# Supplementary material

In this supplementary text, we provide confirmation of our findings in *ISAR Risk* by testing the prognostic value of SAF in three independent post-infarction populations including a total of 2,564 patients:

1.) St. George's Hospital Medical School (SGHMS) Post-infarction Survey
2.) Holter sub-study of the European Myocardial Infarction Amiodarone Trial (EMIAT)
    a. Placebo arm
    b. Amiodarone arm
3.) Multiple Risk Factor Analysis Trial (MRFAT)

**Study characteristics**

The study characteristics of the different populations have been described elsewhere (1-4). Table S1 provides a brief summary of the study characteristics.

**Results**

During follow-up of 2 years (EMIAT, MRFAT) and 3 years (SGHMS), respectively, 82/679 (12.1%), 87/633 (13.7%), 88/625 (14.1%) and 34/597 (5.7%) of the patients died in the SGHMS Post-infarction survey, the placebo- and amiodarone arm of EMIAT, and MRFAT.

*Risk stratification by LVEF*

In the SGHMS post-infarction survey and in MRFAT (i.e. populations without restriction of LVEF), LVEF ≤30% identified only a minority of patients who died during follow up (SGHM 28/82=34%; MRFAT 8/34=24%). In the placebo- and amiodarone-arm of EMIAT (LVEF restricted to ≤ 40%), 65% (57/87) and 61% (54/88) of deaths occurred in patients with LVEF ≤30%, respectively. Cumulative mortality rates of patients with LVEF ≤30% vs. patients with LVEF >30% are shown in panels A, D, G and J of Figure S1 for the different populations. See also tables S2-S4 for details.

*Risk stratification by SAF in patients with LVEF >30%*

In all populations, SAF was a highly significant predictor of death in the subgroups of patients with preserved LVEF (>30%). In the SGHMS Post-infarction survey, SAF identified 29 patients with LVEF >30% , out of whom 11 died during follow-up. In the placebo- and amiodarone arm of EMIAT, SAF identified 27 and 34 patients with LVEF >30%, out of whom 6 and 11 patients died during follow-up. In MRFAT, SAF identified 109 patients with LVEF >30% , out of whom 15 died during follow-up. The mortality rates of patients with preserved LVEF (>30%) but positive SAF findings are shown in the right column of Figure S1 (Panel C, F, I and L). Their mortality risk was not statistically different from that of patients with impaired LVEF (≤30%).

*Risk stratification by SAF in the total populations*

In addition to our primary goal of testing the prognostic power of SAF in the so-called low-risk group of patients with LVEF >30%, we tested the prognostic power of SAF in the total populations. The mortality rates of patients with and without positive SAF findings are shown in the middle column of Figure S1 (panels B, E, H and K). In the SGHMS Post-infarction survey, SAF identified 46 patients, out of whom 18 patients died. In the placebo- and amiodarone arm of EMIAT, SAF identified 76 and 91 patients, out of whom 27 patients died, respectively. In MRFAT, SAF identified 134 patients, out of whom 19 patients died.

*Combination of LVEF ≤30% and SAF for prediction of death*

As shown in the right columns of tables S2-4, combinations of LVEF ≤30% and SAF lead to a significant increase of sensitivity in all populations while the positive predictive accuracies were preserved. Note that the increase of sensitivity in EMIAT is lower because of the restriction to patients with LVEF ≤40% and consequently higher incidence of patients with LVEF ≤30%.

**Conclusion**

Post-hoc analyses of the SGHM Post-infarction survey, the placebo- and amiodarone-arm of EMIAT and MRFAT clearly confirmed the principal findings of *ISAR Risk*. Despite significant differences in study characteristics (Table S1), SAF was a strong predictor of death in all populations. This was not only true for the total populations, but in particular also in the subgroups of patients with preserved LVEF (>30%) – i.e. patient groups not covered by present ICD guidelines. In all populations, SAF was

capable of identifying a high risk group of patients with preserved LVEF, whose prognosis was as worse as of patients with reduced LVEF.

**References**


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**Figure legend**

**Figure S1:** Cumulative mortality curves for patients of the St.George's Medical School (SGHMS) Post-infarction Survey, the Holter sub-study of the European Myocardial Infarction Amiodarone Trial (EMIAT) and the Multiple Risk Factor Analysis Trial (MRFAT) stratified by left ventricular ejection fraction (LVEF; left panels) and stratified by presence of severe autonomic failure (SAF; middle panels). Right panels show cumulative mortality curves for patients with LVEF >30% also stratified by presence of SAF.

**Tables (supplementary material)**

**Table S1** Study characteristics

| | SGHMS | EMIAT (Holter substudy) | MRFAT |
|---|---|---|---|
| N | 679 | 1,258 (625 Plac./ 633 Amiod.) | 597 |
| Start of enrollment | 1984 | 1990 | 1996 |
| Inclusion criteria | Acute MI<br>Age ≤75 years<br>Sinus rhythm | Recent MI<br>Age ≤75 years<br>Sinus rhythm<br>LVEF ≤ 40% | Acute MI<br>Age ≤75 years<br>Sinus rhythm |
| Holter recordings | day 7 after index MI | Pre-randomization | day 7 after index MI |
| Follow-up | Restricted to 3 years | 21 months (median) | Restricted to 2 years |
| Primary endpoint | Death of any cause | Death of any cause | Death of any cause |
| PCI | 0% | 0% | 24% |
| Lysis | 59% | 59% / 56% | 41% |
| Betablockers | 52% | 44% / 45% | 97% |

MI myocardial infarction

**Table S2:** SGHMS Post-infarction survey: Mortality rates, sensitivities and specificities for prediction of all cause mortality by high-risk groups

| | LVEF ≤ 30% | SAF | SAF (in LVEF >30%) | LVEF ≤ 30% or LVEF >30% and SAF |
|---|---|---|---|---|
| Total count | 105 | 46 | 29 | 134 |
| *Prediction of all-cause mortality at 3 years* | | | | |
| All cause deaths | 28 | 18 | 11 | 39 |
| Positive predictive accuracy (%) | 26.7 | 39.1 | 37.9 | 29.1 |
| Negative predictive accuracy (%) | 90.6 | 89.9 | 89.1 | 92.1 |
| Sensitivity (%) | 34.1 | 22.0 | 13.4 | 47.6 |
| Specificity (%) | 87.1 | 95.3 | 97.0 | 84.1 |

LVEF left ventricular ejection fraction; SAF severe autonomic failure; SGHMS St.George's Hospital Medical School

**Table S3:** Placebo- and amiodarone arm of EMIAT: Mortality rates, sensitivities and specificities for prediction of all cause mortality by high-risk groups

| | LVEF ≤ 30% | SAF | SAF (in LVEF >30%) | LVEF ≤ 30% or LVEF >30% and SAF |
|---|---|---|---|---|
| **Placebo Arm (n = 633)** | | | | |
| Total count | 296 | 76 | 27 | 324 |
| *Prediction of all-cause mortality at 2 years* | | | | |
| All cause deaths | 57 | 27 | 6 | 63 |
| Positive predictive accuracy (%) | 19.3 | 35.5 | 22.2 | 19.4 |
| Negative predictive accuracy (%) | 90.4 | 88.6 | 91.9 | 91.9 |
| Sensitivity (%) | 65.5 | 31.0 | 6.9 | 72.4 |
| Specificity (%) | 56.2 | 91.0 | 96.2 | 52.2 |
| **Amiodarone Arm (n = 625)** | | | | |
| Total count | 300 | 91 | 34 | 334 |
| *Prediction of all-cause mortality at 2 years* | | | | |
| All cause deaths | 54 | 27 | 11 | 65 |
| Positive predictive accuracy (%) | 18.0 | 29.7 | 32.4 | 19.5 |
| Negative predictive accuracy (%) | 87.6 | 85.6 | 89.6 | 89.6 |
| Sensitivity (%) | 62.1 | 31.0 | 12.6 | 74.7 |
| Specificity (%) | 54.9 | 88.3 | 95.8 | 50.7 |

LVEF left ventricular ejection fraction; SAF severe autonomic failure; EMIAT European Myocardial Infarction Amiodarone Trial

**Table S4:** MRFAT: Mortality rates, sensitivities and specificities for prediction of all cause mortality by high-risk groups

| | LVEF ≤ 30% | SAF | SAF (in LVEF >30%) | LVEF ≤ 30% or LVEF >30% and SAF |
|---|---|---|---|---|
| Total count | 58 | 134 | 109 | 167 |
| *Prediction of all-cause mortality at 2 years* | | | | |
| All cause deaths | 8 | 19 | 15 | 23 |
| Positive predictive accuracy (%) | 13.8 | 14.2 | 13.8 | 13.8 |
| Negative predictive accuracy (%) | 95.2 | 95.9 | 97.0 | 97.4 |
| Sensitivity (%) | 23.5 | 55.9 | 57.7 | 67.6 |
| Specificity (%) | 91.1 | 79.6 | 81.7 | 74.4 |

LVEF left ventricular ejection fraction; SAF severe autonomic failure; MRFAT Multiple Risk Factor Analysis