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RESEARCH ARTICLE

Association of beta-blocker treatment with mortality following myocardial infarction in patients with chronic obstructive pulmonary disease and heart failure or left ventricular dysfunction: a propensity matched-cohort analysis from the High-Risk Myocardial Infarction Database Initiative

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Aims To determine the influence of baseline beta-blocker use on long-term prognosis of myocardial infarction (MI) survivors complicated with heart failure (HF) or with left ventricular dysfunction and with history of chronic obstructive pulmonary disease (COPD).

Methods and results Among the 28 771 patients from the High-Risk MI Database Initiative we identified 1573 patients with a baseline history of COPD. We evaluated the association between beta-blocker use at baseline (822 with beta-blocker and 751 without) on the rates of all-cause and cardiovascular mortality. On univariable Cox analysis, beta-blocker use was found to be associated with lower rates of both all-cause [hazard ratio (HR) = 0.61, 95% confidence interval (CI) 0.51–0.75, $P < 0.0001$] and cardiovascular mortality (HR = 0.63, 95% CI 0.51–0.78, $P < 0.0001$). After extensive adjustment for confounding, including 24 baseline covariates, COPD patients still benefited from beta-blocker usage (HR = 0.73, 95% CI 0.60–0.90, $P = 0.002$ for all-cause mortality; HR = 0.77, 95% CI 0.61–0.97, $P = 0.025$ for cardiovascular mortality). Adjusting for propensity scores (PS) constructed from the 24 aforementioned baseline characteristics provided similar results. In a cohort of 561 pairs of patients taking or not taking beta-blocker matched on PS using a 1:1 nearest-neighbour matching method, patients treated with beta-blocker experienced fewer all-cause deaths (HR = 0.71, 95% CI 0.56–0.89, $P = 0.003$) and cardiovascular deaths (HR = 0.76, 95% CI 0.59–0.97, $P = 0.032$).

Conclusions In the specific setting of a well-treated cohort of high-risk MI survivors, beta-blockers were associated with better outcomes in patients with COPD.

Keywords Beta-blockers • Chronic obstructive pulmonary disease • Myocardial infarction • Mortality

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Introduction

Beta-blockers are effective at reducing the risk of mortality after a myocardial infarction (MI),[1] and they are given a class I recommendation by current guidelines.[2,3] Despite a gradual improvement in optimal medical therapy at discharge from MI hospitalization, the gap between guidelines and practices in using beta-blockers continues.[4] Patients with chronic obstructive pulmonary disease (COPD) are at higher risk for death after MI[5] and this association seems to be mainly explained by differences in co-morbidities and treatment. Indeed, as already highlighted in an acute heart failure (HF) context,[6] this subset of patients less often receives well-proven secondary preventive medications such as beta-blockers.[7] However, data from large retrospective studies show that patients with COPD receiving beta-blockers had about 40% risk reduction in mortality,[1,8] even in a high-risk setting.[1]

Many clinicians withhold or do not prescribe beta-blockers from patients with COPD because they fear for provoking bronchospasm and inducing respiratory failure; indeed, beta-blockers may cause bronchial hyper-reactivity in patients with other lung diseases such as asthma,[9] and potentially also in COPD patients, in whom provoked bronchial hyper-responsiveness has been reported in about 40% of cases.[10] However, mechanisms potentially able to induce airway constriction in patients with COPD may be different from those in patients with asthma,[11] and beta-blockade may not cause bronchoconstriction in patients with COPD.[12] In addition, cardioselective beta-blockers have been proven to be safe in different cardiovascular settings (HF, coronary artery disease, and hypertension); thus, according to evidence, this class of drug should not be routinely withheld from patients with COPD.[13] Despite the above-cited evidence, a substantial proportion of MI survivors with COPD, ranging roughly from one-fifth to three-fifths of these patients, are still discharged without a beta-blocker.[14,15]

It is very unlikely that a prospective large randomized trial evaluating beta-blocker effect in HF patients with COPD will ever be performed. In the absence of such randomized evidence, evaluating the treatment effect from observational cohorts using specific methods to decrease attribution bias would likely augment evidence regarding the effects of beta-blockers in this specific population.

To further examine the impact of beta-blockers on the long-term prognosis of MI survivors with COPD, we took advantage of the pooled population of four large clinical trials that enrolled high-risk MI survivors.[16]

Methods

High-risk acute myocardial infarction trials pooling project

The rationale for selecting and pooling four trials included in this analysis has been published elsewhere.[16] The High-Risk MI Database Initiative constructed a common database by merging the data from four randomized and double-blinded large trials: the effect of the Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN),[17] Eplerenone's Neurohormonal Efficacy and Survival Study (EPHESUS),[18] the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL)[19] and Valsartan in Acute Myocardial Infarction trial (VALIANT).[20]

Each trial enrolled patients with left ventricular systolic dysfunction, HF, or both between 12 h and 21 days after acute MI. In total, 28 771 patients were enrolled (1959 in CAPRICORN, 6632 in EPHESUS, 5477 in OPTIMAAL, and 14 703 in VALIANT) with a mean follow-up of 2.7 years. In two trials patients were assigned equally to placebo or active therapy (carvedilol or eplerenone),[17,18] added to the usual treatment. In the other two, patients were randomized to experimental therapy (losartan or valsartan) or active control (captopril).[19,20] VALIANT[20] had, in addition, a third treatment arm (captopril plus valsartan).

Beta-blocker usage and chronic obstructive pulmonary disease definition in the High-Risk Myocardial Infarction Database Initiative

With regard to beta-blocker treatment, the database reports the usage of this drug class by coding it 'yes/no', without mentioning the specific active substance. Beta-blocker users were defined at randomization, which occurred throughout the whole acute phase of MI (up to 21 days for CAPRICORN). The presence of clinically recognized COPD was recorded using a yes/no check box by individual site investigators at study entry according to their clinical judgment.

Among the study population, 2390/28771 patients (8.3%) had a history of COPD. Beta-blocker treatment at baseline was not reported in CAPRICORN[17] (being patients randomized to carvedilol or placebo), and left ventricular ejection fraction (LVEF) was not reported in OPTIMAAL.[19] Entering these factors resulted in a further reduction of the sample size from 2390 to 1573 patients (5.4%); that sample was used for sensitivity analysis. Both beta-blocker usage and COPD, as well as all the other data included in this analysis are baseline characteristics at study randomization, which occurred shortly after the index event (ranging from 3 to14 days after admission because of MI in EPHESUS[18] and from 0.5 to 10 days in VALIANT[20]).

Statistical methods

Baseline characteristics of the study population were described as frequency (per cent) for categorical variables and mean ± standard deviation (SD) for continuous variables. In order to correct for potential bias in the selection of patients, a propensity score (PS) analysis was performed[21] to calculate the probability of being prescribed a beta-blocker at baseline. Specifically, a full non-parsimonious logistic regression model was performed to determine the propensity for receipt of beta-blockers (dependent variable) as initial therapy at baseline for each of the 1573 participants, based on the 24 variables presented in *Table 1* (predictor variables) (see the Supplementary material online, *Table S1*, for binary logistic regression model to estimate the effect of each baseline characteristic on the probability of receiving a beta-blocker at baseline). We also undertook further sensitivity analyses matching on propensity scores. A 1:1 nearest-neighbour matching was used.[22] Treatment groups were compared using standardized differences, calculated as the difference in means or proportions expressed as a percentage of the pooled estimate of the SD,[23,24] before and after PS matching. We plotted these standardized differences before and after matching as a Love plot.[25] Typically, a standardized difference of less than 10% suggests inconsequential bias.[23] The pre-specified outcomes were all-cause and cardiovascular mortality.

Table 1 Baseline characteristics according to beta-blocker use in patients with chronic obstructive pulmonary disease before and after propensity matching

	Before matching				After matching			
	Beta-blocker use				Beta-blocker use			
	No ($n = 751$)	Yes ($n = 822$)	Standardized difference*	*P*-value	No ($n = 561$)	Yes ($n = 561$)	Standardized difference*	*P*-value
Anthropometry—lifestyle								
Male gender	69%	75%	12.2%	0.018	71%	72%	2%	0.748
Age (years)	69 ± 9	66 ± 10	26.6%	<0.0001	68 ± 10	68 ± 10	0.6%	0.920
Smoker								
Never	19%	16%	9.6%	0.069	17%	18%	1%	0.875
Past	41%	38%	6%	0.238	40%	39%	2.9%	0.625
Current	40%	46%	12.6%	0.012	43%	44%	2.8%	0.763
Physical examination and ultrasound								
Systolic BP (mmHg)	122 ± 18	121 ± 16	9.2%	0.081	122 ± 17	122 ± 17	1%	0.873
Diastolic BP (mmHg)	71 ± 11	71 ± 11	6.7%	0.182	71 ± 11	71 ± 11	4.4%	0.453
Heart rate (b.p.m.)	80 ± 13	75 ± 12	37.6%	<0.0001	78 ± 13	77 ± 13	6.4%	0.306
eGFR (ml/min.1.73 m^2)	66 ± 21	73 ± 54	13.1%	0.001	67 ± 21	69 ± 23	2.9%	0.226
Killip class ≥3	32%	30%	22.6%	<0.0001	29%	27%	4.2%	0.506
LVEF	33 ± 9	33 ± 9	1.6%	0.753	34 ± 9	34 ± 9	0.8%	0.894
Medical history								
Previous MI	36%	40%	8.6%	0.085	37%	38%	1.5%	0.805
HF hospitalization	55%	52%	6%	0.232	54%	54%	0.1%	0.484
Atrial fibrillation	21%	16%	13.5%	0.011	19%	19%	0.5%	0.940
Stroke	11%	11%	1.2%	0.821	11%	11%	0.1%	0.923
PAOD	18%	19%	2.5%	0.614	18%	18%	0.8%	0.99
Diabetes	30%	31%	2%	0.694	31%	30%	0.8%	0.897
Hypertension	58%	63%	9.5%	0.063	61%	61%	1.5%	0.807
Hyperlipidaemia	41%	52%	21.8%	<0.0001	45%	46%	0.7%	0.905
Renal failure	8%	5%	1.1%	0.832	7%	8%	3.5%	0.577
Medications								
ACEI/ARB	56%	61%	10.3%	0.044	58%	59%	2.2%	0.767
Digoxin	23%	19%	9%	0.084	21%	22%	3.6%	0.560
Aspirin	84%	89%	16.6%	0.003	86%	87%	2.9%	0.665
Calcium channel blockers	21%	10%	36.3%	<0.0001	13%	15%	4.1%	0.547
Diuretics	69%	59%	20.5%	<0.0001	67%	65%	3.3%	0.572
Statins	28%	42%	28.9%	<0.0001	33%	34%	1.4%	0.800

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BP, blood pressure; eGFR, estimated glomerular filtration rate according to the MDRD formula; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAOD, peripheral artery obstructive disease.
Data are expressed as % or means±SD.
*The standardized difference is expressed as a percentage and is the difference between the means for the two groups divided by the mutual standard deviation. *P*-value from chi-square or Student's *t*-test.

Univariable and multivariable Cox proportional hazards models for all-cause and cardiovascular mortality were performed. Three types of Cox models were built: (i) univariable and multivariable Cox adjusted according to age, gender, smoking habit (considered as relevant a priori),[15] Killip class ≥3, co-morbidities, biological variables, LVEF and treatments at baseline; (ii) univariable and multivariable Cox proportional hazards models PS-adjusted, using PS as an alternative way of adjusting for differences in groups of patients taking or not taking beta-blocker (as continuous covariates, PS values were forced into the Cox model with beta-blocker intake, evaluating the effect on outcomes in the whole cohort and across subgroups according to baseline characteristics, also testing for interaction in order to test consistency of treatment effects); (iii) univariable Cox proportional hazards model stratified on PS matched pairs associated with beta-blocker usage. Kaplan–Meier survival curves were built for the matched cohort according to beta-blocker usage. All analyses were performed using SPSS 23.0 (SPSS, Chicago, IL, USA) The two-tailed significance level was set at $P < 0.05$.

Results

Patient characteristics in the whole and propensity matched cohorts

Characteristics of patients with and without COPD are reported in the Supplementary material online (*Table S2*).

The study cohort included 1573 patients with COPD and among them, 822 (52.2%) were on beta-blockers at randomization; overall, mean age was 67 ± 10 years, 28% were female with an average

Table 2 Association of beta-blocker use as initial therapy at baseline with outcomes using Cox proportional hazards models in the whole cohort [adjusted according to clinical models and propensity score (PS)] and in the PS-matched cohort

	All-cause mortality HR (95% CI)	*P*-value	Cardiovascular mortality HR (95% CI)	*P*-value
Whole cohort				
Model adjusted for 24 covariates*	0.73 (0.60–0.90)	0.002	0.77 (0.61–0.97)	0.025
Model adjusted for PS	0.73 (0.60–0.90)	0.003	0.77 (0.61–0.96)	0.022
PS-matched cohort				
Crude analysis	0.71 (0.56–0.89)	0.003	0.76 (0.59–0.97)	0.032

CI, confidence interval; HR, hazard ratio.
*Model is adjusted for age, gender, smoking habit, Killip class ≥3, co-morbidities (myocardial infarction, heart failure, hypertension, renal failure, atrial fibrillation, peripheral artery disease, diabetes, history of cerebrovascular disease), biological variables (systolic and diastolic blood pressure, heart rate, estimated glomerular filtration rate), left ventricular ejection fraction, and treatment at baseline (digoxin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, diuretics, aspirin, calcium channel blocker, statin).

LVEF of 33 ± 9%. Unadjusted baseline characteristic differences between patients on beta-blockers or not were important as assessed by standardized differences (*Table 1*). Generally, patients on beta-blockers were younger, more likely to be male and, as expected, they had a lower heart rate; they were also less likely to have Killip class ≥ 3 (frank pulmonary oedema) or atrial fibrillation at study entry (*Table 1*). In multivariable analysis, a number of variables were significantly associated with the probability of being treated with a beta-blocker, including age, smoking status, diastolic blood pressure, and previous hospitalization owing to HF (*Table S2*).

By application of PS matching, we then assembled a cohort of 561 pairs of patients receiving or not receiving beta-blockers at baseline; standardized differences were reduced to less than 5% for all 24 characteristics except for heart rate, which nevertheless did not exceed 10%, with a substantial improvement in the balance across treatment groups (*Table 1*; see the Supplementary material online, *Figure S1*). Overall, matched patients had a mean age of 68 ± 10 years, 28% were female, and had an average LVEF of 34 ± 9% (*Table 1*).

Impact of beta-blockers on long-term prognosis in the whole cohort

The median length of follow-up after MI was 1.68 years (range 0.01–3.81). Overall, during the follow-up, there were 420 (26.7%) all-cause deaths and 334 (21.2%) cardiovascular deaths in the whole cohort ($n = 1573$). Patients on beta-blockers at randomization ($n = 822$) experienced 176 (21.4%) all-cause deaths, whereas 244 (32.5%) deaths occurred among untreated patients ($n = 751$); similarly, patients on beta-blockers had fewer cardiovascular deaths, with 142 (17.3%) events as opposed to 192 (25.6%) among patients not on beta-blockers. By univariable Cox models, patients with COPD prescribed with a beta-blocker were shown to have a better survival, with lower rates of both all-cause mortality [hazard ratio (HR) = 0.61, 95% confidence interval (CI) 0.51–0.75, $P < 0.0001$] and cardiovascular mortality (HR = 0.63, 95% CI 0.51–0.78, $p < 0.0001$).

Using multivariable Cox models, after extensive adjustment for several baseline characteristics, beta-blocker use was still found to be associated with a better outcome, both in terms of all-cause (HR = 0.73, 95% CI 0.60–0.90, $P = 0.002$) and cardiovascular mortality (HR = 0.77, 95% CI 0.61–0.97, $P = 0.025$) (*Table 2*).

When adjusting for PS expressed as a continuous variable, patients with beta-blockers had lower all-cause death (HR = 0.73, 95% CI 0.60–0.90, $P = 0.003$) and cardiovascular death rates (HR = 0.77, 95% CI 0.61–0.96, $P = 0.022$) (*Table 2*). We evaluated the association of beta-blocker use with survival adjusted on PS across subgroups according to baseline characteristics (*Figure 1*). There was no formal evidence for heterogeneity of treatment effects for any of the subgroups (all treatment subgroup interactions showed $P \geq 0.05$). However, we observed interaction with a *P*-value <0.10 for diastolic blood pressure both for all-cause and cardiovascular mortality, whereas no effect modification was observed according to systolic blood pressure (*Figure 1*). Overall, beta-blocker use was associated with better survival across subgroups for both endpoints (*Figure 1*).

Impact of beta-blockers on long-term prognosis in the propensity-matched cohort

All-cause death occurred in 130 (23.2%) and 174 (31%) of PS matched patients receiving and not receiving beta-blockers as an initial therapy, respectively (crude analysis: HR associated with beta-blockers use = 0.71, 95% CI 0.56–0.89, $P = 0.003$) (*Table 2*). Similarly, with regard to cardiovascular mortality, there were 107 events (19.1%) among patients on beta-blockers as opposed to 134 (23.9%) events in patients not taking beta-blockers; for this outcome, patients on beta-blockers also showed better survival (crude analysis: HR = 0.76, 95% CI 0.59–0.97, $P = 0.032$) (*Table 2*).

For all-cause mortality, 3-year survival for patients on beta-blockers was 67.2 ± 3.2%, compared with 61.3 ± 2.8% in patients not on beta-blockers, with a number needed to treat of 17 (*Figure 2A*). For cardiovascular mortality, 3-year survival of

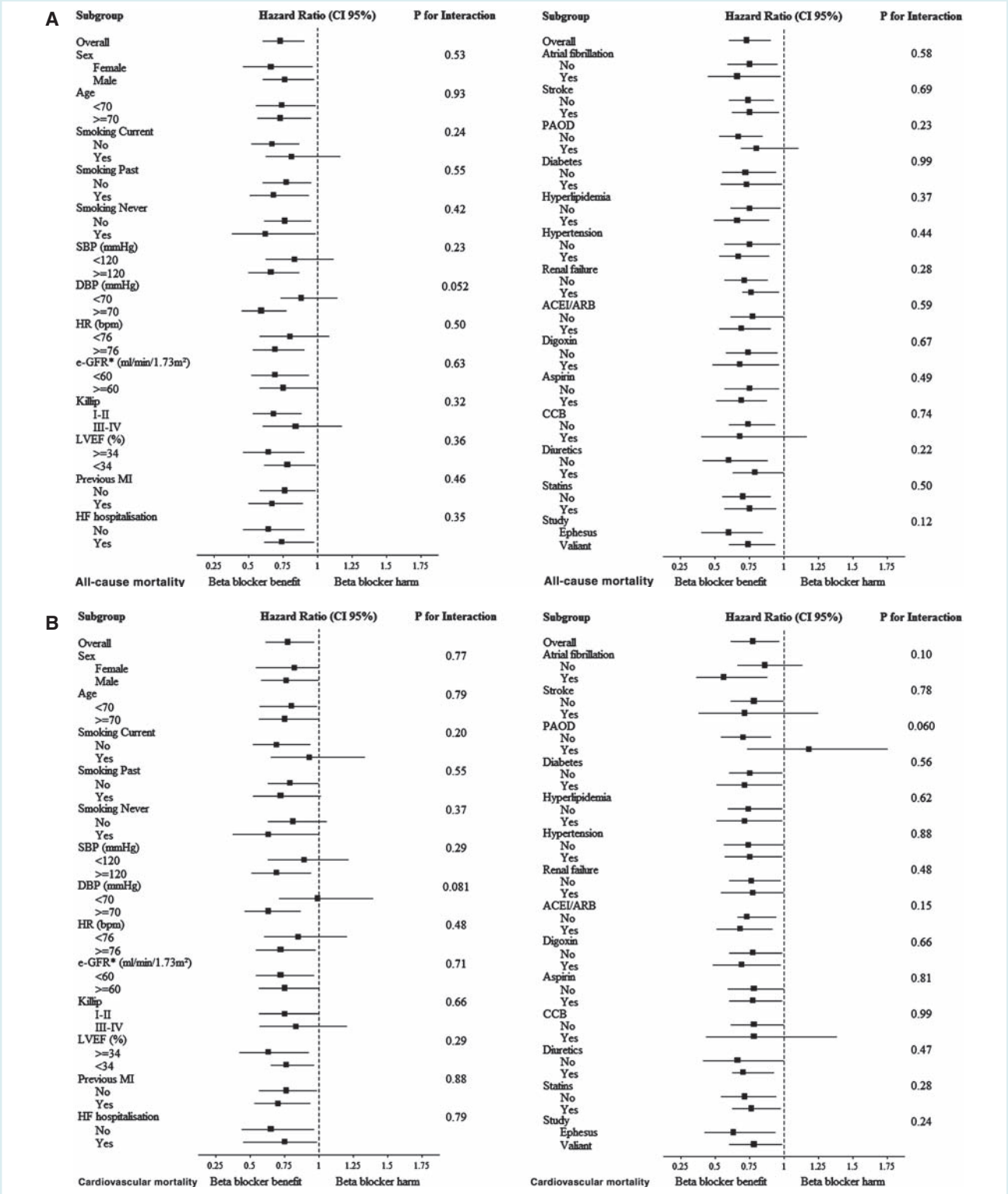

Figure 1 Forest plots for all-cause (*A*) and cardiovascular mortality (*B*): consistency of beta-blocker treatment effects across subgroups according to baseline characteristics. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; CI, confidence interval; DBP, diastolic blood pressure; e-GFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAOD, peripheral artery obstructive disease; SBP, systolic blood pressure.

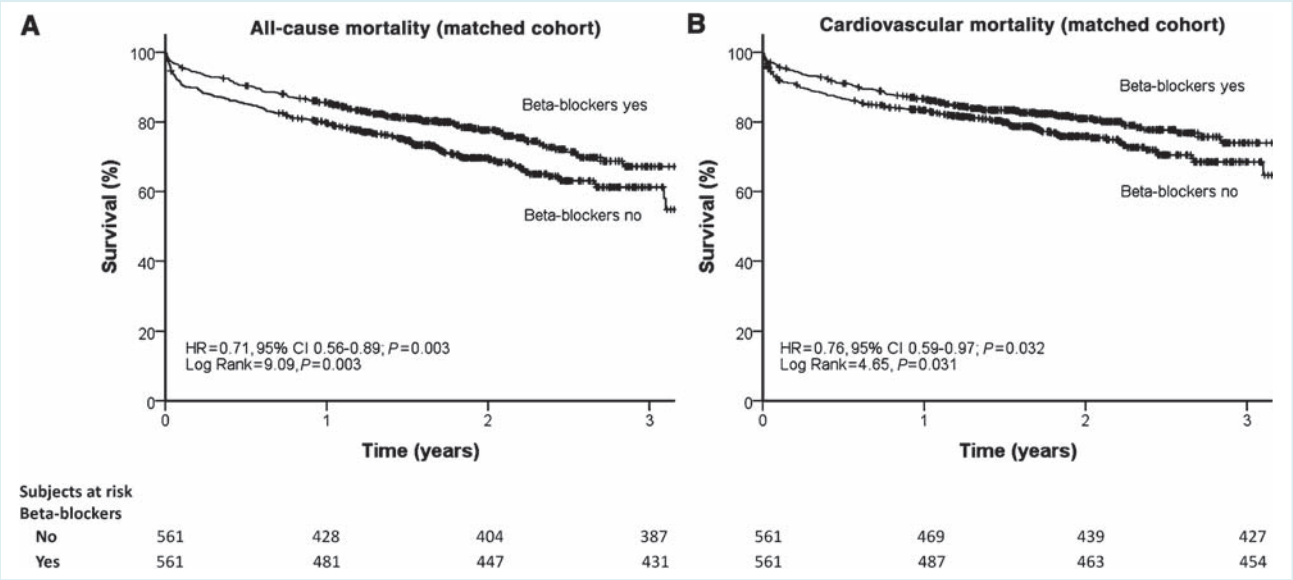

Figure 2 Kaplan-Meier survival curves, restricted cohort, matched pairs (n = 561): plots for all-cause (*A*) and cardiovascular mortality (*B*) in propensity-matched patients receiving and not receiving beta-blockers as initial therapy at baseline. HR, hazard ratio; CI, confidence interval.

patients on beta-blockers was 74 ± 3%, compared with 68.5 ± 2.8% in patients not on beta-blockers, with a number needed to treat of 20 (*Figure 2B*).

Discussion

The present study was designed to evaluate the association of beta-blocker therapy with long-term all-cause and cardiovascular mortality in a cohort of high-risk MI survivors with COPD. In this specific population, where beta-blockers are still deemed to have possible harmful effects by many clinicians,[5,26] our results suggest that beta-blocker treatment may be associated with a reduced mortality risk at long-term follow-up.

Beta-blocker use in post-myocardial infarction patients with chronic obstructive pulmonary disease

Out of the 1573 MI survivors with COPD that we selected for our analysis, 822 patients (52.2%) were on beta-blockers. Similarly, among the 2390 COPD patients available in the entire high-risk database, there were 1125 treated patients (49.6%); taking into account that overall percentages in the entire cohort of EPHESUS[18] and VALIANT[20] (the two studies composing the cohort of 1573 patients) were about 70%, we can immediately observe an under-use of beta-blockers among COPD patients. However, these relatively low percentages of patients refer only to baseline characteristics at study entry, which occurred right after the index MI (up to 14 days after admission owing to MI in EPHESUS[18] and up to 10 days in VALIANT[20]); it cannot be excluded that the proportion of patients on beta-blockers was higher at discharge. We cannot make a direct comparison with other similar studies[14,15,27] as they assessed beta-blocker use at discharge[14,27] or according to different stages (before or throughout hospitalization because of MI);[15] however, in these studies beta-blocker usage also varied widely, with discharge percentages even lower than in our cohort.[15]

First, such an apparent reluctance of physicians to prescribe beta-blockers in this subset of MI patients is likely to occur because COPD patients tend to be older, with more cardiovascular co-morbidities (previous stroke or peripheral artery disease),[8] and especially with previous HF or MI, which is problematic considering that these diseases represent the main indications for beta-blocker treatment. Second, a marked geographic variability[14,28] persists in the use of evidence-based therapies recommended by guidelines for MI[2], including beta-blockers, both overall among MI patients[28] and specifically in the subset with COPD.[14]

Impact of beta-blocker use on long-term prognosis in high-risk myocardial infarction survivors with chronic obstructive pulmonary disease

After adjustment for confounders, the HR for all-cause mortality between groups was about 0.70, both in the whole cohort and in the PS-matched cohort, confirming previous findings in high-risk settings. To this purpose, Quint *et al.*[15] evaluated benefit from beta-blocker usage in a cohort of 1063 patients with COPD having a first MI. Beta-blocker treatment was associated with better long-term survival whether initiated during hospital admission (fully adjusted HR = 0.50, 95% CI 0.36–0.69, $P < 0.001$) or before (HR = 0.59, 95% CI 0.44–0.79, $P < 0.001$); similar results were obtained with PS. Compared with these findings, our results showed greater HRs for all-cause mortality. Possible reasons for this could range from different study population characteristics to

slightly different study designs. Indeed, our cohort was particularly sick, with more than half with a previous hospitalization owing to HF, about 40% with a previous MI, and all had symptomatic HF and/or depressed LVEF. In addition, we also considered strong predictors of prognosis in MI survivors such as age, blood pressure, creatinine, and Killip class [all included in the updated version of the Global Registry of Acute Coronary Events (GRACE) score], which showed to be highly discriminative in predicting death at long term.[29] We also adjusted for LVEF, a well-known predictor of both sudden and non-sudden death after MI.[30] However, we were unable to make a direct comparison in terms of benefit from beta-blockers with previously published studies[14,15,27] as they assessed beta-blocker use at discharge.

Data on beta-blocker use at discharge are not available in high-risk MI database and we do not know exactly how many patients stopped the treatment during hospitalization or started it after randomization; nevertheless, we can obtain some information from a *post-hoc* analysis of VALIANT,[31] which evaluated the prognostic value of beta-blockers according to their usage at randomization or at discharge. Overall, among the 14 703 VALIANT patients, only the subgroup with a persistent use of beta-blockers had a significant survival benefit at long term; indeed, patients on beta-blockers only at randomization or at discharge had mortality rates of not significantly different from those of untreated patients.[31] Thus, this observational study clearly shows that beta-blockers can be used in the early post-MI period in most patients, even in a high-risk setting. In VALIANT, there were 1254 patients with COPD, of which 732 had beta-blockers at randomization and 522 did not. At discharge, beta-blockers were stopped in 139 patients (18.9%) and started in 55 patients (11.7%).[31] Thus, beta-blocker use did not change in the large majority of VALIANT patients. Among these 1254 VALIANT MI survivors with COPD, 963 patients had complete available data and they were used to build our whole cohort of 1573 (with 610 from EPHESUS). Consequently, the survival advantage seen in the present study may mainly result from the effect of maintaining patients on beta-blockers throughout MI hospitalization. With regard to diagnosis of COPD, we have no information on pulmonary function testing, and diagnosis was based on study investigator recording history of COPD, as reported by patients. However, our data are in accord with previously published studies using International Classification of Diseases codes[7] or medical records.[27] Our findings seem to be comparable to those of HF patients with COPD;[32] in addition, a recent study by Staszewsky *et al.*[32] showed that beta-blocker use at baseline was associated with a lower total risk of mortality in a cohort of 2837 acute HF patients with COPD derived from administrative health databases (adjusted HR = 0.74); as reported by the accompanying editorial,[33] even though the use of pulmonary function testing such as spirometry may result in over-diagnosis of COPD in patients with HF because pulmonary fluid overload may compress airways, resulting in significant obstruction.[34] Our cohort includes MI patients with signs of HF and/or left ventricular dysfunction; this means that, in the absence of an established diagnosis of COPD before the index event, repeated pulmonary functional tests might be necessary for an accurate COPD diagnosis, ideally to be performed when patients are stable and euvolaemic.[34]

Limitations and strengths

The main limitation of our study is its *post hoc* nature. Furthermore, there may be unknown or unmeasured confounders that were not considered. We do not have precise information on the timing of beta-blocker treatment initiation as it was evaluated at randomization (occurred up to about 2 weeks after admission owing to MI); thus, some patients might have already been on a beta-blocker before MI hospitalization and others might have started treatment during the hospital stay. Similarly, we do not know exactly how many patients not receiving a beta-blocker at discharge were prescribed thereafter, or if patients actually discharged with a beta-blocker discontinued it during the follow-up. In addition, data on the specific beta-blocker agent and dose were not available and could not be adjusted for. Further studies are therefore needed to better define whether the mortality benefit of beta-blocker treatment in this setting is observed with cardioselective agents, non-cardioselective agents, or both (i.e. beta-1-selective vs. beta-1/beta-2 blockers). As this information was not available, we cannot ascertain the benefit of non-cardioselective agents. The preferential use of beta-1 selective blockers is likely to yield a better safety profile in patients meeting the inclusion criteria of the present study.

Another limitation is that diagnosis of COPD was investigator-derived, obtained from hospital records or pulmonary function test if available, and questioning the patient; in addition, no pre-specified criteria were defined in the investigator brochure. We did not have data on the severity of COPD as we did not have measurements of pulmonary function tests. In the absence of such information we could not verify the diagnosis and severity of COPD. Therefore we were unable to further adjust for this potential confounder as in other studies.[15] The severity of COPD might also have influenced the attitude to prescribe beta-blockers in our cohort. Another limitation is that our COPD cohort might include patients with asthma or patients with asthma–COPD overlapping syndrome, potentially having a different response to beta-blocker therapy. However, previous findings showed a survival benefit associated with beta-blocker treatment at discharge in a mixed cohort of MI patients with COPD or asthma.[27] Overall, we cannot ascertain the absence of residual confounding from the aforementioned limitations. Notably, study investigators were likely to have the same level of information as treating physicians in 'real life', making the lack of precise data regarding COPD diagnosis less relevant. It is also likely that the High-Risk MI database included patients with a well-established diagnosis of COPD (probably those with advanced degrees of COPD). Therefore, this might strengthen our results, confirming a beta-blocker mortality benefit in patients with more severe airflow obstruction.

This study has several methodological strengths. In order to address the issue of confounding by indication, we adjusted for an extensive array of clinical variables (24 clinical covariates) in a multivariable Cox model. In addition, we adopted a propensity score matching approach. Among observational studies, the use of the propensity score ensures the closest design to a clinical trial.[35]

Conclusions

In conclusion, beta-blocker treatment was associated with a better outcome in high-risk MI survivors with COPD, both in terms all-cause and cardiovascular mortality at long-term follow-up. However, owing to the above limitations, we cannot draw any firm conclusions about a causal relationship between beta-blocker use and reduced all-cause and cardiovascular mortality; nevertheless, prescription of beta-blockers in this specific high-risk setting has to be encouraged and, if possible, shortly after admission.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Love plot displaying absolute standardized differences for 24 baseline characteristics.

Table S1. Binary logistic regression for propensity score.

Table S2. Patient characteristics according to COPD history.

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