1. Introduction

Cardiovascular diseases, particularly acute coronary syndromes (ACS), are an important cause of death in Europe [1]. Although mortality rates of ACS decreased in the last decades, due to major improvements in treatment, it stabilized in 3–5% [2]. Some special subsets of patients are at particularly risk and treatment must be optimized in those subgroups.

In previous guidelines, treatment of patients with new or presumably new left bundle branch block (LBBB) should follow recommendations for ST-segment elevation acute myocardial infarction (STEMI), with immediate reperfusion therapy, preferably primary angioplasty [3]. In recent guidelines, this recommendation has been enlarged for right bundle branch block (RBBB) patients [4,5]. However, for RBBB, evidence is less robust, with fewer available clinical studies and a lower level of evidence.

The prevalence of RBBB in the context of ACS is 6–10% [6–12]. In fibrinolysis era, both BBB types had high in-hospital mortality, of around 15–20%, much higher when compared to STEMI patients or other ACS with normal QRS duration [6–8]. In more contemporaneous studies, hospital mortality is still highest in patients with BBB, particularly new-onset RBBB [9–12]. However, those studies have several limitations. Some are derived from small samples, others were performed in non-contemporaneous populations or in randomized (not real-life) populations, some are meta-analysis and, in some cases, there are important ethnic differences.

For that reason, it was our objective to assess, in a contemporaneous real-life population of patients admitted with ACS, the differential impact of LBBB and RBBB in outcome.

1.1. Population and methods

In the present study, we included consecutive adult patients admitted at the Intensive Care Unit of our Cardiology Department with an ACS, between January 2005 and November 2016. Inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS 48 h before admission, with or without new or presumed new significant ST-segment or T-wave changes, LBBB and/or elevated
biomarkers of myocardial necrosis (with a rise and/or fall of levels). Acute myocardial infarction was defined according to type 1 myocardial infarction universal definition [13]. STEMI was defined by the presence of persistent (>30 min) ST-segment elevation. All other cases were considered non-ST-segment elevation ACS (NSTACS).

Patients were included prospectively in the centre’s ACS registry. Data was collected in a dedicated computer database. It included demographic data, clinical and patient management information, as well as in-hospital outcome. Hypertension, diabetes and hyperlipidemia were defined as previously known or on specific therapy. If the patients had smoked during the previous six months, they were classified as smokers and were self-reported. All decisions on patient management strategy (including referral for an invasive strategy and type of revascularization) were left to the attending physician.

Follow-up was obtained by a dedicated nursing team in every patient that survived to discharge and was obtained by telephone interview with the patient or with a close family member and/or by review of the medical record. Follow-up was completed in 99.7% of patients. Our primary endpoint was all-cause mortality during one-year follow-up, counted from admission. Mortality was also analyzed during hospital stay and at 30-day follow-up. Mean hospital stay was 8 days, with a median stay of 6 days and interquartile range of 5–9 days. The authors assert that all procedures contributing to this work comply with the ethical standards of Helsinki Declaration of 1975 and that this research does not involve human and/or animal experimentation.

1.2. Statistical analysis

Patients were divided in three groups according to the presence of LBBB, RBBB or normal QRS duration in the admission ECG. Normality of continuous variables was tested with the Kolmogorov-Smirnov’s test and homogeneity of variance was tested with Leven’s test. Categorical variables are reported as percentages and differences between groups were tested with the chi-square test or Fischer’s exact test, as appropriate. Survival analysis was tested with Kaplan-Meier curves and with Log-rank test. We used Cox-proportional-hazards regression models to identify potential predictors of the primary outcome. We set a p level for inclusion in the multivariate model at 0.05. The estimates of the association between predictors and outcome are presented as hazard ratios (HR) and 95% confidence intervals (CI).

For all statistical analysis, we used the IBM SPSS statistical software package (version 19.0.0.2). All tests were two-sided with a critical value of 0.05 for statistical significance.

2. Results

We included in the present study 3990 patients. QRS duration was normal in the majority of patients. LBBB was present in 3.4% and RBBB in 4.3% of patients. Mean age was 64 (13) years, with a predominance of male gender (72%). Patients with BBB were older and had more cardiovascular risk factors, particularly LBBB patients, with the exception of smoking that was less prevalent in both BBB groups, mainly in LBBB patients (Table 1). RBBB group had more male patients, followed by normal QRS group. Regarding previous medical history, baseline characteristics were also significantly worse in both groups of BBB, particularly in LBBB group, with more frequent history of myocardial infarction and myocardial revascularization. Killip class on admission was also worse in BBB groups. Heart rate and SBP was higher in LBBB.

Pharmacological treatment was similar in all groups; however, coronary angioplasty was less performed in patients with BBB, particularly LBBB (Table 2). Thrombolysis was used in 5.3% of all patients (8.1% of STEMI cases), 3% in RBBB group, 3% in LBBB group and 5% in the group with normal QRS, with most cases being referred to our department for rescue PCI. Complications occurred at a similar rate across all groups, with the exception of cardiac arrest, more frequent in RBBB group. All mortality endpoints were more frequent in BBB, but slightly higher in the RBBB group. In univariate survival analysis, BBB patients had worse outcome (Log-rank, p < 0.001), but similar in LBBB and RBBB (Log-rank, p = 0.597).

Patients with RBBB and NSTACS, compared to patients with STEMI, have more frequently hypertension, previous revascularization, higher systolic blood pressure on admission and better Killip class (Supplemental Table). They received more often statins but were less often submitted to coronary angioplasty. Mortality was higher than usual in both groups (STEMI and NSTACS), particularly in the STEMI group.

In Cox-proportional hazards univariate analysis, both LBBB and RBBB were predictors of all-cause mortality at one-year follow-up (Table 3). The other potential predictors of outcome were age, diabetes,

| Table 1 | Baseline characteristics. |
|---------|--------------------------|
| Age (years) | Total n = 3990 | LBBB n = 133 | RBBB n = 172 | Normal QRS n = 3683 | p-value |
| 64 (13) | 70 (11) | 63 (13) | -0.001 |
| Male gender (%) | 72.0 | 61.9 | 74.4 | 72.3 | 0.025 |
| Risk factors (%) | | | | | |
| Hypertension | 64.3 | 81.5 | 70.3 | 63.6 | -0.001 |
| Hyperlipidemia | 51.3 | 60.7 | 54.7 | 50.8 | 0.052 |
| Diabetes | 25.8 | 43.0 | 34.3 | 24.8 | -0.001 |
| Smoking | 38.4 | 15.6 | 26.2 | 39.8 | -0.001 |
| Previous history (%) | | | | | |
| Myocardial infarction | 14.5 | 31.1 | 19.2 | 13.7 | -0.001 |
| PCI | 10.7 | 17.8 | 13.4 | 10.3 | 0.012 |
| CABG | 3.7 | 14.8 | 5.8 | 3.2 | -0.001 |
| Stroke/TIA | 5.7 | 9.6 | 6.4 | 5.5 | 0.113 |
| PAD | 3.5 | 3.7 | 4.1 | 3.4 | 0.890 |
| COPD | 2.1 | 4.4 | 1.7 | 2.0 | 0.143 |
| STEMI (%) | 65.1 | - | 51.7 | 67.0 | -0.001 |
| Heart rate (bpm) | 78 (20) | 89 (21) | 82 (22) | 78 (20) | -0.001 |
| SBP (mmHg) | 137 (29) | 144 (33) | 135 (32) | 137 (29) | -0.019 |
| Killip class ≥2 (%) | 14.8 | 40.0 | 23.3 | 13.4 | -0.001 |
| Qualitative LVEF (%) | | | | | |
| <50% | 56.2 | 28.1 | 54.7 | 66.6 | -0.001 |
| 50-70% | 31.0 | 37.8 | 35.5 | 26.6 | |
| >70% | 8.9 | 34.1 | 9.9 | 6.8 | |

LBBB – left bundle branch block; RBBB – right bundle branch block; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; TIA – transient ischemic attack; PAD – peripheral artery disease; COPD – chronic obstructive pulmonary disease; STEMI – ST-elevation myocardial infarction; SBP – systolic blood pressure; LVEF – left ventricular ejection fraction.

| Table 2 | Treatment, complications and outcome. |
|---------|--------------------------|
| DAPT (%) | Total n = 3990 | LBBB n = 133 | RBBB n = 172 | Normal QRS n = 3683 | p-value |
| 91.2 | 88.9 | 90.7 | 91.3 | 0.621 |
| ACEI/ARB | 87.4 | 88.1 | 84.9 | 87.3 | 0.588 |
| Beta-blockers | 83.7 | 79.3 | 84.3 | 83.8 | 0.358 |
| Statins | 91.7 | 88.9 | 90.1 | 91.9 | 0.336 |
| PCI | 81.0 | 62.2 | 76.7 | 81.9 | -0.001 |
| Complications (%) | | | | | |
| Mechanical complications | 6.4 | 6.7 | 9.9 | 6.2 | 0.162 |
| Cardiac arrest | 7.4 | 8.1 | 13.3 | 7.0 | 0.016 |
| Complete AV block | 2.6 | 3.0 | 1.2 | 2.6 | 0.474 |
| Major bleeding | 0.4 | 0 | 1.2 | 0.4 | 0.447 |
| Stroke/TIA | 1.0 | 2.2 | 1.2 | 1.0 | 0.338 |
| Outcome (%) | | | | | |
| In-hospital mortality | 5.3 | 8.1 | 10.5 | 5.0 | 0.002 |
| 30-day mortality | 5.7 | 8.1 | 13.4 | 5.7 | -0.001 |
| One-year mortality | 9.3 | 17.0 | 19.2 | 8.6 | -0.001 |

DAPT – double antiplatelet treatment; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; PCI – percutaneous coronary intervention; TIA – transient ischemic attack.
Table 3
Cox proportional hazard regression analysis (unadjusted and adjusted).

|          | Univariate | p-value | Multivariate | p-value |
|----------|------------|---------|--------------|---------|
| Normal QRS | Ref.       | -       | Ref.         | -       |
| LBBB     | 2.06 (1.35–3.15) | 0.001   | 1.13 (0.72–1.79) | 0.584   |
| RBBB     | 2.37 (1.66–3.4)  | <0.001  | 1.66 (1.14–2.40) | 0.007   |

Results are presented as Hazard ratios and 95% confidence intervals. Adjusted for: age, heart rate, systolic blood pressure, previous revascularization, diabetes, Killip class ≥2, double antiplatelet treatment, renin-angiotensin-aldosterone system blocker, beta-blockers, statins, and percutaneous coronary intervention.

In our sample of patients with ACS, 7.7% of the patients had any form of BBB, particularly RBBB in 4.3%. In general, patients with BBB had worse baseline characteristics, particularly regarding demographic variables, cardiovascular risk factors, previous cardiac history, and presentation, with more data in LBBB patients. Treatment was, however, similar in all groups with the exception of coronary angioplasty, less frequently performed in LBBB, followed by RBBB. The outcome was significantly worse in all form of BBB, but patients with BBB had higher mortality. In multivariate analysis, and after adjustment, BBB remains an independent predictor of all-cause mortality but RBBB remains an important predictor (HR 1.66, p = 0.007) (Fig. 1).

3. Discussion

In our sample of patients with ACS and normal QRS (77%) [9]. A large meta-analysis confirmed that RBBB patients had the highest mortality (in-hospital and long-term), but in this analysis there was considerable heterogeneity across included studies [11]. In more recent studies, mortality rates in this subgroup did not improve much, despite substantial improvements in treatment [10–12]. Studies that compared new/old or persistent transient BBB, consistently showed that new and permanent BBB (particularly RBBB), was associated with the worst outcome [6,7,12]. Thus, patients with new and permanent BBB are a subset of patients at particularly higher risk and they represent a substantial proportion of patients. In a cohort of patients from 1998 to 2008, new BBB represented 32.5% of all BBB (36% for RBBB and 27% for LBBB) [6]. A more recent cohort (2006–2008) showed lower incidence, with 16% of all RBBB and 13% of all RBBB being new [8]. Permanent BBB is believed to represent 35% of all new BBB and 40% of all new LBBB [6].

However, those studies have several limitations as already pointed out and a contemporaneous study, with a large real-life population and with head-to-head comparison was necessary to confirm previous information and to validate recent guidelines. Our analysis, in a large cohort of patients, demonstrated that both types of BBB had worse outcome in medium-term follow-up, with in-hospital mortality of 8–10% and one-year all-cause mortality of 17–20%. These results seem to be better that previously reported, probably reflecting the optimized pharmacological treatment with higher use of drugs with important impact in prognosis. However, coronary angioplasty was significantly less performed in BBB patients when compared to normal QRS patients and this is an important cause for the worse results obtained in these groups, particularly in patients with LBBB. In RBBB patients, the outcome was persistently worst, even after adjustment for other independent predictors of mortality. One possible explanation is that these patients had more often cardiac arrest in the index hospitalization. Coronary anatomy might also be an important explanation for the results obtained; in previous studies, angiographic predictors of BBB were proximal occlusion and TIMI flow 0/1 of the infarct related artery, all known predictors of unfavorable outcome [10]. However, in our study, not all patients were submitted to coronary angiography, particularly in BBB groups, and this information is not available in our data registry. For that reason, it was not possible to assess the impact of coronary anatomy in BBB incidence and outcome. We believe that there might be some differences in culprit coronary artery or coronary anatomy related to BBB that might have implications in terms of outcome.

3.1. Limitations

This is a retrospective study, with all the limitations previously described for this type of study. Some information was not possible to collect retrospectively. For instance, it was not possible to assess if BBB was new or old if it was transient or permanent. We also do not have information about concomitant presence of anterior or posterior left hemiblock with RBBB. Another limitation is the lack of detailed information about quantitative left ventricular ejection fraction, troponins, completeness of revascularization, PCI delays, and concomitant causes of BBB (such as pulmonary hypertension, pulmonary embolism or right ventricle myocardial infarction). Our sample of patients with BBB is relatively small. The type of follow-up used in the present study did not allow an analysis of other endpoints, such as myocardial infarction or other cardiovascular events. We only have data for one-year follow-up. A longer follow-up might have provided additional important information.

4. Conclusions

Patients with bundle branch block had worse baseline characteristics, especially patients with left bundle branch block. In long-term
follow-up, they also had worse outcome, with higher all-cause mortality, particularly in the presence of right bundle branch block. Our results support international recommendations. We should be aware and pay special attention to these patients (particularly with right bundle branch block), and treat them at least as aggressively as patients with normal QRS duration, not only concerning pharmacological treatment but also in terms of invasive strategy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.11.006.

Conflict of interests

None to declare.

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