Journal of the Society for Cardiovascular Angiography & Interventions 2 (2023) 101046

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Long-term Safety of Revascularization Deferral Based on Instantaneous Wave-Free Ratio or Fractional Flow Reserve

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ABSTRACT

Background: Deferral of coronary revascularization is safe whether guided by instantaneous wave-free ratio (iFR) or by fractional flow reserve (FFR). We aimed to assess long-term outcomes in patients deferred from revascularization based on iFR or FFR in a large real-world population.

Methods: From 2013 through 2017, 201,933 coronary angiographies were registered in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). We included all patients (n = 11,324) with at least 1 coronary lesion deferred from PCI during an index procedure using iFR (>0.89; n = 1998) or FFR (>0.80; n = 9326). The primary outcome was major adverse cardiac events (MACE) defined as the composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization. A multivariable-adjusted Cox proportional hazards model was used, with analysis for interaction of prespecified subgroups.

Results: Patients presented with stable angina pectoris (iFR 46.9% vs FFR 48.6%), unstable angina or non–ST-elevation myocardial infarction (iFR 37.7% vs FFR 33.1%), ST-elevation myocardial infarction (iFR 1.9% vs FFR 1.6%), and other indications (iFR 12.5% vs FFR 15.7%). The median follow-up was 2 years for both iFR and FFR groups. At the conclusion of the study, the cumulative MACE risks were 26.7 for the iFR group and 25.9% for FFR group. In the adjusted analysis, no difference was found between the 2 groups (adjusted hazard ratio: iFR vs FFR, 0.947; 95% CI, 0.84-1.08; $P = 39$). Consistent with the overall findings, the prespecified subgroups showed no interaction with the FFR/iFR results.

Conclusions: Deferral of revascularization showed similar long-term safety whether based on iFR or on FFR.

Introduction

Physiology-guided percutaneous coronary intervention (PCI) has become an established practice in the management of patients with chronic coronary syndrome[1] and is included in current coronary revascularization guidelines.[2] The DEFER[3] trial with a long-term follow-up[4] has shown that deferral of PCI in hemodynamically nonsignificant lesions is safe based on the fractional flow reserve (FFR). Furthermore, 2 large randomized clinical trials demonstrated that instantaneous wave-free ratio (iFR) and FFR are equally safe in guiding coronary revascularization[5,6] in patients in whom revascularization was deferred. The cumulative risk of major adverse cardiac events (MACE)[7] at 1 year was reported to be ~4%.[8] Clinical trials are often restricted to assessing efficacy in a narrowly selected patient population and time frame, and the adoption of novel treatment strategies outside of trials may not reflect the conditions under which they were evaluated. This may affect

Abbreviations: ACS, acute coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

Keywords: coronary physiology; deferral of revascularization; fractional flow reserve; instantaneous wave-free ratio; SWEDEHEART.

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https://doi.org/10.1016/j.jscai.2023.101046
Received 19 March 2023; Received in revised form 11 May 2023; Accepted 16 May 2023
Available online 4 June 2023

net clinical benefit,[9] and real-world data are necessary to gauge the effectiveness on patient outcome of novel management strategies outside the context of clinical trials.

The objective of this study was to compare iFR and FFR regarding long-term outcomes of coronary revascularization deferral in a large all-comer, real-world population from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.

Methods

Study design and population

This study was performed as a registry-based nonrandomized comparison of the outcome of iFR-based and FFR-based deferral of revascularization. The study is an all-comer study on patient-level. Consecutive patients from the SWEDEHEART registry who underwent coronary angiography from June 2013 through December 2017 were eligible for inclusion (Figure 1 and Central Illustration). SWEDEHEART is a prospective, national registry that reports on all patients undergoing coronary angiography in Sweden at 30 centers, and ≤150 variables are recorded for each patient and procedure,[10] with ~40,000 entries annually. Patients were included in the study if they had undergone coronary angiography during which indication for physiological assessment (index procedure) was established irrespective of indication for the index procedure. Patients who did not undergo intracoronary physiology were excluded. We excluded patients in whom both iFR and FFR measurements were performed. Thus, the final analysis included all patients in the SWEDEHEART registry who had at least 1 deferred coronary lesion during the index procedure, defined as a lesion deemed suitable for physiological assessment with iFR value of >0.89 or FFR of >0.80 and without subsequent ad hoc or planned revascularization. Ethical approval for this study was obtained from the local ethics committee before study initiation.

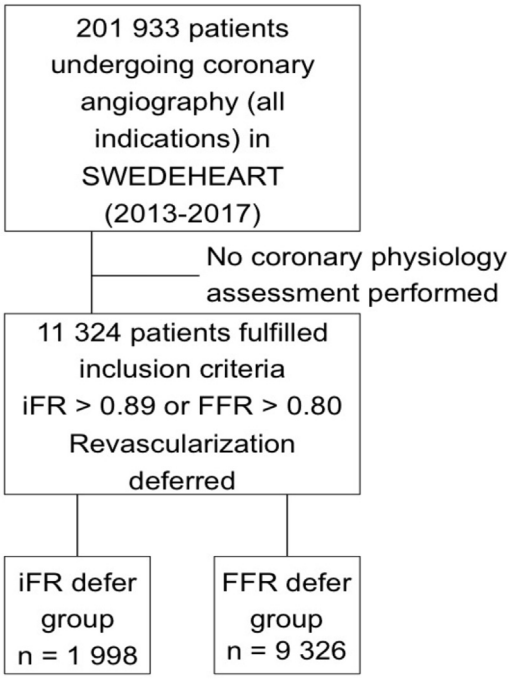


Figure 1.
Study design. From 201,933 patients in the SWEDEHEART registry between 2013 and 2017, 11,324 were included in the final analysis. No patients were lost to follow-up. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

Outcome definition and sampling

The primary end point was MACE, defined as a composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization during the study period. Secondary outcomes were the individual components of the primary end point. Nonfatal myocardial infarction and unplanned revascularization data were obtained from the SWEDEHEART registry.[10] In brief, all patients undergoing coronary angiography or admitted owing to myocardial infarction to a coronary care unit in Sweden are prospectively recorded in the SWEDEHEART database. The definition of myocardial infarction follows the universal definition of myocardial infarction, and the data are entered by a dedicated nurse and monitored by the SWEDEHEART registry, thus ensuring validity of the data. Data on death are obtained by linking the unique Swedish personal identification number with other public registries. All patients were tracked until the end of 2017 with no loss to follow-up.

Statistical analysis

Continuous variables are presented as median (interquartile range) and proportions as counts and percentages. Kaplan-Meier curves were used to visualize failure curves over time and comparisons made with the log-rank test. A Cox proportional hazards model adjusted for age, sex, smoking, procedure indication, and year of index procedure was used to compare the primary outcome of the iFR group with that of the FFR group. Two sensitivity analyses were conducted: (1) excluding patients who underwent PCI during the index procedure and (2) excluding patients who underwent the index procedure for other indications (eg, heart failure, heart transplant surveillance, arrhythmia, and heart valve disease). The prespecified subgroups age, sex, hypertension, hyperlipidemia, diabetes, smoking, and procedure indication were tested for interaction with FFR and iFR. All statistical analyses were performed using STATA version 15 (StataCorp). A 2-sided P value of <.05 was considered statistically significant.

Results

Patients

During a 5-year period from 2013 through 2017, 201,933 coronary angiographies were recorded in the SWEDEHEART registry. A total of 11,324 patients met the inclusion criteria, with 1998 in the iFR group and 9326 in the FFR group (Figure 1). Patient baseline characteristics are summarized in Table 1. No patients were lost to follow-up. The median age was 68 years in the iFR group and 69 years in the FFR group ($P = .30$). In the iFR group, 69.8% were male sex, compared with 68.6% in the FFR group ($P = .29$). The median creatinine level was 81 μmol/L in both groups ($P = .29$). The indications to perform physiologic assessment were as follows: stable angina pectoris (iFR 46.9% vs FFR 48.6%), unstable angina or non–ST-elevation myocardial infarction (iFR 37.7% vs FFR 33.1%), ST-elevation myocardial infarction (iFR 1.9% vs FFR 1.6%), and other indications (iFR 12.5% vs FFR 15.7%) (P-independence = .001; distribution of recorded iFR and FFR values are show in Supplemental Fig. S1). Most of the patients presented with angiographic nonsignificant lesions (<50% stenosis severity) or 1-vessel or 2-vessel disease without left main disease (Supplemental Table S1). Smokers were overrepresented in the

Table 1. Baseline characteristics

	iFR (n = 1998)	FFR (n = 9326)	*P*	% Missing
Male sex	1394 (69.8)	6393 (68.6)	.286	0
Age, y	68 (61-75)	69 (61-75)	.295	0
Creatinine, μmol/L	81 (70-94)	81 (69-94)	.289	9.6
Indication			<.001	1
Stable angina	936 (46.9)	4530 (48.6)		
STEMI	37 (1.9)	153 (1.6)		
Other	250 (12.5)	1461 (15.7)		
NSTEMI/unstable angina	754 (37.7)	3088 (33.1)		
Year			<.001	0
2013	52 (2.6)	914 (9.8)		
2014	291 (14.6)	1667 (17.9)		
2015	597 (29.9)	2000 (21.5)		
2016	490 (24.5)	2326 (24.9)		
2017	568 (28.4)	2419 (25.9)		
Smoking			<.001	3.4
Never	750 (37.5)	3767 (40.4)		
Previous smoker	915 (45.8)	4019 (43.1)		
Current smoker	306 (15.3)	1187 (12.7)		
Unknown	27 (1.4)	353 (3.8)		
Diabetes	452 (22.6)	2224 (23.9)	.112	0.9
Hypertension	1498 (75.0)	7018 (75.3)	.842	1.4
Hyperlipidemia	1384 (69.3)	6416 (68.8)	.439	1.4
Previous myocardial infarction	688 (34.4)	3027 (32.5)	.225	0
Previous PCI	788 (39.4)	3614 (38.8)	.660	0
Previous coronary artery bypass grafting	95 (4.8)	504 (5.4)	.538	0
Aspirin before procedure	1818 (91.0)	8443 (90.5)	.731	0.1
Ticagrelor before procedure	983 (49.2)	3488 (37.4)	<.001	0.1
Bivalirudin during procedure	58 (2.9)	101 (1.1)	<.001	0.1
Heparin during procedure	1875 (93.8)	8345 (89.5)	<.001	0.1
Artery approach			.006	0.8
Femoral	216 (10.8)	1182 (12.7)		
Radial	1774 (88.8)	8063 (86.5)		
PCI during index procedure			.008	0
Yes	420 (21)	1721 (18.4)		
No	1578 (78)	7605 (81.6)		

Values expressed as number (%) or median (IQR).
FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

iFR group (iFR 15.0% vs FFR 12.8%; $P < .001$), and there were significant differences in the annual proportions undergoing iFR vs FFR. There were proportionately more patients prescribed ticagrelor before procedure in the iFR group. Although, overall, 19% of the patients underwent concomitant PCI during the index procedure (Table 1 and Supplemental Table S2), there was a small but significantly higher proportion in the iFR group (the distribution of disease is summarized in Supplemental Table S1). We also observed minor but significant differences in the use of bivalirudin and heparin during the index procedure and in the use of radial approach (Table 1).

Outcome

The median follow-up was 2 years for both the iFR and FFR groups. At 1 year, the cumulative MACE risk for iFR was 9.4% and 9.9% ($P = .51$) for FFR, and the cumulative MACE risk at the end of the study period was 26.7% for iFR and 25.9% for FFR ($P = .27$) (Table 2). Kaplan-Meier failure curves for the long-term composite outcome for the iFR and FFR groups (Figure 2) did not reveal any difference between the 2 groups (unadjusted). In the adjusted survival analysis, we found no difference in the MACE hazard ratio (death, myocardial infarction, or unplanned revascularization) between the 2 groups during the long-term follow-up (adjusted hazard ratio: iFR vs FFR, 0.947; 95% CI, 0.84-1.08; $P = .39$). Moreover, both the 1-year and the long-term cumulative risks of the individual components of the composite primary end point (mortality, myocardial infarction, and unplanned revascularization) did not differ between the groups (Figure 3A-C; Table 2). The sensitivity analyses yielded findings consistent with the primary analysis, excluding patients who underwent PCI during the index procedure, yielded an adjusted MACE hazard ratio between iFR and FFR groups of 0.907 (95% CI, 0.79-1.05; $P = .19$; n = 9183)

Subgroup analysis

The analysis of the prespecified subgroups did not reveal significant interactions except for patients with stable angina, demonstrating

Table 2. Cumulative risks of primary and secondary outcomes at 1 and 4 years

	1 year			4 years		
	iFR	FFR	*P* (log-rank)	iFR	FFR	*P* (log-rank)
MACE	9.4	9.9	0.507	26.7	25.9	0.269
Death	2.5	2.3	0.736	10.7	9.6	0.889
Myocardial infarction	0.9	1.1	0.292	3.1	3.0	0.436
Unplanned revascularizton	7.1	7.6	0.457	17.4	18.1	0.338

Cumulative risk (in percentages from the Kaplan-Meier analysis) of the primary outcome of MACE, defined as the composite of all-cause mortality, nonfatal myocardial infarction, or unplanned revascularization, and the individual components of the primary outcome at 1 and 4 years. *P* value for difference is shown for the log-rank test.
FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MACE, major adverse cardiac events.

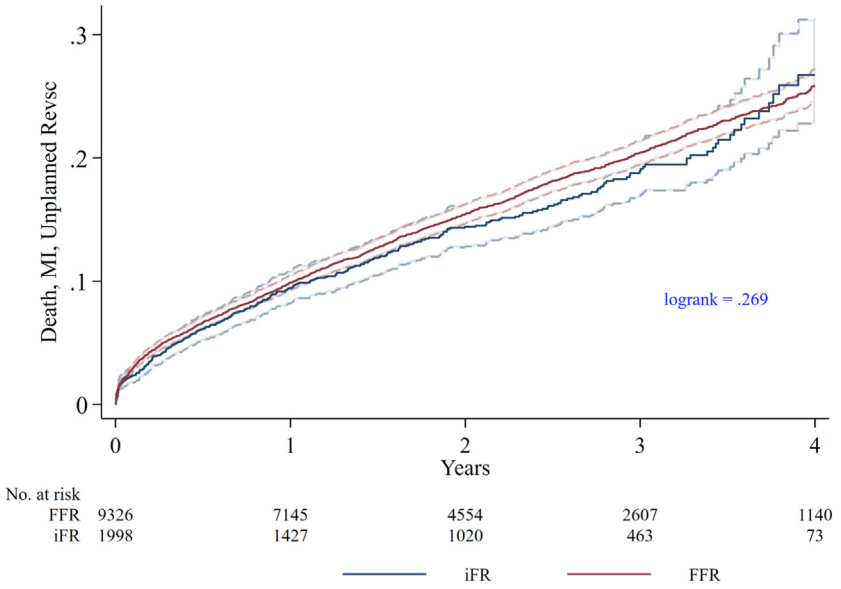


Figure 2.

Cumulative risk of the primary end point (death, myocardial infarction, or unplanned revascularization in patients deferred from revascularization). Kaplan-Meier failure curves showing the composite end point of death, myocardial infarction, or unplanned revascularization during the long-term follow-up in patients deferred from revascularization based on iFR or FFR. Dotted lines show the 95% CIs. FFR, fractional flow reserve; iFR. instantaneous wave-free ratio.

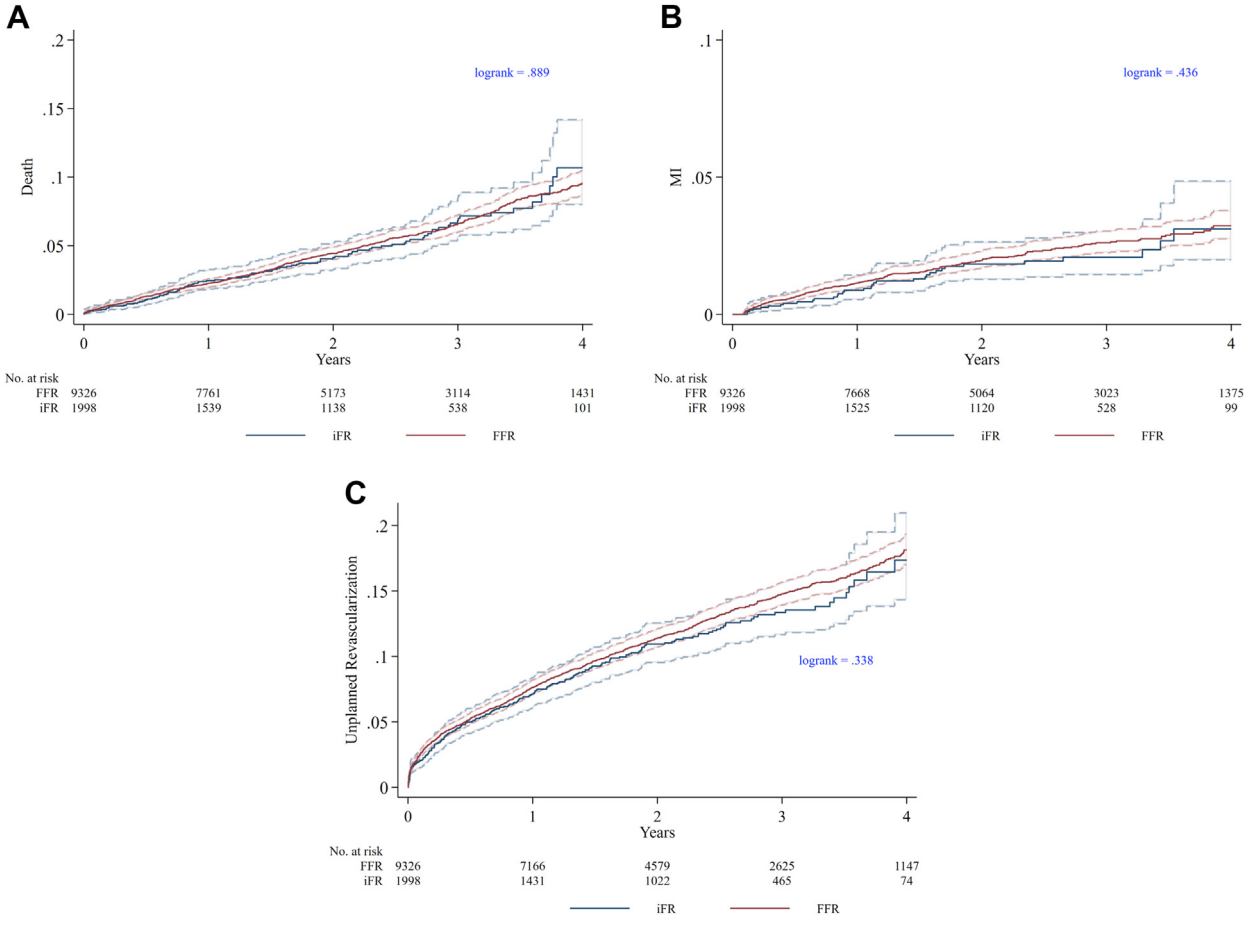


Figure 3.

Kaplan-Meier failure curves for mortality, myocardial infarction, and unplanned revascularization in patients deferred from revascularization based on iFR or FFR. (**A**) Long-term follow-up for death. (**B**) New myocardial infarction during the long-term follow-up. (**C**) Unplanned revascularization during the long-term follow-up. Dotted lines show the 95% CIs. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MI, myocardial infarction.

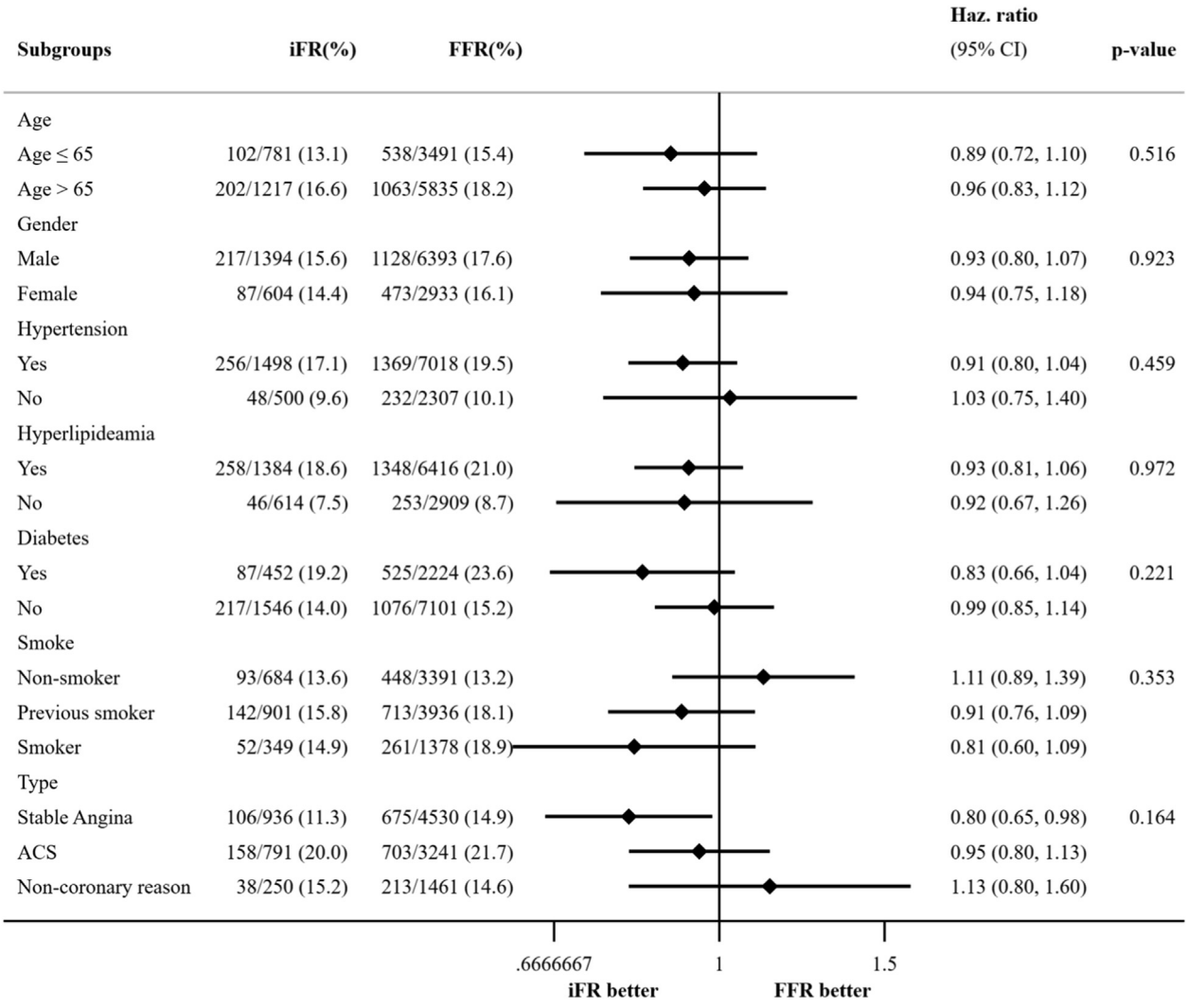


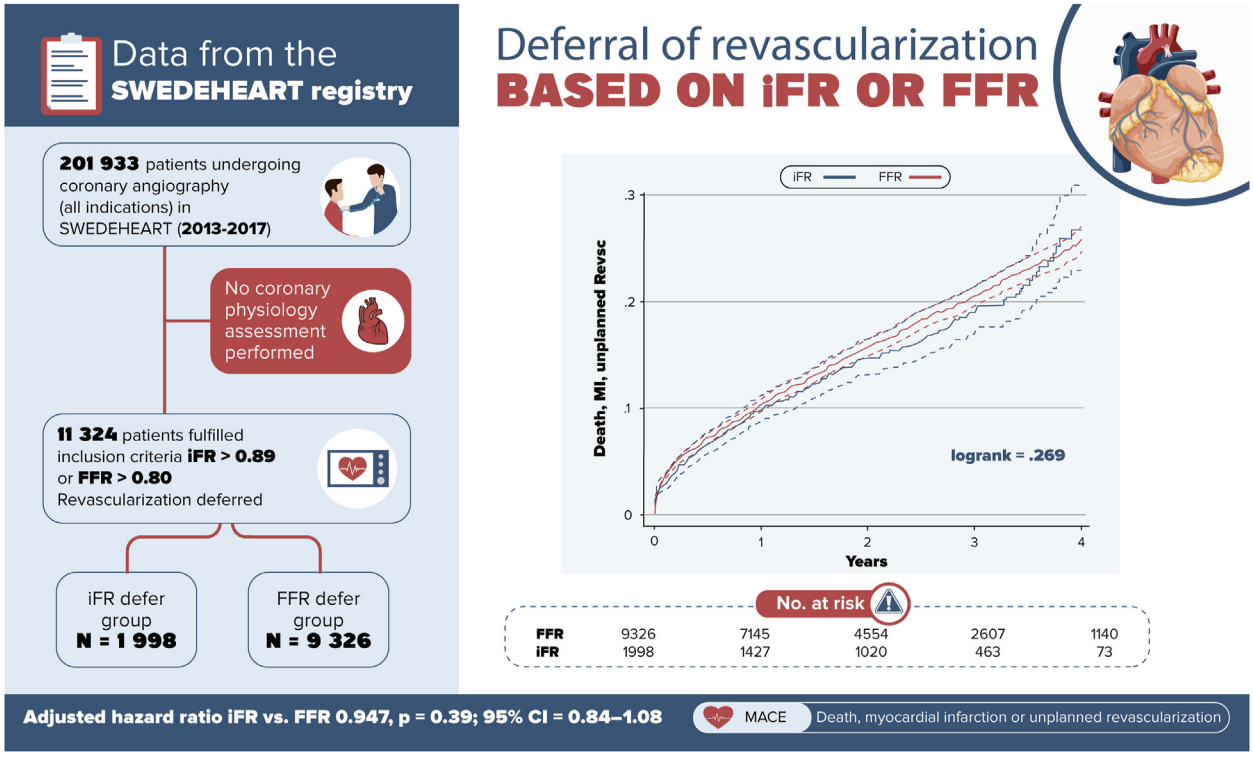
Figure 4.
Subgroup analysis. Forest plot showing the interaction of prespecified subgroups age, sex, hypertension, hyperlipidemia, diabetes, smoking, and indication with FFR vs iFR. ACS, acute coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

consistency with the overall findings (Figure 4). Although there was no overall difference found between iFR and FFR, we performed an exploratory analysis in the stable angina subgroup and found an adjusted hazard ratio of the composite end point at 4 years of 0.835 (95% CI, 0.68-1.027; iFR vs FFR), with a *P* value of .088, suggesting no difference when adjusting for known confounders.

Discussion

This study examined the safety of deferring revascularization based on intracoronary physiology measurements from a large, unselected cohort of patients with a long-term follow-up using either iFR or FFR. The DEFER[3] trial established the basis for intracoronary physiology-guided revascularization because it showed that deferral of PCI is safe in patients with intermediate coronary lesions and no ischemia documented by FFR. A recent meta-analysis of 19 studies comprising 3097 patients corroborated these findings.[7] When the iFR-SWEDEHEART and DEFINE-FLAIR trials were concluded, showing noninferiority of an iFR-based revascularization strategy versus an FFR-based strategy, there was a larger proportion of patients being deferred from revascularization based on iFR versus FFR.[5,6] With a numerical but nonsignificant number of excess deaths in the iFR group from both trials, it has been a topic of scrutiny if deferral of PCI based on iFR should be considered as safe as deferral based on FFR.[11] A pooled analysis of all deferred patients from both studies (N =2130 patients; iFR group = 1117 patients; FFR group =1013 patients) could not find any difference in the safety of deferral between iFR and FFR with a follow-up of 1 year.[8] Furthermore, 5-year outcomes after the iFR-SWEDEHEART trial were published recently, showing no difference in outcome between an iFR-based revascularization strategy versus an FFR-based strategy.[12] In this study, we examined 11324 patients with a coronary physiology registration, selected from a cohort of all 201933 angiographies performed in Sweden during a 4-year period, with PCI deferred based on either iFR (>0.89; n = 1998) or FFR (>0.80; n = 9326). The data underlying this study are pooled from all 30 PCI centers in Sweden contributing to the SWEDEHEART registry irrespective of hospital size, academic or university affiliation, or operator skill. With a follow-up period exceeding that of iFR-SWEDEHEART and DEFINE-FLAIR, our findings in a real-world population strongly support equal safety of deferring coronary revascularization whether based on iFR or FFR.

Randomized trials are often limited to a narrow, highly selected patient population. In a cross-sectional study of 220 clinical trials published in 2017, only 15% could be replicated using available real-world data,[9] limiting generalizability from clinical trials to a real-world setting.[13] Thus, the net effect of an intervention in a randomized trial



Central Illustration.
Study overview and main findings. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

could be underestimated or overestimated. Therefore, there is a need for real-world data to complement clinical trials when implementing novel therapies. In this study, we found an overall similar outcome between iFR-based and FFR-based deferral strategies compared with that of the aforementioned clinical trials. However, we also found a substantially higher cumulative MACE risk in our study population in both groups (Table 2). In the previous trials, cumulative MACE risks were ~4% in deferred patients with a follow-up of 1 year, with a higher risk in patients presenting with acute coronary syndrome (ACS) versus stable angina.[8] We found a cumulative risk of MACE more than twice as high, that is, 9%-10% at 1 year (Figure 1; Table 2), in our study for both the iFR and the FFR groups. This may be explained by the fact that patients in this study were older (median age, 69 years), and thus with an inherent poorer prognosis, than patients in DEFINE-FLAIR[5] and iFR-SWEDEHEART[6] (median age, ~66 years). The increased risk seen in our study may also be attributed to the fact that ~40% of the patients in this study recorded ACS as presenting indication, compared with ~20% in DEFINE-FLAIR and iFR-SWEDEHEART. We cannot exclude other reasons for the discrepancies in the MACE risks, and further follow-up of the clinical trials are needed to evaluate long-term differences in deferral risks between the present study and DEFINE-FLAIR and iFR-SWEDEHEART.

Potential discrepancies in the performance of iFR and FFR have been the subject of scrutiny, and patient characteristics showing dissimilarities in iFR and FFR results have been examined; with some suggestion of possible influence of sex, vessel size, and presence of diabetes mellitus.[7,14] In this study, we did not find an interaction of age, sex, hypertension, hyperlipidemia, diabetes, smoking, or procedure indication with FFR or iFR on the overall results (Figure 4). Although the exploratory subgroup analysis did point to a better outcome with deferral based on iFR rather than FFR for patients with stable angina (Figure 4, bottom of the Forest plot), an adjusted analysis could not confirm this hypothesis-generating finding. Of notice, we also included patients with other indications than stable angina or ACS, such as heart failure, heart transplant surveillance, arrhythmia, and heart valve disease, underscoring the heterogeneity of the study.

In summary, guidelines recommend the use of pressure-derived ischemia measurements to guide revascularization in intermediate angiographic lesions.[2] Despite 2 large randomized trials showing noninferiority of iFR compared with FFR, there has been a query regarding the safety of patients being deferred from revascularization with an iFR-based strategy versus an FFR-based strategy. In agreement with DEFINE-FLAIR and iFR-SWEDEHEART, this study of a large real-world population reiterated equal safety of deferral of revascularization based on iFR compared with FFR up to 4 years after the index examination. The observed cumulative MACE risks for both iFR and FFR groups in our study were twice those of the aforementioned clinical trials, which should warrant consideration when deferring patients from revascularization using coronary physiology in the setting of ACS.

Limitations

There are several limitations to this study. The study included patients in whom invasive coronary physiology could be performed, likely omitting patients with heavy calcification or tortuous vessels. Continuous pressure measurements were transformed to a dichotomous variable guiding revascularization. There may have been factors weighed in the decision to defer revascularization that were not considered. Owing to the observational nature of registry data, there may have been unmeasured confounders; however, we applied robust statistical methods to adjust for known confounders. We could not include information on left ventricular ejection fraction because this is not recorded in patients in SWEDEHEART undergoing coronary angiography based on stable angina.

Conclusions

In this large, real-world, nationwide registry study, deferral of revascularization has similar safety over the long-term whether based on iFR or on FFR. The findings are consistent with findings from recent trials and current guidelines.

Acknowledgments

The authors thank the staff members of all coronary care units and PCI centers in Sweden for their work collecting data to the SWEDEHEART registry. The authors also thank the SWEDEHEART organization and its committees for their work upholding the framework and infrastructure in the registry.

Declaration of competing interest

All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. Matthias Götberg reports receiving lecture fees from Philips Volcano, consulting fees and lecture fees from Boston Scientific, and fees for serving on an advisory board from Medtronic. No other disclosures pertaining to this article were reported.

Funding sources

This study was supported by the Swedish Heart and Lung Foundation, Swedish Scientific Research Council, Knut and Alice Wallenberg Foundation, ALF, the Bundy Academy, and Skåne University Hospital.

Ethics statement and patient consent

The local ethical review board approved this study. All patients in SWEDEHEART are informed about their participation in the registry and may at any time without inquiry decide to opt out of the registry.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101046.

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