ORIGINAL ARTICLE

Temporal changes of noninvasive electrocardiographic risk factors for sudden cardiac death in post-myocardial infarction patients with preserved ejection fraction: Insights from the PRESERVE-EF study

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Abstract

Background: Several noninvasive risk factors (NIRFs) have been proposed for sudden cardiac death risk stratification in post-myocardial infarction (post-MI) patients with preserved ejection fraction (EF). However, it remains unclear if these factors change over time.

Methods: We evaluated seven electrocardiographic NIRFs as they were described in the PRESERVE-EF trial in 80 post-MI patients with EF $\geq$ 40%, at least 40 days after revascularization and 1 year later.

Results: Mean patient age was 56 ± 10 years, and 88% were men. Mean EF was $50 \pm 5\%$. The prevalence of (a) positive late potentials (27.5% vs. 28.8%, $p = .860$), (b) >30 premature ventricular complexes/hour (8.8% vs. 11.3%, $p = .598$), (c) nonsustained ventricular tachycardia (8.8% vs. 5%, $p = .349$), (d) standard deviation of normal RR intervals <75 ms (3.8% vs. 3.8%, $p = 1.000$), (e) QTc derived from 24-hr electrocardiography >440 ms (men) or >450 ms (women) (17.5% vs. 17.5%, $p = 1.000$), (f) deceleration capacity ≤ 4.5 ms and heart rate turbulence onset $\geq 0\%$ and slope ≤ 2.5 ms (2.5% vs. 3.8%, $p = 1.000$), and (g) ambulatory T-wave alternans ≥ 65 μ V in two Holter channels (6.3% vs. 6.3%, $p = 1.000$) were similar between the two measurements. However, five patients (6.3%) without any NIRFs during the first assessment had at least one positive NIRF at the second assessment and six patients (7.5%) with at least one NIRF at baseline had no positive NIRFs at 1 year.

Conclusions: While the prevalence of the examined electrocardiographic NIRFs between the two examinations was similar on a population basis, some patients without NIRFs at baseline developed NIRFs at 1 year and vice versa, highlighting the need for risk factor reassessment during follow-up.

KEYWORDS

myocardial infarction, noninvasive risk factors, preserved EF, sudden cardiac death

1 | INTRODUCTION

The role of electrocardiographic noninvasive risk factors (NIRFs) for assessing the risk for sudden cardiac death (SCD) in post-myocardial infarction (post-MI) patients with preserved left ventricular ejection fraction (LVEF) has received limited study. Implementation of NIRFs or risk models that predict the risk for SCD in this group of patients is of critical importance, since most patients who experience SCD have mildly or moderately reduced LVEF (Gorgels & Gijssbers, 2003; Makikallio et al., 2005; Stecker et al., 2006).

Currently, approximately 85% of MI patients maintain a preserved LVEF (>40%), explaining why the absolute number of patients who are in danger for SCD in this group is higher compared with the group of patients with reduced LVEF, even though the incidence of SCD in the latter group is higher (Makikallio et al., 2005). However, current guidelines recommend the prophylactic use of an implantable cardioverter-defibrillator (ICD) in post-MI patients with LVEF $\leq$ 35% excluding in practice patients with higher LVEF (Al-Khatib et al., 2018; Priori et al., 2015).

To overcome the limitations of LVEF for SCD risk stratification, several NIRFs derived from the patients' electrocardiogram (ECG) have been tested and have shown promising results (Gatzoulis et al., 2017; Wellens et al., 2014). However, none of these have been shown to be a specific predictor of sudden cardiac death and it remains unclear whether these factors change over time and need to be reevaluated (Dagres & Hindricks, 2013).

PRESERVE-EF study proposed a two-step SCD risk stratification approach, by combining noninvasive/invasive risk stratification approach in patients who suffered from MI and had preserved systolic function after revascularization (LVEF $\geq$ 40%). Patients with at least on positive NIRF (premature ventricular complexes, nonsustained ventricular tachycardia, late potentials, prolonged QTc, increased T-wave alternans, reduced heart rate variability, and abnormal deceleration capacity with abnormal turbulence) underwent programmed ventricular stimulation (PVS), and if they were inducible, they had an ICD implanted. Of the 575 patients included in the study, 204 (35.5%) had at least one positive NIRF. Forty-one of 152 patients who underwent PVS were inducible (7.1% of total study population) with thirty-seven of them receiving an ICD. During a 32-month mean follow-up, nine patients (1.6% of the total population) had an appropriate ICD activation meeting the study primary endpoint (sustained ventricular tachycardia/fibrillation, appropriate ICD activation, or SCD). None of the noninducible patients and patients without NIRFs met the primary endpoint.

We investigated the temporal changes in electrocardiographic NIRFs in post-MI patients with preserved LVEF ($\geq$ 40%) included in the PRESERVE-EF who had been recruited in one of the seven cardiology departments participating in the trial.

2 | METHODS

From April 2014 to July 2018, 575 consecutive patients in seven hospitals in Greece were enrolled in the prospective, observational cohort PRESERVE-EF study (clinicaltrials.gov identifier NCT02124018) (Gatzoulis et al., 2019). In one hospital (Attikon University Hospital), systematic follow-up with a second Holter assessment was performed 1 year after the initial assessment. Between October 2014 and November 2017, 82 consecutive eligible patients were enrolled at this center. Two patients did not return for the second assessment and were excluded, leaving 80 patients for the analysis. All patients had suffered a prior MI as defined by the third universal definition of MI and had undergone angioplasty of the culprit lesion (Thygesen et al., 2012). At least 40 days after the MI, patients had their LVEF evaluated by rest echocardiography and were considered eligible if it was $\geq$ 40%. All patients had been completely revascularized or otherwise had a negative stress test (if they had one or more remaining lesions of >50% after the initial angiography), before being assessed with Holter monitoring.

Seven electrocardiographic NIRFs were evaluated at least 40 days after the event and were considered positive according to the following criteria as they are described in PRESERVE-EF trial: (a) 2/3 positive criteria for late potentials (LPS), either conventional or modified (Breithardt et al., 1991; Gatzoulis et al., 1995), on 45-min electrocardiographic recording during resting, (b) >30 premature ventricular complexes (PVCs)/hour on 24-hr electrocardiography (Crawford et al., 1999; Sajadieh et al., 2006), (c) presence of non-sustained ventricular tachycardia (NSVT) on 24-hr electrocardiography (Buxton et al., 2000; Makikallio et al., 2005; Moss et al., 1996), (d) Standard deviation of normal RR intervals (SDNN) $\leq$ 75 ms on the 24-hr electrocardiography (La Rovere et al., 2001), (e) QTc derived from 24-hr electrocardiography >440 ms (men) or >450 ms (women) (Arsenos et al., 2011), (f) Deceleration capacity (DC) $\leq$ 4.5 ms and heart rate turbulence onset (TO) $\geq$ 0% and heart rate turbulence slope (TS) $\leq$ 2.5 ms on 24-hr electrocardiography (Bauer et al., 2009), and (g) Ambulatory T-wave alternans (TWA) $\geq$ 65 μ V in two Holter channels, on 24-hr electrocardiography (Verrier et al., 2011). Use of antiarrhythmic drugs other than β -blockers was an exclusion criterion. The complete study design can be found in the original PRESERVE-EF manuscript (Gatzoulis, Tsiachris, Arsenos, Dilaveris, et al., 2014). The CardioMem CM 4000 Multi-channel ECG Recorder (GE healthcare) was used for the recordings, and the CardioDay 2.4 (GE healthcare) software was used for the analysis.

Patients who underwent PVS were considered inducible if they developed (a) sustained monomorphic ventricular tachycardia (monomorphic QRS complexes with rate between 120–220 bpm, lasting for more than 30 s) or (b) ventricular flutter (monomorphic QRS complexes with rate $\geq$ 220 bpm, not degenerating to ventricular fibrillation) or (c) polymorphic ventricular tachycardia (constantly

TABLE 1 Patients' baseline characteristics

Basic characteristics	N = 80
Age (years) ^a	56 ± 10
Male gender (%)	88 (70)
BMI (kg/m ²) ^a	27 ± 4
Smoking (current) (%)	75 (60)
Diabetes (%)	23 (18)
Dyslipidemia (%)	71 (57)
Hypertension (%)	44 (35)
STEMI (%)	61 (49)
One-vessel disease (%)	81 (65)
Culprit vessel (%)	
LAD (%)	39 (29)
RCA (%)	39 (29)
LCX (%)	21 (16)
Ramus (%)	1.3 (1)
NYHA I (%)	90 (72)
Hb (g/dl) ^a	14.1 ± 1.1
Glu (mmol/L) ^b	5.88 (5.16, 7.77)
Cr (μmol/L) ^b	70.7 (61.9, 88.4)
K (meq/Lt) ^b	4.3 (4.1, 4.6)
LDL (mmol/L) ^b	3.2 (2.4, 3.8)
HDL (mmol/L) ^b	0.96 (0.83, 1.1)
TG (mmol/L) ^b	1.3 (1.0, 1.7)
B-blockers (%)	94 (75)
ACE inhibitors/ARB (%)	88 (70)
Statin (%)	99 (79)
Aspirin (%)	100 (80)
P2Y12 inhibitors (%)	100 (80)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; Cr, creatinine; Glu, glucose; Hb, hemoglobin; HDL, high-density lipoprotein; K, potassium; LAD, left anterior descending artery; LCX, circumflex artery; LDL, low-density lipoprotein; NYHA, New York Heart Association; RCA, right coronary artery disease; STEMI, ST-segment elevation myocardial infarction; TG, triglycerides.

^aMean ± SD.

^bMedian (interquartile range).

changing morphologies and axis, degenerating to ventricular fibrillation).

2.1 | Statistical analysis

Categorical variables were expressed as percentages and were compared using Pearson's chi-square test or 2-tail Fisher's exact test. Continuous variables were presented as mean ± SD or median (interquartile range, IQR) and were compared using *t* test or Wilcoxon rank-sum test, as appropriate. All statistical analyses were performed with JMP 14.0 (SAS Institute, Cary, North Carolina). A two-sided *p* value of .05 was considered statistically significant.

3 | RESULTS

Patients' baseline characteristics are summarized in Table 1. Mean age was 56 ± 10 years, and 88% were men. They had high prevalence of dyslipidemia (71%), smoking (75%), and diabetes (23%). Most patients were New York Heart Association (NYHA) class I (90%), had one-vessel disease (65%), and had suffered more frequently from ST-segment elevation MI than non-ST-segment elevation MI (61% vs. 49%). The most common target vessel was the left anterior descending artery and right coronary artery (39% for both). Implementation of evidence-based medicine was high in the study population with 94% of the patients taking b-blockers, 88% angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, 99% statins, and 100% dual antiplatelet therapy. Median time from myocardial infarction to the first assessment was 49 (IQR 44, 65) days.

LVEF did not change between the two assessments (50%±5% vs. 52%±6%, *p* = .169), and all the patients had LVEF ≥40% at the second assessment that took place 1 year later (mean 365 ± 32 days apart). In addition, similar was the mean heart rate (68 ± 8 vs. 70 ± 9, *p* = .165) as it was derived by the 24-hr electrocardiography between the two assessments, as it were all the measurements of the basic electrocardiographic intervals derived from the resting ECG (Table 2).

The prevalence of (a) positive LPS (27.5% vs. 28.8%, *p* = .860), (b) >30 PVCs/h (8.8% vs. 11.3%, *p* = .598), (c) presence of NSVT (8.8% vs. 5%, *p* = .349), (d) SDNN < 75 ms (3.8% vs. 3.8%, *p* = 1.000), (e) QTc derived from 24-hr electrocardiography >440 ms (men) or >450 ms (women) (17.5% vs. 17.5%, *p* = 1.000), (f) Deceleration capacity ≤4.5 ms and heart rate turbulence onset ≥0% and heart rate turbulence slope ≤2.5 ms (2.5% vs. 3.8%, *p* = 1.000), and (g) Ambulatory TWA ≥ 65 μV in two Holter channels (6.3% vs. 6.3%, *p* = 1.000) was similar at the time of the initial and repeat assessment. Furthermore, there was no difference in the absolute values of means/medians of NIRFs (Table 3). However, five patients (6.3%) with no positive NIRFs during the first assessment had at least one positive NIRF present at the second assessment and six patients (7.5%) with at least one positive NIRF at the first examination had no positive NIRFs during the second.

Patients who had the first assessment before 49 day after MI (40–49 days) had numerically higher rate of positive NIRFs compared to patients who had the first assessment after 49 days (61% vs. 49%, *p* = .271). However, no statistically significant difference was found between the first and the second assessment regarding the prevalence of NIRFs in patients who had the initial assessment before (61% vs. 63%, *p* = .820) and after 49 days (49% vs. 44%, *p* = .650) from MI.

Patients, who initially had LVEF < 50% (*n* = 27), had higher prevalence of positive NIRFs at the first assessment compared with patients with LVEF ≥ 50% (*n* = 53), (74% vs. 45%, *p* = .014). Although no statistically significant difference was reached, the rate of patients with initial LVEF < 50% and at least one positive NIRF was reduced by 11% during the second assessment (74% vs. 63%, *p* = .379), while

Echocardiographic measurements/HR, basic electrocardiographic intervals	First assessment	Second assessment	p-value
EF(%) ^a	50 ± 5	52 ± 6	.1690
LVEDD (mm) ^a	48 ± 5	48 ± 4	.8723
HR (bpm) ^a	68 ± 8	70 ± 9	.1650
QRS (ms) ^b	88 (80, 100)	89 (80, 100)	.4848
P (ms) ^b	100 (80, 116)	108 (87, 120)	.0772
PR (ms) ^b	160 (140, 180)	159 (140, 170)	.8707
QT (ms) ^b	413 (400, 440)	402 (400, 420)	.1934
RR (ms) ^a	1,001 ± 131	966 ± 135	.0951

Abbreviations: HR, heart rate; EF, ejection fraction; LVEDD, left ventricular end diastolic diameter.

^aMean ± SD.

^bMedian (interquartile range).

TABLE 2 Comparison between echocardiographic measurements, heart rhythm, and basic electrocardiographic intervals between the first and the second assessment

Noninvasive risk factors	First assessment	Second assessment	p-value
LPS			
fQRS (ms) ^a	97 (89, 104)	99 (90, 108)	.4223
LAS (ms) ^a	32 (24, 39)	34 (26, 40)	.3296
RMS μ V ^a	36 (17, 69)	28 (15, 69)	.3936
LPS positive (%)	27.5	28.8	.8604
PVCs ^a	12 (2, 139)	19 (2, 343)	.5227
>30 PVCs/hr (%)	8.8	11.3	.5982
NSVT (%)	8.8	5	.3486
SDNN (ms) ^a	127 (108, 148)	128 (112, 154)	.7548
Abnormal SDNN (%)	3.8	3.8	1.0000
QTc (ms) ^b	425 ± 19	426 ± 16	.8853
QTc > 440 ms men, >450 ms women (%)	17.5	17.5	1.0000
TO (%) ^a	-0.02 (-0.04, -0.01)	-0.02 (-0.04, -0.01)	.6720
TS (ms/rri) ^a	9.7 (5.5, 14.9)	8.8 (4.6, 17.4)	.8631
DC (ms) ^a	6.7 (4.75, 8.8)	6.9 (5.1, 8.1)	.8417
Abnormal HR turbulence/DC (%)	2.5	3.8	1.0000
T-wave alternans ($\geq 65 \mu$ V) (%)	6.3	6.3	1.0000

Abbreviations: DC, deceleration capacity; HR, heart rate; fQRS, filtered QRS; LAS, low amplitude (<40 μ V) signal duration; LPS, late potentials; NSVT, nonsustained ventricular tachycardia; PVCs, premature ventricular complexes; RMS, terminal (last 40 ms) QRS root means square voltage; SDNN, standard deviation of normal to normal heart beat; TO, turbulence onset; TS, turbulence slope.

^aMedian (interquartile range).

^bMean ± SD.

TABLE 3 Comparison of noninvasive risk factors between the first and the second assessment

the rate of patients with LVEF $\geq 50\%$ and at least one positive NIRF was slightly increased (45% vs. 49%, $p = .697$).

We performed an analysis comparing diabetic versus nondiabetic patients (Figure 1). In both the initial (67% vs. 52%, $p = .258$) and the follow-up (61% vs. 52%, $p = .477$) assessment, diabetic patients had numerically higher prevalence of NIRFs. The number of positive NIRFs was marginally statistically significant higher for the diabetic patients

at the initial assessment (1.2 for diabetic vs. 0.6 for nondiabetic patients, $p = .05$) but not at the follow-up assessment (1.1 vs. 0.7, $p = .199$).

Eighteen patients underwent PVS, eight were inducible and seven of them had an ICD implanted (one patient declined).

During the 1-year period between the two examinations, two patients developed an acute coronary syndrome (one case of unstable angina and one case of non-ST-elevation myocardial infarction) and

FIGURE 1 Comparison of the prevalence of noninvasive electrocardiographic risk factors between diabetic versus nondiabetic patients of the study at the initial (Panel a) and follow-up assessment (Panel b)

one patient stable angina. All three patients underwent coronary angiography and percutaneous coronary intervention and had the culprit vessel revascularized. One patient had positive LPs during the first and the second assessment, while the two remaining patients had no positive NIRFs both times. Regarding arrhythmic events, one patient who had positive LPs at the initial assessment experienced an episode of ventricular tachycardia (VT) that was successfully terminated with shock given by the ICD, as the patient had previously undergone programmed ventricular stimulation according to the PRESERVE-EF protocol which induced monomorphic VT and had an ICD implanted. During the second Holter assessment, the patient had again positive LPs and one episode of NSVT (Figure 2). This was the only recorded arrhythmic event in our study.

4 | DISCUSSION

To the best of our knowledge, this is the first study that evaluated at serial time points after MI the prevalence of NIRFs, focusing exclusively in post-MI patients with preserved EF who are practically excluded from SCD risk stratification.

The main findings of our study are the following: (a) In post-MI patients with characteristics similar to the present study, there is a high prevalence of the evaluated NIRFs, both during the first and the second assessment. (b) LPs were the NIRF that was found more often positive, followed by QTc. (c) Although there was no statistically significant difference in the prevalence of any of the NIRFs between the two measurements, over 5% of the patients who initially

FIGURE 2 Panel a. Positive late potentials (3/3) as they were recorded on 45-min electrocardiographic recording during resting in a patient with EF > 40%, 40-days after suffering a myocardial infarction. Panel b. The same patient after one-year follow-up presented again with positive late potentials (2/3)

had no positive risk factors found to have at least one positive NIRF at the second measurement.

PRESERVE-EF trial demonstrated that the NIRFs that were evaluated in our substudy can be used as a very useful initial screening test in a two-step approach for arrhythmic risk stratification of post-MI patients with LVEF $\geq$ 40%: Patients who had at least one positive risk factor underwent PVS, and if the study was positive, a cardioverter-defibrillator was implanted (Gatzoulis et al., 2019; Gatzoulis, Tsiachris, Arsenos, Dilaveris, et al., 2014).

Although the percentage of inducible patients in our substudy was higher than in the PRESERVE-EF (42% vs. 27% of the patients who underwent PVS), the percentage of patients who met the primary endpoint was similar (1.3% vs. 1.6% of the total study

population) and none of the patients with negative NIRFs or negative PVS experienced any arrhythmic events.

However, our knowledge about when these risk factors should be measured and if they change in the long-term is limited.

Exner et al showed that the assessment of TWA and heart rate turbulence (HRT) between 2 and 4 weeks after MI did not predict cardiac death or resuscitated cardiac arrest during the follow-up in patients with EF < 50% (Exner et al., 2007). However, 10–12 weeks after MI, the combination of the same NIRFs reliably identified patients at risk of serious events, proving a variation in the diagnostic value of the same noninvasive parameters regarding the time of measurement. These findings were at least in part explained by the fact that LVEF significantly increased over the initial 2 months after MI in the

population of this trial. Based on this study, European guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend against the use of noninvasive tests for risk stratification in the early phase after MI (Priori et al., 2015). According to the design of our study, all the initial measurements took place at least 40 days after MI, excluding to a great extent LV remodeling that is promoted by revascularization as the causative factor of the changes in the values of the evaluated NIRFs.

Huikuri et al in their study demonstrated that attenuated recovery of autonomic function early after MI, as estimated by the assessment of HRT and heart rate variability (HRV) in two post-MI cohorts in two separate Holter-recordings in each cohort (5–21 days and 6 weeks after the event in the first and 2–4 weeks and 10–14 weeks in the second), was associated with serious arrhythmic events (Huikuri et al., 2010; Huikuri, Mahaux, & Bloch-Thomsen, 2003). Interestingly, Sandercock et al showed that in patients with coronary artery disease and following MI, cardiac rehabilitation led to significant increase in SDNN, showing that effective therapies as cardiac rehabilitation can improve autonomic nervous system function (Sandercock, Grocott-Mason, & Brodie, 2007).

Verozini et al performed signal-averaged electrocardiograms (SA-ECG's) in 220 post-MI patients before hospital discharge (16 ± 6 days) and then at regular intervals during the following year (6 weeks, 3, 6 and 12 months): 28.2% of the patients had initially positive LPS, close to the 27.5% we described in our study with the difference that our initial assessment took place at least 40 days after the event. There was no significant difference in terms of mean LVEF between patients who presented with positive LPS (group 1) and those who initially had negative LPS (group 2) ($40\% \pm 14\%$ vs. $45\% \pm 15\%$, $p = \text{NS}$). In contrast to our study, a percentage of patients in both previously mentioned groups had $\text{EF} < 40\%$ (46% vs. 35% , $p = \text{NS}$). In addition, 20% of the patients normalized their LPS after 6 months, compared with 18% after 1 year, in our study. Similarly to our findings, the investigators of this study stated that mean fQRS, LAS, and RMS values did not change significantly but at each follow-up assessment between 15% and 28% of the patients did change group (Verzoni et al., 1989).

The role of electrophysiologic study (EPS) is limited in current clinical practice. While the seminal Multicentre Automatic Defibrillator Implantation Trial I (MADIT-I) required electrophysiologic testing for inducible ventricular tachycardia before ICD implantation, Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II) showed that prophylactic ICD in post-MI patients with systolic dysfunction ($\text{EF} \leq 30\%$) reduced all-cause mortality compared to standard medical therapy without requiring the performance of PVS (Moss et al., 1996, 2002). Based on the outcomes of MADIT-II and SCD-HeFT trial (which included patients with $\text{EF} \leq 35\%$ and either ischemic or non-ischemic cardiomyopathy), current American and European guidelines recommend the prophylactic use of ICD in patients with prior MI and $\text{EF} \leq 35\%$, at least 40 days after MI without requiring a positive PVS prior (Bardy et al., 2005). Practically, the use of EPS in post-MI patients is limited in those with EF between 35%–40% and NSVT (Al-Khatib et al., 2018; Priori et al., 2015): Driven by the results of Multicenter

Unsustained Tachycardia trial (MUSTT), guidelines recommend the performance of PVS in patients with NSVT and EF between 35% and 40% and the implantation of ICD in inducible patients, ignoring patients with $\text{EF} > 40\%$ (Al-Khatib et al., 2018; Buxton et al., 2000; Priori et al., 2015).

The usefulness of EPS-guided risk stratification approach in post-MI patients with $\text{LVEF} > 35\%$ –40% and positive NIRFs has also been shown in prior studies (Gatzoulis, Tsiachris, Arsenos, Archontakis, et al., 2014; Gatzoulis et al., 2013). Combined with the results of the current substudy and PRESERVE-EF, PVS seems to have an emerging role in SCD risk stratification in post-MI patients with preserved LVEF. However, multicenter randomized controlled clinical trials are needed before the implementation of PVS in clinical practice for patients with preserved EF and positive NIRFs.

The single use of NIRFs for guiding prophylactic ICD implantation is not justified by current data. The ongoing REFINE-ICD trial (NCT00673842) examines the benefit of prophylactic ICD therapy in patients with EF between 36% and 50% and abnormal HRV plus TWA without having prior undergone EPS (Bauer, 2017; Perkiomaki et al., 2015).

The main limitation of our study was the limited number of patients that made our study underpowered for the NIRFs with low prevalence like SDNN and HRT and DC. Furthermore, for the estimation of SDNN cutoff value, heart rate was not taken under consideration.

5 | CONCLUSION

While the prevalence of the examined electrocardiographic NIRFs between the two examinations was similar on a population basis, few patients will present with a positive risk factor at the second measurement while they originally had no positive risk factors, implying the need for long-term follow-up with reevaluation of the risk factors. The present data are not sufficient to suggest that the selection of the risk markers should be tested after a year. The optimal timing of the second assessment and serial reevaluations remains unknown and justifies further study.

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