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PhD THESIS

PREDICTIVE FACTORS FOR THE PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY PCI

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Keywords: acute myocardial infarction, percutaneous coronary intervention, independent predictors of outcome

1. INTRODUCTION - MOTIVATION

In Europe, cardiovascular diseases (CVD) represent 37% of all deaths, Romania, while in Romania this percentage is 63%. The principal cause of death in patients with coronary artery disease (CAD) is represented by acute myocardial infarction (AMI). In our country, about 13,000 persons suffer every year an AMI, while the mortality rate gains worrying amounts. The mortality rate decreases considerably afterwards, from 19% during the first 24 hours to 8% the next days. About 21% of deaths occur during the first month post-myocardial infarction (MI).

In the last decade, the treatment procedures of patients with myocardial infarction (MI) has improved in Romania too, as a result of the efforts made by the Romanian Society of Cardiology to implement progress in accordance with the European Society of Cardiology (ESC) guidelines. The reperfusion strategies performed in the first hours after the onset of AMI with ST-segment elevation contributed to a notably decrease in the mortality rate. The mortality rate further decreased after a change in reperfusion approach, from fibrinolysis to primary percutaneous coronary intervention (PCI).

In Romania, no predictors of mortality have been yet established in patients with AMI treated by an early PCI. This is an important issue, as Romanian patients may present some particular features in terms of clinical presentation and CV risk factors compared with the AMI patients in other European states.

Therefore, the aim of our study was to evaluate the independent predictors for LV remodeling, heart failure and death in AMI patients with (STEMI)- or without ST-segment elevation (NSTEMI) treated by an early, $<$ 12 hours from the symptoms onset percutaneous coronary intervention (PCI).

2. GENERAL PART

In Romania, CVD represent 63% of all deaths. This is more almost double compared to the rest of Europe (37%). According to the European Commission's 2018 report on health policies, Romania has the second highest mortality rate in the EU, with 1,530 deaths per 100,000 inhabitants, compared to an EU average of 1,036 cases. The most common cause of death is the disease of the circulatory system (cardiovascular, cerebrovascular). This state of health is associated with the level of health expenditure, i.e. EUR 983 per person per year.

AMI is the principal cause of death in patients with ischemic heart disease (IHD). In our country, approximately 13,000 persons experience an AMI every year, the mortality rate getting upsetting levels. The death rate decreases remarkably in time, from 19% during the first 24 hours to 8% the next day. Ultimately, 21% of deaths occur during the first month after the AMI.

Among the significant geographical variations that have been reported, Romania presents some interesting features. Firstly, cardiovascular disease was responsible for a significantly higher percentage of total deaths (55.5%). Secondly, death rates from cardiovascular disease were about three times higher in Romania compared to the rest of the world. And thirdly, the cardiovascular mortality rate (per 100,000 people) has increased in the last decade from 681 [95% confidence interval (CI) 677-685] in 2007 to 745 (95% CI 716- 774) in 2017, as opposed to the general downward trend. But, from 1994 to 2017, acute myocardial infarction age-standardized mortality rates decreased significantly in Romania between 1994 and 2017 in close correlation to the implementation of national healthcare programs.

Percutaneous coronary intervention (PCI) is the most commonly done and the best revascularization strategy all over the world. The best results are obtained when it is performed within the first 120 minutes from STEMI diagnosis by an experienced medical team. Over the last twenty years, the managing of CAD has been revolutionized by the progresses achieved in the PCI practice, tools, and associated therapies, increasing the procedural security and efficacy, and decreasing the needness for emergency surgery by coronary bypass artery graft (CABG), as well as the cardiovascular mortality. The demographics of patients in which PCI is performed has changed in the last decade, they being older and having a higher comorbidity burden. Despite these modifications in patients' clinical profiles, the data regarding the cardiac and noncardiac causes of death after PCI are lacking.

The data regarding the worldwide trend of total and cause-specific mortality in the short- and long-term amongst patients undergoing PCI in more recent years are controversial. Patient features, such as increasing age and a higher burden of comorbidities may favor noncardiac causes of death. But other reasons for lowering the long-term cardiac mortality are the progresses achieved in the revascularization technology, the high procedural success rates, and use of secondary cardiovascular prevention therapies.

Additional studies are necessary to add best methods to reduce the amount of noncardiac causes of death into clinical best practices guidelines regarding cardiac and noncardiac health.

Until now, there is no evidence from large randomized clinical trials specifically in patients with ACS, examining the benefit of lifestyle modifications, including regular physical activity, healthy diet, and weight loss, but overall results in other populations (like people with no CVD or post-MI patients) show consistent results. So these strategies are considered to be positive when in ACS patients.

3. SPECIFIC PART

3.1. SCOPE AND OBJECTIVES

This research thesis aims to establish through four case-control observational studies the independent predictors of in-hospital mortality, as well as of the 1-year mortality and readmission rates in acute myocardial infarction patients (both STEMI and high-risk NSTEMI), treated by PCI within the first 12 hours from the onset of symptoms.

The objectives of this thesis are:

1. To assess the prognostic role of systolic blood pressure and heart rate on the in-hospital mortality level in STEMI patients after primary PCI. Cardiac deaths were regarded those due to acute pulmonary edema, cardiogenic shock, ventricular fibrillation or cardiac rupture. Non-cardiac deaths were regarded those having an extra-cardiac cause, such as sepsis, acute renal failure, stroke.
2. To reveal clinical parameters that are correlated with in-hospital deaths in patients with acute coronary syndrome. The new Canadian-ACS risk score was used as a simple risk assessment tool for these patients. In-hospital mortality was the primary endpoint of the study. Mortality was defined by deaths from any cause of ACS patients during hospitalization
3. To seal the gaps in information, by a thorough analyze of a group of elderly AMI patients (aged ≥ 80 years) as part of the entire patients cohort admitted with acute myocardial infarction. The principal endpoint consisted of in-hospital mortality, defined as the death of whichever cause in the course of hospitalization for the AMI. The secondary endpoints were mortality and readmission rates in the course of the 1-year follow-up phase.
4. To evaluate the clinical, echocardiographic, biochemical, and angiographic factors linked with LV remodeling following an AMI. We enrolled AMI patients with LVEF ≥ 40% after successful PCI that was done within the first 12 hours from the symptoms` onset. We wanted to find the most notable independent predictors of LV remodeling, as well as their corresponding cut-off values. The study end-point was the appearance of echocardiographycally determined LV remodeling at the 6- months re-evaluation. Corresponding to the occurrence of LV remodeling, the patients were separated into the remodeling or the non-remodeling group. LV remodeling was diagnosed once the 6-month follow-up showed an increase of the LV end-systolic volume (LVESV) by more than 20% from the initial amount.

3.2. MATERIAL AND METHODS

3.2.1. From January to April 2017, 326 patients diagnosed with STEMI were hospitalized at the Institute of Cardiovascular Diseases Timisoara. The hospitalization took place in the first 12 hours within symptoms onset of the AMI. Of these, 294 patients underwent primary PCI and were enrolled in the research. According to the value of the systolic blood pressure (SBP) at admission, its value, patients were divided into 5 groups: group I, with SBP ≤105 mmHg; group II, with SBP 105-125 mmHg, group III, with SBP 126-140mmHg, group IV, with SBP 141-158 mmHg, and group V, with SBP ≥159 mmHg. An increased heart rate (HR) at admission was defined as a HR ≥80 beats per minute (BPM).

3.2.2. The study included all patients hospitalized with acute coronary syndromes (ACS), from January 2000 to December 2015 in the Cardiology Clinic of the Municipal Clinical Hospital Timisoara. STEMI patients were enrolled in the subgroup ACS-STEMI, while patients with unstable angina (UA) and those with AMI without ST-segment elevation were included in the ACS-NSTEMI group. Using the Canada-ACS risk score, we assessed the baseline risk of in-hospital mortality. The discriminatory capacity of this score was estimated. C-ACS risk score of all patients with ACS was calculated, and afterwards the same statistic was performed on the subgroups of ACS (NSTEMI-ACS and STEMI-ACS), separately. The predicted mortality rate was compared with those observed in different studies.

3.2.3. All consecutive patients that were admitted with AMI at the Timisoara Institute of Cardiovascular Disease between 1st January and 31st December of 2019, were evaluated for enrolling in this study. In the absence of contraindications, percutaneous coronary intervention (PCI) was done within the first 12 hours from the symptoms onset in all STEMI and in the high-risk NSTEMI patients. As high-risk NSTEMI were stated those patients with at minimum one of the following parameters: a GACE-score > 140, a relative rise or fall in cardiac enzymes, or dynamic changes of the ST-segment/ T wave. High-risk NSTEMI subjects in whom PCI could not be done within the first 12 hours of the symptoms onset were not included enrolled in the trial. The PCI and the associate pharmacological treatment were performed according to the ESC guidelines. Medical treatment records were accomplished during hospitalization, at discharge and after one year. The origin of death was established from hospital records, or by inquiring the patient`s physician. All readmissions were registered throughout the 1- year follow-up phase and their causes were established from the hospital records.

3.2.4. This study started in the Cardiology Clinic of the Institute of Cardiovascular Disease and completed in the Cardiology Clinic of the Municipal Emergency Hospital, in Timisoara.It enrolled all successive patients hospitalized for a first acute myocardial infarction January 2019 to January 2020 and could be effectively treated by a PCI done in the first 12 hours from the symptoms` onset, had a LVEF ≥40%, and were in sinus rhythm. The PCI was performed corresponding to the standard procedures (143), without surpassing the 12 hours interval from the symptoms` onset, in the STEMI and high-risk NSTEMI patients. Echocardiography was accomplished at starting point (as soon as possible following the PCI) and at 6 months. LV remodeling was outlined as an increase of > 20% in the biplane LV end-systolic volume from the initial evaluation to the 6-month`s measurement. As harmed or infarct-related segments were stated those segments showing at the initial examination longitudinal strains weaker than -15%.

3.3. RESULTS

3.3.1. Of the 294 STEMI patients that underwent primary PCI intervention, 218 (74%) were men. Their mean age was 62 ± 17 years (33-95 years. The basic features and cardiovascular history present in the 5 AMI patient groups are presented in Table 1. Compared to groups II-V, the group I patients (having admission SBP values <105 mmHg) were more often smokers (P = 0.026), elderly (P = 0.033), with systemic hypertension (P = 0.023), a history of old MI (P = 0.003), chronic renal failure (P = 0.0200) or diabetes (P = 0.041), more often their HR values were ≥80 bpm (P = 0.028), and their Killip were 3 or 4 at the time of admission (P = 0.020). Patients in group V, with SBP values ≥159 mmHg at admission, were more often diabetics and hypertensive. In patients in group I, the culprit injuries that triggered acute myocardial infarction were placed in the left coronary artery, right coronary artery, , or in at least two blood vessels, the maximum level of the enzyme creatine phosphokinase being significantly higher.Patients in group I had a higher mortality rate in the hospital, compared to patients in group V. During baseline hospitalization, there were 18 deaths (6%). 11 of these had cardiac causes (3.7%), while the rest of 7 had non-cardiac causes (3.3%). The main cardiac causes of in-hospital death were acute pulmonary edema, cardiogenic shock, myocardial rupture and ventricular fibrillation, which were the most common causes in group I patients. The appearance of cardiogenic shock and rupture of the free myocardial wall led more frequent to the death in group I AMI patients. Group I patients (n = 60) experienced an in-hospital all-cause death mortality rate of 15%, notably higher than in the other groups (P = 0.018). Among the other groups, the differences regarding the mortality rates were not important. Cardiac causes of death were more common in group I (P = 0.032), while non-cardiac causes of deaths were similarly distributed. In patients with an admission SBP value <105 mmHg at admission, the relative risk of death of all causes was 4.9 (95% CI 1,977–12,205, P = 0.006), while the relative risk of death with a cardiac cause was 5, 4 (95% CI 1.723–17.249, P = 0.003). Heart rate ≥80 bpm was also found to be an alternative prognostic factor for death in STEMI. The multivariable analysis called logistic regression selected these variables using the predictive power of the risk of in-hospital death. Considering the mortality risk in STEMI patients after PCI, the strongest predictor was SBP ≤105 mmHg (AUC = 0.804, 95% CI 0.712–0.896, P <0.0001), trailed by diabetes mellitus (AUC = 0.697, 95% CI 0.582–0.813, P = 0.0013), a history of hypertension (AUC = 0.554, 95% CI 0.439–0.670, P = 0.0009), and a HR ≥80 bpm (AUC = 0.664, 95% CI 0.541–0.747, P = 0.0272). Notable differences between the areas under the ROC curve, signifying important differences between their predictive capacities, were observed between diabetes and hypertension (0.143, 95% CI 0.0033–0.283, P = 0.044). Regarding the risk of cardiac death in patients with post-PCI ST-segment elevation myocardial infarction, the strongest variable was the Killip class ≥3 at the time of admission (AUC = 0.896, 95% CI 0.872–0.919, P = 0.0429) , followed by SBP ≤105 mmHg (AUC = 0.791, 95% CI 0.669–0.913, P = 0.0057), peripheral artery disease (PAD), (AUC = 0.648, 95% CI 0.498–0.798, P = 0.0015), and the HR ≥80 bpm (AUC = 0.756, 95% CI 0.727–0.785, P = 0.0023). Notable differences between the areas under the ROC curves were also observed when comparing the HR≥80 bpm with a Killip class ≥3 (0.140, 95% CI 0.106–0.173, P <0.0001) and when comparing the Killip class ≥3 with PAD (0.248, 95% CI 0.0955–0.399, P = 0.0014).

3.3.2. The study population consisted of 960 patients with ACS, 78% being men. The average age was 68 ± 11 years (between 35 and 85 years), 22.7% were over 75 years old. Of the total group of patients with ACS, 42.6% were stated with STEMI and 57.4% with NSTEMI. Comorbidities were common in these patients. We noticed that patients with STEMI tended to be younger, male, smokers or with a history of smoking, with higher HR and lower SBP at admission. The C-ACS risk score for all patients with acute coronary syndrome was 0.62 ± 0.78, being notably bigger in patients with STEMI vs. NSTEMI-SCA (P <0.001). In-hospital mortality was 11.8% in the study group, significantly higher in the subgroup of patients with STEMI (14.9%) than in the group of patients with NSTEMI-SCA (9.6%), P <0.02. Patients over 75 years had a higher mortality rate than those under 75 years in the total study group (OR = 1.71, 95% CI: 1.16-2.54, P = 0.006) and in the STEMI subgroup (OR = 4.25, 95% CI: 2.57-7.01, P <0.0001). A gradual increase in the in-hospital mortality correlated with the increase in the C-

ACS risk score in all hospitalized patients with acute coronary syndrome was observed. The predicted mortality was slightly higher than the observed one in ACS patients, but the difference was not notable. The mortality in patients with ACS was higher in elderly, women, smokers, and in those presenting at admission a Killip class>.1. a HR > 100 BPM and a SBP< 100 mmHg. The mean C-SCA risk score was significantly higher in patients who died of ACS (3.02 vs. 0.54, P <0.0001). Patients with STEMI who died were frequently older, hypertensive, smokers, with Killip class> 1, dyslipidaemia, and more frequently had TAS <100mmHg and a HR of over 100 bpm. The mean C-SCA risk score in these patients was 2.80 vs. 0.61 in STEMI surviving patients (P< 0.0001). Patients with NSTEMI-SCA who did not survive were more frequently women with diabetes mellitus, Killip class> 1, low SBP at admission and high HR values. Their mean C-SCA risk score was 3.3, compared with 0.48 in NSTEMI-SCA survivors (P <0.0001).Two independent predictors of in-hospital mortality were found in patients with acute coronary syndrome, using multivariable logistic regression: C-SCA risk score (P <0.0001) and age over 75 years (P = 0.016). The C-SCA risk score showed the best discrimination capability in the whole group of patients with ACS, with a statistical C of 0.94 (95% CI: 0.92-0.95). Statistic C for over age 75 years was 0.70 (95% CI: 0.67-0.73).

3.3.3. 297 patients were admitted with AMI and 277 were registered in the trial. The mean age was 67.38±13.4 years (32-95 years). 173 (63%) were males. According to the age at admission, AMI patients were divided into two groups: group I (≥80 years, n=63), and group II (< 80 years, n=214). The group I patients were less often men, smokers, and had more often a history of hypertension, stroke, heart failure, and kidney disease. They also presented more frequently a LEVF<50% and a higher Killip functional class at admission. No angiography was performed in 4% of the octogenarians and in 0.5% patients of the younger patients (*P*=0.66), for the reason of critical kindney failure. Group I patients presented significantly more frequent a 3-vessel coronary disease (*P* =0.01), and were significantly less frequent treated with myocardial revascularization by PCI (48% vs. 78%, (*P*<0.0001). The proportion of CABG was 2% in the octogenarians and 3% in the younger group II (*P*=0.67). Concerning the associated drugs, the octogenarians received more often diuretics and oral anticoagulants (*P*<0.001). The entire all-cause mortality percentage, counting in-hospital and 1-year mortality, was 12.6% (n=35). Among the octogenarians 18 (28%) died, while among the younger AMI patients the mortality rate was 17 (8%), P<0.0001. The octogenarians had a relative risk to die of 3.5 (95% CI 1.94 to 6.46, P<0.0001). All-cause deaths had a relative risk for in-hospital mortality of 3.2 in the octogenarians (95% CI 2.08 to 5.18, P<0.0001), and the cardiac deaths of 2.9 (95% CI 1.11 to 7.83, P=0.029). .In univariate analysis, the parameters linked with in-hospital death risk were age ≥80 years (*P* < 0.0001), diabetes (*P* < 0.0001), male sex (*P* < 0.0001), a Killip class ≥3 (*P* < 0.0001),a previous MI (*P* < 0.001), an LVEF <40% at admission (*P* < 0.0001), and a three-vessel CAD (*P* < 0.01). The multivariate logistic regression selected three parameters that acted as independent predictors for the risk of in-hospital mortality. These parameters were: an age ≥ 80 years [*P*<0.0001, 95% CI 3.05 to 16.20, odds ratio (OR) 7.03], a Killip class 3 or 4 (P<0.0001, 95% CI 1.06 to 5.51, OR=2.41).and a LVEF < 40% at admission (P<0.0001, 95% CI 0.99 to 4.59, OR=2.1). The comparison of ROC cu rves for these parameters showed that an LVEF< 40% at admission was the most potent predictor for in-hospital death, with an AUC of 0.687, followed by the age ≥ 80 years (AUC=0.672) and the Killip class ≥ 3 (AUC=0.665). In the cohort group of patients with STEMI, following multivariable logistic regression, we identified two independent predictive factors of in-hospital mortality: C-SCA risk score ($P < 0.0001$) and dyslipidemia ($P = 0.005$). The highest discriminative power was stated for the C-SCA risk score (AUC=0.92, 95% CI: 0.98-0.94).In the cohort of NSTEMI patients, multivariable logistic regression identified two independent predictive factors of in-hospital deaths the C-SCA risk score ($P < 0.001$) and the female gender ($P = 0.016$). Both independent indicators had discriminatory power: C-SCA risk score AUC=0.97, 95% CI: 0.95-0.98; female gender with AUC=0.75, 95% CI: 0.73-0.78).

3.3.4. 24% patients were detected to have LV remodeling and were included in group II, while 66% were included in group I. The patients presenting LV remodeling were found to be older, more frequent hypertensive, with higher peak values of CPK-MB isoenzymes and upper Killip functional classes, but lower values of the estimated glomerular filtration rate. They also had more frequently multivessel CAD. The percentage of STEMI patients was superior in group II, but the difference was not notable (94% vs. 89%). Concerning the echocardiogray data, we established that baseline LVESV and LVEDV were notably lower in the remodeling group. The differences between LVEF, stoke volume indexes, E/A ratios, and wall motion score indexes were not important. At the 6-month echocardiography, the LVESV and the WMS indexes were notably higher in the remodeling group, while the LVEF and stroke volume indexes were importantly lower compared to group I. The odds ratio of LV remodeling occurrence was 1.81 in STEMI patients (95% CI: 0.66-5.00, $P=0.24$). In univariate logistic regression, we found 15 predictors for LV remodeling ($P<0.001$) in AMI patients revascularized by PCI and having a midrange or preserved LVEF. These included age, systemic hypertension, hypercholesterolemia, smoking history, systolic and diastolic blood pressure at admission, the Killip class, the estimated glomerular filtration rate, the peak values of CK-MB isoenzymes, the 2- and 3 vessel CAD found at angiography, the LVEDV, and the LVESV, as well as HLS and the HLSR. The multivariate logistic regression selected 5 independent predictors for LV remodeling, and these were: the Killip class, the 3-vessel CAD, and the baseline LVESV, HLS, and HSR.

4. DISCUSSION AND CONCLUSIONS

The objectives of the study were fully met, the results obtained being positive, but especially in accordance with those in the literature.

4.1. The first study highlights that vital signs (SBP and HR) measured in the emergency-room in STEMI patients might offer valuable information regarding the risk of in-hospital death followind a primary PCI intervention. Admission SBP ≤105 mmHg and/or HR ≥80 bpm are correlated with a high risk of death, while SBP ≥159 mmHg and/or HR <80 bpm are correlated with a better outcome. Diabetes mellitus and systemic hypertension were identified as independent predictors for every-cause mortality, while Killip class ≥ 3 class and multivessels CAD were outlined as independent predictors for cardiac-related in-hospital mortality in STEMI.

4.2. The Canada- Acute Coronary Risk Score used in the second study showed to be succesful when used to assess patients with acute coronary syndrome, using only clinical parameters measured at the first medical examination of the patient. The predicted mortality was slightly higher than the mortality observed in the hospital in ACS patients, but the difference was not important. A gradual increase in the in-hospital mortality correlated was observed with the increase in the C-SCA risk score in all hospitalized ACS patients. C-ACS was the most powerful independent predictor for in-hospital mortality in the entire group of ACS-patients, as well in the STEMI and NSTEMI subgroups.

4.3. The main findings of the third study, that evaluated the treatament strategies and outcomes in octogenarians with AMI, were as follows: AMI patients aged ≥ 80 years were less frequently treated by a revascularization method within the first 12 hours from the symptoms onset of and they have a worse prognosis when compared with those aged <80 years. Interventional revascularization by a PCI was done less frequent in the elderly ($P<0.0001$), while coronary artery by-pass graft was performed in about 2% of all AMI patients, regardless of the age-group. The risk of in-hospital death was 3 times higher in the elderly. Our study identified three independent predictors for in-hospital mortality in AMI patients: the age ≥ 80 years, the LVEF < 40% at admission, and the Killip class 3 or 4. the 1-year mortality was 12 % in the elderly, while the 1-year readmission rate was 18%. Both the 1-year mortality and the 1-year readmission rate were significantly higher in the elderly ($P<0.001$, and $P<0.01$, respectively). The most frequent causes of 1-year death and/or readmission were recurrent myocardial infarction and aggravated heart failure, suggesting that the AMI in elderly patients is the result of more extensive atherosclerosis and a more severe coronary artery disease.On the subject of the concomitant medication, the diuretics and the oral anticoagulants were more often prescribed in the elderly, as they presented more often heart failure and atrial fibrillation, respectively. Although the elderly received more often oral anticoagulants, the in-hospital bleeding rate in the elderly was not significantly different from that of the younger AMI patients, probably because the radial approach represents the preferred method of vascular access in our hospital. At discharge, the proportion of patients receiving oral anticoagulants was again higher among the elderly, and their 1-year mortality rate due to bleeding or stroke was higher ($P=0.04$). This fact can be explained the higher prevalence of oral anticoagulant treatment, of female gender and of chonic kidney disease in the elderly, all these conditions being risk factors for bleeding.

4.4. The fourth study, a case-control observational study, confirmed the predictive value of 2D-STE for the early detection of LV remodeling in AMI patients with a midrange or preserved LVEF after successful reperfusion by PCI. At the 6-month echocardiography, 61 patients (24%) were identified by this method as presenting LV remodeling. The odds ratio of LV remodeling occurrence was 1.81 in STEMI patients compared with the high-risk NSTEMI patients ($P=0.24$). The multivariate logistic regression selected 5 independent predictors for LV remodeling. The most potent predictors of LV remodeling were the HLS ($P<0.001$), and the HLSR ($P<0.001$). The other independent predictors were the LVEDV ($P<0.001$), the Killip class ($P<0.001$), and the 3-vessel CAD ($P<0.001$). The detected cut-off values predicting LV remodeling at baseline 2D-STE examination were -11% for the HLS and -0.65 s^{-1} for the HLSR. At Cox-regression analysis, the coefficients for LV remodeling were 1.4 for a baseline infarct-related LS weaker than -11% ($P<0.0001$, and 2.16 for a infarct-related baseline LSR lower than -0.65s^{-1} ($P<0.001$). 2D-STE was demonstrated to be an effective, practical, and trustworthy noninvasive technique able to predict LV remodeling in this cohort of patients.