Relationship Between Beta-Blocker and Angiotensin-Converting Enzyme Inhibitor Dose and Clinical Outcome Following Acute Myocardial Infarction

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Background: Benefit of β-blockers (BB) and angiotensin-converting-enzyme inhibitors (ACEI) on mortality following acute myocardial infarction (MI) is well demonstrated. This study assessed the impact of BB and ACEI doses administered following ST-elevation MI on mortality and outcome up to 1 year.

Methods and Results: The French prospective observational cohort “RIMA” included 1,461 MI patients. Dosing of BB and ACEI given at 24 h and at time of discharge was assessed as follows: no treatment; <50% of target dose; or ≥50% of target dose. For in-hospital mortality, after MI, the use of BB in the first 24 h, but not ACEI, was associated with significantly lower event rate on multivariate analysis (OR, 5.78; 95% CI: 2.62–12.76, P<0.001). In contrast at 1 year, use of higher doses of ACEI, but not BB, was associated with significantly lower CV mortality, readmission for heart failure and the composite of CV mortality and readmission for heart failure (HR, 2.65; 95% CI: 1.32–5.31, P=0.006 for absence of ACEI at discharge).

Conclusions: Prescription of BB in the first 24 h was independently associated with a lower in-hospital mortality following MI. There appeared to be a significant dose effect on outcome with regard to <50% vs. ≥50% of target dose, which requires confirmation in further large-scale clinical studies. (Circ J 2015; 79: 632–640)

Key Words: Angiotensin-converting enzyme inhibitor; Beta-blocker; Heart failure; Myocardial infarction; Target dose

Several studies have proven the beneficial effects of β-blockers (BB) and angiotensin-converting enzyme inhibitors (ACEI) in reducing major adverse cardiac events (MACE) and mortality following myocardial infarction (MI). Particular benefits were observed among patients with high-risk features, such as heart failure during hospitalization or left ventricular ejection fraction (LVEF) <40%. Most of these studies took place before modern medicine’s reperfusion era, and European Society of Cardiology guidelines advocate BB following MI with a class IIb recommendation and ACEI with a class IIa recommendation. In patients with LV dysfunction, the level of recommendation is class Ia for both drug groups. A recent, nationwide, French study reported improved prescription rates of BB and ACEI following ST-elevation MI in the years 2008–2010, yet did not provide any detail regarding the doses given. Some registries noted that BB and ACEI were used at lower doses than in clinical trials. In contrast to the heart failure indication, the prognostic impact of these 2 evidence-based therapies at lower doses has not yet been assessed in MI registries.

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The first objective of this study was to assess the association between early BB or ACEI treatment following MI and in-hospital mortality. The second part of the analysis was to detect any link between the prescription of these therapies, dose used at discharge from hospital, and mortality and MACE over 1-year follow-up.

Methods

Patients and Data
The RIMA registry (Registre des infarctus du Maine-Anjou)
prospectively included all patients admitted for MI at participating sites, namely the University Hospital of Angers and the secondary care hospitals of Cholet, Saumur, and Chateauroux, France, between January 2003 and December 2009. Acute MI was diagnosed based on the following symptoms suggestive of MI: persistent ST elevation ≥0.1 mV in 2 contiguous peripheral leads and V5, V6, or ≥0.2 mV in 2 contiguous leads from V1 to V4, as well as elevation of cardiac biomarkers.

Basic demographics, cardiovascular risk factors, medication, and hospitalization information were all prospectively collected. LVEF was assessed on echocardiography using biplane Simpson’s method during hospitalization. Revascularization at acute phase included primary percutaneous coronary intervention (PCI) and fibrinolysis procedures. PCI at acute phase included primary PCI and rescue PCI procedures.

We also took note of specific information regarding the absence or presence of BB and ACEI at the first hospital day. The type and daily dosage of BB and ACEI at the time of discharge and at 1 year were recorded. Specific reasons for not using these treatments at discharge were noted. The target dose was in line with BB and ACEI doses used in large randomized trials, defined as follows: metoprolol, 200 mg/day; carvedilol, 50 mg/day; atenolol, 100 mg/day; acebutolol, 400 mg/day; propanolol, 180 mg/day; captopril, 150 mg/day; lisinopril, 10 mg/day; ramipril, 10 mg/day; perindopril, 10 mg/day; trandolapril, 4 mg/day. Treatment with valsartan, up to 320 mg/day as the target dose, was categorized as ACEI. All information on statins, dual antiplatelet agents, and optimal therapy, defined according to association with BB, ACEI, antiplatelet agents, and statins, as at time of discharge and at 1 year, were collected.

In-hospital data on mortality, reinfarction, heart failure, stroke, major bleeding defined as hemorrhagic stroke, digestive hemmorhage, vascular surgical repair, and transfusion were recorded. One-year follow-up data on all-cause mortality, 1-year cardiovascular mortality, 1-year reinfarction, 1-year readmission for heart failure, 1-year stroke, and 1-year revascularization with angioplasty or bypass surgery were collected as well. Heart failure was defined clinically in accordance with the guidelines of the European Society of Cardiology. During follow-up, data on drug prescription and dose were also recorded. The data were collected during follow-up consultation at 6 months and 1 year or by phone if the patient was followed up at a center other than the participating center. In-hospital and post-discharge outcomes were systematically adjudicated by the referring physicians (W.A.-K., S.D., F.P., A.F., S.G., J.-M.B., P.L.-C., C.R.) from the intensive care unit. The data were collected prospectively during 1-year follow-up with the cause of death attributed by the referring physician.

The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of University Hospital of Angers.

Statistical Analysis
Patient characteristics were compared with regard to in-hospital mortality. Outpatient characteristics and 1-year events were compared for each treatment with regard to the following: no treatment; <50% of target dose; and ≥50% of target dose. Particular focus was placed on patients with LVEF <40% or history of heart failure, named the LV dysfunction group and corresponding to a class I level A recommendation for BB and ACEI prescription following ML. For categorical variables, patient characteristics were compared using chi-squared test and expressed as frequencies and percentages. Continuous variables are expressed as median (IQR). Analysis of continuous variables was made using Mann-Whitney U-test for 2-comparison groups and Kruskal-Wallis test for 3-group comparison.

Univariate and multivariate analysis with binomial logistic regression were used in order to identify independent factors associated with in-hospital mortality. Variables used in univariate analysis were age, female gender, body mass index (BMI), history of hypertension, prior MI, prior coronary disease, acute revascularization, systolic blood pressure (SBP) at admission, heart rate at admission, anterior location of MI, creatinine, in-hospital heart failure, LVEF and absence of ACEI and BB after the first hospital day. The variables that were significantly (P<0.05) associated with the endpoints on univariate analysis were entered into multivariate analysis. The Hosmer-Lemeshow statistic was used to assess the goodness of fit of the logistic model.

An exploratory Cox proportional hazards model was applied to identify variables independently associated with 1-year all-cause mortality, 1-year cardiovascular mortality, 1-year readmission due to heart failure and composite endpoint (1-year cardiovascular mortality and 1-year readmission due to heart failure). The variables entered into the model were age, gender, history of hypertension, smoking status, dyslipidemia, diabetes, BMI, prior infarction, prior coronary artery disease, creatinine, both SBP and heart rate at admission, in-hospital heart failure, time from symptoms to admission, 3-vessel disease, anterior location, major bleeding, LVEF, and absence of BB and ACEI at discharge. Then a model with BB and ACEI doses was similarly tested. Factors that differed significantly on univariate analysis (P<0.05) were included in multivariate models. The same analysis was performed in the LV dysfunction subgroup. The proportional-hazard assumptions were tested by analyzing the Schoenfeld residuals for every significant parameter in the Cox model.

Logistic regression analysis was also performed in order to identify the variables associated with the use of <50% of the target dose among patients treated at discharge.

Unadjusted Kaplan-Meier survival analysis was conducted using log-rank test to determine cumulative incidence of 1-year all-cause mortality, 1-year cardiovascular mortality, and 1-year readmission for heart failure according to BB and ACEI doses at discharge.

Statistical analysis was carried out using SPSS version 17.0 (SPSS, Chicago, IL, USA). P<0.05 was considered statistically significant.

Results
In-Hospital Events
In the subject group of 1,461 patients, median age was 65 years (IQR, 52–78 years), 25.8% were diabetic, and 67.4% had undergone revascularization at acute phase. Median LVEF was 50% (IQR, 40–55%). A total of 114 patients (7.8%) died during hospitalization, and 376 (25.9%) had heart failure. The main characteristics are summarized in Table 1. The median length of stay was 6 days (IQR, 4–10 days). Compared to other patients, those who died during hospitalization were older and had more cardiovascular risk factors; they had a more severe presentation at admission. They had a lower prevalence of acute revascularization by fibrinolysis, PCI, or bypass surgery. The ischemic complications and major bleeding were more frequent.

Patients not receiving BB (16.7%) or ACEI (31.1%) on the first hospital day were older, more often female, and had a
### Table 1. Subject Characteristics

|                          | Total n=1,461 | In-hospital death n=114 (7.8%) | Discharged alive n=1,347 (92.2%) | P-value† |
|--------------------------|--------------|---------------------------------|----------------------------------|----------|
| **Cardiovascular risk factors** |              |                                 |                                  |          |
| Age (years)              | 65 (52–78)   | 79.5 (66.8–85)                  | 64 (52–77)                       | <0.001   |
| Male                     | 71.5         | 57.9                            | 72.7                             | 0.001    |
| Hypertension             | 49.8         | 63.3                            | 48.7                             | 0.003    |
| Diabetes mellitus        | 25.8         | 25.9                            | 25.8                             | NS       |
| Dyslipidemia             | 47.9         | 41.7                            | 48.4                             | NS       |
| Smoker                   | 34.2         | 17.3                            | 35.5                             | <0.001   |
| BMI (kg/m²)              | 26.2 (23.9–29.1) | 24.6 (22.8–27.7)              | 26.3 (23.9–29.1)                     | NS       |
| Prior CAD                | 44.5         | 48.2                            | 44.2                             | NS       |
| Prior MI                 | 10.2         | 18.6                            | 9.4                              | 0.002    |
| **Clinical data at admission** |            |                                 |                                  |          |
| Heart rate (beats/min)   | 76 (65–90)   | 80 (66.5–100)                   | 75 (65–90)                       | 0.026    |
| SBP (mmHg)               | 137 (120–155) | 120 (97–140)                   | 138 (120–157)                     | <0.001   |
| **MI characteristics**   |              |                                 |                                  |          |
| Time from symptoms to admission (h) | 3.2 (2–6.5) | 4.5 (2.3–13.7) | 3.2 (2–6.2) | 0.015 |
| Anterior location        | 47.0         | 46.1                            | 47                               | NS       |
| 3-vessel disease         | 21.3         | 44.7                            | 19.8                             | <0.001   |
| Acute revascularization  | 67.4         | 49.1                            | 68.9                             | <0.001   |
| Fibrinolysis             | 19.4         | 10.5                            | 20.1                             | 0.013    |
| PCI at acute phase       | 60.7         | 48.2                            | 61.8                             | 0.005    |
| CABG                     | 2.5          | 1.8                             | 2.5                              | NS       |
| Final TIMI flow 3        | 91.6         | 65.0                            | 93.1                             | <0.001   |
| LVEF (%)                 | 50 (40–55)   | 40 (30–50)                      | 50 (40–57)                       | <0.001   |
| Creatine phosphokinase peak (U/L) | 1,475 (662–2,677) | 1,628 (774–2,887) | 1,467 (660–2,667) | NS |
| Creatinine (μmol/L)      | 84 (71–100)  | 100 (79–135)                    | 83 (70–98)                       | <0.001   |
| **In-hospital events**   |              |                                 |                                  |          |
| HF                       | 25.9         | 63.1                            | 22.8                             | <0.001   |
| Reinfarction             | 1            | 0.9                             | 1.0                              | NS       |
| Stroke                   | 1.8          | 7.9                             | 1.3                              | <0.001   |
| Major bleeding           | 5.9          | 14.9                            | 5.1                              | <0.001   |

Data given as % or median (IQR). †Comparison between in-hospital death and discharged alive (Mann-Whitney or chi-squared test). BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIMI, Thrombolysis in Myocardial Infarction.

### Table 2. Multivariate Analysis for In-Hospital Mortality

|                         | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | P-value             | OR (95% CI)           |
| Age (per 1 year)        | <0.001              | NS                    |
| Female                  | <0.001              | NS                    |
| Smoker                  | <0.001              | NS                    |
| Prior MI                | 0.003               | 4.8 (1.96–11.79)      |
| SBP at admission (per 1 mmHg) | <0.001          | 0.98 (0.97–0.99)      |
| Heart rate at admission (per 1 beats/min) | 0.017             | NS                    |
| In-hospital HF          | 0.001               | 3.00 (1.14–7.92)      |
| Creatinine (per 50 μmol/L) | <0.001            | NS                    |
| 3-vessel disease        | <0.001              | NS                    |
| LVEF (per 1%)           | <0.001              | NS                    |
| No ACEI on first hospital day | <0.001      | NS                    |
| No BB on first hospital day | <0.001         | 5.78 (2.62–12.76)    |

ACEI, angiotensin-converting enzyme inhibitor; BB, β-blocker. Other abbreviations as in Table 1.
Beta-Blocker and ACEI Dose Following MI

The prevalence of renal failure was higher, SBP was lower, and there was a higher prevalence of anterior infarct and 3-vessel disease. Among patients without BB treatment on the first hospital day there were 57 (23.4%) in-hospital deaths vs. 50 (4.2%) among those who received BB (P<0.001).

Independent variables associated with in-hospital mortality were prior MI, in-hospital heart failure, low blood pressure at admission and absence of BB on first hospital day, with the latter being the strongest factor (OR, 5.78; 95% CI: 2.62–12.76; Table 2).

Outpatients and 1-Year Events
Mean follow-up was 305±107 days. Of the 1,347 patients discharged alive, 82.2% received optimal treatment, such as BB, ACEI, statins, and antiplatelet agents. 93.4% received BB, and 92.7% ACEI. This is compared with 90.2%, and 77.1%, respectively, at 1 year. When BB were not administered, the following reasons were given: pulmonary disease, such as asthma or severe chronic obstructive pulmonary disease, in 26.7% of cases; conduction disorders in 20%; hypotension in 15%; coronary spasm in 12.2%; and unknown causes in 26.1%. To explain absence of ACEI prescription, reasons given were: normal LVEF in 24% of cases; hypotension in 21.2%; renal failure in 16.2%; and unknown causes in 38.6%.

Of the patients treated with BB, 22.6% received <50% of target dose at discharge, as did 21.1% of patients receiving ACEI. Only 34.9% of patients treated with BB, and 21.1% of those receiving ACEI, were administered the target dose at discharge.

Table 3. One-Year Events in Outpatients vs. Discharge BB Dose

| Cardiovascular risk factors | No BB at discharge (n=89 (6.6%)) | <50% of target dose (n=304 (22.6%)) | ≥50% of target dose (n=954 (70.8%)) | P-value† |
|----------------------------|-----------------------------------|------------------------------------|-----------------------------------|---------|
| Age (years)                | 72 (57–81)                        | 72.5 (57–81)                       | 61 (50–74)                        | <0.001  |
| Male                       | 60.7                              | 62.2                               | 77.1                              | <0.001  |
| Hypertension               | 56.2                              | 53.6                               | 46.5                              | 0.033   |
| Diabetes mellitus          | 27.9                              | 22.1                               | 26.7                              | NS      |
| Dyslipidemia               | 40.7                              | 46.7                               | 49.6                              | NS      |
| Smoker                     | 30.6                              | 27.2                               | 38.6                              | 0.001   |
| BMI (kg/m²)                | 26 (231–29.5)                     | 25.6 (23–28.5)                     | 26.5 (4.2–29.3)                   | 0.005   |
| Prior CAD                  | 51.7                              | 42.1                               | 44.2                              | NS      |
| Prior MI                   | 9                                 | 10.5                               | 9.1                               | NS      |
| Clinical data at admission |                                   |                                    |                                   |         |
| Heart rate (beats/min)     | 74 (55–98.5)                      | 77 (61.5–94)                       | 75 (65–88)                        | NS      |
| SBP (mmHg)                 | 136 (110–160)                     | 135 (144–154)                      | 140 (120–157)                     | 0.034   |
| In-hospital HF             | 33.7                              | 37.3                               | 17.2                              | <0.001  |
| MI characteristics         |                                   |                                    |                                   |         |
| Time from symptoms to admission (h) | 3.6 (2.3–12.8) | 3 (2–5.9)                         | 3.2 (2–6.1)                      | NS      |
| Anterior location          | 40.3                              | 39.7                               | 48.1                              | NS      |
| 3-vessel disease           | 19.2                              | 21.2                               | 18.6                              | NS      |
| Acute revascularization    | 57.3                              | 63.8                               | 71.1                              | 0.002   |
| Fibrinolysis               | 15.7                              | 19.7                               | 20.7                              | NS      |
| PCI at acute phase         | 53.9                              | 55.6                               | 64.4                              | 0.006   |
| CABG                       | 4.5                               | 4.0                                | 1.9                               | NS      |
| Final TIMI flow 3          | 91.8                              | 94.8                               | 92.7                              | NS      |
| LVEF (%)                   | 45 (40–55)                        | 45 (32–55)                         | 50 (45–60)                        | <0.001  |
| Creatinine (µmol/L)        | 90 (70.5–107.8)                   | 85 (71–104)                        | 82 (70–96)                        | 0.002   |
| Creatine phosphokinase peak (UI/L) | 1,434 (669–2,314) | 1,116 (418–2,230) | 1,596 (737–2,780) | <0.001 |
| 1-year treatment           |                                   |                                    |                                   |         |
| Statins                    | 79.1                              | 89.2                               | 93.4                              | <0.001  |
| Dual antiplatelet agent    | 49.2                              | 71                                 | 77.2                              | <0.001  |
| Optimal treatment          | 16.9                              | 64.1                               | 73.2                              | <0.001  |
| 1-year events              |                                   |                                    |                                   |         |
| 1-year all cause mortality | 14                                | 8.0                                | 2.8                               | <0.001  |
| 1-year cardiovascular mortality | 9.3                        | 5.4                                | 2.2                               | <0.001  |
| 1-year reinfection         | 2.9                               | 3.0                                | 2                                 | NS      |
| 1-year readmission for HF  | 8.5                               | 12.5                               | 4.4                               | <0.001  |
| 1-year stroke              | 1.5                               | 0.4                                | 0.9                               | NS      |
| 1-year revascularization   | 8.7                               | 7.6                                | 10.1                              | NS      |
| 1-year PCI                 | 8.7                               | 7.2                                | 7.6                               | NS      |
| 1-year CABG                | 0.0                               | 0.4                                | 3                                 | 0.018   |

Data given as % or median (IQR). †Comparison between the 3 groups (Kruskal-Wallis or chi-squared test). Abbreviations as in Tables 1,2.
der and lower heart rate at admission were independent variables related to prescription of BB at <50% of target dose (OR, 1.59; 95% CI: 1.13–2.23, P=0.007; OR, 0.99; 95% CI: 0.98–0.99, P=0.023, respectively). Among patients treated with ACEI at discharge, independent variables associated with prescription of ACEI at <50% of the target dose were prior MI (OR, 1.86; 95% CI: 1.16–2.96, P=0.010) and lower LVEF (OR, 0.98; 95% CI: 0.97–1, P=0.048) (Tables S1, S2).

At 1 year, 109 patients had been lost to follow-up (7.5%). There were 63 deaths (4.8%), 45 cardiovascular deaths (3.6%), and 76 readmissions due to heart failure (5.2%). Patients who received none or <50% of the target dose of BB or ACEI had higher incidence rates of 1-year all-cause mortality, 1-year cardiovascular mortality, and 1-year readmission due to heart failure (Tables 3, 4).

### Table 4. One-Year Events in Outpatients vs. Discharge ACEI Dose

| Cardiovascular risk factors | No ACEI at discharge n=100 (7.4%) | <50% of target dose n=284 (21.1%) | ≥50% of target dose n=963 (71.5%) | P-value† |
|-----------------------------|------------------------------------|-----------------------------------|----------------------------------|---------|
| Age (years)                 | 68.5 (55–80)                       | 63.5 (53–77)                      | 64 (51–76)                       | 0.045   |
| Male                        | 58                                 | 70.1                              | 75                               | 0.001   |
| Hypertension                | 57                                 | 44.5                              | 49.1                             | NS      |
| Diabetes mellitus           | 24.7                               | 17.1                              | 28.4                             | 0.001   |
| Dyslipidemia                | 49.5                               | 46.1                              | 48.9                             | NS      |
| Smoker                      | 30.2                               | 37.4                              | 35.5                             | NS      |
| BMI (kg/m²)                 | 27.1 (24.2–29.6)                   | 25.7 (23.2)                       | 26.4 (24.1)                      | 0.045   |
| Prior CAD                   | 48                                 | 40.4                              | 45                               | NS      |
| Prior MI                    | 14                                 | 8.5                               | 9.3                              | NS      |

### Clinical data at admission

| Heart rate (beats/min)      | 76 (62–92)                         | 76 (64–90)                        | 75 (65–90)                       | NS      |
| SBP (mmHg)                  | 131 (110–150)                      | 130 (113–150)                     | 140 (120–160)                    | <0.001  |
| In-hospital HF              | 27                                 | 28                                | 20.8                             | 0.024   |

### MI characteristics

| Time from symptoms to admission (h) | 3.7 (3.2–11.2) | 3.5 (2.1–6.7) | 3.1 (2.5–9) | NS |
| Anterior location              | 31.2              | 48.2             | 49           | 0.007 |
| 3-vessel disease               | 28.8                | 22.2             | 18.4         | 0.047 |
| Acute revascularization        | 55                  | 67.3             | 70.9         | 0.004 |
| Fibrinolysis                   | 11                  | 20.1             | 21.1         | NS    |
| PCI at acute phase             | 50                  | 60.9             | 63.2         | 0.003 |
| CABG                          | 9                   | 2.5              | 1.9          | <0.001 |
| Fibrinolysis                   | 88.3                | 91.5             | 93.9         | NS    |
| LVEF (%)                      | 50 (43–60)          | 50 (40–55)       | 50 (40–57)   | NS    |
| Creatinine (μmol/L)           | 88 (76.5–109)       | 81.5 (70–96.7)   | 83 (70–97)   | 0.013 |
| Creatine phosphokinase peak (UI/L) | 1,266 (578–2,126) | 1,559 (643–2,789) | 1,473 (674–2,666) | NS |

### 1-year treatment

| Statins                      | 85                  | 92.4             | 92.1         | NS    |
| Dual antiplatelet agent      | 55.8                | 64.6             | 78.9         | <0.001 |
| Optimal treatment            | 32                  | 68.7             | 70.7         | <0.001 |

### 1-year events

| 1-year all cause mortality   | 13.5                | 5.8              | 3.5          | <0.001 |
| 1-year cardiovascular mortality | 14.3                | 4.4              | 2.2          | <0.001 |
| 1-year reinfarction          | 2.6                 | 3.5              | 1.9          | NS    |
| 1-year readmission for HF    | 14.5                | 9                | 4.9          | 0.023 |
| 1-year stroke                | 1.3                 | 0.8              | 0.8          | NS    |
| 1-year revascularization     | 7.8                 | 9.3              | 9.6          | NS    |
| 1-year PCI                   | 6.5                 | 7.8              | 7.6          | NS    |
| 1-year CABG                  | 1.3                 | 2.3              | 2.3          | NS    |

Data given as % or median (IQR). †Comparison between the 3 groups (Kruskal-Wallis or chi-squared test). Abbreviations as in Tables 1–3.
Beta-Blocker and ACEI Dose Following MI

Exploratory Multivariate Analysis
Independent variables associated with 1-year cardiovascular mortality were female sex, in-hospital major bleeding, LVEF, and lower dose or absence of ACEI (Tables 5, S5). Treatment with ACEI was associated with a significant reduction in overall cardiovascular mortality, regardless of the dose (<50% or ≥50% of the target dose; Figure 1A).

Independent variables associated with 1-year readmission due to heart failure were age, in-hospital heart failure, LVEF, creatinine and lower dose or absence of ACEI (Tables 6, S6). Treatment with ≥50% of target dose was associated with a significant reduction in readmission due to heart failure at 1 year (Figure 1B). Independent variables associated with the composite endpoint were in-hospital heart failure, in-hospital major bleeding, creatinine, LVEF and absence of ACEI at discharge (HR, 2.65; 95% CI: 1.32–5.31, P=0.006) (Tables S3, S4).

One-Year Events and History of Heart Failure or LVEF <40%
In this subgroup of 477 patients with history of heart failure or LVEF <40% (32.6%), there were 45 deaths (9.4%), 36 cardiovascular deaths (7.5%), and 50 readmissions due to heart failure (10.5%) at 1 year. The variables independently related with 1-year all-cause mortality were target dose of BB (HR, 0.48; 95% CI: 0.26–0.89, P=0.019) and older age (HR, 1.06; 95% CI: 1.01–1.10, P=0.011). Treatment with ≥50% of target dose was associated with a significant reduction in 1-year all-cause mortality (Figure 2A).

Independent variables related with 1-year readmission for heart failure were in-hospital heart failure (HR, 9.9; 95%CI: 3.04–32.26, P=0.001), lower LVEF (HR, 0.96; 95%CI: 0.93–0.98, P=0.003), and target dose of ACEI (HR, 0.41; 95% CI: 0.27–0.62, P=0.001; Figure 2B). Treatment with ≥50% of the target dose was associated with a significant reduction in 1-year readmission for heart failure.

Discussion
The primary finding of the present study was that not prescribing BB in the first 24h following admission was independently associated with in-hospital death. The COMMIT trial proved that early injection of metoprolol did not improve mortality in MI due to increased cardiogenic shock, despite a reduction in ventricular arrhythmias observed. Yet high meta-

Table 5. Multivariate Analysis for 1-Year Cardiovascular Mortality

| Variable                                      | P-value Univariate Analysis | P-value Multivariate Analysis | HR (95% CI) Multivariate Analysis |
|-----------------------------------------------|----------------------------|-------------------------------|----------------------------------|
| Age (per 1 year)                              | <0.001                     | NS                            | 3.74 (1.58–8.88)                |
| Female                                        | <0.001                     | 0.029                         | 2.37 (1.08–5.1)                 |
| Hypertension                                  | <0.001                     | NS                            | 0.95 (0.91–0.98)                |
| Smoker                                        | 0.001                      | NS                            | 0.46 (0.27–0.76)                |
| Heart rate at admission (per 1 beats/min)     | <0.001                     | NS                            |                                  |
| In-hospital HF                                | <0.001                     | NS                            |                                  |
| Creatinine (per 50 μmol/L)                    | <0.001                     | 0.003                         | 0.95 (0.91–0.98)                |
| LVEF (per 1%)                                 | <0.001                     | NS                            |                                  |
| No BB vs. <50% vs. ≥50% target dose           | <0.001                     | NS                            |                                  |
| No ACEI vs. <50% vs. ≥50% target dose         | <0.001                     | 0.003                         | 0.46 (0.27–0.76)                |

Abbreviations as in Tables 1, 2.
prolol doses were administered, maximum at 200 mg per day on the second day of treatment, which could account for some cardiogenic shock occurrence. In the TIMI II-B study, early BB treatment proved beneficial in patients aged <70 years, without anterior infarct or heart failure, and with SBP >100 mmHg. In the present study, LVEF was moderately altered, and the patients were relatively young. A recent non-randomized study conducted by Hirschl et al confirmed a reduction in in-hospital mortality among ST-elevation MI patients who benefitted from treatment with bisoprolol very early following diagnosis. In contrast with some studies, the RIMA registry found that early ACEI treatment was not related to in-hospital mortality. ACEI have been shown to be particularly beneficial in reducing post-infarct remodeling of the LV, with benefits in mortality and heart failure more evident on long term follow-up. Similar effects of angiotensin receptor blockers have been reported, particularly with the use of valsartan. In-hospital heart failure was also an independent factor associated with in-hospital mortality; it is possible that the effect of absence of BB prescription on the day of admission on in-hospital mortality is explained in part by worse clinical status at admission, particularly heart failure, which limits treatment with BB.

Another relevant finding of the present study was that few patients were at target dose at the time of discharge, with only 34.8% at target for BB, and 21.7% for ACEI. In line with the present findings, Kvan and Reikvam reported that only 34% of patients left hospital with evidence-based dosing of BB. In addition, in 2007 Goldberger et al reported that only 17% of patients received >50% of the target dose of ACEI at discharge. In the present study, we found that 33% were at >50% of target dose for ACEI. A Danish registry including 55,300 patients with acute MI found that most patients received approximately 50% of target dose of ACEI and BB at discharge. As in the present study, during the 2-year follow-up conducted in that registry, the 2 treatment doses did not increase, indicating that the dose at time of discharge constituted the final dose of treatment in the majority of patients. These data are consistent with EUROASPIRE III concerning the decrease in prescription rates of ACEI and BB during follow-up. In the present study, independent factors related with BB dose at discharge were found to be female gender and lower heart rate at admission as well as prior MI and lower LVEF for ACEI doses, respectively. Underutilization of evidence-based therapies for women, associated with poorer prognosis in acute MI, has been well-established.

### Table 6. Multivariate Analysis for 1-Year Readmission for HF

|                      | Univariate analysis |         | Multivariate analysis |         |
|----------------------|---------------------|---------|-----------------------|---------|
|                      | P-value             |         | HR (95% CI)           |         |
| Age (per 1 year)     | <0.001              | 0.012   | 1.04 (1.01–1.06)      |         |
| Female               | 0.002               | NS      |                       |         |
| Hypertension         | <0.001              | NS      |                       |         |
| Smoker               | 0.002               | NS      |                       |         |
| Heart rate at admission (per 1 beats/min) | <0.001 | NS      |                       |         |
| In-hospital HF       | <0.001              | <0.001  | 3.23 (1.76–5.95)      |         |
| Creatinine (per 50 μmol/L) | <0.001 | <0.001 | 1.52 (1.22–1.88)      |         |
| LVEF (per 1%)        | <0.001              | <0.001  | 0.95 (0.93–0.98)      |         |
| No BB vs. <50% vs. ≥50% target dose | <0.001 | NS      |                       |         |
| No ACEI vs. <50% vs. ≥50% target dose | 0.001 | 0.001  | 0.54 (0.38–0.77)      |         |

Abbreviations as in Tables 1, 2.
Lower rate of BB and ACEI prescription in women has been found in a recent Japanese study.\textsuperscript{27} A Canadian registry on acute coronary syndrome found that female gender was an independent predictive factor of not receiving ACEI or lipid-modifying agents.\textsuperscript{28} In that registry, women were also less frequently treated with BB when compared to men.

Finally, the present study confirmed that the absence of ACEI prescription at discharge was associated with 1-year cardiovascular mortality. This result is in line with clinical trials assessing the effects of ACEI in an acute MI setting.\textsuperscript{3, 13, 14} The benefits of ACEI in these studies were particularly marked among patients with LV dysfunction or clinical heart failure. In the resent study, considering patients with LVEF <40% or in-hospital heart failure, ACEI ≥50% of target dose was related with absence of 1-year hospitalization due to heart failure. Also with regard to heart failure, Chen et al noted that patients receiving a higher dose of lisinopril had a reduction in mortality.\textsuperscript{29} The ATLAS trial found a reduction in mortality and hospitalization due to heart failure with high-dose vs. low-dose lisinopril among patients with heart failure.\textsuperscript{30} To our knowledge, the RIMA registry is the first to demonstrate the relevance of target dose of ACEI on cardiovascular mortality in an unselected MI population, as well as on hospitalization for heart failure among those with LV dysfunction.

With regard to BB therapy, a treatment dose <50% of target dose at discharge was independently associated with 1-year all-cause mortality among patients with LV dysfunction (LVEF <40% or in-hospital heart failure), but not in patients with preserved LVEF. As is the case for ACEI effects, data concerning the effect of low-dose BB following acute MI are scarce. Most information available concerning treatment doses originates from publications on heart failure. The MOCHA study noted a close link between carvedilol dose and survival in systolic heart failure.\textsuperscript{31} As in the present study, the COMET trial found a significant correlation between high metoprolol or carvedilol dose and reduction in mortality after 2 years of follow-up.\textsuperscript{32}

### Study Limitations

The present study had some limitations. Although prospective, this is an observational registry and the use/dosage of therapy is subject to considerable confounding factors, both at the patient and at the physician level that cannot be fully addressed. We also deplore the absence of monitoring of the prescription and of uptitration of BB or ACEI during follow-up. Second, this was a regionwide registry conducted in a rural area, potentially indicating a bias of selection, particularly with regard to reperfusion therapy modalities. The present results may be specific to the our dataset and potential discrepancies should be disclosed when considering patients from distinct origins and levels of income. It represents, however, a specific interest in complete long term follow-up and a focus on very specific variables such as therapy dose, which may be harder to achieve in a nationwide registry.

Finally, the reasons for the absence of uptitration are uncertain and may constitute the key limitation of the present study. Indeed it may reflect the misuse of evidence-based therapy, or may indicate the presence of patients with more severe clinical status with lower blood pressure and drug intolerance. Prospective randomized studies should be tailored to determine the feasibility, the causes and the results of uptitration in a real-life setting.

### Conclusions

Early treatment with BB following MI was associated with lower in-hospital mortality. At discharge, ACEI ≥50% of target dose was associated with lower hospitalization due to heart failure, regardless of LVEF. For patients with LV dysfunction, dose ≥50% of BB or ACEI target doses administered at discharge should have a beneficial effect on all-cause and cardiovascular mortality. The present study indicates the importance of early prescription of BB after MI, as well as (in line with the requirement of evidence-based therapies) of being as close as possible to the target dose to provide maximum protection against MACE during follow-up. But, given that lower dose could also be representative of drug intolerance, uptitration should be conducted progressively according to clinical status. This strategy has to be confirmed in clinical randomized trials.

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### Disclosures

Conflict of Interest: None declared.

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