Cardiac imaging characteristics of patients with COPD: prognostic implications

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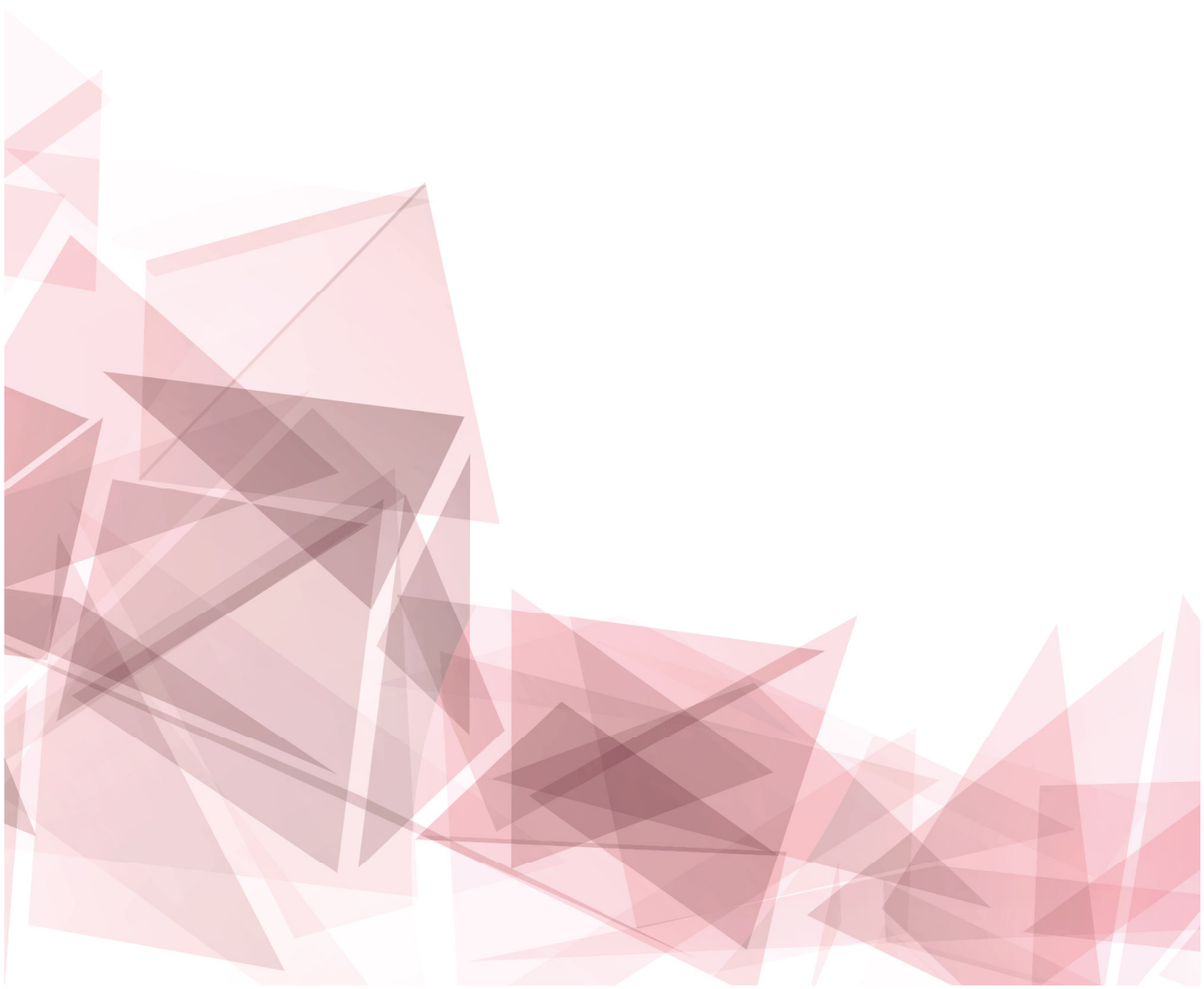

Chapter 3

Left Ventricular Global Longitudinal Strain and Long-term Prognosis in Patients With Chronic Obstructive Pulmonary Disease after Acute Myocardial Infarction

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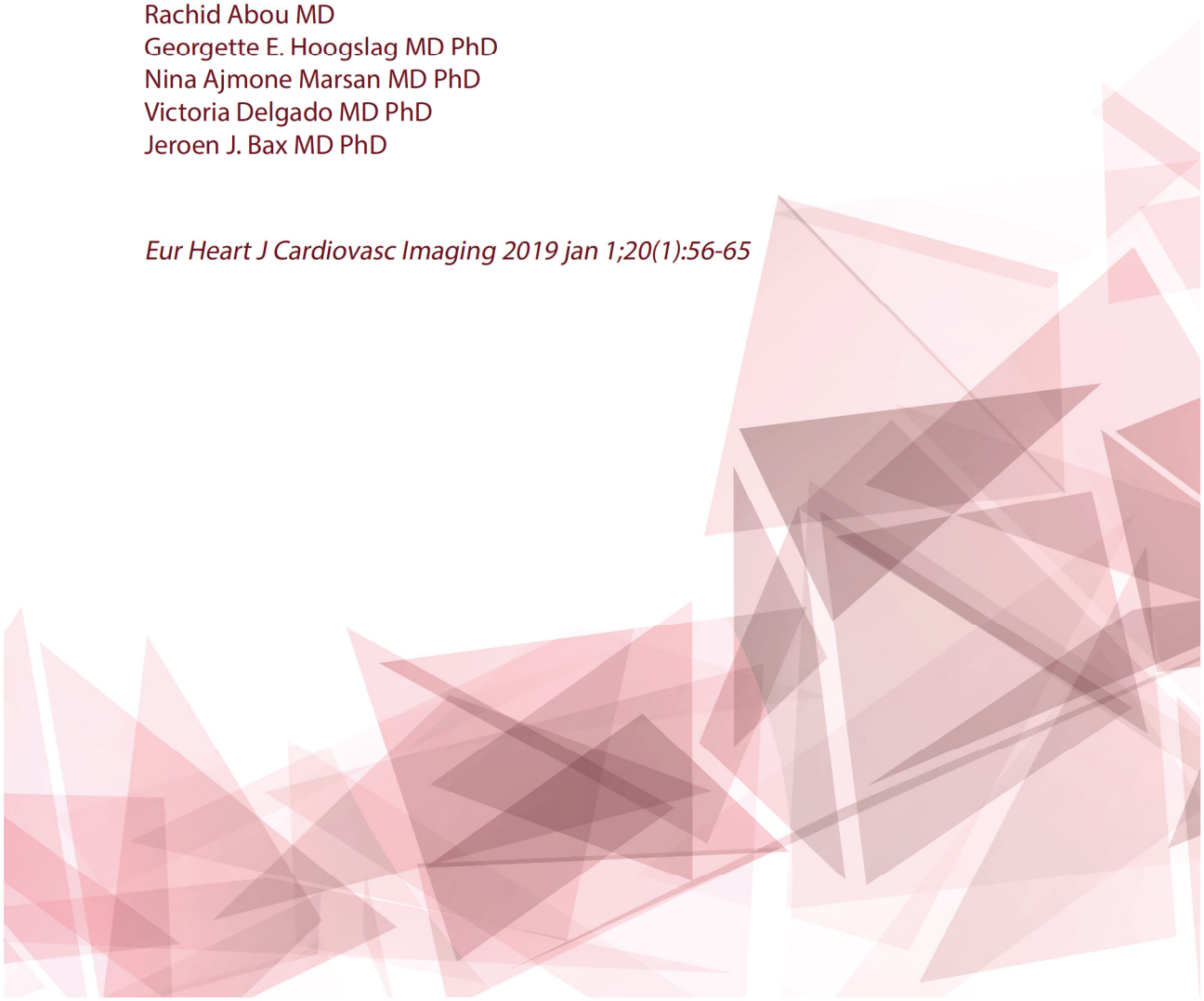


Abstract

Aims LV systolic function is a known prognostic factor after ST-segment elevation myocardial infarction (STEMI). We evaluated the prognostic value of left ventricular (LV) global longitudinal strain (GLS) in patients with chronic obstructive pulmonary disease (COPD) after STEMI.

Methods and results 143 STEMI patients with COPD (mean age 70±11 years, 71% male), were retrospectively analysed. LVEF and LV GLS were measured on transthoracic echocardiography within 48 hours of admission. Patients were followed for the occurrence of all-cause mortality and the combined endpoint of all-cause mortality and heart failure hospitalization. After a median follow-up of 68 (IQR 38.5-99) months, 66 (46%) patients died and 70 (49%) patients reached the combined endpoint. The median LV GLS was -14.4%. Patients with LV GLS >-14.4% (more impaired) showed higher cumulative event rates of all-cause mortality (19%, 26% and 44% vs 7%, 8% and 18% at 1, 2 and 5 years follow-up, log-rank p=0.004) and the combined endpoint (26%, 34% and 50% vs 8%, 10% and 20% at 1, 2 and 5 years follow-up, log-rank p=0.001) as compared to patients with LV GLS ≤-14.4%. In multivariate analysis, LV GLS >-14.4% was independently associated with increased all-cause mortality and the combined endpoint (hazard ratio 2.07; p=0.02 and hazard ratio 2.20; p=0.01, respectively) and had incremental prognostic value over LVEF demonstrated by a significant increase in $\chi 2$ (p=0.023 and p=0.011, respectively).

Conclusion Impaired LV GLS is independently associated with worse long-term survival in STEMI patients with COPD and has incremental prognostic value over LVEF.

Keywords: Prognosis; COPD; myocardial infarction; global longitudinal strain; speckle tracking echocardiography

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of hospitalization and death due to cardiovascular diseases.[1] Particularly, among patients with ST-segment elevation myocardial infarction (STEMI), the presence of COPD has been independently associated with higher mortality as compared to patients without COPD.[2-4] The underlying factors explaining this mortality difference include delayed diagnosis and reperfusion treatment of a STEMI and underuse of secondary prevention therapy.[5] These may lead to large left ventricular (LV) infarct size and adverse remodelling (dilation) during follow-up, increasing the risk of heart failure and cardiovascular mortality. Left ventricular ejection fraction (LVEF) is frequently used in clinical practice as a marker of the myocardial damage (infarct size) after STEMI and is a well-known prognostic determinant. However, in a recent large cohort of STEMI patients, COPD patients had comparable LVEF as patients without COPD.[6] Two-dimensional (2D) speckle tracking echocardiography is an advanced technique to assess myocardial deformation. In contrast to LVEF which reflects a change in LV volume, 2D speckle tracking echocardiography evaluates the active contraction of the myocardium reflecting directly the myocardial function. LV global longitudinal strain (GLS) measured with 2D speckle tracking echocardiography is currently one of the most frequent variables to reflect LV systolic function and has been associated with prognosis after STEMI.[7] In contrast to LVEF, LV GLS showed that STEMI patients with COPD had larger myocardial damage than patients without.[6] Therefore, LV GLS may have more discriminative power than LVEF to identify the patients with increased mortality risk after STEMI. The present study evaluated the prognostic value of LV GLS in STEMI patients with COPD and investigated whether LV GLS has incremental value over conventional echocardiographic parameters for LV systolic function.

Methods

Patient population and data collection

From an ongoing registry of patients admitted with acute STEMI and treated with primary percutaneous coronary intervention at the Leiden University Medical Center (Leiden, the Netherlands) between 2004 and 2013, patients with COPD were identified. When pulmonary function tests were available, COPD was defined according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines (ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) <0.7).[8] Otherwise, a documented history of COPD was taken into consideration. Patients were treated according to the guideline based institutional STEMI protocol (MISSION!) as described previously.[9-11] Optimal medical therapy was initiated during hospitalization and echocardiography was performed within 48 hours of admission. Clinical and echocardiographic data were collected prospectively in the departmental Cardiology information system (EPD-

vision) and echocardiographic database, respectively. All data were retrospectively analysed. For this retrospective analysis, the Institutional Review Board waved the need for patient written informed consent. Patients were excluded if they had a documented history of asthma, when the echocardiographic image quality was not suitable for LV GLS measurement using two-dimensional speckle tracking echocardiography or when patients died before echocardiography was performed.

Clinical data

Demographic and clinical characteristics were recorded. Diabetes mellitus was defined as having a history of diabetes mellitus and subsequent medical therapy with insulin, oral glucose-lowering drugs or diet. Hypertension was defined as previous use of antihypertensive medication or a systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg.[12] Hypercholesterolemia was defined as having a documented history of hypercholesterolemia and/or statin use. During invasive coronary angiography, the culprit vessel was identified and multivessel disease was defined as more than one vessel with >50% luminal stenosis.

Transthoracic echocardiography

Images were obtained using a commercially available system (Vivid 7 and E9, GE Healthcare, Horten, Norway) with the patient at rest, in left lateral decubitus position. A 3.5 MHz or M5S transducer was used to obtain parasternal, apical and subcostal views and images were digitally stored in cine-loop format. Standard 2D, M-mode, color, pulsed- and continuous-wave Doppler images were acquired according to the recommendations by the American Society of Echocardiography.[13] Data analysis was performed off-line using the EchoPac software (version BT13, GE Medical Systems, Horten, Norway).

LV dimensions were measured in the parasternal long-axis view and LV mass was calculated using the Devereux's formula.[13] In apical two- and four -chamber views, LV volumes were measured and LVEF was calculated using the biplane Simpson's method.[13] Furthermore, the LV was divided into 16 segments for calculation of the wall motion score index (WMSI). Each individual segment was scored based on systolic thickening and motion (1=normokinesia, 2=hypokinesia, 3=akinesia, 4=dyskinesia).[13] Subsequently, the WMSI was calculated as the sum of all individual segments divided by the number of segments.[13] LV diastolic function was assessed by obtaining peak early (E) and late (A) diastolic velocities and E-wave deceleration time on pulsed-wave Doppler recordings of the transmitral flow.[14] LV filling pressures were evaluated by calculating the E/e' ratio using the average e', measured at both the septal and lateral side of the mitral annulus with tissue Doppler imaging at the apical 4-chamber view.[14] To assess global right ventricular (RV) systolic function, tricuspid annular plane systolic excursion (TAPSE) according to current recommendations.[13] The systolic pulmonary arterial pressure (SPAP) was estimated by calculating the RV pressure from the peak velocity of the tricuspid regurgitant jet according

to the Bernoulli equation and adding the right atrial pressure.[13] The right atrial pressure was determined according to the diameter and inspiratory collapse of the inferior vena cava.[13]

Two-dimensional speckle tracking echocardiography

Analysis of transthoracic echocardiography by 2D speckle tracking echocardiography was performed offline and blinded to clinical data. To quantify LV GLS, standard routine gray-scale images were used from the apical 2-, 3- and 4-chamber views, with a frame rate ≥40 frames/sec. The LV endocardial border was traced at end-systole at the three apical views, and the automatically created region of interest was manually adjusted to the thickness of the myocardium. Subsequently, the myocardium was tracked throughout the cardiac cycle and segments with poor tracking were (manually) excluded. LV GLS was provided by the software as the average peak systolic strain of the three apical views and presented in a 17-segment "bull's eye" plot.[15] To correct for the potential effect of the RV pressure overload secondary to COPD on the myocardial strain of the septal segments and subsequently on the LV global longitudinal strain, the average of regional longitudinal strain of 5 septal segments was calculated (Figure 1). The value of longitudinal strain of the remaining segments was averaged and compared to the average value of the septal segments. Intra- and inter-observer variability of LV GLS analysis in our laboratory have been previously reported.[7]

Follow-up and endpoint definitions

Patients were followed at the outpatient clinic according to the institutional care track protocol.[9] The occurrence of adverse events (all-cause mortality and heart failure hospitalization) at long-term follow-up was prospectively recorded through telephone interviews and requesting medical records when indicated. Data on mortality was collected through municipal civil registries, which contain up-to-date mortality data. All-cause mortality was the primary endpoint. The secondary endpoint was a composite of all-cause mortality and heart failure hospitalization. Heart failure hospitalization was defined as hospitalization for new-onset or worsening of heart failure. Follow-up was obtained for all study patients.

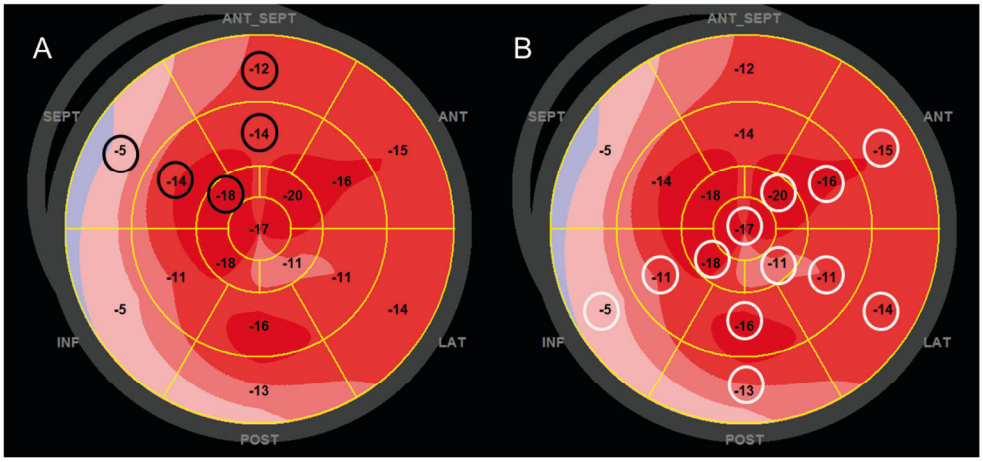


Figure 1. Segmental longitudinal strain analysis. Example of an automatically generated 17 segment "bulls-eye" plot, derived from 2-dimensional speckle tracking echocardiography. Septal strain was calculated as the average of the 5 septal segments (A) and non-septal strain as the average of the remaining 12 segments (B).
Abbreviations: ANT, anterior wall; ANT_SEPT, anteroseptal wall; INF, inferior wall; LAT, lateral wall; POST, posterior wall; SEPT, septal wall.

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous data are presented as mean ± standard deviation or median and interquartile range, as appropriate. Patients were divided into two groups, based on their survival status. To compare categorical data between survivors and non-survivors, chi-square ($\chi 2$) tests or Fisher's exact were performed, as appropriate. Continuous data were compared using the unpaired Students t-test or Mann-Whitney U test, as appropriate.

Furthermore, Kaplan-Meier analysis was performed for survival and cumulative event rates. For the combined endpoint, patients were censored at the occurrence of the first event. The study population was divided into two groups according to the median LV GLS (-14.4%) and the cumulative event rates were compared with log-rank tests.

Finally, the association of clinical and echocardiographic variables with the primary and secondary endpoints were tested using the Cox proportional hazards analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. Due to the relatively small number of events, the number of covariates added into the multivariate models was adjusted to avoid overfitting. Clinically relevant and/or statistically significant predictors in the univariable Cox regression analysis ($p \leq 0.05$) were included in multivariable models. The final multivariable model for the primary endpoint consisted of clinical (age, diabetes and β-blocker use) and echocardiographic variables of LV and RV systolic function (TAPSE, LVEF, WMSI and LV GLS). For the secondary endpoint, the same clinical variables were used and E/e' ratio was added to the echocardiographic parameters. To evaluate the

incremental value of LV GLS over clinical and conventional echocardiographic variables, nested regression models were created and the change in global $\chi 2$ values was calculated. A two-sided p-value of <0.05 was statistically significant. All statistical analyses were performed using SPSS software (version 24, IBM SPSS statistics for Windows, Armonk, New York).

Results

Of 173 STEMI patients with COPD treated with primary percutaneous coronary intervention, 30 patients were excluded due to transfers to other hospitals before echocardiography was performed (n=20), death within 48 hours (n=2) or LV GLS measurement not feasible due to image quality (n=8) (Figure 2). Therefore, the total study population consisted of 143 consecutive patients (mean age 70±11 years, 71% male). Segmental strain analysis was feasible in 131 out of 143 study patients (92%) due to variation in heart rate or frame rate between the 3 apical views. After a median follow up of 68 (IQR 38.5-99) months, 66 patients (46%) died and 70 patients (49%) reached the composite endpoint. The population was divided into two groups, based on survival status.

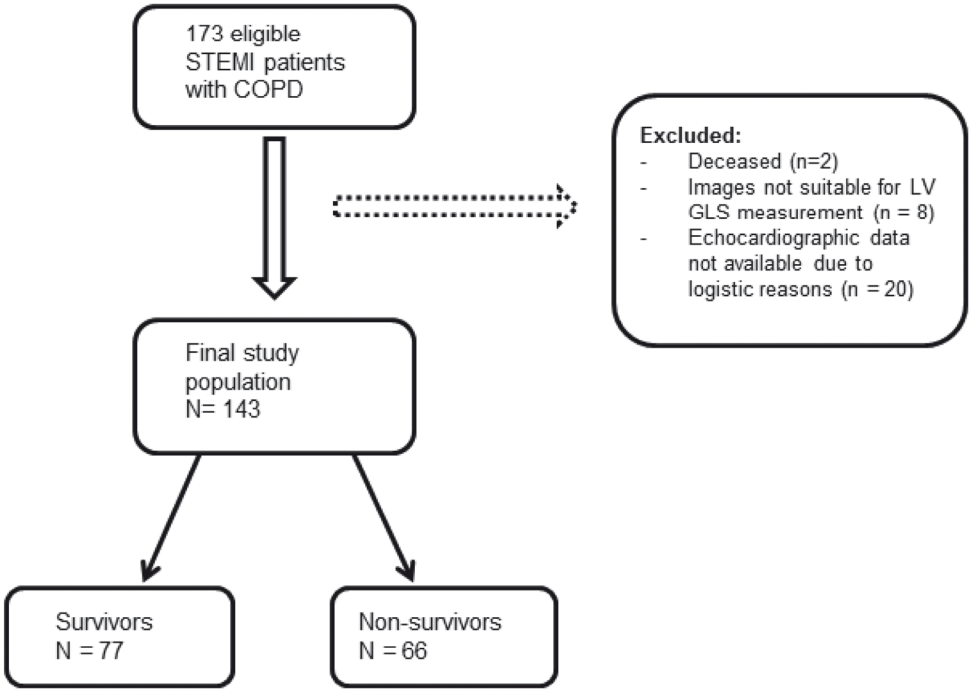


Figure 2. Flowchart of patient selection.
Abbreviations: COPD, chronic obstructive pulmonary disease; LV GLS, left ventricular global longitudinal strain; STEMI, ST-segment elevation myocardial infarction.

Clinical characteristics

Baseline clinical characteristics are reported in Table 1 for the total study population, survivors and non-survivors. Almost half of the patients (53%) had multivessel disease and the right coronary artery was the most frequently involved culprit vessel (40%). One fifth of the population had impaired renal function (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2). Nearly all patients received the medication as recommended by the most recent European Society of Cardiology STEMI guidelines, except for β-blockers which were prescribed in 85% of the patients.[11]

When comparing survivors versus non-survivors, patients who died were significantly older (74±10 vs. 66±10 years, p<0.001), more often diabetics (21% vs. 7%, p=0.010), had a slightly lower diastolic blood pressure (80±19 vs. 87±15 mmHg, p=0.011) and less frequent prescription of β-blockers after discharge (82 vs 95%, p=0.017), as compared to survivors.

Table 1. Clinical characteristics of the total population, survivors and non-survivors.

	Total population (n=143)	**Survivors (n=77)**	**Non-survivors (n=66)**	**p-value***
Age (years, SD)	70 ± 10.6	66 ± 10	74 ± 10	<0.001
Male (n%)	102 (71)	51 (66)	51 (77)	0.146
Current smoking (n%)	74 (51)	41 (53)	32 (49)	0.570
Hypertension (n%)	62 (43)	34 (44)	28 (42)	0.835
Diabetes (n%)	19 (13)	5 (7)	14 (21)	0.010
Family history of CVD (n%)	50 (35)	32 (43)	17 (27)	0.048
Hypercholesterolaemia (n%)	31 (22)	16 (22)	15 (23)	0.837
Peripheral vascular disease (n %)	13 (9)	4 (5)	9 (14)	0.080
Previous myocardial infarction (n%)	14 (10)	5 (7)	9 (14)	0.152
Killip class ≥2 (n%)	12 (8)	3 (4)	9 (14)	0.038
Systolic BP (mmHg)	140 ± 29	144 ± 28	134 ± 29	0.055
Diastolic BP (mmHg)	84 ± 17	87 ± 15	80 ± 19	0.011
Heart rate (at discharge)	74 ± 13	73 ± 10	75 ± 15	0.485
BSA	1.93 ± 0.20	1.95 ± 0.21	1.90 ± 0.19	0.102
Multivessel disease (n%)	76 (53)	39 (51)	37 (57)	0.455
Culprit lesion (n%)				0.312
LAD	54 (38)	25 (33)	29 (45)	
RCA	58 (40)	33 (43)	24 (37)	
RCx	29 (20)	18 (24)	11 (17)	
LM	1 (1)	0 (0)	1 (2)	
Peak CK (U/l)	1291 [597 – 2123]	1227 [513 -2161]	1395 [626 – 2109]	0.747
Peak troponin T (µg/l)	3.2 [1.3 – 7.2]	3.1 [1.0 – 6.0]	3.8 [1.9 – 8.0]	0.117
eGFR <60 ml/min/1,73m^2 (n%)	28 (19)	13 (18)	15 (23)	0.419
Glucose	7.5 [6.1 – 10.1]	7.5 [6.4 – 9.3]	8.0 [6.1 – 11.1]	0.593
Medication at discharge:				
Aspirin (n%)	134 (97)	76 (100)	57 (93)	0.037
Thienopyridines (n%)	137 (95)	76 (100)	60 (98)	0.445
B-blockers (n%)	123 (85)	72 (95)	50 (82)	0.017
ACEi/ARB (n%)	134 (93)	76 (100)	57 (95)	0.083
Statin (n%)	138 (96)	77 (100)	61 (100)	-

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BSA, body surface area; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LAD, left anterior descending; LM, left main; RCA, right coronary artery; RCx, ramus circumflex. Continuous data are presented as mean±SD or median [25th-75th percentile]. *p-values contribute to differences between survivors and non-survivors.

Echocardiographic characteristics

Baseline echocardiographic characteristics for the total study population, survivors and non-survivors are reported in Table 2. In the total study population, mean LVEF and LV GLS were 46±10% and -13.8±4.0%, respectively. Mean LV filling pressures were increased (E/e' ratio 15.7±7.8).

Patients who died had a significantly lower LVEF and more impaired LV GLS shortly after myocardial infarction (43±9 vs. 48±9%; p=0.001 and -12.9±4.3 vs -14.6±3.4%; p=0.011, respectively) as compared to patients who survived. Furthermore, patients who died had higher LV filling pressures (E/e' ratio 17.5±9.5 vs. 14.3±5.6, p=0.021). The segmental analysis showed that longitudinal strain values of both septal and non-septal segments were more impaired in patients who died as compared to survivors (Table 2). There were no differences in SPAP between the groups. Patients who died had a significantly lower TAPSE compared to survivors (16.9±4.6 vs. 18.5±3.4 mm, p=0.020), although the values were within normal ranges.

Survival analysis

Kaplan-Meier curves for all-cause mortality are shown in Figure 3A, with the population divided into two groups by the median LV GLS (-14.4%). The cumulative survival rates at 5 years were significantly lower for patients with LV GLS >-14.4% (more impaired) as compared to patients with LV GLS ≤-14.4% (52% vs. 78%, log-rank p=0.004).

Similarly, the 5-year cumulative event-free survival rates for the combined endpoint (all-cause mortality and heart failure hospitalization) were significantly lower for patients with LV GLS >-14.4% (more impaired) as compared to patients with LV GLS ≤-14.4% (50% vs. 80%, log-rank p=0.001; Figure 3B).

Table 2. Baseline echocardiographic measurements of the total population, survivors and non-survivors.

	Total population (n=143)	**Survivors** (n=77)	**Non-survivors** (n=66)	**p-value**
LVEDD (mm)	46 ± 7	47 ± 6	45 ± 8	0.089
LVESD (mm)	32 ± 7	32 ± 7	32 ± 8	0.919
PWT (mm)	11.5 ± 2.2	11.5 ± 1.9	11.6 ± 2.5	0.723
IVSD (mm)	11.3 ± 2.3	11.0 ± 2.1	11.7 ± 2.5	0.067
LVEDV (mL)	99 ± 38	99 ± 32	100 ± 45	0.926
LVESV (mL)	54 ± 26	51 ± 20	58 ± 32	0.101
LV mass (g)	200 ± 74	198 ± 61	203 ± 88	0.698
LVMI (g/m^2)	103 ± 34	100 ± 25	106 ± 41	0.326
LVEF (%)	46 ± 10	48 ± 9	43 ± 10	0.001
WMSI	1.44 [1.25 – 1.71]	1.38 [1.22 – 1.60]	1.50 [1.25 – 1.75]	0.053
LV GLS (%)	-13.3 ± 3.8	-13.9 ± 3.5	-12.3 ± 4.1	0.012
Septal segments (%)*	-12.9 ± 6.6	-14.3 ± 6.1	-11.2 ± 6.9	0.007
Non-septal segments (%)*	-11.4 ± 4.9	-12.3 ± 4.5	-10.3 ± 5.2	0.017
E (cm/s)	66 ± 18	64 ± 17	67 ± 19	0.381
A (cm/s)	76 ± 21	72 ± 17	80 ± 24	0.030
E/A ratio	0.84 [0.69 – 1.06]	0.86 [0.72 – 1.09]	0.83 [0.64 – 0.96]	0.189
E' (cm/s)	4.8 ± 1.8	4.9 ± 1.6	4.6 ± 1.9	0.329
E/e' ratio	15.7 ± 7.8	14.3 ± 5.6	17.5 ± 9.5	0.021
DT (ms)	213 ± 84	205 ± 72	224 ± 97	0.193
TAPSE (mm)	17.8 ± 4.1	18.5 ± 3.4	16.9 ± 4.6	0.020
SPAP (mmHg)	30 ± 8	30 ± 8	31 ± 8	0.317

A, A-wave peak velocity; DT, deceleration time; E, E-wave peak velocity; IVSD, interventricular septum diameter; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; LV GLS, left ventricular global longitudinal strain; PWT, posterior wall thickness; WMSI, wall motion score index. Data are presented as mean±SD or median [25th-75th percentile]. *Data available for 131 patients.

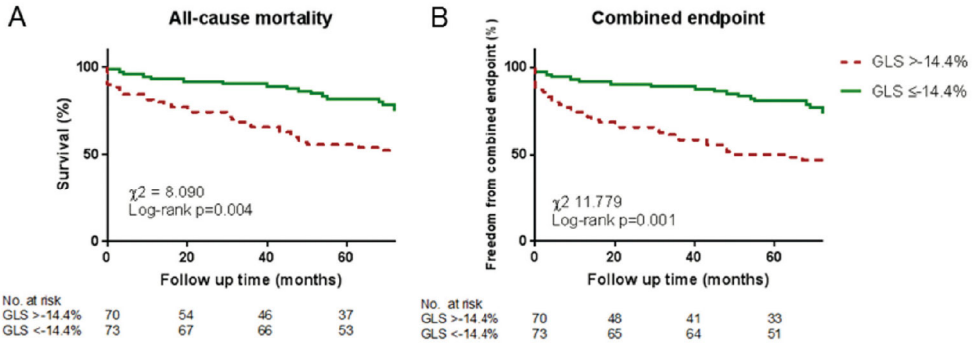


Figure 3. Kaplan-Meier estimates of all-cause mortality (A) and combined endpoint (B). Cumulative event rates were compared between patients with left ventricular global longitudinal strain (LV GLS) >-14.4% (dotted line) and patients with LV GLS ≤-14.4% (solid line).

Prognostic value of LV GLS in COPD patients after STEMI

Table 3 summarizes the significant univariable associates of all-cause mortality and the combined endpoint (all-cause mortality and heart failure hospitalization). Age, diabetes, β-blocker use, TAPSE, LVEF, WMSI and LV GLS >-14.4% were introduced into a multivariable model to identify independent associates of all-cause mortality. The correlation coefficient for LV GLS and LVEF was 0.484, for LV GLS and WMSI, 0.445 and for LVEF and WMSI, 0.535 ($p<0.001$ for all). Therefore, no evidence of multicollinearity was found and these variables could be introduced into the same multivariable model. Age, diabetes and LV GLS >-14.4% were independently associated with all-cause mortality (Table 3).

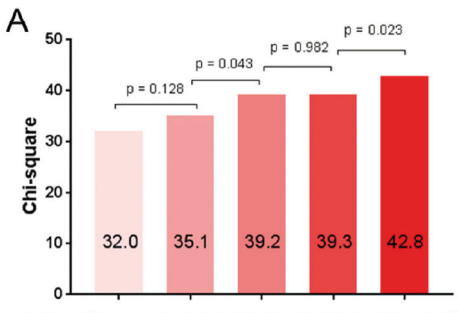
In addition, to identify independent associates of the combined endpoint, age, diabetes, β-blocker use, E/e' ratio, TAPSE, LVEF, WMSI and LV GLS >-14.4% were introduced into multivariable analysis. Only age and LV GLS >-14.4% were independently associated with the combined endpoint (Table 3).

Table 3. Uni- and multivariate cox regression analyses to identify independent clinical and echocardiographic associates of all-cause mortality and combined endpoint.

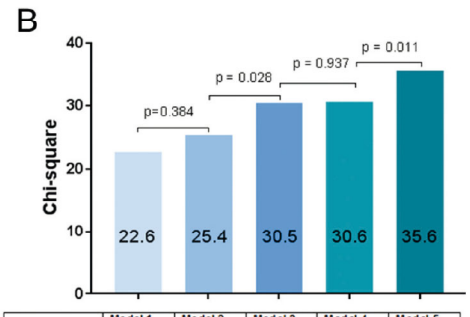
	Univariate analysis			Multivariate analysis		
All-cause mortality	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**HR**
Age, per 1 year increase	1.08	1.05-1.11	<0.001	1.07	1.04 - 1.11	<0.001
Male sex yes/no	1.44	0.81-2.57	0.21			
Diabetes yes/no	2.94	1.61-5.36	<0.001	2.27	1.13 - 4.55	0.02
Killip class ≥2 yes/no	2.68	1.31-5.46	0.01			
DBP, per 5 units increase	0.93	0.86-0.997	0.04			
β-blocker use yes/no	0.48	0.25-0.92	0.03	0.52	0.24 - 1.12	0.09
E/e', per 1 unit increase	1.05	1.02-1.08	<0.001			
LVEF, per 1 unit increase	0.95	0.93-0.98	0.001	0.98	0.94 - 1.01	0.22
WMSI, per 0.1 unit increase	1.08	1.00-1.17	0.05	0.67	0.24 – 1.84	0.44
LV GLS >-14.4% yes/no	2.02	1.23-3.31	0.01	2.07	1.11 - 3.86	0.02
TAPSE, per 1 unit increase	0.93	0.87–0.99	0.04	0.97	0.90 – 1.05	0.40
SPAP, per 1 unit increase	1.02	0.98-1.06	0.22			
Combined endpoint						
Age, per 1 year increase	1.06	1.03 - 1.09	<0.001	1.05	1.02-1.08	0.004
Male sex yes/no	1.32	0.76 - 2.28	0.392			
Diabetes yes/no	2.54	1.40 - 4.59	0.002	1.94	0.96-3.90	0.06
Killip class ≥2 yes/no	3.51	1.82 - 6.76	<0.001			
DBP, per 5 units increase	0.93	0.87 - 0.99	0.03			
β-blocker use yes/no	0.49	0.26 - 0.91	0.02	0.52	0.25 - 1.08	0.08
E/e', per 1 unit increase	1.05	1.02 - 1.08	0.002	1.00	0.96 - 1.05	0.89
LVEF per 1 unit increase	0.96	0.93 - 0.98	0.001	0.98	0.95 - 1.02	0.26
WMSI, per 0.1 unit increase	1.07	0.99 - 1.16	0.06	0.75	0.27 – 2.07	0.57
LV GLS >-14.4% yes/no	2.26	1.40 - 3.66	0.001	2.20	1.19 – 4.04	0.01
TAPSE, per 1 unit increase	0.95	0.89– 1.01	0.08	0.98	0.91 – 1.05	0.64
SPAP, per 1 unit increase	1.03	0.99– 1.06	0.15			

CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; WMSI, wall motion score index.

LV GLS had incremental prognostic value as demonstrated by a significant increase of global χ^2 to a model containing clinical and conventional echocardiographic parameters for both RV and LV systolic function (Figure 4).



	Model 1	Model 2	Model 3	Model 3	Model 4
		+ TAPSE	+ LVEF	+ WMSI	+ LV GLS
Age	1.07 (1.04-1.11)	1.07 (1.04-1.11)	1.07 (1.03-1.10)	1.07 (1.03-1.10)	1.07 (1.04-1.11)
Diabetes	2.23 (1.00-3.91)	2.14 (1.08-4.24)	2.12 (1.06-4.23)	2.12 (1.06-4.23)	2.27 (1.13-4.55)
B-blocker use	0.53 (0.25-1.12)	0.53 (0.25-1.14)	0.55 (0.26-1.18)	0.55 (0.26-1.18)	0.52 (0.24-1.12)
TAPSE		0.95 (0.88-1.02)	0.97 (0.90-1.04)	0.97 (0.90-1.04)	0.97 (0.90-1.05)
LVEF			0.97 (0.90-1.00)	0.97 (0.94-1.00)	0.98 (0.94-1.01)
WMSI				0.99 (0.39-2.54)	0.67 (0.24-1.84)
LV GLS >-14.4%					2.07 (1.11-3.86)



	Model 1	Model 2	Model 3	Model 4	Model 5
		+ E/e' ratio & TAPSE	+ LVEF	+ WMSI	+ LV GLS
Age	1.05 (1.02-1.09)	1.05 (1.02-1.08)	1.04 (1.01-1.08)	1.04 (1.01-1.08)	1.05 (1.02-1.08)
Diabetes	1.78 (0.91-3.50)	1.88 (0.95-3.72)	1.81 (0.91-3.61)	1.82 (0.91-3.63)	1.94 (0.96-3.90)
B-blocker use	0.53 (0.26-1.08)	0.54 (0.26-1.10)	0.55 (0.27-1.14)	0.55 (0.27-1.14)	0.52 (0.25-1.08)
E/e' ratio		1.01 (0.97-1.05)	1.01 (0.97-1.05)	1.01 (0.97-1.06)	1.00 (0.96-1.05)
TAPSE		0.96 (0.89-1.03)	0.98 (0.92-1.06)	0.98 (0.92-1.06)	0.98 (0.91-1.06)
LVEF			0.97 (0.94-1.00)	0.97 (0.94-1.00)	0.98 (0.95-1.02)
WMSI				1.04 (0.39-2.75)	0.75 (0.27-2.07)
LV GLS> -14.4%					2.20 (1.19-4.04)

Figure 4. Incremental value of left ventricular global longitudinal strain. Bar graphs illustrate the incremental value of echocardiographic parameters over clinical parameters on all-cause mortality (**A**) and combined endpoint (**B**), displayed by χ2 values on the y-axis. LVEF indicates left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index. Data are presented as hazard ratios and 95% confidence intervals.

Discussion

The present study demonstrates that in STEMI patients with COPD an impaired LV GLS is independently associated with worse long-term prognosis. Furthermore, LV GLS has incremental prognostic value over LVEF. This suggests that, in this specific patient population, LV GLS is more sensitive than LVEF to identify patients at risk for adverse events.

Prognosis of COPD patients after STEMI

Mortality rates are higher in patients with COPD after acute myocardial infarction as compared to patients without COPD.[2, 16] The higher mortality rates are frequently ascribed to the delayed diagnosis and reperfusion therapy of acute myocardial infarction.[5] Furthermore, underuse of β-blockers in COPD patients, due to the fear of bronchoconstriction, has been related to the higher mortality rates.[5, 17] However, data

from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) comparing 1,258 COPD patients with 13,445 non-COPD patients showed a 14% increased risk of mortality after myocardial infarction among COPD patients, irrespective of β -blocker use.[4] The present study showed that the underuse of β-blockers was associated with worse outcomes. However, after correcting for other variables such as age, diabetes and LV GLS, β-blockers use was not independently associated with all-cause mortality or the combined endpoint. This suggests that LV myocardial damage, as reflected by more impaired LV GLS, is a stronger prognostic determinant than β-blocker use.

Prognostic importance of GLS versus LVEF after STEMI

Echocardiographic assessment of infarct size has frequently relied on LVEF and WMSI.[18, 19] More recently, LV GLS has emerged as a good surrogate of myocardial infarct size[20, 21] and has incremental prognostic value over LVEF in the general population.[7] In STEMI patients with COPD, LV GLS has shown to be more sensitive than LVEF to evaluate the extent of myocardial damage.[6] In a retrospective series including 133 COPD patients and 1,617 patients without COPD, cardiac biomarkers and conventional echocardiographic parameters of infarct size (LVEF and WMSI) were similar in both groups whereas LV GLS was significantly more impaired in COPD patients as compared with patients without COPD.[6] Therefore, evaluation of LV GLS might be sensitive to detect myocardial damage after STEMI in patients with COPD.

It has been shown that the chronic inflammatory-catabolic state of COPD patients may be the underlying pathophysiology explaining the larger myocardial damage in these patients.[22] Increased levels of pro-inflammatory mediators and oxidative stress are recognized in COPD patients and have also been associated with reperfusion injury, leading to increased myocardial damage even shortly after myocardial infarction.[23, 24] Furthermore, patients with COPD exhibit increased circulating levels of matrix metalloproteinases (MMP's) which have been involved in the pulmonary remodelling process as well as in the LV remodelling after myocardial infarction.[25, 26] Figure 5 demonstrates a schematic overview of the association between systemic inflammation in COPD patients and the occurrence and consequences of STEMI.

Parallel to chronic inflammation resulting in cardiac remodelling, COPD is characterized by hypoxia causing increased pulmonary vascular resistance.[27] This increase in pulmonary vascular resistance can lead to an increase in pulmonary arterial pressures and subsequent RV dysfunction. This phenomenon has even been described in patients with mild COPD.[28] In our patient cohort, SPAP and RV function (using TAPSE) were evaluated with echocardiography, showing that TAPSE was significantly associated with all-cause mortality. However, after correcting for various factors, RV function was not independently associated with mortality. Interestingly, LV GLS did have a significant prognostic association with both endpoints, even after correction for RV function.

This is the first study evaluating the prognostic implications of LV GLS and its incremental prognostic value over conventional parameters such as TAPSE, LVEF and WMSI in STEMI patients with COPD. Patients with an LV GLS >-14.4% had significantly worse outcome than patients with LV GLS ≤-14.4%. These findings suggest that, LV GLS might be a more sensitive marker to identify the COPD patients at the highest risk of adverse events at the moment of discharge after STEMI, than the conventional LVEF.

Study limitations

Several study limitations should be acknowledged. This is a single centre, retrospective study limiting generalizability of the results. Furthermore, pulmonary function tests were not available for every patient to confirm the COPD status as stated in medical records. Therefore we could not assess differences between patients with different GOLD stages. However, previous studies have used the same definition of COPD in the absence of structural testing of pulmonary function in day to day practice.[2, 3]

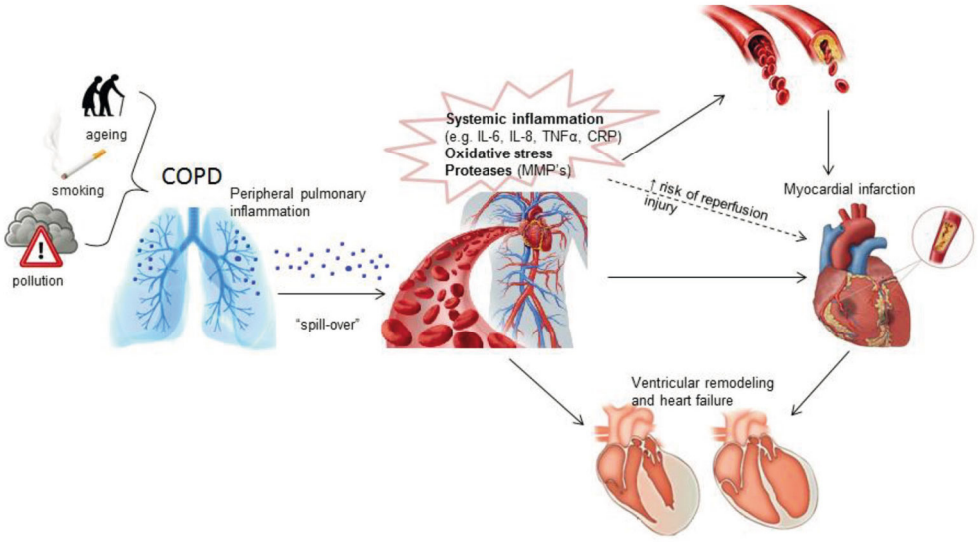


Figure 5. Cardiovascular disease in COPD patients. The peripheral pulmonary inflammation that occurs in COPD induces a systemic inflammation status due to the release to the systemic circulation of interleukines (IL-6 and IL-8), tumor necrosis factor (TNF)-α and C-reactive protein (CRP), increased oxidative stress and increase of proteases involved in the remodelling process of the vasculature and myocardium. These factors accelerate the atherosclerosis process, increasing the risk of myocardial infarction. During myocardial infarction, these factors also may increase the risk of reperfusion injury, and at follow-up, may influence the LV remodelling process leading to heart failure.

Conclusion

In STEMI patients with concomitant COPD, impaired LV GLS is independently associated with worse long-term prognosis. Importantly, LV GLS has incremental prognostic value over established risk factors and LVEF.

Conflicts of interest

The Department of Cardiology of the Leiden University Medical Centre received grants from Biotronik, Medtronic, Boston Scientific Corporation and Edwards Lifesciences. Victoria Delgado received speaker fees from Abbott Vascular.

References

1. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E, Jr., et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;16:63-70.
2. Campo G, Guastaroba P, Marzocchi A, Santarelli A, Varani E, Vignali L, et al. Impact of COPD on long-term outcome after ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention. *Chest* 2013;144:750-757.
3. Stefan MS, Bannuru RR, Lessard D, Gore JM, Lindenauer PK,Goldberg RJ. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest* 2012;141:1441-1448.
4. Hawkins NM, Huang Z, Pieper KS, Solomon SD, Kober L, Velazquez EJ, et al. Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *Eur J Heart Fail* 2009;11:292-298.
5. Rothnie KJ, Smeeth L, Herrett E, Pearce N, Hemingway H, Wedzicha J, et al. Closing the mortality gap after a myocardial infarction in people with and without chronic obstructive pulmonary disease. *Heart* 2015;101:1103-1110.
6. Goedemans L, Abou R, Hoogslag GE, Ajmone Marsan N, Taube C, Delgado V, et al. Comparison of Left Ventricular Function and Myocardial Infarct Size Determined by 2-Dimensional Speckle Tracking Echocardiography in Patients With and Without Chronic Obstructive Pulmonary Disease After ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2017;120:734-739.
7. Antoni ML, Mollema SA, Delgado V, Atary JZ, Borleffs CJ, Boersma E, et al. Prognostic importance of strain and strain rate after acute myocardial infarction. *Eur Heart J* 2010;31:1640-1647.
8. Gómez FP,Rodriguez-Roisin R. Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2002;8:81-86.
9. Liem S-S, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14. e1-11.
10. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-e140.
11. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-2619.
12. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315-81.

13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-271.
14. Nagueh SF, Smiseth OA, Appleton CP, Byrd IIIBF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321-1360.
15. Negishi K, Negishi T, Kurosawa K, Hristova K, Popescu BA, Vinereanu D, et al. Practical Guidance in Echocardiographic Assessment of Global Longitudinal Strain. *JACC: Cardiovasc Imaging* 2015;8:489-492.
16. Andell P, Koul S, Martinsson A, Sundström J, Jernberg T, Smith JG, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart* 2014;1:e000002.
17. Quint JK, Herrett E, Bhaskaran K, Timmis A, Hemingway H, Wedzicha JA, et al. Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013;347:f6650.
18. Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *J Am Coll Cardiol* 2002;39:30-6.
19. Baron T, Flachskampf FA, Johansson K, Hedin EM,Christersson C. Usefulness of traditional echocardiographic parameters in assessment of left ventricular function in patients with normal ejection fraction early after acute myocardial infarction: results from a large consecutive cohort. *Eur Heart J Cardiovasc Imaging* 2016;17:413-20.
20. Cimino S, Canali E, Petronilli V, Cicogna F, De Luca L, Francone M, et al. Global and regional longitudinal strain assessed by two-dimensional speckle tracking echocardiography identifies early myocardial dysfunction and transmural extent of myocardial scar in patients with acute ST elevation myocardial infarction and relatively preserved LV function. *Eur Heart J Cardiovasc Imaging* 2013;14:805-11.
21. Thorstensen A, Amundsen BH, Dalen H, Hala P, Kiss G, Aase SA, et al. Strain rate imaging combined with wall motion analysis gives incremental value in direct quantification of myocardial infarct size. *Eur Heart J Cardiovasc Imaging* 2012;13:914-21.
22. Sabit R, Bolton CE, Fraser AG, Edwards JM, Edwards PH, Ionescu AA, et al. Sub-clinical left and right ventricular dysfunction in patients with COPD. *Resp Med* 2010;104:1171-1178.
23. Blancke F, J. Claeys M, Jorens P, Vermeiren G, Bosmans J, L. Wuyts F, et al. Systemic Inflammation and Reperfusion Injury in Patients With Acute Myocardial Infarction. *Med Inflamm* 2005;6:385-389.

24. Maclay JD,MacNee W. Cardiovascular Disease in COPD: Mechanisms. *Chest* 2013;143:798-807.
25. MacNee W. Systemic inflammatory biomarkers and co-morbidities of chronic obstructive pulmonary disease. *Ann Med* 2013;45:291-300.
26. Phatharajaree W, Phrommintikul A,Chattipakorn N. Matrix metalloproteinases and myocardial infarction. *Can J Cardiol* 2007;23:727-33.
27. Tannus-Silva DG,Rabahi MF. State of the Art Review of the Right Ventricle in COPD Patients: It is Time to Look Closer. *Lung* 2017;195:9-17.
28. Hilde JM, Skjorten I, Grotta OJ, Hansteen V, Melsom MN, Hisdal J, et al. Right ventricular dysfunction and remodeling in chronic obstructive pulmonary disease without pulmonary hypertension. *J Am Coll Cardiol* 2013;62:1103-1111.

3