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Background **The aim of our study is to assess the effect of bundle branch block (BBB) on mortality and left ventricular ejection fraction (LVEF) in ST-elevation myocardial infarction (STEMI) patients treated in the current era of percutaneous reperfusion therapy.**

Patients and methods **In this retrospective cohort study, a total of 1123 STEMI patients treated in the University Medical Center Groningen from January 2011 until May 2013 were included. The follow-up duration was 2–4 years. Transthoracic echocardiography was performed within 2 weeks after STEMI.**

Results **In total, 23 (2.0%) patients presented with left BBB and 49 (4.4%) patients presented with right BBB. Two-year mortality after STEMI was 25.0% ($n = 18$) in patients with BBB and 9.2% ($n = 97$, $P < 0.001$) in patients without BBB. Patients with BBB had more frequently a severely reduced LVEF (< 30%) [20.0% ($n = 6$) compared with 4.2% ($n = 21$), $P = 0.002$] and less frequently a normal LVEF [16.7% ($n = 5$) compared with 35.7% ($n = 179$), $P = 0.046$]. After multivariable analysis, BBB did not remain an independent predictor of mortality, but was an independent predictor of reduced LVEF.**

Conclusion **The presence of a BBB was an independent predictor of a reduced LVEF. However, we found no effect of BBB on 2-year mortality in the current era of percutaneous reperfusion therapy.** *Coron Artery Dis* **28:232–238**

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Keywords: bundle branch block, percutaneous reperfusion therapy, ST-elevation myocardial infarction

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Introduction

Previous studies in the prethrombolytic [1–3] and thrombolytic era [4–11] showed that patients with a bundle branch block (BBB) had higher in-hospital and long-term unadjusted mortality following myocardial infarction (MI) irrespective of whether this was a left bundle branch block (LBBB) or a right bundle branch block (RBBB). In addition, some studies suggested that MI patients with BBB had a lower left ventricular ejection fraction (LVEF) at discharge [10,12,13]. LVEF is a predictor of 6-month mortality in MI patients treated with thrombolysis [14]. However, most of these findings are from the thrombolysis era. Since the introduction of primary angioplasty in the 1990s, outcome after ST-elevation MI (STEMI) has improved significantly [15–17]. In recent studies, patients with BBB were less likely to receive primary angioplasty when presenting with acute MI [7,12,13,18]. Studies investigating the mortality rate in MI patients with BBB treated with primary angioplasty report inconsistent results. The limitations of these studies are a short follow-up duration of a maximum of 1 year and the lack of LVEF as an outcome variable [19–21]. In light of the above, whether the presence of a BBB still represents an impaired outcome in the contemporary era is unknown and therefore we aim to study the impact of a BBB on mortality and LVEF in patients presenting with an acute STEMI.

Patients and methods

In total, 1282 patients older than 18 years of age with STEMI treated in the University Medical Centre Groningen between 1 January 2011 and 31 May 2013 were included in this study. All patients underwent coronary angiography and were excluded when no significant coronary artery disease was found ($n = 51$) or when no percutaneous coronary intervention (PCI) was performed ($n = 108$). No PCI was performed in case of death ($n = 27$), emergency coronary artery bypass surgery (CABG) ($n = 50$), a good flow in the coronary arteries ($n = 15$), or no possibilities for intervention ($n = 14$). For two patients, no reason was found. The remaining 1123 patients were included for further analysis.

An interventional cardiologist reviewed the ECG assessments of all patients. Because of the small number of patients with LBBB and RBBB, these groups were merged. The ECG change suggestive of STEMI was new ST elevation at the J point in two contiguous leads

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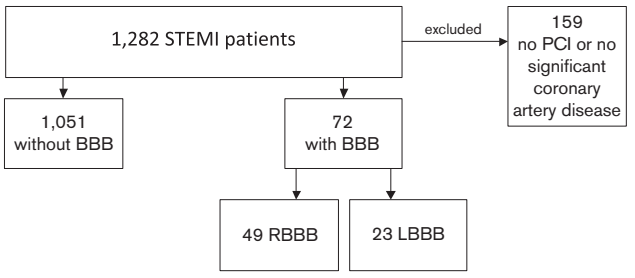
with the cut-points: greater than or equal to 0.1 mV in all leads other than leads V_2–V_3, where the following cut-points apply: greater than or equal to 0.2 mV in men of 40 years or older, greater than or equal to 0.25 mV in men of less than 40 years, or greater than or equal to 0.15 mV in women [22]. LBBB was defined as follows [23]: a QRS-complex of at least 120 ms; a broad notched or slurred R wave in leads 1, aVL, V_5, and V_6; and an RS pattern in V_5 and V_6 attributed to displaced transition of QRS-complex and absent Q waves in leads I, V_5, and V_6. RBBB had the following ECG characteristics: a QRS-complex of at least 120; Rsr′, rsR′, or rSR′ in leads V_1 or V_2; and normal R peak time in leads V_5 and V_6, but greater than 50 ms in lead V_1.

The outcome variables were mortality and LVEF. Mortality was obtained from the municipal personal records database. Categorization of LVEF into groups was performed on the basis of the 2015 recommendations for cardiac chamber quantification by echocardiography in adults [24]: in men, the normal range was 52–72%, the mildly reduced range was 41–51%, the moderately reduced range was 30–40%, and the severely reduced range was less than 30%. In women, the normal range was 54–74%, the mildly reduced range was 41–53%, the moderately reduced range was 30–40%, and the severely reduced range was less than 30%. LVEF was measured by eyeballing or the Biplane Simpson method. The first available echocardiographic assessment within 2 weeks after STEMI was used for analysis.

Baseline characteristics were obtained from the medical files of the patients and heart rate and blood pressure were measured at presentation. Measurement of creatine kinase (CK), myocardial band of CK (CK-MB), and high-sensitivity troponin-T was performed according to local hospital standards on standard laboratory assays (Roche Modular, Mannheim, Germany) as part of standard care. Enzyme release of CK, CK-MB, and high-sensitivity troponin-T was measured routinely during the stay at the coronary care unit after primary PCI. Peak values were determined over the first 36 h after PCI. Successful PCI was defined as a TIMI flow 3 after PCI [25] and ischemia time was defined as time from the onset of symptoms to the first coronary intervention.

Fig. 1



Study population. BBB, bundle branch block; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; STEMI, ST-elevation myocardial infarction.

Table 1 Baseline characteristics of no bundle branch block and bundle branch block

Variables	No BBB ($n=1051$)	BBB ($n=72$)	*P*-value
Male (%)	71.9	77.8	0.284
Age (years) (mean ± SD)	62 ± 23	70 ± 13	**< 0.001**
Risk factors			
BMI (kg/m^2) (mean ± SD)	27.0 ± 4.0	26.4 ± 4.0	0.276
Hypertension (%)	36.1	44.4	**0.023**
Diabetes (%)	17.1	29.6	**0.008**
Hypercholesterolemia (%)	32.8	30.6	0.371
Current smoker (%)	47.2	27.8	**0.002**
Family history of CVD (%)	41.2	27.8	**0.022**
Medical history (%)			
MI	12.3	23.6	**0.018**
PCI	10.1	11.1	0.053
CABG	2.5	6.9	**0.002**
CVA	3.8	8.3	0.152
VF	7.6	12.5	0.284
Malignancy	7.3	16.7	**0.015**
PAD	14.1	22.9	0.356
Medication (%)			
β-Blocker	20.7	31.9	0.064
ACE-inhibitors	11.3	26.4	**0.001**
Angiotensin II receptor antagonist	7.9	9.7	0.813
Diuretics	11.9	12.5	0.953
Calcium channel blockers	8.5	13.9	0.270
Antiarrythmic	0.6	5.6	**< 0.001**
Insulin	5.2	9.7	0.227
Metformin	7.1	20.8	**< 0.001**
Lab values [median (interquartile range)]			
Peak CK in hospital (U/l)	1174 (465–2716)	1968 (817–4328)	**< 0.001**
Peak CK-MB in hospital (U/l)	151 (63–296)	269 (109–493)	**< 0.001**
Peak troponin in hospital (μg/l)	2342 (838–5579)	5279 (2327–9756)	**< 0.001**
Physical examination [*n* (%)]			
Heart rate (beats/min)	77.7 (18.0)	84.1 (20.7)	**0.004**
Systolic blood pressure (mmHg)	136.4 (26.1)	133.8 (30.8)	0.463
Diastolic blood pressure (mmHg)	85.0 (14.7)	84.9 (17)	0.933
Infarct location (%)			
RCA	40.1	27.8	**0.039**
LMCA	1.0	2.8	0.145
CX	18.5	16.7	0.704
LAD	39.4	45.8	0.280
Successful PCI (%)	88.7	77.5	**0.033**
Ischemia time (min) [median (interquartile range)]	168 (114–270)	189 (126–344)	0.287
Discharge medication (%)			
β-Blocker	90.4	84.4	**0.012**
ACE-inhibitors	66.0	65.6	0.357
Aspirin	90.6	87.5	0.096
Statin	92.1	90.6	0.130
Clopidogrel/ticagrelor	90.2	83.3	0.063

Bold values are significant. ACE-inhibitors, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; CK, creatine kinase; CVA, cerebral vascular accident; CVD, cardiovascular disease; CX, circumflex coronary artery; LAD, left anterior descending artery; LMCA, left main coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; RCA, right coronary artery; VF, ventricular fibrillation.

Dichotomous variables were presented as percentages and continuous variables were presented as mean with SD. Continuous variables not normally distributed were presented as medians with their interquartile ranges. The

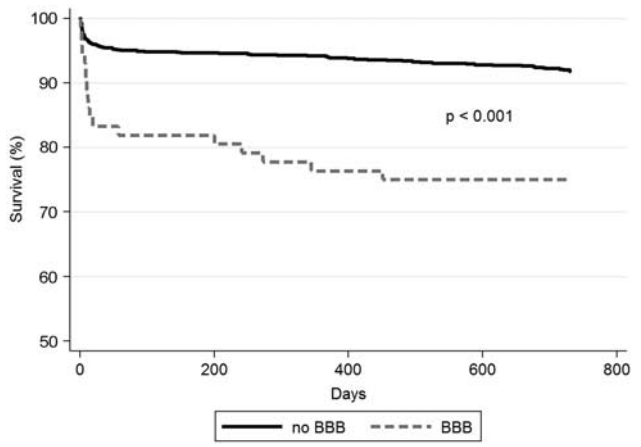
Table 2 Univariate and multivariate Cox regression: 2-year mortality

	Univariate Cox regression			Multivariate Cox regression		
Variables	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI
BBB	**< 0.001**	3.433	2.063–5.713			
Male	0.218					
Age (per year)	**< 0.001**	1.051	1.034–1.067	**0.009**	1.069	1.017–1.123
Risk factors						
BMI (per kg/m^2)	0.339					
Hypertension	**< 0.001**	1.265	1.208–1.324			
Diabetes	0.101					
Hypercholesterolemia	**< 0.001**	1.257	1.201–1.316			
Current smoker	**< 0.001**	1.275	1.215–1.338			
Family history of CVD	**< 0.001**	1.290	1.231–1.350			
Medical history						
MI	0.253					
PCI	0.738					
CABG	0.989					
CVA	0.471					
Previous VF	**0.002**	1.270	1.130–1.427			
Malignancy	0.608					
PAD	0.149					
Medication at presentation						
β-Blocker	**< 0.001**	1.154	1.092–1.219			
ACE-inhibitors	**< 0.001**	1.147	1.086–1.212			
Angiotensin II receptor antagonist	**< 0.001**	1.151	1.090–1.215			
Diuretics	**< 0.001**	1.166	1.106–1.228			
Calcium channel blockers	**< 0.001**	1.161	1.103–1.224			
Antiarrhythmic	**< 0.001**	1.148	1.088–1.211			
Insulin	0.111					
Metformin	0.324					
Lab values						
Peak CK in hospital (per 100 U/l)	**< 0.001**	1.014	1.011–1.017			
Peak CK-MB in hospital (per 100 U/l)	**< 0.001**	1.002	1.001–1.002			
Peak troponin in hospital (per 100 U/l)	**< 0.001**	1.002	1.001–1.002			
Physical examination						
Heart rate (per 10 beats/min)	**< 0.001**	1.250	1.133–1.30	**0.006**	1.338	1.086–1.650
Systolic blood pressure (per 1 mmHg)	**< 0.001**	0.978	0.969–0.987	**0.006**	0.9714	0.951–0.991
Diastolic blood pressure (per 1 mmHg)	**< 0.001**	0.961	0.945–0.977			
Infarct location						
RCA	0.187					
LMCA	**0.054**	3.958	1.254–12.485			
CX	0.198					
LAD	0.383					
Successful PCI	0.113					
Ischemia time	0.982					
Discharge medication						
β-Blocker	0.901					
ACE-inhibitors	0.830					
Aspirin	0.409					
Statin	0.754					
Clopidogrel/ticagrelor	**< 0.001**	0.057	0.038–0.084	**< 0.001**	0.107	0.038–0.307
LVEF group						
Normal LVEF (reference)	**< 0.001**					
Mildly reduced LVEF	0.292					
Moderately reduced LVEF	**0.008**	16.899	2.113–135.123			
Severely reduced LVEF	**< 0.001**	52.108	5.806–400.758	**0.013**	17.094	1.818–160.704

Bold values are significant. ACE-inhibitors, angiotensin-converting enzyme inhibitors; BBB, bundle branch block; CABG, coronary artery bypass grafting; CI, confidence interval; CK, creatine kinase; CVA, cerebral vascular accident; CVD, cardiovascular disease; CX, circumflex coronary artery; LAD, left anterior descending artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; VF, ventricular fibrillation.

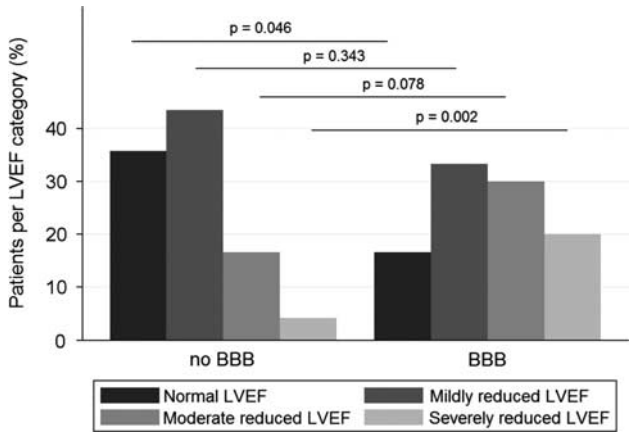
χ^2-test was used to compare frequencies of events in patients with and without a BBB. Differences in continuous variables between patients with and without BBB were ascertained using a *t*-test. Fisher's exact test was used to compare the percentages of patients in LVEF categories. The log-rank test was used to compare mortality between patients with and without BBB. Univariable and multivariable Cox regression analyses were carried out to determine correlates of baseline variables and 2-year mortality. These variables include risk factors for coronary artery disease, medical history, medication use, laboratory measures, physical examination, infarct location, PCI procedural success, discharge medication, and LVEF. Univariate regression analysis was reported with a *P*-value and when significant, concomitant hazard ratio and confidence interval. The 10 most significant variables in univariate analyses were included in the multivariable Cox regression. Stepwise

Fig. 2



Two-year Kaplan–Meier survival curve. The black solid line shows the survival of STEMI patients without BBB ($n = 1051$). The grey dashed line shows the survival of patients with BBB ($n = 72$). BBB, bundle branch block; STEMI, ST-elevation myocardial infarction.

Fig. 3



Division LVEF category in patients with and without BBB. From left to right (and from dark to light). Normal LVEF, $n = 184$. Mildly reduced LVEF, $n = 228$. Moderate reduced LVEF, $n = 92$. Severely reduced LVEF, $n = 27$. BBB, bundle branch block; LVEF, left ventricular ejection fraction.

backward multivariable Cox regression analyses were carried out to determine independent predictors of 2-year mortality (cut-off for entry 0.10; and removal 0.05). To validate the models, forward-stepwise multivariable Cox regression was also performed (cut-off for entry and removal set at a significance level of 0.05). For regression analysis of LVEF, downwards-stepwise ordered logistic regression was used and validated with forward-stepwise ordered logistic regression. For all analyses, a *P*-value up to 0.05 was considered to be statistically significant. All statistical analyses were carried out using Stata, version IC 11 (StataCorp, College Station, Texas, USA).

Results

Figure 1 shows the study population. In total, 23 (2.0%) patients presented with LBBB and 49 (4.4%) patients presented with RBBB.

Baseline characteristics of patients with and without BBB are presented in Table 1. Patients with BBB were older compared with patients without BBB. Peak CK, CK-MB, and high-sensitivity troponin-T were significantly higher in patients with BBB. Also, patients with BBB more often had hypertension, diabetes, a history of MI, CABG, or cancer, but were less often smokers or less often had a family history of cardiovascular disease. At presentation, patients with BBB used more medication (angiotensin-converting enzyme inhibitors, antiarrhythmic, or metformin). Patients with BBB less often had a successful PCI and less frequently used β-blockers at discharge.

Patients with BBB showed a higher 2-year mortality. In the group with BBB, 18 (25%) patients died within 2 years compared with 97 (9.2%) patients in the group without BBB. Univariate analysis shows that a BBB is associated with increased mortality (Table 2). Figure 2 shows the Kaplan–Meier estimates for mortality in the two groups. In a multivariable Cox regression model including BBB, age, smoking, family history, peak lab value of CK-MB, heart rate, systolic and diastolic blood pressure, clopidogrel or ticagrelor at discharge, and LVEF, the difference in mortality between the two groups did not remain significant. Exclusion of LVEF from multivariable analysis did not result in the inclusion of BBB in the model. Table 2 shows the independent predictors of 2-year mortality after STEMI.

In total, 531 patients underwent echocardiography within 2 weeks after STEMI. Patients with BBB less frequently had a normal LVEF ($n = 5$, 16.7%) compared with patients without a BBB ($n = 179$, 35,7%, $P = 0.046$). Patients with BBB had more often a severely reduced LVEF after STEMI ($n = 6$, 20%) compared with patients without BBB ($n = 21$, 4.2%, $P = 0.002$). Between mildly and moderate reduced LVEF, no difference was found between patients with and without BBB ($n = 10$, 33.3% and $n = 9$, 30%, $P = 0.343$ vs. $n = 218$, 43.5%, and $n = 83$, 16.6%, $P = 0.078$; Fig. 3). Table 3 presents univariate and multivariable ordered logistic regression and shows that BBB is an independent predictor of lower LVEF.

Discussion

The major findings of this study were as follows: (i) differences at baseline between patients with and without a BBB; (ii) no significantly higher mortality in the BBB group when adjusted for covariates; and (iii) an increased risk of reduced LVEF in patients with BBB.

Table 3 Ordered logistic regression: the left ventricular ejection fraction group

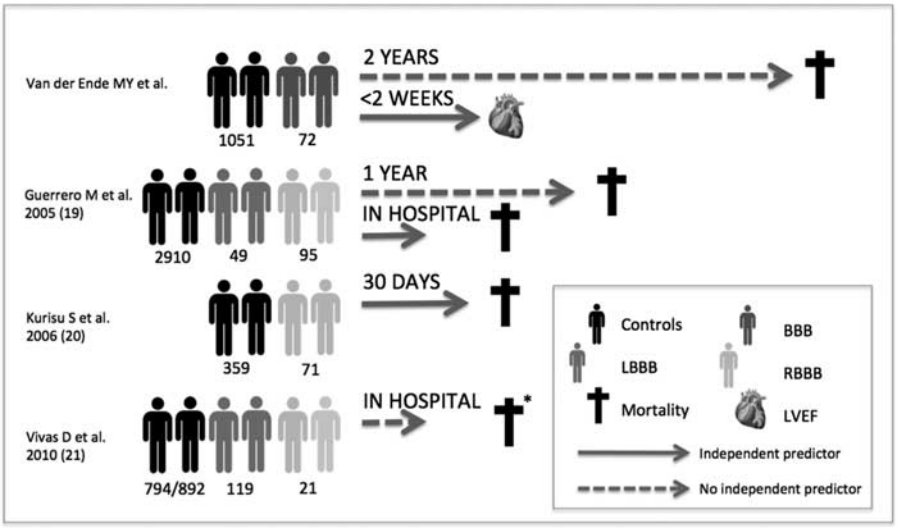
	Univariate ordered logistic regression				Multivariate ordered logistic regression		
Variables	*P*-value	Coefficient	95% CI	R^2	*P*-value	Coefficient	95% CI
BBB	**< 0.001**	1.351	0.645–2.057	0.011	**0.002**	1.152	0.427–1.878
Male	0.415						
Age (per year)	**0.013**	0.017	0.003–0.031	0.005			
Risk factors							
BMI (per kg/m^2)	0.278						
Hypertension	**0.078**	0.082	−0.009 to 0.174	0.003			
Diabetes	**0.005**	0.705	0.218–1.192	0.006			
Hypercholesterolemia	**0.083**	0.062	−0.008 to 0.133	0.002			
Current smoker	**0.100**	0.097	−0.018 to 0.212	0.002			
Family history of CVD	0.186						
Medical history							
MI	**< 0.001**	1.839	1.063–2.615	0.017			
PCI	0.115						
CABG	0.346						
CVA	0.108						
Previous VF	0.444						
Malignancy	0.497						
PAD	**0.063**	0.809	−0.044 to 1.663	0.006			
Medication							
β-Blocker	0.537						
ACE-inhibitors	0.461						
Angiotensin II receptor antagonist	0.550						
Diuretics	0.592						
Calcium channel blockers	0.568						
Antiarrhythmic	0.373						
Insulin	**0.019**	1.152	0.191–2.113	0.004			
Metformin	**0.052**	0.904	−0.004 to 1.812	0.003			
Lab values							
Peak CK in hospital (per 100 U/l)	**< 0.001**	0.035	0.028–0.043	0.080	**< 0.001**	0.032	0.024–0.039
Peak CK-MB in hospital (per 100 U/l)	**< 0.001**	0.013	0.010–0.017	0.080			
Peak troponin in hospital (per 100 U/l)	**< 0.001**	0.013	0.010–0.017	0.080			
Physical examination							
Heart rate (per 10 beats/min)	**< 0.001**	0.025	0.016–0.035	0.023	**< 0.001**	0.017	0.008–0.027
Systolic blood pressure (per 1 mmHg)	**0.043**	−0.007	−0.013 to 0.000	0.004			
Diastolic blood pressure (per 1 mmHg)	0.383						
Infarct location							
RCA	**< 0.001**	−0.936	−1.272 to 0.600	0.024			
LMCA	**0.052**	1.571	0.052–3.089	0.003			
CX	**0.001**	−0.675	−1.086 to 0.263	0.008	**0.045**	−0.496	−0.981 to 0.010
LAD	**< 0.001**	1.283	0.943 to 1.622	0.046	**< 0.001**	0.920	0.535–1.306
Successful PCI	**0.005**	−0.774	−1.316 to 0.232	0.008			
Ischemia time (per 10 min)	**0.002**	0.001	−0.001 to 0.003	0.002			

Bold values are significant. ACE-inhibitors, angiotensin-converting enzyme inhibitors; BBB, bundle branch block; CABG, coronary artery bypass grafting; CI, confidence interval; CK, creatine kinase; CVA, cerebral vascular accident; CVD, cardiovascular disease; CX, circumflex coronary artery; LAD, left anterior descending artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; RCA, right coronary artery; VF, ventricular fibrillation.

STEMI patients with BBB have more co-morbidities compared with patients without BBB. Patients with BBB were older, more often had diabetes or hypertension, and were more likely to have a history of MI, CABG, or cancer. These findings are in agreement with other studies [6–8,10,12,13,19–21,26] and suggest a higher clinical risk profile in patients with BBB, which contributes toward the poor outcome of STEMI patients with BBB.

Mortality was higher in STEMI patients with BBB treated with the current improved reperfusion therapy compared with patients without BBB. However, in multivariable analyses, BBB did not remain an independent predictor of mortality. This is in contrast with most studies reporting BBB as an independent predictor of in-hospital and future mortality [5,6,8,9,13,18,19]. In previous studies, patients with BBB did not or less frequently underwent PCI [7,12,13]; this difference in treatment could be an explanation for the reported higher mortality rates in earlier studies. In our study, BBB patients were less likely to receive β-blockers at discharge, probably because of an already existing conduction delay. Otherwise, there were no differences in medical treatment compared with patients without BBB. These results suggest that patients with BBB may have an improved outcome when treated with PCI compared with thrombolytic therapy. In a similar study in which all patients underwent PCI, a higher mortality was found in patients with LBBB compared with patients with RBBB [19]. Because of the low prevalence of LBBB and RBBB among STEMI patients, we did not make a distinction between LBBB and RBBB. Further research has to be performed to establish possible differences between

Fig. 4



Comparison between studies carried out in the era of primary PCI. *Combined endpoint of in-hospital mortality and reinfection and only persistent BBB as an independent predictor of mortality. BBB, bundle branch block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RBBB, right bundle branch block.

these two groups. The higher mortality among BBB patients in our study seemed to be determined by the higher percentage of lower LVEF in this patient group, together with the older age and more co-morbidities. Therefore, therapy of STEMI patients with BBB should be focused on aggressive treatment of heart failure.

A BBB is an independent predictor of lower LVEF. There is a paucity of data on the effect of BBB on LVEF in patients with MI. In a study of Stenestrand and colleagues, it is suggested that MI patients with BBB are at a higher risk of developing clinical signs of heart failure [10,12]. Because of a lack of pre-STEMI data, we could not make a distinction between new-onset and pre-existent BBB. BBB can be a manifestation of an underlying heart disease and appears to be associated with reduced LVEF [27–29]. Whether the more reduced LVEF in BBB patients is a result of STEMI or pre-existing heart disease is unknown. However, patients with BBB had higher enzymatic infarct size and less often had successful PCI (defined as TIMI flow 3 after PCI), both predictive of poor LVEF and outcome [30].

Figure 4 shows a comparison between this study and other studies carried out in the era of primary PCI [19–21]. This figure shows that our study by van der Ende and colleagues provides novel insights into the outcome of patients with STEMI and BBB because of the long follow-up duration of mortality compared with previous studies. In addition, our study exclusively has LVEF as the second outcome variable.

There are a few limitations in our study. The sample size was the main limitation and did not enable an analysis of the differences between LBBB and RBBB and between transient and persistent BBB. Because of the lack of pre-STEMI ECG data, we could not make a distinction between new-onset and pre-existent BBB and between transient and persistent BBB. Previous studies suggest that the likelihood for death higher is in patients with persistent BBB than in those with transient BBB and that new BBB results in higher mortality than known BBB [5,7,31]. In this study, LVEF was often determined within a range because of poor echocardiography image quality. Some ranges overlapped with two LVEF categories, whereby a bias could have occurred. By consistently placing the same ranges in the same groups, the bias was maintained as small as possible.

Conclusion

In the current reperfusion area, BBB is an independent predictor of reduced LVEF after STEMI, but not an independent predictor of mortality.

Impact on daily practice

The higher mortality rate among BBB patients in our study seemed to be determined by the higher percentage of reduced LVEF in this patient group, together with the older age and more co-morbidities. Therefore, the treatment therapy of STEMI patients with BBB should be focused on more aggressive treatment to prevent the development of heart failure.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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