Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

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BACKGROUND The instantaneous wave-free ratio (iFR) is an index used to assess the severity of coronary artery stenosis. The index has been tested against fractional flow reserve (FFR) in small trials, and the two measures have been found to have similar diagnostic accuracy. However, studies of clinical outcomes associated with the use of iFR are lacking. We aimed to evaluate whether iFR is noninferior to FFR with respect to the rate of subsequent major adverse cardiac events.

METHODS We conducted a multicenter, randomized, controlled, open-label clinical trial using the Swedish Coronary Angiography and Angioplasty Registry for enrollment. A total of 2037 participants with stable angina or an acute coronary syndrome who had an indication for physiologically guided assessment of coronary-artery stenosis were randomly assigned to undergo revascularization guided by either iFR or FFR. The primary end point was the rate of a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months after the procedure.

RESULTS A primary end-point event occurred in 68 of 1012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates, 0.7 percentage points; 95% confidence interval [CI], − 1.5 to 2.8; P = 0.007 for noninferiority; hazard ratio, 1.12; 95% CI, 0.79 to 1.58; P = 0.53); the upper limit of the 95% confidence interval for the difference in event rates fell within the prespecified noninferiority margin of 3.2 percentage points. The results were similar among major subgroups. The rates of myocardial infarction, target-lesion revascularization, restenosis, and stent thrombosis did not differ significantly between the two groups. A significantly higher proportion of patients in the FFR group than in the iFR group reported chest discomfort during the procedure.

CONCLUSIONS Among patients with stable angina or an acute coronary syndrome, an iFR-guided revascularization strategy was noninferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac events at 12 months.

即時冠狀動脈流速差 (instantaneous wave-free ratio) 和血流儲備分數 (fractional flow reserve) 導引在經皮冠狀動脈介入治療 (percutaneous coronary intervention) 的角色

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冠狀動脈血管重建術（revascularization）對於具有血流動力學重要性的狹窄病灶（hemodynamically important）才有必要。許多大型隨機臨床試驗已證實血流儲備分數（fractional flow reserve, FFR）對於偵測具有血流動力學重要性的狹窄病灶的能力優於血管造影，且血流儲備分數導引（FFR-guided）的冠狀動脈血管重建術能改善臨床預後。血流儲備分數的測量是利用壓力導絲（pressure guidewire）在投予藥物 adenosine 達到充血（hyperemia）狀態下，測量狹窄病灶遠近兩端的壓力差。

許多研究已證實，靜止指數（resting indexes）（未投予藥物測得的靜止壓力）對於心肌缺血有與血流儲備分數相似的診斷準確性。及時冠狀動脈流速差（instantaneous wave-free ratio, iFR）是近年來發展用以評估狹窄嚴重性的生理指數（physiological index）。它的計算方式是測量在舒張分期中，微血管阻力最低且穩定的時期，病灶兩端的靜止壓力差。它的好處是不需投藥就能得到即時的病灶評估結果。雖然及時冠狀動脈流速差測得的結果與血流儲備分數有點差異，但許多大型的臨床試驗並未證實這樣的差異是否有臨床意義。這個試驗的目的是研究依照及時冠狀動脈流速差或血流儲備分數等生理評估具有是否須血管重建術治療的患者臨床預後是否有所差異。

方法

臨床試驗設計

iFR-SWEDEHEART (The Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) 是個多中心，隨機控制開放性的研究，並透過國家登記來收集病人的資料與追蹤。所有的病人都登錄在 SCAAR（Swedish Coronary Angiography and Angioplasty Registry）試驗中。研究包含了 30 個瑞典和 1 個冰島的冠狀動脈介入治療中心。

病人族群

收錄個案包含穩定性心絞痛，不穩定心絞痛及非 ST 段上升心肌梗塞同時合併眼視評估冠狀動脈約 40%~80% 左右狹窄的病人；懷疑穩定心絞痛的病人，將評估所有的病灶；不穩定心絞痛或是非 ST 段上升心肌梗塞的病人，只評估非致病病灶（nonculprit lesion）。

隨機分配

經由 SCAAR 網路平台，隨機分配病人接受及時冠狀動脈流速差與血流儲備分數。

侵入手術

兩族群在壓力導絲評估病灶前，都會接受經冠狀動脈注射硝酸甘油（nitroglycerin）。病灶若有 80% 以上的狹窄，將直接處理而不評估生理指數。只有狹窄介於 40%~80% 才會使用及時冠狀動脈流速差或是血流儲備分數。血流儲備分數都會經冠狀動脈（intracoronary）或是靜脈給予藥物達到充血狀態。血管重建術（revascularization）只在 iFR ≦ 0.89 或是 FFR ≦ 0.80 的情況下才會進行。

資料收集，終點評估（end points），追蹤

初級終點（primary end point）包含了所有原因的死亡（all cause mortality），非致命性的心肌梗塞，或是手術後 12 個月內非計畫性的再次血管重建（unplanned revascularization）。非計畫性的再次血管重建術定義為第一次手術過後，60 天內發生非預定的分期手術（staged procedure）。次級終點（secondary end points）

則包含了初級終點、手術中的胸悶、目標病灶的再次血管重建術（target-lesion revascularization）、支架內血栓及再狹窄。

統計分析

所有的終點評估都基於實際治療分析（per-protocol）的理論。組間不同的事件史（time-to-event）差異則使用對數一等級（log-rank）分析。Kaplan-Meier 評估組間初級事件發生率則是透過 Machin&Gardner 過去提出的方法。若是 95% 信賴區間的上界低於 3.2 百分點，及時冠狀動脈流速差則認為不劣於血流儲備分數。風險比值的計算是利用 Cox 比例風險模式（Cox proportional-hazards models）。組間平均值差異則是透過雙尾學生 t 檢驗（two-tailed Student's t-test）。卡方檢定（Chi-square）或是費雪精確檢定（Fisher's exact test）則用來比較兩組比例的差異。若雙尾 p 值小於 0.05 則認定具有統計學上的意義。初級終點則利用比例風險模式做次族群間分析並運算得到交互作用 p 值（interaction p value），其以風險比值和 95% 信賴區間表示。

結果

基本資料及血管造影結果

這研究由 13 家瑞典醫院，1 家丹麥醫院及 1 家冰島醫院共同執行。研究期間從 2014 年五月至 2015 年十月，約 20.3% 病人起初以穩定心絞痛，不穩定心絞痛，或非 ST 段上升心肌梗塞病症表現。總計 2037 位病人，其中 1019 人接受及時冠狀動脈流速差，1018 人接受血流儲備分數。18 名病患因為錯誤族群分配、無法忍受藥物副作用、技術上問題或是其他種種原因而退出研究。剩餘 2019 名的結果如（圖一）所示。兩組間的危險因子、血管造影的適應症、冠狀動脈病變程度、臨床及基本特徵皆類似（如表一）。平均年紀為 68 歲，21.8% 的病人有糖尿病，62% 有穩定心絞痛，33% 之前有心肌梗塞病史。

手術相關的特徵如（表二）所示。及時冠狀動脈流速差共評估了 1568 個病灶（平均每位病人 1.55 個病灶），血流儲備分數則有 1436 個病灶（每位病人有 1.43 個病灶）（p=0.002）。及時冠狀動脈流速差測得的平均值 ± 標準差為 0.91±0.10，血流儲備分數是 0.82±0.10。在及時冠狀動脈流速差族群中，29.1% 的病灶具有血行動力重要性，在血流儲備分數族群則是 36.8%（p<0.001）。及時冠狀動脈流速差的族群中，536 位病人接受血管重建手術，血流儲備分數族群則有 569 位（p=0.11）。PCI 在接受血管重建手術的病人中佔了 81.4%。

初級終點

初級終點事件在及時冠狀動脈流速差的 1012 位病患族群中共有 68 位（6.7%），1007 位血流儲備分數病患中則有 61 位（6.1%）（差了 0.7 百分比；95% 信賴區間為 -1.5~2.8；p=0.007）（圖二）。事件發生比率的 95% 信賴區間上界落於 3.2 百分點的不劣性區間。使用非校正（unadjusted）Cox 回歸模型得到的風險比值為 1.12（95% 信賴區間為 0.79-1.58；p=0.53）（表三）。在次族群分析中，治療效果沒有顯著的異質性（heterogeneity）。

次級終點

12 個月後所有原因的死亡在兩組中，並沒有顯著差異。（及時冠狀動脈流速差族群有 15 位，其中 6 位死於心血管原因；血流儲備分數族群裡共有 12 位，其中有 6 位死於心血管原因。p=0.57）（表三）。兩組間的非致命性心肌梗塞，非計畫性的再次血管重建，目標血管的再次血管重建並無顯著差異。確定支架內血栓的病患在及時冠狀動脈流速差族群中有一位，在血流儲備分數族群中有 2 位。支架內再狹窄比例在及時冠狀動脈流速差族群有 1.9%，在血流儲備分數族群有 1.8%（p=0.87）。手術進行中，在及時冠狀動脈流速差族群裡有 3% 發生胸口不舒服，在血流儲備分數族群中則有 68.3%（p<0.001）。

討論

在穩定心絞痛，不穩定心絞痛或非 ST 段上升心肌梗塞的病人中，及時冠狀動脈流速差導引的血管重建術，在主要心血管事件（major adverse cardiac outcomes）中，並不差於血流儲備分數的族群，且較少有胸口不舒服的症狀。

及時冠狀動脈流速差的族群中有顯著較多的病灶接受評估。這可能是因為病患在接受血流儲備分數的藥物刺激時產生胸口不舒服症狀，導致醫師傾向不再評估其他血管病灶。這也暗示了血流儲備分數族群的

病人因為預期的藥物副作用影響並沒有完全遵照研究設計。

血流儲備分數族群有較多的病灶具有血流動力學的重要性，造成兩組置放的支架數目只有輕微的差異。兩組血流動力學的病灶差異可能來自於病灶的分類。過去的 80%~85% 的研究認定測得及時冠狀動脈流速差的值小於 0.89 具有臨床生理意義，但測量結果介於灰色地帶時，便容易產生意見分歧。然而，這樣的變異性對於預後並不具有特別重要的臨床意義，因為觀察到血流儲備分數數值接近 0.80 的病人，死亡率和心肌梗塞並沒有增加。數據顯示，及時冠狀動脈流速差和血流儲備分數測量病灶分類不同時，及時冠狀動脈流速差是比較精確的。在 JUSTIFY-CFR（Jointed Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve）的研究也發現有同樣的結果。血流儲備分數也容易高估病灶的嚴重程度，原因是因為充血狀態下即使正常的冠狀動脈血流也會造成壓力下降低於閥值。過去及時冠狀動脈流速差的相關研究已證實及時冠狀動脈流速差的診斷正確性是和血流儲備分數類似甚至更好。血流儲備分數的閥值定在 0.75 會比 0.80 有更好的心肌缺血關連性。

血流儲備分數導引的血管重建術從臨床預後，已證實優於只單純依賴血管造影的心導管手術。儘管有這些證據支持還有 American College of Cardiology Foundation—American Heart Association-Society for Cardiovascular Angiography and Interventions 的建議，血流儲備分數的臨床使用率仍偏低。部份的原因來自於藥物 Adenosine 造成的併發症。鑒於本研究的結果，及時冠狀動脈流速差因為不需使用藥物，大幅增加其測量病灶的使用率。

總結，適合評估病灶血管生理的病人，術後 12 個月發生主要心血管事件的比率上，及時冠狀動脈流速差導引的心導管並不劣於血流儲備分數導引的心導管手術。

Table 1. Baseline Characteristics of the Patients.*

Characteristic	iFR Group (N=1019)	FFR Group (N=1018)
Age — yr	67.6±9.6	67.4±9.2
Male sex — no. (%)	756 (74.2)	766 (75.2)
Body-mass index†	27.6±4.3	27.6±4.3
Indication for angiography — no. (%)		
Stable angina	632 (62.0)	632 (62.1)
Unstable angina	211 (20.7)	208 (20.4)
NSTEMI	176 (17.3)	178 (17.5)
Angina class — no./total no. with stable angina (%)‡		
I	153/632 (24.2)	121/632 (19.1)
II	355/632 (56.2)	343/632 (54.3)
III	49/632 (7.8)	74/632 (11.7)
IV	0	3/632 (0.5)
Missing data	75/632 (11.9)	91/632 (14.4)
Diabetes mellitus — no. (%)	232 (22.8)	213 (20.9)
Hypertension — no. (%)	730 (71.6)	710 (69.7)
Hyperlipidemia — no. (%)	733 (71.9)	704 (69.2)
Smoking status — no. (%)		
Never smoked	351 (34.4)	368 (36.1)
Former smoker	501 (49.2)	467 (45.9)
Current smoker	159 (15.6)	167 (16.3)
Missing data	8 (0.8)	16 (1.6)
Previous myocardial infarction — no. (%)	337 (33.1)	335 (32.9)
Previous percutaneous coronary intervention — no. (%)	429 (42.1)	425 (41.7)
Previous coronary-artery bypass grafting — no. (%)	49 (4.8)	43 (4.2)
Angiographic findings — no. (%)§		
Nonsignificant coronary artery disease	203 (20.0)	198 (19.4)
One-vessel disease	452 (44.3)	453 (44.5)
Two-vessel disease	256 (25.1)	267 (26.2)
Three-vessel disease	108 (10.6)	101 (9.9)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in baseline characteristics. FFR denotes fractional flow reserve, iFR instantaneous wave-free ratio, and NSTEMI non–ST-segment elevation myocardial infarction.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Angina was classified among the patients with stable angina according to the Canadian Cardiovascular Society functional classification; classes range from I to IV, with higher classes indicating greater limitations of physical activity owing to angina.

§ Significant coronary artery disease was defined as the presence of at least 50% stenosis. Classification of one-vessel, two-vessel, or three-vessel disease was based on visual estimation.

▲ 表 1

Table 2. **Procedural Characteristics in the Per-Protocol Population.***

Characteristic	iFR Group (N=1012)	FFR Group (N=1007)	P Value
Radial-artery approach — no. of patients (%)	841 (83.1)	811 (80.5)	0.13
Contrast material used per patient — ml			0.10
Median	110	115	
Interquartile range	80–155	80–160	
Procedure time — min†			0.09
Median	50.8	53.1	
Interquartile range	13.8–87.8	18.1–88.1	
Fluoroscopy time — min			0.57
Median	10.5	10.2	
Interquartile range	6.3–16.8	6.5–16.0	
Intravenous adenosine administered — no. of patients (%)	NA	695 (69.0)	
Total no. of lesions evaluated	1568	1436	
No. of lesions evaluated per patient	1.55±0.86	1.43±0.70	0.002
Hemodynamically important lesions — no. (% of total lesions evaluated)‡	457 (29.1)	528 (36.8)	<0.001
No. of hemodynamically important lesions per patient‡	0.45±0.71	0.52±0.68	0.05
Mean iFR	0.91±0.10	NA	
Mean iFR in hemodynamically important lesions‡	0.80±0.13	NA	
Mean FFR	NA	0.82±0.10	
Mean FFR in hemodynamically important lesions‡	NA	0.72±0.08	
Lesion complexity according to the ACC–AHA class — no./total no. of treated lesions (%)§¶			0.73
A	61/915 (6.7)	73/980 (7.4)	
B1	304/915 (33.2)	320/980 (32.7)	
B2	284/915 (31.0)	300/980 (30.6)	
C	139/915 (15.2)	165/980 (16.8)	
Missing data	127/915 (13.9)	122/980 (12.4)	
Lesions treated in the vessel — no./total no. of treated lesions (%)¶			0.68
Left main coronary artery	14/915 (1.5)	16/980 (1.6)	
Left anterior descending artery	434/915 (47.4)	469/980 (47.9)	
Left circumflex artery	176/915 (19.2)	179/980 (18.3)	
Right coronary artery	164/915 (17.9)	196/980 (20.0)	
Missing data	127/915 (13.9)	120/980 (12.2)	
Total no. of stents placed	698	787	
No. of stents placed per patient undergoing PCI	1.58±1.08	1.73±1.19	0.05
Stent length per patient — mm	34.2±21.9	36.8±24.5	0.10
Stent diameter — mm	2.97±0.47	3.01±0.49	0.27
Drug-eluting stents placed — no. (% of total stents placed)‖	696 (99.7)	770 (97.8)	0.50
PCI as primary revascularization procedure — no. of patients (%)	443 (43.8)	456 (45.3)	0.50
CABG as primary revascularization procedure — no. of patients (%)	93 (9.2)	113 (11.2)	0.13
Revascularization performed — no. of patients (%)	536 (53.0)	569 (56.5)	0.11

* Plus–minus values are means ±SD. The per-protocol population included all patients who underwent assessment for coronary-artery stenosis. CABG denotes coronary-artery bypass grafting, NA not applicable, and PCI percutaneous coronary intervention.
† Data on procedure time were available for only 904 patients.
‡ An iFR of 0.89 or lower and an FFR of 0.80 or lower indicated hemodynamically important stenosis.
§ Lesion complexity was classified according to the American College of Cardiology (ACC)–American Heart Association (AHA) classification; class A indicates a simple lesion, B1 and B2 a moderately complex lesion, and C a complex lesion.
¶ Treated lesions were lesions for which PCI was performed, including those that did not undergo physiologically guided assessment.
‖ Only second-generation drug-eluting stents were used.

▲ 表 2

Table 3. End Points at 12 Months in the Per-Protocol Population.

End Point	iFR Group (N=1012)	FFR Group (N=1007)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary end point: death from any cause, nonfatal myocardial infarction, or unplanned revascularization	68 (6.7)	61 (6.1)	1.12 (0.79–1.58)	0.53
Death from any cause	15 (1.5)	12 (1.2)	1.25 (0.58–2.66)	0.57
Nonfatal myocardial infarction	22 (2.2)	17 (1.7)	1.29 (0.68–2.44)	0.42
Unplanned revascularization	47 (4.6)	46 (4.6)	1.04 (0.69–1.57)	0.84
Target-lesion revascularization	29 (2.9)	27 (2.7)	1.21 (0.70–2.07)	0.49
Restenosis	19 (1.9)	18 (1.8)	1.05 (0.55–2.01)	0.87
Stent thrombosis*	1 (0.1)	2 (0.2)		
Chest discomfort during procedure				<0.001†
None	982 (97.0)	319 (31.7)		
Mild	26 (2.6)	316 (31.4)		
Moderate	2 (0.2)	285 (28.3)		
Severe	2 (0.2)	87 (8.6)		

* Stent thrombosis was defined as the presence of stent occlusion on angiography and an acute clinical presentation.
† P value was calculated by means of the Wilcoxon rank-sum test.

▲ 表 3

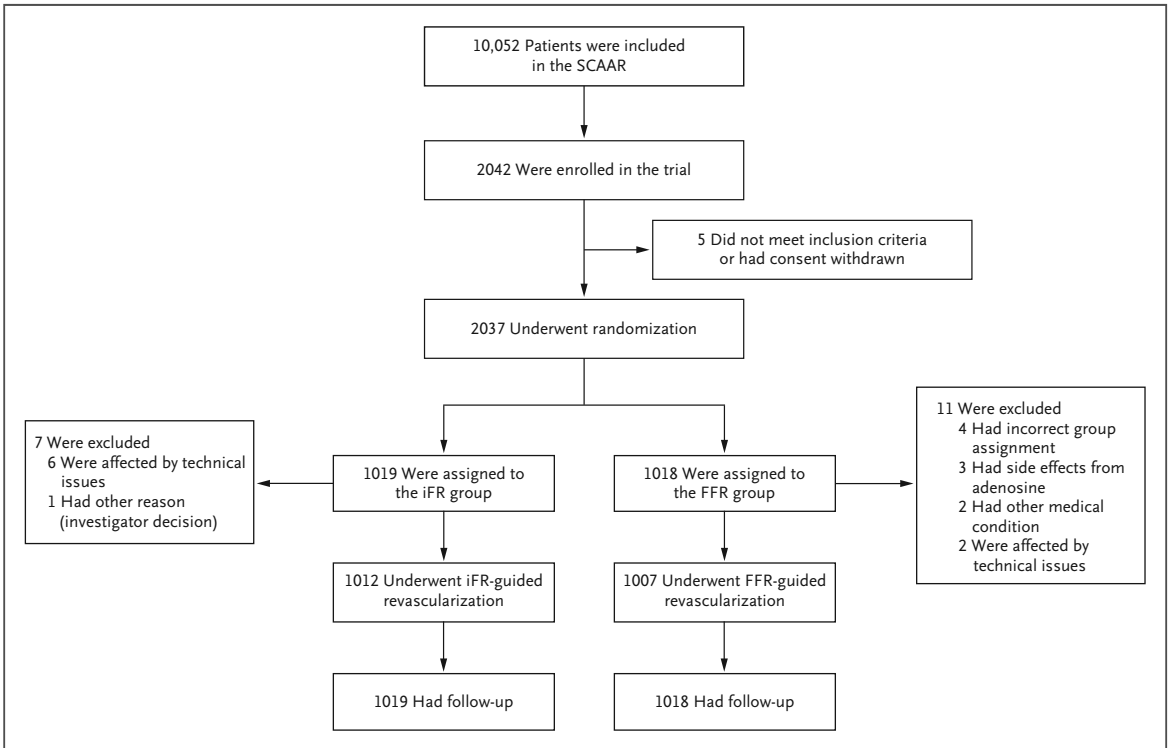
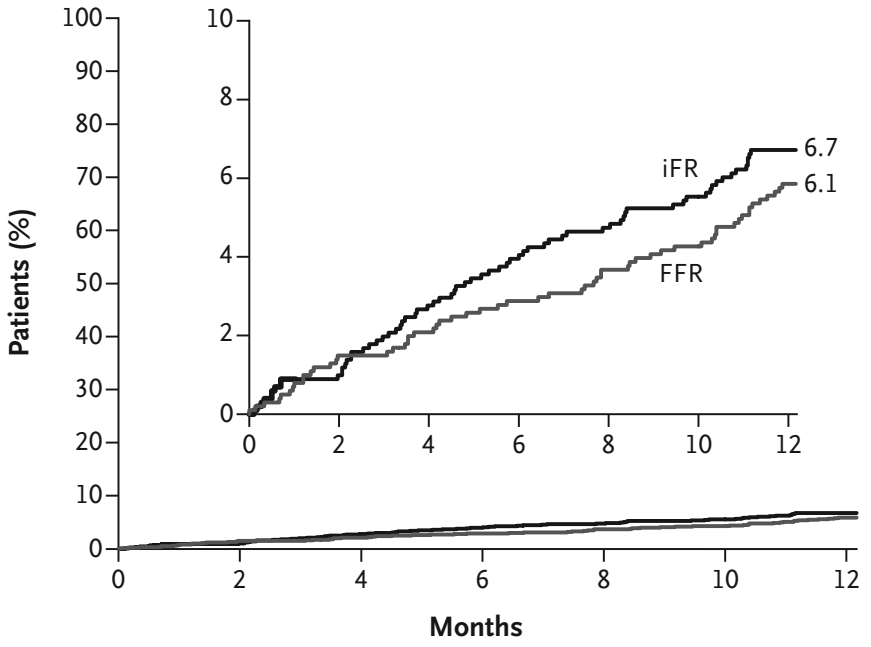


Figure 1. Enrollment, Randomization, and Follow-up.
FFR denotes fractional flow reserve, iFR instantaneous wave-free ratio, and SCAAR Swedish Coronary Angiography and Angioplasty Registry.

▲ 圖 1



No. at Risk

iFR	1012	1002	984	971	963	956	944
FFR	1007	990	984	976	968	961	946

Figure 2. Kaplan–Meier Curves for the Primary End Point.

Shown are Kaplan–Meier curves for the cumulative risk of the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months after the index procedure. The inset shows the same data on an enlarged y axis.

▲ 圖二