JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 24, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.07.021

Nonculprit Stenosis Evaluation Using Instantaneous Wave-Free Ratio in Patients With ST-Segment Elevation Myocardial Infarction

Troels Thim, MD, PhD,[a] Matthias Götberg, MD, PhD,[b] Ole Fröbert, MD, PhD,[c] Robin Nijveldt, MD, PhD,[d] Niels van Royen, MD, PhD,[d] Sergio Bravo Baptista, MD,[e] Sasha Koul, MD, PhD,[b] Thomas Kellerth, MD, DMSc,[c] Hans Erik Bøtker, MD, DMSc,[a] Christian Juhl Terkelsen, MD, PhD, DMSc,[a] Evald Høj Christiansen, MD, PhD,[a] Lars Jakobsen, MD, PhD,[a] Steen Dalby Kristensen, MD, DMSc,[a] Michael Maeng, MD, PhD[a]

ABSTRACT

OBJECTIVES The aim of this study was to examine the level of agreement between acute instantaneous wave-free ratio (iFR) measured across nonculprit stenoses in patients with ST-segment elevation myocardial infarction (STEMI) and iFR measured at a staged follow-up procedure.

BACKGROUND Acute full revascularization of nonculprit stenoses in STEMI is debated and currently guided by angiography. Acute functional assessment of nonculprit stenoses may be considered.

METHODS Immediately after successful primary culprit intervention for STEMI, nonculprit coronary stenoses were evaluated with iFR and left untreated. Follow-up evaluation with iFR was performed at a later stage. iFR <0.90 was considered hemodynamically significant.

RESULTS One hundred twenty patients with 157 nonculprit lesions were included. Median acute iFR was 0.89 (interquartile range [IQR]: 0.82 to 0.94; n = 156), and median follow-up iFR was 0.91 (interquartile range: 0.86 to 0.96; n = 147). Classification agreement was 78% between acute and follow-up iFR. The negative predictive value of acute iFR was 89%. Median time from acute to follow-up evaluation was 16 days (IQR: 5 to 32 days). With follow-up within 5 days after STEMI, no difference was observed between acute and follow-up iFR, and classification agreement was 89%. With follow-up ≥16 days after STEMI, acute iFR was lower than follow-up iFR, and classification agreement was 70%.

CONCLUSIONS Acute iFR evaluation appeared valid for ruling out significant nonculprit stenoses in patients with STEMI undergoing primary percutaneous coronary intervention. The time interval from acute to follow-up iFR influenced classification agreement, suggesting that inherent physiological disarrangements during STEMI may contribute to classification disagreement. (J Am Coll Cardiol Intv 2017;10:2528–35) © 2017 by the American College of Cardiology Foundation.

During primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), nonculprit coronary stenoses may be identified on acute coronary angiography (1). Current guidelines generally recommend that these stenoses not be treated during acute CAG but reevaluated later (e.g., at follow-up CAG), when these stenoses

From the [a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Cardiology, Lund University, Skåne University Hospital, Lund, Sweden; [c]Örebro University, Faculty of Health, Department of Cardiology, Örebro, Sweden; [d]Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands; and the [e]Cardiology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal. This work was supported by an unrestricted research grant from Volcano Europe BVBA/SPRL. Dr. Nijveldt has received financial support from the Netherlands Organisation for Health Research and Development (grant 90714544). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 21, 2017; revised manuscript received May 24, 2017, accepted May 24, 2017.

can be further evaluated and treated if necessary (2–5).

On acute CAG, coronary stenoses are typically evaluated on the basis of angiography alone (6,7). On follow-up CAG, angiographic images can be supplemented with other diagnostic tools for decision support, and some patients do not require further revascularization on the basis of this evaluation (1).

SEE PAGE 2536

Functional assessment by fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) may be used as a supplementary diagnostic modality on follow-up CAG (1,8). FFR requires pharmacological stimulation of the coronary circulation and has not become standard clinical practice for the assessment of nonculprit lesions at the time of acute CAG. iFR does not require pharmacological stimulation of the coronary circulation and can thereby more easily be applied during acute CAG. However, the agreement between iFR measurements performed on acute versus follow-up CAG is not known.

The aim of this study was to assess the level of agreement between iFR measured across nonculprit stenoses on acute CAG in patients with STEMI compared with iFR and FFR measured on follow-up CAG.

METHODS

STUDY DESIGN. We performed a prospective multicenter evaluation of nonculprit coronary stenoses using iFR in patients with STEMI, with follow-up evaluation of the same stenoses with iFR and FFR. The study was approved by the ethics committees of the participating centers. Participants were informed about the study by the physician responsible for the acute procedure and provided informed consent before participation.

The study was prospective and observational. Participants were given standard treatment in accordance with current guidelines and institutional standards. Study-related intracoronary pressure measurements were performed during coronary angiographic studies carried out for standard clinical indications.

PARTICIPANTS. The inclusion criteria were: 1) acute CAG for STEMI with successful primary PCI treatment of the culprit lesion; 2) the presence of 1 or more nonculprit coronary stenoses that, according to the usual clinical standards of the institution, indicated follow-up CAG with evaluation of the nonculprit stenoses; and 3) age ≥18 years. The exclusion criteria were: 1) inability to provide informed consent; 2) clinical condition of the patient indicating full revascularization on acute CAG (e.g., cardiogenic shock); and 3) clinical condition of the patient precluding intracoronary pressure measurements on acute CAG.

Participants were included at Aarhus University Hospital, Skåne University Hospital, Örebro University Hospital, VU University Medical Center, and Hospital Prof. Doutor Fernando Fonseca between June 25, 2015, and November 17, 2016.

ABBREVIATIONS AND ACRONYMS

CAG = coronary angiography
FFR = fractional flow reserve
iFR = instantaneous wave-free ratio
IQR = interquartile range
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

NONCULPRIT LESION EVALUATION. After successful primary PCI of the culprit lesion, acute iFR measurements were performed across the nonculprit stenoses. Pressure wire position was documented by angiography. Follow-up iFR and FFR measurements were performed using the same pressure wire position. The time interval between the acute evaluation and the follow-up evaluation was at the discretion of the treating physicians, to be in agreement with usual institutional standards.

Before intracoronary pressure measurements, intracoronary nitroglycerin was administered to avoid epicardial coronary artery spasm. Pressure wire and guiding catheter tip pressure measurements were normalized before the pressure wire was placed distal to the lesion. All iFR measurements were repeated until 3 stable consecutive measurements were obtained, and the stable value was recorded. At follow-up, iFR was measured first and followed by FFR measurement using intravenous adenosine (140 μg/kg body weight/min) during FFR measurements. Pressure wires were always controlled for drift of normalized values before acceptance of the obtained iFR and FFR measurements. Drift of 0.02 or less was considered acceptable. When drift was more than 0.02, measurements were repeated. Pressure measurements were performed using Verrata pressure wires (Volcano Europe BVBA/SPRL, Zaventem, Belgium).

Nonculprit lesion quantitative CAG was performed using QAngio XA version 7.3.38.0 (Medis Medical Imaging Systems, Leiden, the Netherlands).

STATISTICAL METHODS. Demographic variables were entered at the patient level, whereas pressure wire measurements and angiographic variables were entered at the lesion level. Continuous demographic variables (age and body mass index) are summarized as mean ± SD, while continuous lesion characteristics (reference artery diameter, minimal luminal diameter, percentage diameter stenosis, iFR, and FFR) and time between acute and follow-up CAG are summarized as medians and interquartile ranges (IQRs), because these variables did not have a normal

TABLE 1 Baseline Patient Characteristics (n = 120)

Age, yrs	66 ± 11
Male	88 (73)
Body mass index, kg/m^2	27 ± 5
Family history of ischemic heart disease	41 (34)
Current smoking	39 (33)
Hypertension*	48 (40)
Hypercholesterolemia†	30 (25)
Diabetes‡	11 (9)
Previous acute myocardial infarction	11 (9)
Previous percutaneous coronary intervention	15 (13)
Previous coronary artery bypass grafting	1 (1)

Values are mean ± SD or n (%). *Treatment with blood pressure–lowering agents. †Treatment with lipid-lowering agents. ‡Treatment with antidiabetic drugs or diet.

TABLE 2 Characteristics of Nonculprit Stenoses

Acute	
Reference artery diameter, mm (n = 154)	2.3 (2.0–2.8)
Minimal luminal diameter, mm (n = 154)	1.2 (0.9–1.5)
Percentage diameter stenosis, % (n = 154)	50 (41–59)
iFR (n = 156)	0.89 (0.82–0.94)
Follow-up	
iFR (n = 147)	0.91 (0.86–0.96)
FFR (n = 146)	0.81 (0.75–0.88)

Values are median (interquartile range).
FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

distribution. Dichotomous demographic variables (sex, family history of ischemic heart disease, current smoking, hypertension, hypercholesterolemia, diabetes, previous acute myocardial infarction, previous percutaneous coronary intervention, and previous coronary artery bypass grafting) are presented as count (frequency).

Agreement between acute and follow-up iFR measurements was examined using scatterplots and Bland-Altman plots (9). The differences between acute and follow-up iFR measurements were not normally distributed, and the difference between acute and follow-up iFR was examined using the sign test, overall and stratified according to time between acute and follow-up iFR. We evaluated the between-center variance in iFR data using the Kruskal-Wallis test. In addition, acute iFR measurements were plotted against follow-up FFR measurements in a scatterplot.

Subsequently, iFR measurements were dichotomized into hemodynamically significant (<0.90) or nonsignificant (≥0.90) values (10,11). Likewise, FFR measurements were dichotomized into significant and nonsignificant values, using both the ≤0.80 cutoff (12,13) and the <0.75 cutoff (14,15). We cross-tabulated the dichotomized acute iFR versus follow-up iFR and FFR to evaluate the degree of classification agreement.

Data were summarized and analyzed using Stata/IC version 13.1 for Windows (StataCorp, College Station, Texas).

RESULTS

PARTICIPANTS. We included 120 patients with culprit lesions in the left main stem (n = 1), left anterior descending coronary artery including diagonal branches (n = 44), left circumflex coronary artery including obtuse marginal branches (n = 24), and right coronary artery (n = 51). The mean participant age was 66 years, and 73% of participants were men.

In these 120 patients, we included 157 nonculprit lesions in the left main stem (n = 2), left anterior descending coronary artery including diagonal branches (n = 80), left circumflex coronary artery including obtuse marginal branches (n = 46), and right coronary artery (n = 29). In 87 patients, 1 nonculprit lesion was evaluated. In 29 patients, 2 nonculprit lesions were evaluated. And in 4 patients, 3 nonculprit lesions were evaluated. In 1 patient, a wire-induced dissection of the nonculprit lesion led to acute intervention precluding pressure wire assessment.

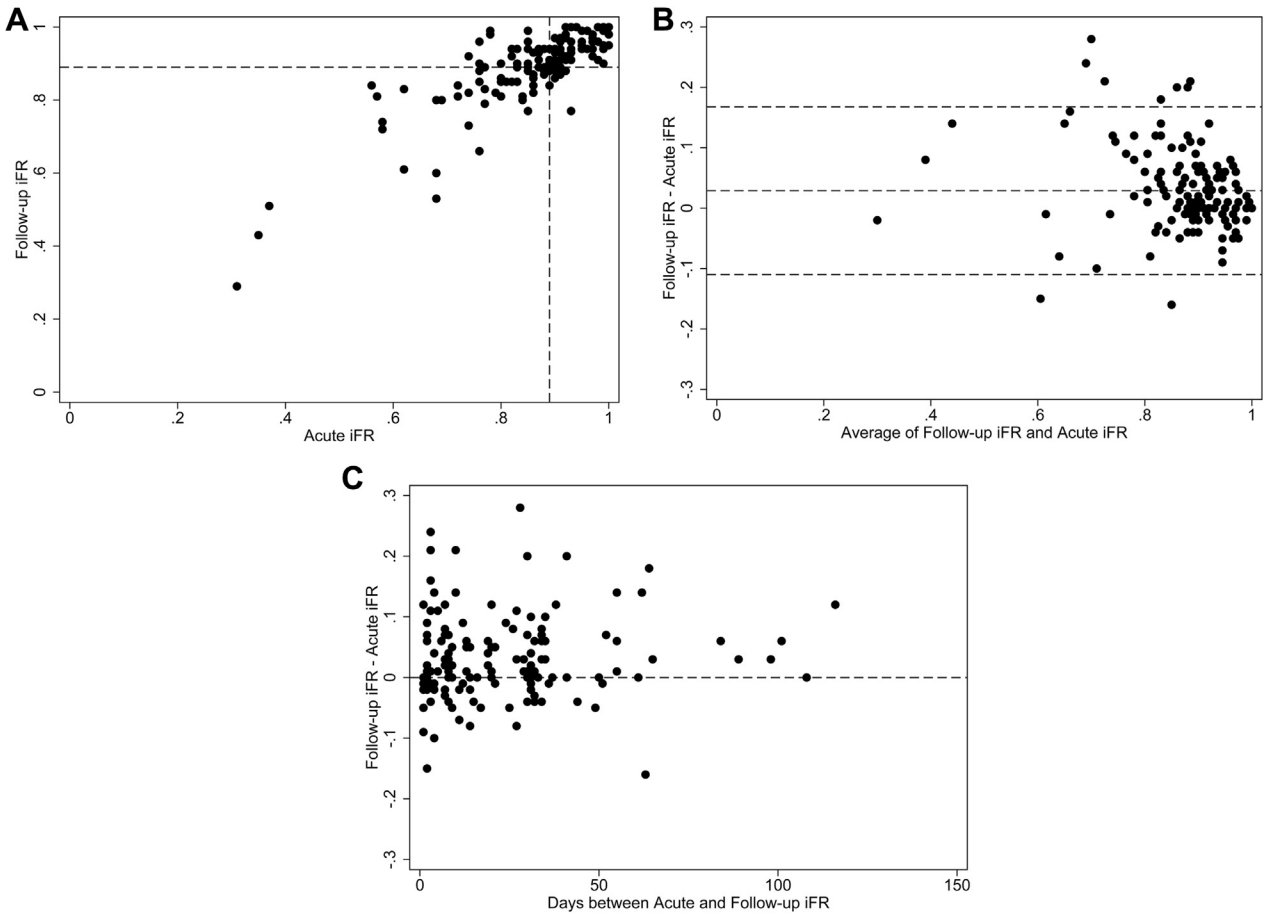
Of 119 patients with acute iFR assessment of 156 nonculprit lesions, follow-up iFR was completed for 113 patients with 147 nonculprit lesions. One of these patients had asthma and thus had 1 nonculprit lesion evaluated with iFR but not FFR at follow-up. Follow-up iFR and FFR were not available for 6 patients. Of these 6 patients, 3 died during the initial admission, 1 died after out-of-hospital cardiac arrest 6 days after discharge from the acute admission, and 2 patients declined follow-up with invasive lesion assessment. Among the 6 patients without follow-up, 3 had 1 nonculprit lesion and 3 had 2 nonculprit lesions.

Baseline clinical characteristics of participants are summarized in **Table 1**.

NONCULPRIT LESION EVALUATION. Data from participants without follow-up were included in the summaries of acute lesion characteristics but not in the subsequent analyses. Angiographic data were missing from 3 participants.

Lesion characteristics are summarized in **Table 2**. Acute iFR was <0.90 in 81 of 156 lesions (52%). Acute and follow-up iFR measurements are plotted in **Figure 1A** and cross-tabulated in **Table 3**. Agreement between acute and follow-up iFR is illustrated in **Figure 1B**. We found classification agreement (significant vs. nonsignificant) between acute and follow-up

FIGURE 1 Acute and Follow-Up Instantaneous Wave-Free Ratio



(A) Scatterplot of acute and follow-up instantaneous wave-free ratio (iFR). The **horizontal and vertical lines** at 0.89 on both axes indicate the border between significant (<0.90) and non-significant (≥0.90) iFR values. **(B)** Bland-Altman plot of acute and follow-up iFR. The **horizontal lines** indicate the mean difference between the 2 measurements and 95% confidence intervals (mean ± 2 SDs). **(C)** Plot of the difference between acute and follow-up iFR over time between acute and follow-up iFR.

iFR in 78% of lesions (115 of 147). With follow-up iFR as reference, acute iFR had sensitivity of 87%, specificity of 72%, positive predictive value of 68%, and negative predictive value of 89%. There was no significant between-center variance in acute iFR ($p = 0.57$), follow-up iFR ($p = 0.38$), or difference between follow-up iFR and acute iFR ($p = 0.25$).

TABLE 3 Acute and Follow-Up Instantaneous Wave-Free Ratio

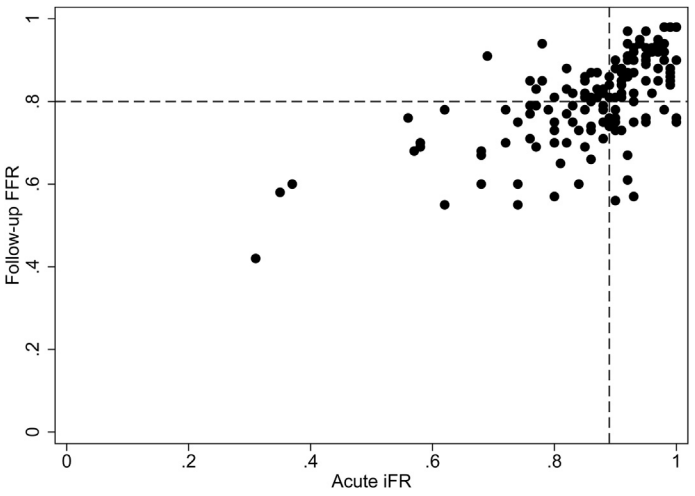
	Acute iFR		
Follow-Up iFR	**≥0.90**	**<0.90**	**Total**
≥0.90	63	24	87
<0.90	8	52	60
Total	71	76	147

iFR = instantaneous wave-free ratio.

Acute iFR measurements are plotted against follow-up FFR measurements in Figure 2 and cross-tabulated in Tables 4 and 5. With follow-up FFR ≤0.80 as reference, acute iFR had sensitivity of 76%, specificity of 68%, positive predictive value of 67%, and negative predictive value of 77%. With follow-up FFR <0.75 as reference, acute iFR had sensitivity of 83%, specificity of 58%, positive predictive value of 38%, and negative predictive value of 91%.

We identified 8 lesions in 8 patients with acute iFR ≥0.90 and follow-up iFR <0.90. Among these, 6 were in the left anterior descending coronary artery including diagonal branches, 1 was in the left circumflex coronary artery including obtuse marginal branches, and 1 was in the right coronary artery. In 7 of these lesions, follow-up iFR was in the range of 0.86 to 0.89. In 1 lesion follow-up iFR was 0.77.

FIGURE 2 Acute Instantaneous Wave-Free Ratio and Follow-Up Fractional Flow Reserve



Scatterplot of acute instantaneous wave-free ratio (iFR) and follow-up fractional flow reserve (FFR). The **vertical line** at iFR = 0.89 indicates the border between significant (<0.90) and nonsignificant (≥0.90) lesions. The **horizontal line** at FFR = 0.80 indicates the border between significant (≥0.80) and nonsignificant (>0.80) lesions.

The patient with this lesion reported unstable symptoms between acute and follow-up angiography, and follow-up angiography showed clear signs of rapid lesion progression.

We recognized 24 lesions in 23 patients with acute iFR <0.90 and follow-up iFR ≥0.90. Among these, 11 were in the left anterior descending coronary artery including diagonal branches, 8 were in the left circumflex coronary artery including obtuse marginal branches, and 5 were in the right coronary artery.

TIMING OF FOLLOW-UP AND iFR AGREEMENT. Figure 1C illustrates the relation between the difference between acute and follow-up iFR (follow-up − acute) and time between acute and follow-up iFR. Overall, the median difference in iFR was 0.01 (IQR: −0.01 to 0.06); that is, follow-up iFR was higher than acute iFR (sign test $p < 0.0001$). Median time from acute assessment to follow-up assessment was 16 (IQR: 5 to 32 days).

Examining the plot in Figure 1C, the differences between acute and follow-up iFR were distributed more evenly around zero with shorter intervals between acute and follow-up iFR compared with longer intervals where follow-up iFR was more often higher than acute iFR. When follow-up iFR was performed within 16 days (n = 73), the median difference was 0.01 (IQR: −0.02 to 0.06; sign test p = 0.11), and classification agreement between acute and follow-up iFR was 86% (63 of 73). When follow-up iFR was performed after ≥16 days (n = 74), the median difference was 0.03 (IQR: 0.00 to 0.06; sign test $p < 0.0001$), and classification agreement between acute and follow-up iFR was 70% (52 of 74). When follow-up iFR was performed within 5 days (n = 35) (i.e., a time interval equivalent to in-hospital reevaluation), the median difference was 0.00 (IQR: −0.02 to 0.07; sign test p = 1.00), and classification agreement between acute and follow-up iFR was 89% (31 of 35). However, when follow-up was performed after ≥5 days, the median difference was 0.02 (IQR: −0.04 to 0.06; sign test $p < 0.0001$), and classification agreement between acute and follow-up iFR was 75% (84 of 112). See Online Tables 1 to 4 for cross-tabulation according to time interval between acute and follow-up iFR.

TABLE 4 Acute Instantaneous Wave-Free Ratio and Follow-Up Fractional Flow Reserve

	Acute iFR		
Follow-Up FFR	**≥0.90**	**<0.90**	**Total**
>0.80	54	25	79
≤0.80	16	51	67
Total	70	76	146

Abbreviations as in Table 2.

TABLE 5 Acute Instantaneous Wave-Free Ratio and Follow-Up Fractional Flow Reserve

	Acute iFR		
Follow-Up FFR	**≥0.90**	**<0.90**	**Total**
≥0.75	64	47	111
<0.75	6	29	35
Total	70	76	146

Abbreviations as in Table 2.

DISCUSSION

The findings of the present study are as follows: 1) in patients with STEMI, iFR assessment of nonculprit lesions immediately after treatment of the culprit lesion was feasible; 2) classification agreement between acute and follow-up iFR was high when acute iFR was ≥0.90 but only moderate when acute iFR was <0.90; and 3) acute iFR was, overall, lower than follow-up iFR. With shorter time intervals between acute and follow-up iFR, the differences between acute and follow-up iFR were minor, whereas the differences between acute and follow-up iFR increased with longer time intervals. This latter finding suggests that inherent physiological

disarrangements during STEMI may contribute to classification disagreement.

iFR FOR ACUTE ASSESSMENT OF FUNCTIONAL SIGNIFICANCE OF NONCULPRIT STENOSES IN STEMI. Previous studies have reported agreement of approximately 80% between iFR and FFR in patients in stable condition when comparing the revascularization decision by these methods using an iFR cutoff of <0.90 and an FFR cutoff of ≤0.80 (11). In patients in stable condition, disagreement between the methods is most commonly detected in the intermediate range close to the dichotomous cutoff values (11). Despite these classification disagreements between iFR and FFR, 2 large recent trials have reported equal patients outcomes with iFR- and FFR-guided PCI, with fewer stents used with iFR-guided PCI (16,17).

In our study in patients with STEMI with nonculprit lesions, 8 nonculprit lesions with acute iFR ≥0.90 had changed to <0.90 at follow-up. Of these, 7 changed to iFR values just below the cutoff. These minor variations around the cutoff may reflect methodological variations related to, for example, wire positioning, minor drift within the accepted 0.02 limit, or differences in physiological parameters, such as coronary artery tone and flow (18). The only patient with a larger deviation from the <0.90 discrimination limit was a patient whose condition became unstable between acute and follow-up iFR. On angiography, this patient had rapid lesion progression, a well-known phenomenon in atherothrombosis (19). Our interpretation is that acute iFR reliably rules out nonculprit lesion significance.

Moreover, acute iFR correctly classified 87% of the stenoses with follow-up iFR <0.90. Again, the aforementioned methodological and physiological variations probably explain some of the cases with lack of agreement. It is, however, noteworthy that approximately one-third of the lesions that were hemodynamically significant by acute iFR were no longer hemodynamically significant when evaluated by follow-up iFR. Our results suggest that inherent physiological disarrangements during STEMI contribute to classification disagreement and results in a lower acute iFR and that these conditions do not change within the first 5 to 16 days after STEMI. Accordingly, we found that the reproducibility of iFR was high (89%) when reevaluated within 5 days but relatively low (70%) when patients were reexamined ≥16 days after STEMI. In previous studies, nonculprit stenosis severity was reported to be exaggerated during acute CAG compared with follow-up CAG (1,18,20).

Our findings have several potential clinical implications. First, acute iFR assessment of nonculprit lesions can be used to defer revascularization or staged follow-up evaluation. In our cohort, 48% of nonculprit stenoses had acute iFR ≥0.90, indicating that almost one-half of the patients could have been deferred from staged evaluation. Thus, acute iFR assessment of nonculprit lesions will most likely reduce the risk, costs, and patient-related concerns associated with staged follow-up procedures.

Second, acute iFR may be a tool to guide acute full revascularization. Although iFR guidance may be an improvement compared with angiography-guided intervention (6,7), our data suggest that acute iFR-guided intervention may lead to treatment of more intermediate lesions compared with a strategy with staged iFR-guided complete revascularization with follow-up ≥16 days after STEMI. Thereby, our data support the current recommendation of staged reevaluation.

Third, iFR seems to have acceptable reproducibility, while the physiological conditions, which apparently changed from acute to extended follow-up, may explain some of the observed disagreements.

ACUTE AND STAGED FULL REVASCULARIZATION OF PATIENTS WITH STEMI. The guidelines generally recommend staged reevaluation and treatment of nonculprit lesions (2–5). Meta-analyses of previous studies evaluating strategies for evaluation and treatment of nonculprit lesions suggest that staged evaluation and treatment of nonculprit lesions was superior to culprit lesion intervention only as well as to complete primary revascularization (21,22). This finding is supported by registry studies (23,24).

However, this recommendation is debated on the basis of recent trials in which primary complete revascularization was superior to culprit lesion revascularization only (6,7,25).

Our data provide a basis for prospective randomized studies comparing acute full revascularization with functional evaluation of nonculprit stenoses versus staged full revascularization with functional (invasive or noninvasive) evaluation of nonculprit stenoses.

STUDY LIMITATIONS. The cutoffs for iFR and FFR used in this study are based on previous studies and current clinical practice (4,11,12,14) and derived from patients in stable condition and may not be directly transferable to patients with STEMI. The lack of a true gold standard for ischemia detection is also a limitation.

Intentionally, the patients constituted a consecutive cohort. However, not all patients eligible for inclusion during the study period were actually

included. This reflects the clinical scenario including complex nonculprit lesion morphology, the need for heart team consultation, and overall procedure risk including total x-ray and contrast exposure that may have precluded inclusion (1). Also, the attending physician may have decided not to include some patients because of other inbound patients with STEMI during off hours.

Additional patient characteristics such as ejection fraction and peak troponin levels could have enhanced the patient population characterization. However, the collection of such data was not protocolized.

CONCLUSIONS

Acute iFR evaluation appeared valid for ruling out significant nonculprit stenoses in patients with STEMI. Time interval from acute to follow-up iFR had a substantial influence on classification agreement, suggesting that inherent physiological disarrangements during STEMI may contribute to classification disagreement.

ADDRESS FOR CORRESPONDENCE: Dr. Troels Thim, Aarhus University Hospital, Department of Cardiology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. E-mail: troels.thim@clin.au.dk.

PERSPECTIVES

WHAT IS KNOWN? Nonculprit stenoses are frequently encountered in patients with STEMI. Although guidance of coronary intervention with pressure wire assessment of stenoses improves outcomes in elective patients, this is currently not standard in the acute setting in patients with STEMI and nonculprit stenoses.

WHAT IS NEW? We evaluated acute pressure wire assessment of nonculprit stenoses using iFR in patients with STEMI. Acute iFR evaluation appeared to be a valid tool for ruling out significant nonculprit stenoses in patients with STEMI. Moreover, time interval from acute to follow-up iFR had a substantial influence on classification agreement.

WHAT IS NEXT? Future studies are needed to clarify whether iFR-guided acute intervention toward nonculprit stenoses improves the treatment of patients with STEMI.

REFERENCES

1. Thim T, Egholm G, Olesen KK, et al. Staged re-evaluation of non-culprit lesions in ST segment elevation myocardial infarction: a retrospective study. Open Heart 2016;3:e000427.

2. Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.

3. American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

4. Authors/Task Force Members, Windecker S, Kolh P, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

5. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2016;67:1235–50.

6. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115–23.

7. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963–72.

8. Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2010;3:1274–81.

9. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.

10. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59:1392–402.

11. Petraco R, Escaned J, Sen S, et al. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. EuroIntervention 2013;9:91–101.

12. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

13. Pijls NH, Fearon WF, Tonino PA, et al. 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;56:177–84.

14. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.

15. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol 2007;49:2105–11.

16. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional

flow reserve in PCI. N Engl J Med 2017;376:1824–34.

17. Gotberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017;376:1813–23.

18. Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization. J Am Coll Cardiol 2002;40:911–6.

19. Thim T, Hagensen MK, Bentzon JF, Falk E. From vulnerable plaque to atherothrombosis. J Intern Med 2008;263:506–16.

20. Donmez E, Koc M, Seker T, Icen YK, Cayli M. The assessment of non culprit coronary artery lesions in patients with ST segment elevated myocardial infarction and multivessel disease by control angiography with quantitative coronary angiography. Int J Cardiovasc Imaging 2016;32:1471–6.

21. Bainey KR, Mehta SR, Lai T, Welsh RC. Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. Am Heart J 2014;167:1–14.e2.

22. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. J Am Coll Cardiol Intv 2017;10:315–24.

23. Jensen LO, Thayssen P, Farkas DK, et al. Culprit only or multivessel percutaneous coronary interventions in patients with ST-segment elevation myocardial infarction and multivessel disease. EuroIntervention 2012;8:456–64.

24. Iqbal MB, Nadra IJ, Ding L, et al. Culprit vessel versus multivessel versus in-hospital staged intervention for patients with ST-segment elevation myocardial infarction and multivessel disease: stratified analyses in high-risk patient groups and anatomic subsets of nonculprit disease. J Am Coll Cardiol Intv 2017;10:11–23.

25. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665–71.

KEY WORDS complete primary revascularization, FFR, full revascularization, iFR, primary PCI

APPENDIX For supplemental tables, please see the online version of this paper.