0.22, 95% CI: 0.05–0.99, $P = 0.03$. This was almost exclusively due to less target vessel-related infarctions (*Figure 2*). Patients with a baseline FFR ≥ 0.75 had a significantly lower rate of MI compared with patients with an FFR < 0.75 (6.1 vs. 12.5%, RR 0.49, 95% CI: 0.24–1.00, $P = 0.044$).

Repeat revascularization

Revascularization occurred in 42.9% of the Defer group, 34.4% of the Perform group, and 44.4% of the Reference group, thereby showing a trend towards higher revascularization rate in the Defer group (Defer vs. Perform $P = 0.245$). However, when looking at

total cumulative events, no difference was observed (47 vs. 49 events) regarding PCI, as shown in *Table 3*. In other words, the mean number of percutaneous coronary interventions per patient was not statistically different in both groups.

Table 1 Baseline characteristics

	FFR ≥ 0.75		FFR < 0.75
	Defer group (n = 91)	Perform group (n = 90)	Reference group (n = 144)
Age (years)	61 ± 9	61 ± 11	60 ± 9
Gender (%)			
Male	65	63	80
Female	35	37	20*
Risk factors (%)			
Diabetes	15	9	13
Hypertension	36	34	42
Hyperlipidaemia	43	48	49
Current smoker	27	23	29
Family history of CAD	56	46	45
Ejection fraction (%)	67 ± 9	67 ± 10	68 ± 9
Angiography			
Reference diameter (mm)	3.00 ± 0.64	2.94 ± 0.57	2.97 ± 0.58*
DS (QCA) (%)	48 ± 9	48 ± 10	57 ± 12
MLD (mm)	1.55 ± 0.37	1.50 ± 0.36	1.28 ± 0.39*
Lesion length (mm)	9.8 ± 5.4	10.2 ± 4.3	9.5 ± 3.9*
FFR	0.87 ± 0.07	0.87 ± 0.06	0.56 ± 0.16*

*$P < 0.05$ for comparison between Defer and Perform groups vs. Reference group. CAD, coronary artery disease; DS, diameter stenosis; FFR, fractional flow reserve; MLD, minimum luminal diameter. Reprinted with permission of the American Heart Association.[14]

Discussion

The DEFER randomized controlled trial investigated the safety of deferring PCI for an angiographically significant but functionally non-significant coronary stenosis as indicated by an FFR ≥ 0.75. Our results show that even after 15 years of follow-up, the prognosis of functionally non-significant deferred lesions is excellent, that PCI of such stenoses has no advantage and even results in more MIs when compared with medical therapy. Our novel results extend earlier findings from the DEFER study at 2- and 5-year follow-up.[14,15] This is the longest follow-up of a randomized trial using fractional flow reserve for decision making and calls for a number of discussion points.

First, our results show a significant increase in rates of MI if a functionally non-significant stenosis is treated by PCI compared with medical therapy alone. These MIs not only were peri-procedural but also occurred throughout the complete follow-up, with the majority arising later than 5 years after the index procedure (*Figure 2*). Interestingly, in the Defer group only one MI was possibly related to the study vessel, thereby confirming the excellent natural history of a functionally non-significant stenosis with optimal medical treatment. In contrast, in the Perform group, the majority of MIs occurred in the stented artery, suggesting a possible role of neo-atherosclerosis as underlying cause.

Second, despite the increased rate of MI in the Perform group, there was no increased mortality compared with the Defer group. In this respect, it should be noted that after a very long-term follow-up mortality is more related to advanced age (average age of 78.0 years at mean follow-up) and non-cardiac causes than to cardiac death. Therefore, the potential effects of deferral vs. performance of PCI on mortality dilute over time. However, the present data

Table 2 Clinical outcome after 15 years

	Defer group (n = 91)	Perform group (n = 90)	Reference group (n = 144)	*P*-value	
				Defer vs. Perform	Defer and perform vs. Reference
Mortality					
All cause	30 (33.0%)	28 (31.1%)	52 (36.1%)	0.789	0.441
Cardiac	5 (5.5%)	4 (4.4%)	15 (10.4%)	1.000	0.062
Unknown	13 (14.3%)	11 (12.2%)	10 (6.9%)	0.682	0.065
Non-cardiac	12 (13.2%)	13 (14.4%)	27 (18.8%)	0.806	0.228
MI					
All	2 (2.2%)	9 (10.0%)	18 (12.5%)	0.033	0.044
Target vessel[a]	1 (1.1%)	8 (8.9%)	12 (8.3%)	0.018	0.221
Revascularization					
All	39 (42.9%)	31 (34.4%)	64 (44.4%)	0.245	0.294
Target vessel	33 (36.3%)	25 (27.8%)	51 (35.4%)	0.221	0.522

[a]Target vessel = target vessel + unknown vessel.

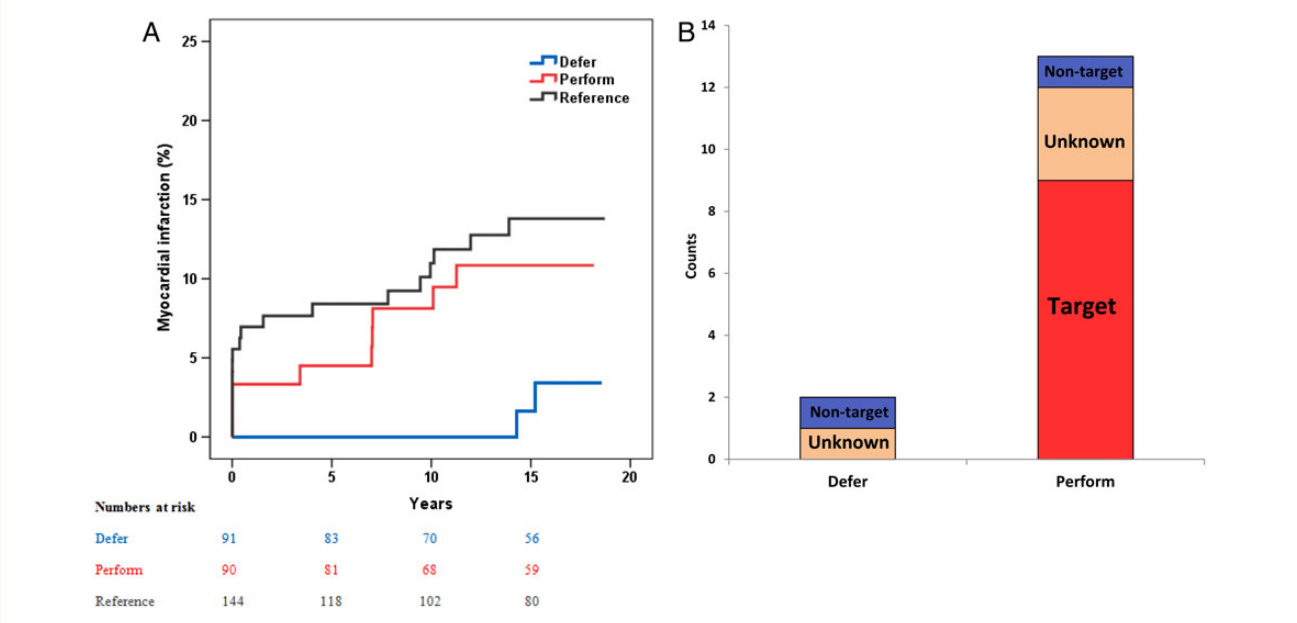


Figure 2 Kaplan–Meier of myocardial infarction (*A*) and relation of myocardial infarction with study vessel territory (*B*).

Table 3 Cumulative adverse events after 15 years

	Defer group ($n = 91$)	Perform group ($n = 90$)	Reference group ($n = 144$)
MI			
All	2	13	19
Target vessel	0	9	13
Unknown vessel	1	3	1
Non-target vessel	1	1	5
PCI			
All	49	47	66
Target vessel	30	28	38
Non-target vessel	19	19	28
CABG			
All	11	7	23
Target vessel	10	7	22
Non-target vessel	1	0	1

show that concerns about increased mortality after deferral of angiographically significant but functionally non-significant coronary lesions are not justified.[10,12,13]

Third, deferring PCI of functionally non-significant stenoses does not result in a significant increase or 'catch-up' of revascularization compared with PCI on the long term. There was a trend towards revascularization occurring in more patients in the Defer group compared with the Perform group, but when looking at total cumulative events no difference was observed (*Table 3*).

Fourth, the current study provides unique insights into the natural course of coronary artery disease over the very long term when treated medically according to FFR guidance. Several studies have described the follow-up of medically treated coronary stenoses in stable angina, but none of them exceeded 10 years.[18–20] Direct comparison of our results with other studies should be done with caution due to differences in baseline characteristics. Deferral of PCI in angiographically significant but functionally non-significant lesions is safe during the very long term. The current study presents rates of MI in the Defer group of 2.2% after 15 years, compared with MI rates of 11.2% after 5 years in COURAGE, and 4.5% after 7 years in RITA-2, when FFR was not used in comparable patients.[18,21] In the FAME study, of 513 deferred lesions based on an FFR > 0.80, only one infarction related to a deferred lesion occurred after 2 years, in line with our extended DEFER results.

Limitations

The present study also has several limitations. First, the study was not designed for a follow-up of 15 years and was therefore not explicitly powered for the reported endpoints.

Second, PCI was performed in an era when drug-eluting stents were not yet available. With contemporary second-generation stents the rate of MI might have been lower in the Perform group.[22] Yet, the excellent outcome in the Defer group, with only two MIs, is hard to surpass (*Figure 2*).

Third, although treatment was randomized, neither the patients nor the physician was blinded. This might have created a bias towards more revascularization in the Defer group at follow-up.

Fourth, in contrast to contemporary patients, the majority of patients in the DEFER study had single vessel disease. Extrapolating our long-term data to patients with multivessel disease should be done with caution. Nevertheless, comparable results with respect

to deferral of functionally non-significant lesions up to 5 years have been described in patients with multivessel disease in the FAME and FAME 2 studies.[5,7] Therefore, even in multivessel disease it might be expected that PCI can be safely deferred in functionally non-significant lesions.

Finally, when using FFR to identify ischaemic stenoses, a grey zone exists between 0.75 and 0.80. In the DEFER study, the lower limit of that grey zone was used, whereas presently the upper limit of the grey zone is used (0.80) to make decisions, thereby increasing sensitivity to almost 100% at the cost of a decreased specificity. We do not believe this choice fundamentally influenced the outcome of the DEFER study because of a continuous relationship between the FFR value and clinical outcomes for both deferral and performance of PCI, as documented recently in a large meta-analysis.[3]

Conclusion

In conclusion, among patients with stable chest pain, coronary stenoses that are not responsible for inducible ischaemia as indicated by FFR $\geq$ 0.75 have an excellent outcome when treated medically, even after 15 years of follow-up. Performing PCI of such functionally non-significant stenosis has no benefit compared with medical treatment.

Authors' contributions

F.M.Z., P.v.S., G.J.W.B., N.P.J.: performed statistical analysis. N.H.J.P.: handled funding and supervision. F.M.Z., A.F., L.X.v.N., J.E., P.A., R.E., V.L., H.C.G., W.S.R., P.R.S., P.v.S., G.J.W.B., B.D.B., N.H.J.P.: acquired the data. N.H.J.P., B.D.B., G.J.W.B.: conceived and designed the research. F.M.Z., N.H.J.P.: drafted the manuscript. F.M.Z., A.F., N.P.J., L.X.v.N., J.E., P.A., R.E., V.L., H.C.G., W.S.R., P.R.S., P.v.S., G.J.W.B., B.D.B., N.H.J.P.: made critical revision of the manuscript for key intellectual content.

Conflict of interest: B.D.B. reports that his institution receives grant support and consulting fees on his behalf from St Jude Medical. N.H.J.P. reports that he receives institutional research grants from St Jude Medical, is consultant for St Jude Medical, Boston Scientific, and Opsens Medical and holds equity interest in Philips, General Electric, and Heartflow.

Funding

This study was supported by an unrestricted grant from Radi Medical System, Uppsala, Sweden (presently St Jude Medical), and the Friends of the Heart Foundation (Stichting Vrienden van het Hart), Eindhoven, the Netherlands. N.P.J. reports that he receives research grants from St Jude Medical and Volcano Corporation.

References

1. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–2907.
2. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011;**32**:1012–1024.
3. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di SL, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodes-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;**64**:1641–1654.
4. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol* 2004;**11**:171–185.
5. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nuesch E, Juni P. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;**371**:1208–1217.
6. Park SJ, Ahn JM, Park GM, Cho YR, Lee JY, Kim WJ, Han S, Kang SJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice. *Eur Heart J* 2013;**34**:3353–3361.
7. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;**56**:177–184.
8. Hodgson JM. What part of the FFR link don't we understand? *J Am Coll Cardiol* 2014;**64**:1655–1657.
9. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di MC, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
10. Mercado N, Maier W, Boersma E, Bucher C, de Valk V, O'Neill WW, Gersh BJ, Meier B, Serruys PW, Wijns W. Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty or coronary stenting. Implications for mechanical plaque sealing. *Eur Heart J* 2003;**24**:541–551.
11. Arbab-Zadeh A, Fuster V. The myth of the 'vulnerable plaque': transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015;**65**:846–855.
12. Stone GW, Maehara A, Lansky AJ, De Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
13. Meier B. Plaque sealing by coronary angioplasty. *Heart* 2004;**90**:1395–1398.
14. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;**103**:2928–2934.
15. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, De Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;**49**:2105–2111.
16. De Bruyne B, Pijls NH, Barbato E, Bartunek J, Bech JW, Wijns W, Heyndrickx GR. Intracoronary and intravenous adenosine 5′-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation* 2003;**107**:1877–1883.
17. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and

after percutaneous transluminal coronary angioplasty. *Circulation* 1993;**87**: 1354–1367.
18. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**: 1503–1516.
19. Hannan EL, Samadashvili Z, Cozzens K, Walford G, Jacobs AK, Holmes DR Jr, Stamato NJ, Gold JP, Sharma S, Venditti FJ, Powell T, King SB III. Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation* 2012;**125**: 1870–1879.
20. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005;**111**: 2906–2912.
21. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;**42**:1161–1170.
22. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, Cangiano E, Minarelli M, Scalone A, Cavazza C, Marchesini J, Parrinello G. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). *JACC Cardiovasc Interv* 2014;**7**: 20–28.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehv379
Online publish-ahead-of-print 18 August 2015

A 45-year-old woman with chest pain after coronary stenting

Marina Leitman[1,2]*, Ruthie Shmueli[1,2], Victor Rubchevsky[2,3], Alberto Hendler[1,2], and Zvi Vered[1,2]

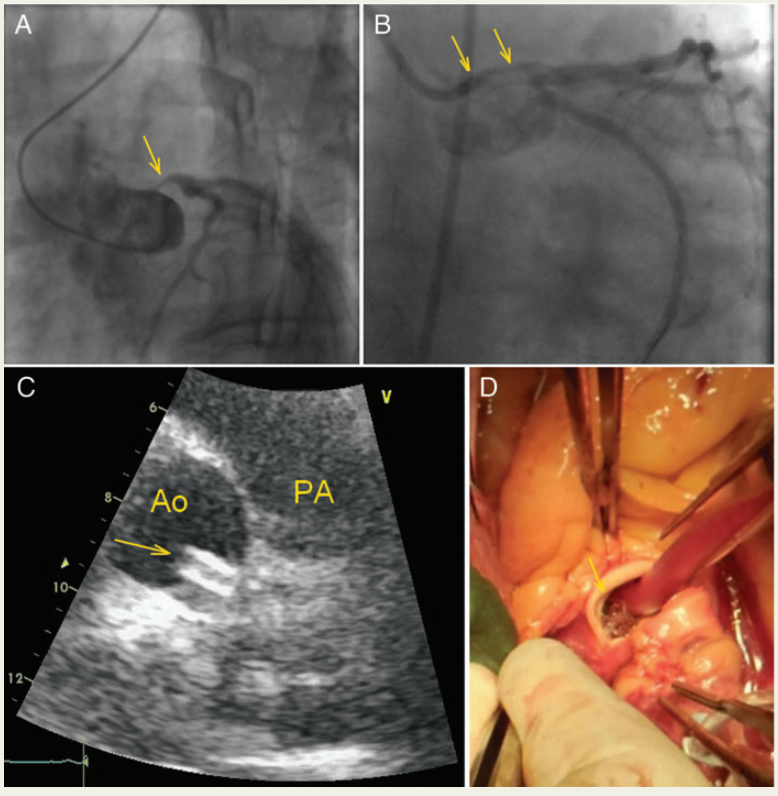
[1]Department of Cardiology, Assaf Harofeh Medical Center, Zerifin 70300, Israel; [2]Sackler School of Medicine Tel Aviv University, Tel Aviv, Israel; and [3]Department of Cardiac Surgery, Rabin Medical Center, Petah Tikva, Israel

* Corresponding author. Tel: +972 89779736, Fax: +972 89778412, Email: marina.leitman@gmail.com

A 45-year-old woman with history of diabetes mellitus and smoking underwent coronary angiography due to unstable angina. During the intubation of the left main coronary artery, pressure drop was observed and ostial left main stenosis was found (*Panel A*). The patient complained of chest pain and immediate stenting of the left main coronary artery was performed guided by intravascular ultrasound. A Resolute Integrity-zotarolimus eluting stent 15 × 4 mm was inserted. Due to dissection distally to the stent, a second stent Resolute Integrity 9 × 4 mm was inserted in the distal left main (*Panel B*).

Next morning the patient complained of chest pain, resolved by isosorbide dinitrate. Bedside echocardiography revealed a metallic shadow 12 × 4 mm, which protruded into the aorta (Ao) on a parasternal short-axis view at the level of the pulmonary artery (PA) and was consistent with migrated coronary stent (*Panel C*).

The patient underwent urgent surgery that showed the coronary stent protruding out of left main coronary artery into the aorta (*Panel D*). The stent was removed and coronary artery bypass grafting was performed. Subsequent course was uneventful.



Incidence of stent loss is rare, 0.2%, but may lead to serious complications including cerebrovascular embolic events, myocardial infarction and death, but may be asymptomatic and occur up to 2 years after the implantation. Risk factors for stent migration are tortuous and calcified artery, short stent at an aorto-ostial location, and drug eluting stent with delayed endothelial coverage.

Z.V. handled funding and supervision. R.S., A.H., and V.R. acquired the data. M.L. and Z.V. conceived and designed the research. M.L. drafted the manuscript. Z.V. made critical revision of the manuscript for key intellectual content.