








Association of non-invasive electrocardiographic risk factors with left ventricular systolic function in post-myocardial infarction patients with mildly reduced or preserved ejection fraction: Insights from the PRESERVE-EF study

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Abstract

Background: Electrocardiographic non-invasive risk factors (NIRFs) have an important role in the arrhythmic risk stratification of post-myocardial infarction (post-MI) patients with preserved or mildly reduced left ventricular ejection fraction (LVEF). However, their specific relation to left ventricular systolic function remains unclear. We aimed to evaluate the association between NIRFs and LVEF in the patients included in the PRESERVE-EF trial.

Methods: We studied 575 post-MI ischemia-free patients with LVEF \geq 40% (mean age: 57.0 \pm 10.4 years, 86.2% men). The following NIRFs were evaluated: premature ventricular complexes, non-sustained ventricular tachycardia (NSVT), late potentials (LPs), prolonged QTc, increased T-wave alternans, reduced heart rate variability, and abnormal deceleration capacity with abnormal turbulence.

Results: There was a statistically significant relationship between LPs (Chi-squared = 4.975; $p < .05$), nsVT (Chi-squared = 5.749, $p < .05$), PVCs ($r = -.136$; $p < .01$), and the LVEF. The multivariate linear regression analysis showed that LPs ($p = .001$) and NSVT ($p < .001$) were significant predictors of the LVEF. The results of the multivariate logistic regression analysis indicated that LPs (OR: 1.76; 95% CI: 1.02–3.05; $p = .004$) and NSVT (OR: 2.44; 95% CI: 1.18–5.04; $p = .001$) were independent predictors of the mildly reduced LVEF: 40%–49% versus the preserved LVEF: \geq 50%.

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Conclusion: Late potentials and NSVT are independently related to reduced LVEF while they are independent predictors of mildly reduced LVEF versus the preserved LVEF. These findings may have important implications for the arrhythmic risk stratification of post-MI patients with mildly reduced or preserved LVEF.

KEYWORDS

late potentials, left ventricular ejection fraction, non-invasive risk factors, non-sustained ventricular tachycardia, risk stratification

1 | INTRODUCTION

Sudden cardiac death (SCD) represents a principal cause of mortality in post-myocardial infarction (post-MI) patients with mildly reduced or preserved left ventricular ejection fraction (LVEF) (Pannone et al., 2021; Vaduganathan et al., 2017). Several electrocardiographic non-invasive risk factors (NIRFs) for SCD risk stratification in post-MI patients with mildly reduced or preserved LVEF have been examined but their exact and relative value remains unclear. However, the implementation of NIRFs or risk models that predict the risk for SCD in this group of patients is of particular importance, since most of the post-MI patients who suffer SCD have mildly reduced or preserved LVEF (Gorgels et al., 2003; Mäkikallio et al., 2005; Stecker et al., 2006).

Currently, most of the MI patients maintain a mildly reduced or preserved LVEF, explaining why the absolute number of patients who are at risk for SCD in this group is higher compared to those with depressed LVEF, although the incidence of SCD in the latter group is greater (Mäkikallio et al., 2005; Stecker et al., 2006). The recently published PRESERVE-EF study was a multicenter, observational cohort study which implemented a two-step risk stratification approach in post-MI patients with LVEF $\geq 40\%$ (Gatzoulis et al., 2019). Namely, patients with at least one positive NIRF were referred for programmed ventricular stimulation (PVS), and those who were inducible were offered an implantable cardioverter defibrillator (ICD). Of note, 24% of the patients who received an ICD had an appropriate activation during the 32-month follow-up, while none of the patients without NIRFs or those with who were not inducible suffered a major arrhythmic event (Gatzoulis et al., 2019).

Whether the severity of left ventricular systolic dysfunction in post-MI patients with LVEF $\geq 40\%$ is related to the presence of specific NIRFs is not known. Also, the impact of reduced LVEF on the relative incidence of NIRFs in this setting has not been studied. We, therefore, investigated the association between LVEF and NIRFs in the patients included in the original PRESERVE-EF trial.

2 | METHODS

Post-angiographically proven MI patients, at least 40 days after the event (90 days after surgery if they underwent coronary artery bypass grafting), with LVEF $\geq 40\%$ (also assessed after 40 or 90 days, respectively, from the index event), either revascularized or not—but without any evidence of active ischemia (following negative myocardial

scintigraphy/exercise treadmill test/stress echocardiography in the previous 6 months), on optimal tolerated medical therapy, were enrolled. A detailed description of the PRESERVE EF population as well as the exclusion criteria have been previously described in detail (Gatzoulis et al., 2014, 2019). The patients were divided into two groups according to the LVEF; LVEF: 40%–49% (mildly reduced), LVEF $\geq 50\%$ (preserved). The LVEF was measured using the biplane Simpson's method while the patients were on a stable hemodynamic condition.

The demographic and clinical characteristics of the patients were carefully recorded. Besides a baseline 12-lead electrocardiogram, all participants underwent a 24-h digital ambulatory electrocardiographic recording followed by a 45-min high-resolution digital recording for the signal averaged electrocardiography. A GE Healthcare GETEMED CardioDay Holter system was used in all patients (recorder CardioMem CM4000 and software CardioDay v.2.4, GE Healthcare). Patients were initially stratified according to the presence of at least one electrocardiographic NIRF and then proceeded to PVS since they considered to be at high arrhythmic risk (Gatzoulis et al., 2014, 2019).

Specifically, the presence or not of the following electrocardiographic NIRFs was carefully examined: (1) >30 premature ventricular complexes (PVCs)/hour on 24-h Holter monitoring (HM), (2) presence of non-sustained ventricular tachycardia (NSVT) on HM, (3) 2/3 positive criteria for late potentials (LPs), either conventional or modified, obtained through the 45-min high-resolution digital ECG recording, (4) QTc derived from HM >440 ms (men) or >450 ms (women), and (5) Ambulatory T-wave alternans (TWA) ≥ 65 μV , Abnormal heart rate variability indicated by SDNN <75 ms on the 24-h HM, Deceleration capacity ≤ 4.5 ms, and heart rate turbulence (HRT) onset $\geq 0\%$ and HRT slope ≤ 2.5 ms.

Continuous variables are expressed as mean \pm SD, or as median [interquartile range] if their values were not normally distributed. The examination of normality was performed by the Kolmogorov–Smirnov test. Comparisons of the continuous variables were performed using the unpaired Student's *t*-test or the non-parametric Mann-Whitney *U*-test, as appropriate. The categorical variables are presented as absolute numbers and frequencies and compared using the Chi-squared test, followed with the Fisher correction when examining 2×2 tables. A two-tailed *p* value $< .05$ was considered significant.

In order to examine the association between the LVEF and other scale parameters (age, sex, etc.), we performed a Pearson's correlation analysis, while for NIRFS, due to their categorical nature, we utilized Chi-squared test of independence prior to the univariate logistic regression. We also performed a predefined multivariate

logistic regression analysis to investigate the predictive ability of the NIRFs over the binary LVEF (LVEF 40%–49% vs. LVEF \geq 50%). The level of significance for the variables of the univariate analysis was defined at 0.05. All analyses were performed using the SPSS software (version 25.0; SPSS Inc.).

3 | RESULTS

The study population consisted of 575 patients (mean age: 57 ± 10.4 years, 86.2% men). The demographic and clinical characteristics of the patients as well as of the two groups are presented in Table 1 while the echocardiographic and baseline 12-lead electrocardiographic parameters are presented in Table 2. The data regarding electrocardiographic NIRFs are summarized in Table 3. The presence of LPs, PVCs, and NSVT were more prevalent in patients with mildly reduced LVEF compared to those with preserved LVEF (Table 3).

There was a statistically significant relationship between LPs (Chi-squared = 4.975; $p < .05$), nsVT (Chi-squared = 5.749, $p < .05$), PVCs ($r = -.136$; $p < .01$), and the LVEF. The multivariate linear regression analysis showed that LPs ($p = .01$) and NSVT ($p < .01$) were significant predictors of the LVEF. The results of the multivariate logistic regression analysis indicated that LPs (OR: 1.76; 95% CI: 1.02–3.05; $p = .04$) and NSVT (OR: 2.44; 95% CI: 1.18–5.04; $p = .01$) were independent predictors of the binary LVEF; namely, predictors of the mildly reduced LVEF: 40%–49% vs. the preserved LVEF: \geq 50% (Table 4).

4 | DISCUSSION

The present study examined for the first time the association of NIRFs with the left ventricular systolic function in post-MI patients with ischemic cardiomyopathy and preserved or mildly reduced LVEF. We performed a sub-analysis of data obtained by the

TABLE 1 Demographic and clinical characteristics of the two groups

| Parameters | | ALL Patients (N = 575) | LVEF 40%–49% (N = 345) | LVEF \geq 50% (N = 230) | p-Value |
|------------------------------|---|---------------------------|---------------------------|---------------------------|---------|
| Age | | 57.0 \pm 10.4 | 57.9 \pm 10.4 | 55.9 \pm 10.1 | <.05 |
| Gender (% male) | | 86.2 | 89.6 | 81.4 | <.01 |
| BMI | | 27.9 \pm 3.8 | 27.9 \pm 4.0 | 27.8 \pm 3.4 | .61 |
| Smoking (% yes) | | 57.7 | 54.8 | 62.2 | .10 |
| Diabetes (% yes) | | 17.7 | 20.3 | 14.0 | .07 |
| Hypertension (% yes) | | 56.0 | 58.7 | 52.3 | .13 |
| Dyslipidemia (% yes) | | 65.1 | 66.9 | 62.2 | .29 |
| Type of infraction (% STEMI) | | 66.3 | 73.8 | 54.6 | <.01 |
| Number of vessels | 0 | 1,9 | 0,9 | 3,7 | <.05 |
| | 1 | 63,7 | 60,2 | 69,4 | |
| | 2 | 22,4 | 22,7 | 21,5 | |
| | 3 | 12,0 | 16,3 | 5,5 | |
| NYHA (%) | 1 | 92.70 | 90.6 | 95.9 | <.05 |
| | 2 | 6.80 | 8.8 | 3.6 | |
| | 3 | 0.20 | 0.3 | 0.0 | |
| | 4 | 0.40 | 0.3 | 0.5 | |
| β -blockers (% yes) | | 85.0 | 87.5 | 81.2 | .05 |
| ACEI or ARB (% yes) | | 73.1 | 73.8 | 72.1 | .73 |
| Statins (% yes) | | 98.1 | 97.7 | 98.7 | .61 |
| Aspirin (% yes) | | 97.9 | 98.0 | 97.7 | 1.00 |
| Hemoglobin (gr/dl) | | 14.1 \pm 1.8 | 14.1 \pm 2.1 | 14.2 \pm 1.4 | .55 |
| Creatinine (mg/dl) | | 1.0 \pm 0.2 | 1.0 \pm 0.2 | 1.0 \pm 0.2 | .37 |
| Potassium (mmol/L) | | 4.4 \pm 0.41 | 4.4 \pm 0.4 | 4.4 \pm 0.37 | .21 |
| Sodium (mmol/L) | | 138.7 \pm 9.1 | 138.6 \pm 9.5 | 138.9 \pm 8.6 | .71 |
| LDL (mg/dl) | | 112.2 \pm 38.3 | 110.7 \pm 38.0 | 114.8 \pm 38.7 | .22 |
| HDL (mg/dl) | | 41.1 \pm 12.3 | 41.7 \pm 13.5 | 40.1 \pm 10.0 | .15 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; STEMI, ST-elevation myocardial infarction.

| Parameters | All Patients (N = 575) | LVEF 40–49% (N = 345) | LVEF ≥50 (N = 230) | p-Value |
|------------|---------------------------|--------------------------|-----------------------|---------|
| LVEDD (mm) | 50 ± 4 | 50.6 ± 5.5 | 48.6 ± 4.6 | <.01 |
| LA (mm) | 39 ± 5 | 39.7 ± 4.5 | 38.3 ± 4.7 | <.01 |
| IVS (mm) | 10.0 (9.0–11.0) | 10.0 (9.0–11.0) | 10.0 (9.0–11.0) | .23 |
| PW (mm) | 10.0 (9.0–11.0) | 10.0 (9.0–11.0) | 10.0 (9.0–11.0) | .67 |
| QRS | 89 ± 18 | 89.6 ± 19.7 | 87.4 ± 15.1 | .19 |
| P (msec) | 97 ± 24 | 96.1 ± 24.7 | 98.8 ± 23.6 | .25 |
| QT MAX | 405 ± 36 | 404 ± 37.3 | 404.5 ± 34.7 | .88 |
| RR | 923 ± 156 | 923.2 ± 154.3 | 921.6 ± 158.3 | .91 |
| PR (msec) | 162 ± 27 | 161 ± 28 | 162 ± 25 | .90 |

Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

TABLE 2 Baseline echocardiographic and electrocardiographic parameters of the two groups

| Parameters | All Patients (N = 575) | LVEF 40%–49% (N = 345) | LVEF ≥50 (N = 230) | p-Value |
|-------------------------|---------------------------|---------------------------|-----------------------|---------|
| PVC (% >30) | 10.8 | 12.8 | 7.6 | .07 |
| LPs (% yes) | 13.8 | 16.4 | 9.4 | <.05 |
| FQRS (% yes) | 12.6 | 15.2 | 8.0 | <.05 |
| LAS (% yes) | 20.7 | 23.8 | 15.3 | <.05 |
| RMS (% yes) | 19.0 | 22.5 | 13.1 | <.05 |
| FQRS msec | 101.4 ± 44.1 | 104.5 ± 54.4 | 95.9 ± 13.6 | <.05 |
| LAS msec | 38.9 ± 143.5 | 43.4 ± 180.6 | 31.0 ± 12.1 | .36 |
| RMS 40 mV | 44.6 ± 30.5 | 41.2 ± 28.5 | 50.9 ± 32.8 | <.05 |
| NSVT (%) | 8.6 | 11.1 | 4.9 | <.05 |
| QTc (%) | 13.6 | 15 | 11.3 | .26 |
| TWA (%) | 6.9 | 8.2 | 4.9 | .19 |
| Abnormal HRV (%) | 2.8 | 3.2 | 2.2 | .67 |
| Abnormal HRT/ DC (%) | 2.8 | 3.2 | 2.3 | .68 |

Abbreviations: DC, deceleration capacity; HRT, heart rate turbulence; HRV, heart rate variability; LPs, late potentials; NIRF, non-invasive risk factor; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; TWA, T-wave alternans.

TABLE 3 Electrocardiographic NIRFs in the two groups

PRESERVE-EF study which applied a two-step approach for the SCD risk stratification in this setting.

Our findings indicate that LPs, PVCs, and NSVT have a correlation with LVEF in patients with mildly reduced or preserved LVEF. However, only LPs and NSVT were independently related to reduced LVEF. Also, the multivariate analysis showed that LPs and NSVT are independent predictors of mildly reduced LVEF versus the preserved LVEF. These results imply the different relative impact of the NIRFs in the risk stratification of these patients.

The current SCD risk stratification schemes for patients with heart failure are far from ideal, especially for patients with mildly reduced or preserved LVEF (Gatzoulis, Sideris, et al., 2017; Pannone et al., 2021). In this context, it has been argued that the use of LVEF as the sole tool for risk stratification in this setting is insufficient and may result in unnecessary overuse of ICDs (Tung & Josephson, 2009). Indeed, in trials where patient selection was based only on

the LVEF, the 3-year absolute risk reduction regarding mortality was low (9% and 5.6% in MADIT II and SCD-HeFT, respectively) (Betts et al., 2013). With regard to ECG indexes, namely, the NIRFs, when used individually have low positive predictive value that increases substantially when examined in combination (Gatzoulis, Sideris, et al., 2017). It seems that a multivariate approach using multiple modalities (non-invasive and invasive) may provide enhanced risk stratification and increase the relative benefit of ICDs (Deyell et al., 2015; Gatzoulis, Sideris, et al., 2017). In other words, there seems to be an interplay between LVEF and other risk factors that imply an arrhythmogenic substrate. Although current guidelines refer to patients with LVEF <35%, it is well known that certain patients with mildly reduced or preserved LVEF may have an increased risk of SCD (Gatzoulis, Sideris, et al., 2017). The relative impact and value of each specific NIRF and its association with LVEF have not been well studied.

TABLE 4 Univariate and multivariable analysis of predictive ability of the studied parameters over the binary LVEF (LVEF 40%–49% vs. LVEF \geq 50%)

| Non-invasive risk factors | Univariate | | | Multivariate | | |
|---------------------------|------------|---------------|---------|--------------|---------------|---------|
| | OR | 95% CI | p-Value | OR | 95% CI | p-Value |
| LPs | 1.883 | 1.105 – 3.209 | .020 | 1.760 | 1.015 – 3.049 | .044 |
| PVCs | 1.783 | 0.991 – 3.208 | .054 | | | |
| NSVT | 2.409 | 1.204 – 4.820 | .013 | 2.444 | 1.184 – 5.042 | .016 |
| QTc | 1.388 | 0.832 – 2.316 | .209 | | | |
| Abnormal HRV | 1.449 | 0.497 – 4.228 | .497 | | | |
| Abnormal HRT/DC | 1.442 | 0.494 – 4.209 | .503 | | | |
| TWA | 1.719 | 0.837 – 3.527 | .140 | | | |

Abbreviations: DC, deceleration capacity; HRT, heart rate turbulence; HRV, heart rate variability; LPs, late potentials; NIRF, non-invasive risk factor; NSVT, non-sustained ventricular tachycardia; OR, odds ratio; PVCs, premature ventricular complexes; TWA, T-wave alternans.

Taking into account the findings of the present study, it seems that the presence of LPs and/or NSVT imply a more malignant arrhythmogenic substrate that accounts for the ventricular tachycardia induction during the PVS in post-MI patients with LVEF \geq 40% (Gatzoulis et al., 2019; Trachanas et al., 2021). On the other hand, it is evident that the other studied NIRFs, namely PVCs, increased QTc interval, presence of TWA, decreased heart rate variability, and abnormal HRT are not significantly associated with mildly reduced LVEF. As demonstrated in the PRESERVE-EF study, the patients with LVEF \leq 50% were more likely to have a positive PVS compared to patients with LVEF $>$ 50% (OR: 10.7, 95% CI: 3.1–36.9) (Gatzoulis et al., 2019). It is, therefore, reasonable to assume that the aforementioned NIRFs are not associated with an increased arrhythmogenic potential in post-MI patients with LVEF \geq 50%.

The presence of NSVT represents a well-known arrhythmic risk factor in patients with structural heart disease and is related with adverse outcomes, especially in patients with severe left ventricular impairment (Hashimoto et al., 2021; de Sousa et al., 2008; Zecchin et al., 2005). In the MADIIT-I and MUSTT clinical studies which included patients with ischemic cardiomyopathy who had severely depressed LVEF and NSVT, there was a high yield of a positive PVS and a significant benefit from a subsequent ICD implantation (Betts et al., 2013). However, the correlation of NSVT with LVEF has not been well studied, especially in patients with mildly reduced or preserved LVEF (Pannone et al., 2021).

The LPs, recorded by signal-averaged electrocardiography, represent delayed local ventricular depolarization indicating areas of scar/fibrosis that have slow conduction (Gatzoulis et al., 2018). In fact, the LPs are very prevalent in post-MI patients and have been associated with a history of sustained monomorphic VT (Gatzoulis et al., 2018; Hashimoto et al., 2021). Although their positive predictive value in these patients is far from ideal, they have a very good negative predictive value in the post-MI setting and also, they seem to be useful when incorporated in multifactorial risk stratification algorithms (Gatzoulis et al., 2018). Interestingly, an older study showed no association between LPs and left ventricular dysfunction in patients who

suffered a recent acute myocardial infarction (8 ± 5 days after the index event) (Gomes et al., 1987).

Based on the results of the present study, it could be suggested that particular NIRFs, namely LPs and NSVT, may have a significant impact in risk stratification of patients with mildly reduced or preserved LVEF. Thus, these NIRFs should possibly regularly be checked especially in patients with left ventricular dysfunction or in patients with declining LVEF over time, who do not fulfill the current indications for ICD implantation. Interestingly, another very recent analysis of 80 post-MI patients included in the PRESERVE-EF study showed that the prevalence of the electrocardiographic NIRFs was not significantly changed 1 year after the initial assessment (Xenogiannis et al., 2020). Nevertheless, some patients without positive NIRFs at the baseline evaluation became positive in the 12-month re-evaluation and vice versa (Xenogiannis et al., 2020). Therefore, despite being on a stable clinical condition, post-MI patients with LVEF \geq 40% should undergo regular evaluation of the electrocardiographic NIRFs in order to have an optimal long-term risk stratification (Xenogiannis et al., 2020). Specifically, it seems sensible to refer patients with NSVT and/or LPs for further evaluation with PVS according to the two-step protocol of the PRESERVE EF study. The PRESERVE-EF study indicated that patients who had at least one positive NIRF and considered to be of high arrhythmic risk benefited since they subjected to PVS, and those who had a positive study received an ICD (Gatzoulis et al., 2019). Indeed, patients of the PRESERVE-EF study having positive NIRFs and a positive PVS study were at a particularly high risk for SCD (Gatzoulis et al., 2019). In support of this notion, a recent retrospective study from our group showed that in hospitalized patients with mildly reduced LVEF, including post-MI and dilated cardiomyopathy patients, the two-step approach for risk stratification based on the NIRFs guided PVS effectively predicts the risk for future major adverse events (Arsenos et al., 2020). Of note, in the original PRESERVE-EF study, no primary endpoint events occurred in patients with LVEF $>$ 50%. Thus, the results of the present study have a particular importance in patients with

mildly reduced LVEF (40–49%) indicating specific NIRFs that are correlated with the left ventricular systolic dysfunction and at the same time implying a potentially arrhythmogenic substrate that should be further explored by PVS.

Some potential limitations should be acknowledged. Firstly, our study was a post hoc analysis of the data obtained by the PRESERVE-EF study and the studied electrocardiographic risk factors were limited according to the initial protocol. However, these NIRFs are representative and of clinical value in the setting of post-MI cardiomyopathy. Secondly, the evaluation using a 24-h digital ambulatory electrocardiographic recording may underestimate the true prevalence of the NIRFs. Longer recordings and sequential re-evaluation of these parameters could potentially reveal a different relative impact and different associations with LVEF. Thirdly, our patient population age was not too old. Elderly patients with more comorbidities may have a different arrhythmogenic substrate. Finally, we do not have data from advanced imaging modalities, such as cardiac magnetic resonance (Gatzoulis, Antoniou, et al., 2017; Kariki et al., 2020; YALIN et al., 2014). The incorporation of other NIRFs such as electrocardiographic markers of repolarization heterogeneity, markers of autonomic dysfunction, as well as magnetic resonance imaging markers of fibrosis, in this risk stratification schemes is a subject of future research.

5 | CONCLUSION

In post-MI patients, the presence of LPs, PVCs, and NSVT is more prevalent in patients with mildly reduced LVEF compared to those with preserved LVEF. Of note, these NIRFs have a correlation with LVEF in patients with mildly reduced or preserved LVEF. However, only LPs and NSVT are independently related to reduced LVEF while they are independent predictors of mildly reduced LVEF versus the preserved LVEF. Therefore, these particular NIRFs should be carefully and regularly checked during the follow-up of post-MI patients who do not fulfill the current criteria for ICD implantation which are mainly based to LVEF. There may be a specific value for those who experience a gradual decrease in LVEF over time being in the range of preserved or mildly reduced LVEF. The meticulous investigation, especially for these NIRFs, should guide the referral for further arrhythmic risk stratification by means of PVS according to the two-step approach.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KG, PA, DT, and C-K.A conceived of the presented idea. SS, PD, EK, NF, AS, EI, DT, KT, and TK developed the theory and performed the computations. KT, NF, and KPT collected the data. KK, SS, and KT verified the analytical methods. KPT wrote the manuscript with support from PK and ID. All authors discussed the results and contributed to the final manuscript.

ETHICAL APPROVAL

Hereby, I, Konstantinos A. Gatzoulis, consciously assure that for the manuscript “Association of noninvasive electrocardiographic risk factors with left ventricular systolic function in post-myocardial infarction patients with mildly reduced or preserved ejection fraction: Insights from the PRESERVE-EF study” the following is fulfilled: This post hoc analysis was approved by the Ethical Committee of the Hippokrateion General Hospital, Athens, Greece, and followed the ethical Declaration of Helsinki. Patients gave informed consent for their participation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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