## INCLUSION AND EXCLUSION CRITERIA

### Inclusion criteria

DEFINE-FLAIR study

1. Age > 18 years.
2. Willing to participate and able to understand, read and sign the informed consent document before the planned procedure.
3. Eligible for coronary angiography and/or percutaneous coronary intervention.
4. Coronary artery disease in one or more native major epicardial vessels or their branches by coronary angiogram with visually assessed de novo coronary stenosis in which the physiological severity of the lesion is in question (typically 40-70% diameter stenosis).
5. Stable angina or ACS (non-culprit vessels only and outside of primary intervention during acute STEMI).

iFR-SWEDEHEART study

1. Provision of informed consent prior to any study specific procedures.
2. Patient must be ≥ 18 years old.
3. Patients with suspected stable angina pectoris or unstable angina pectoris/NSTEMI who are scheduled to undergo coronary angiography, and where there is an indication for physiology guided assessment of coronary lesions (recommend assessment of lesions with a stenosis grade of 40-80%).
4. In patients with suspected stable angina pectoris, any lesion may be assessed. In patients with unstable angina pectoris/NSTEMI only the non-culprit lesion may be assessed.

### Exclusion criteria

DEFINE-FLAIR study

1. Previous CABG with patent grafts to the interrogated vessel.
2. Significant left main stenosis (>50% narrowing).
3. Tandem stenoses separated by more than 10 mm that require separate pressure guide wire interrogation or PCI (not to be interrogated or treated as a single stenosis).
4. Total coronary occlusions (CTOs). NOTE: Patients with CTOs can be included if i) treatment of the CTO is completed first ii) the CTO PCI is successful and iii) the physiological lesion is in another vessel.

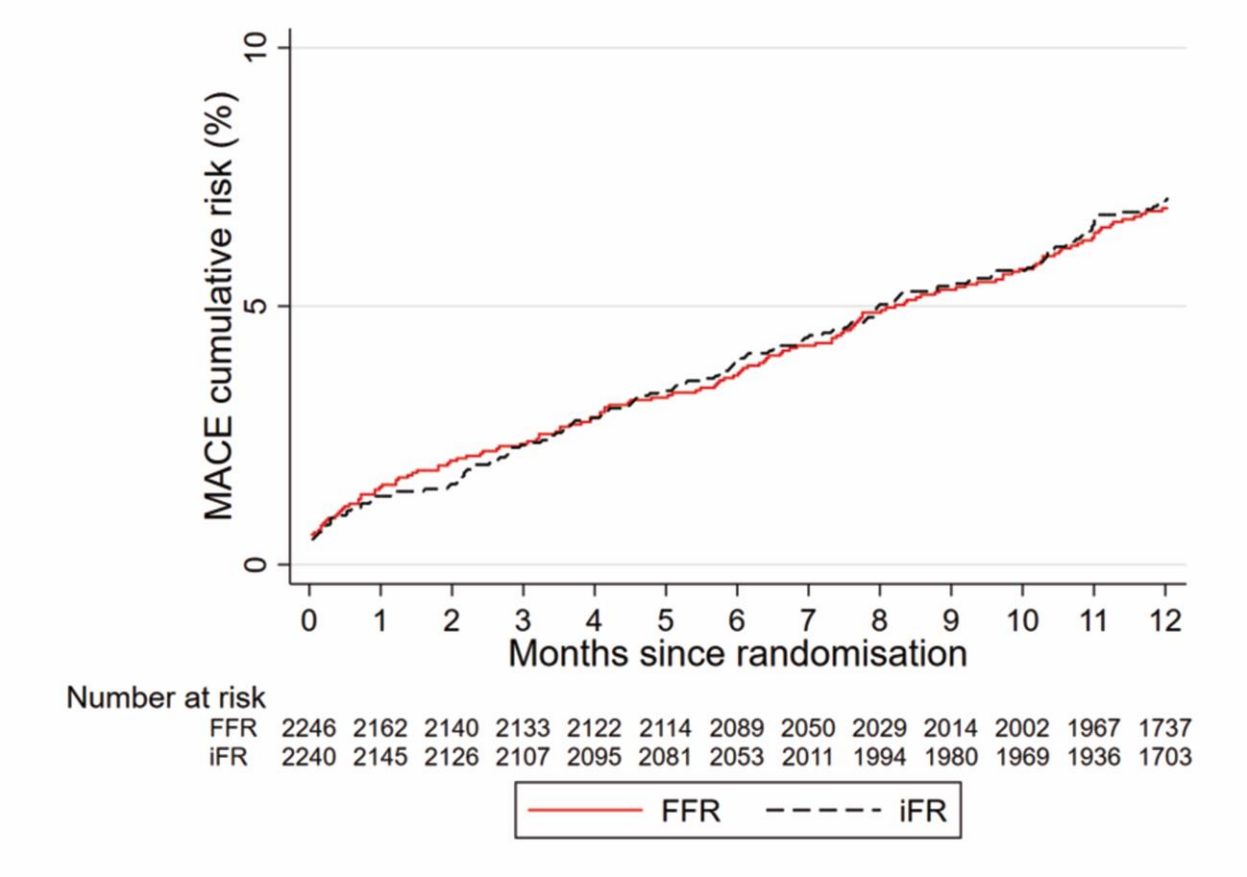
5. Restenotic lesions.
6. Haemodynamic instability at the time of intervention (heart rate<50 beats per minute, systolic blood pressure <90mmHg), balloon pump.
7. Significant contraindication to adenosine administration (e.g. heart block, severe asthma).
8. Contraindications to PCI or drug-eluting stent (DES) implantation.
9. Heavily calcified or tortuous vessels.
10. Significant hepatic or lung disease (chronic pulmonary obstructive disease), and/or malignant disease with unfavourable prognosis that may influence survival within the next 5 years.
11. Pregnancy.
12. STEMI within 48 hours of procedure.
13. Severe valvular heart disease.
14. ACS patients in whom more than one target vessel is present.

<u>iFR-SWEDEHEART study</u>

1. Previous CABG with patent grafts to the interrogated vessel.
2. Inability to provide informed consent.
3. Previous randomization in the iFR-SWEDEHEART trial.
4. Known terminal disease with a life expectancy of less than one year.
5. In patients with multi-vessel disease and other indication than stable angina pectoris, difficulty in assessing which is the culprit lesion.
6. Patient with unstable hemodynamics (Killip class III-IV).
7. Inability to tolerate adenosine.
8. Heavily calcified or tortuous vessels where inability to cross the lesion with a pressure wire is expected.

**SUPPLEMENTARY FIGURE LEGEND**

**Figure 1:** Cumulative risk of primary endpoint MACE by physiological technique in the overall population



## SUPPLEMENTARY TABLES

**Table 1. Baseline Characteristics of the overall population**

| | **iFR (N=2240)** | **FFR (N=2246)** |
|---|---|---|
| Age (years) | 66.5 ±10.3 | 66.2 ±10.1 |
| Male | 76.0% (1703/2240) | 74.8% (1680/2246) |
| Body mass index ($kg/m^2$) | 27.7 ±4.7 | 27.5 ±4.7 |
| Diabetes mellitus | 27.1% (606/2240) | 26.0% (585/2246) |
| Hypertension | 70.9% (1589/2240) | 70.4% (1582/2246) |
| Hyperlipidaemia | 67.6% (1514/2240) | 66.0% (1482/2246) |
| Current smoker | 17.9% (400/2240) | 18.8% (422/2246) |
| Previous MI | 30.8% (689/2240) | 31.3% (703/2246) |
| Previous PCI | 40.6% (910/2240) | 42.0% (943/2246) |
| Clinical presentation | | |
| Acute coronary syndrome | 27.6% (619/2240) | 26.7% (600/2246) |
| Stable coronary disease | 71.6% (1604/2240) | 72.8% (1635/2246) |
| No information | 0.8% (17/2240) | 0.5% (11/2246) |

iFR = instantaneous wave-free ratio, FFR= fractional flow reserve, MI = myocardial infarction, PCI = percutaneous coronary intervention.

**Table 2. Outcomes in the overall population according to iFR or FFR.**

| Outcome | iFR (N=2240) | FFR (N=2246) | HR iFR vs FFR (95% CI) | p-value |
|---|---|---|---|---|
| MACE, % (n) | 6.47% (145/2240) | 6.41% (144/2246) | 1.03 (0.81-1.31) | 0.81 |
| All-cause death, % (n) | 1.61% (36/2240) | 1.11% (25/2246) | 1.46 (0.88-2.44) | 0.14 |
| Cardiovascular death, % (n) | 0.67% (15/2240) | 0.45% (10/2246) | 1.52 (0.68-3.39) | 0.30 |
| Non-cardiovascular death, % (n) | 0.94% (21/2240) | 0.67% (15/2246) | 1.42 (0.73-2.76) | 0.30 |
| Myocardial infarction, % (n) | 2.37% (53/2240) | 2.00% (45/2246) | 1.19 (0.76-1.85) | 0.45 |
| Unplanned revascularisation, % (n) | 4.15% (93/2240) | 4.85% (109/2246) | 0.91 (0.69-1.21) | 0.53 |

HR denotes hazard ratio; MACE, major adverse cardiac events. Other abbreviations as in Table 1

**Table 3: Outcomes in the overall population according to clinical presentation (SAP vs. ACS)**

| | | | Non-adjusted | Fully adjusted | |
|---|---|---|---|---|---|
| **Outcome** | **SAP (N=3239)** | **ACS (N=1219)** | **HR SAP vs ACS (95% CI)** | **HR SAP vs ACS (95% CI)** | **p-value** |
| MACE, % (n) | 5.96% (193/3239) | 7.71% (94/1219) | 0.74 (0.57-0.95) | 0.72 (0.55-0.93) | 0.01 |
| All-cause death, % (n) | 1.11% (36/3239) | 1.97% (24/1219) | 0.57 (0.34-0.96) | 0.56 (0.33-0.94) | 0.03 |
| Cardiovascular death, % (n) | 0.40% (13/3239) | 0.98% (12/1219) | 0.41 (0.19-0.91) | 0.39 (0.18-0.89) | 0.02 |
| Non-cardiovascular death, % (n) | 0.71% (23/3239) | 0.98% (12/1219) | 0.74 (0.37-1.48) | 0.71 (0.35-1.45) | 0.35 |
| Myocardial infarction, % (n) | 2.07% (67/3239) | 2.54% (31/1219) | 0.65 (0.41-1.03) | 0.66 (0.41-1.07) | 0.09 |
| Unplanned revascularisation, % (n) | 4.23% (137/3239) | 5.25% (64/1219) | 0.86 (0.63-1.16) | 0.82 (0.60-1.12) | 0.63 |

ACS denotes acute coronary syndrome; SAP, stable angina pectoris. Other abbreviations as in Table 2.