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

Stefano **Coiro**, 1,2; Nicolas **Girerd**,1; Patrick **Rossignol**, 1; João Pedro **Ferreira**,1,3; Aldo **Maggioni**,4; Bertram **Pitt**,5; Isabella **Tritto**, 2; Giuseppe **Ambrosio**, 2; Kenneth **Dickstein**,6; Faiez **Zannad*** 1

1 INSERM, Centre d'Investigations Cliniques 9501, Université de Lorraine, CHU de Nancy, Institut Lorrain du cœur et des vaisseaux, Nancy, France and INI-CRCT (Cardiovascular and Renal Clinical Trialists) F-CRIN network, Nancy, France

2 Division of Cardiology, University of Perugia, Ospedale S. Maria della Misericordia, Via S. Andrea delle fratte, Perugia, Italy

3Department of Physiology and Cardiothoracic Surgery, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto, Portugal;

4ANMCO Research Centre, Firenze, Italy

5Cardiology Division, University of Michigan School of Medicine, Ann Arbor, MI, USA

6 University of Bergen, Bergen, Norway -Stavanger University Hospital, Stavanger, Norway

* Corresponding author. INSERM CHU de Nancy, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, 4 Rue du Morvan, 54500 Vandoeuvre lès Nancy, France; Tel: +33 3 83 15 74 96, Fax: +33 3 83 15 73 24, Email: f.zannad@chu-nancy.fr

Auhors' email addresses: stefano.coiro@hotmail.it; nicolas_girerd@yahoo.com; p.rossignol@chu-nancy.fr; jp7ferreira@hotmail.com maggioni@anmco.it;bpitt@med.umich.edu; isabella.tritto@unipg.it; giuseppe.ambrosio@ospedale.perugia.it ; trout@online.no; f.zannad@chu-nancy.fr

Short title: beta-blocker in post-MI patients with COPD

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Structured abstract

Aims: The aim of the study was to determine the influence of baseline beta-blocker intake 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: In the 28,771 patients high risk MI collaborative database, 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 n=751 without) on the rate of all-cause death and cardiovascular death. By univariable Cox analysis, beta-blocker intake was associated with lower rates of both all-cause death (HR=0.61, 0.51-0.75, p<0.0001) and cardiovascular death (HR=0.63, 0.51-0.78, p<0.0001). After extensive adjustment for confounding including 24 baselines covariates, COPD patients still benefit from beta-blocker usage (HR=0.73, 0,60-0.90, p=0.002 for all-cause death; HR=0.77, 0.61-0.97, p=0.025 for cardiovascular death). Adjusting on a propensity scores (PS) constructed from the 24 aforementioned baseline characteristics provided similar results. In a cohort of 561 pairs of patients taking or not beta-blocker matched on PS using a 1:1 nearest neighbor matching method, patients treated with beta-blocker experienced less all-cause deaths (HR=0.71, 0.56-0.89, p=0.003) and cardiovascular deaths (HR=0.76, 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

Introduction

Beta-blockers are effective at reducing risk of mortality after a myocardial infarction [1] (MI), 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 to exist [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 as beta-blockers [7]. However, data from large retrospective studies show that patients with COPD receiving beta-blockers had about 40% risk reduction for mortality [1,8], even in a high-risk setting [1].

Yet, many clinicians withhold or do not prescribe beta-blockers from patients with COPD because they fear for provoking bronchospasm and induce respiratory failure; indeed, beta-blockers may cause bronchial hyper reactivity in patients with other lung disease 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 broncoconstriction in patients with COPD [12]. Additionally, cardio-selective beta-blockers have been proven to be safe in different cardiovascular setting (heart failure, coronary artery disease and hypertension); thus, according to evidences, this class of drug should not be routinely withheld from patients with COPD [13]. However, although the above cited evidences, a substantial proportion of MI survivors with COPD are still currently discharged without a beta-blocker, roughly ranging from one to three fifth of these patients [14,15].

It is very unlikely that that a prospective large randomized trial evaluating beta-blocker effect in HF with COPD will ever be performed. In the absence of such randomized evidence, evaluating treatment effect

from observational cohorts using specific methods to decrease attribution bias would increase evidence regarding beta-blocker effect in this specific population.

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

Methods

High risk acute MI 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 4 randomized and double-blinded large trials: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN) [17], Eplerenone's Neurohormonal Efficacy and Survival Study (EPHESUS) [18], 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, 28771 patients were enrolled (1959 in CAPRICORN; 6632 in EPHESUS; 5477 in OPTIMAAL and 14703 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 blockers usage and COPD definition in The High-Risk MI Database

With regard to beta-blocker treatment, the database reports the usage of this drug class 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 trial).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 intake at baseline was not reported in CAPRICORN [17] (being patients randomized to carvedilol or placebo), and left ventricle 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 MI admission 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 (percent) for categorical variables and mean ± standard deviation for continuous variables. In order to correct for potential bias in the selection of patients, a propensity score (PS) analysis was performed [21] in order to calculate the probability for being prescribed a beta-blocker at baseline. Specifically, a full non-parsimonious logistic regression model was performed to determine the propensity for the receipt of beta-blockers (dependent variable) as an initial therapy at baseline for each of the 1573 participants, based on the 24 variables presented in Table 1 (predictor variables) (see Supplementary material on line, Table S1, for binary logistic regression model to estimate the effect of each baseline characteristics on the probability of receiving a beta-blocker at baseline). We also undertook further sensitivity analyses matching on propensity scores. A 1:1 nearest-neighbor matching was used [22]. Treatment groups were compared using standardized differences, calculated as the difference in means or proportions expressed as a percent of the pooled estimate of the standard deviation [23,24], before and after PS matching. We plot 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 considered outcomes were all-cause death and cardiovascular death.

Univariable and multivariable Cox proportional hazard models for all-cause death and cardiovascular death were performed. Three types of Cox models were built: 1) univariable and multivariable Cox adjusted according on age, gender, smoking habits, considered relevant a priori [15]), Killip classe 3, co-morbidities,, biological variables, LVEF and treatment at baseline; 2) univariable and multivariable Cox proportional hazards models PS-adjusted, using PSs as an alternative way of adjusting for differences in groups of patients taking or not beta-blocker. As continuous covariates, PSs 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; 3) 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 (Chicago, Illinois) The two-tailed significance level was set to $p<0.05$.

Results

Patients' characteristics in the whole and in propensity matched cohort

Characteristics of patients with and without COPD are reported in 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 LVEF of 33%±9. Unadjusted baseline characteristics differences between patients on beta-blockers or not were important as assessed by standardized differences (Table 1). Generally, patients with beta-blockers were younger, more likely to be male and, as expected, they had a lower heart rate; additionally they were less likely to have at least a 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 BP and prior heart failure hospitalization (Table S2).

By application of PS matching, we then assembled a cohort of 561 pairs of patients receiving or not beta-blockers at baseline; the standardized differences were reduced to less than 5% for all 24 characteristics but heart rate, who nevertheless did not exceed 10%, demonstrating substantial improvement of the balance across the treatment groups. (Table 1) (Figure S1). Overall, matched patients had a mean age of 68± 10 years, 28% were female, with 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 with beta-blocker use at randomization (N=822) experienced 176 (21.4%) all-cause deaths, with 244 (32.5%) deaths among not treated patients (N=751); similarly, patients with beta-blockers had less cardiovascular deaths, with 142 (17.3%) events as opposed to 192 (25.6%) among patients without beta-blockers. By univariable Cox models, patients with COPD prescribed a beta-blocker showed a better survival, with lower rates of both all-cause death (HR=0.61, 0.51 to 0.75, p<0.0001) and cardiovascular death (HR=0.63, 0.51 to 0.78, p<0.0001) (Table 2).

By multivariable Cox models, after extensive adjustment for several baseline characteristics grouped in three models as mentioned above, patients with beta-blockers were still associated with a better survival, both in terms of all-cause death (HR=0.73, 0,60 to 0.90, p=0.002) and of cardiovascular death (HR=0.77, 0.61 to 0.97, p=0.025) (Table 2).

When adjusting on PSs expressed as a continuous variable, patients with beta-blockers had lower all-cause death (HR=0.73, 0.60 to 0.90, p=0.003) and cardiovascular death rates (HR=0.77, 0.61 to 0.96, p=0.022) (Table 2). We evaluated the association of beta-blocker intake with with survival adjusted on PS across subgroups according to baseline characteristics (Figure 1 for all-cause death and Figure 2 for CV

death). There was no formal evidence for heterogeneity of treatment effects for any of the subgroups (all treatment subgroup interactions showed a Pe0.05). However, we observed interaction with p value <0.10 for diastolic BP both for all-cause and cardiovascular mortality, whereas no effect modification was observed according to systolic BP (Figure 1 and 2). Overall, beta-blocker intake was associated with better survival across subgroups for both endpoints (Figure 1 and 2).

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 intake =0.71, 0.56 to 0.89, p=0.003) (Table 2). Similarly, with regard to cardiovascular death, there were 107 events (19.1%) among patients with beta-blockers as opposed to 134 (23.9%) events in patients not taking beta-blockers; also for this outcome, patients with beta-blockers were associated to a better survival (crude analysis HR=0.76, 0.59 to 0.97), p=0.032) (Table 2).

As regards all-cause death, 3 years survival for patients with beta-blockers was 67.2±3.2%, compared to 61.3±2.8% of patients without, with a number needed to treat corresponding at 16.94 (Figure 3A). For cardiovascular death, 3 years survival of patients with beta-blockers was 74±3%, compared to 68.5 ±2.8% of patients without, with a number needed to treat equivalent to 20 (Figure 3B).

Discussion

The present study was designed to evaluate the association of beta-blockers therapy with long-term follow-up mortality (all-cause and cardiovascular) 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 treatment may be associated with a reduced mortality risk at long-term follow-up.

Beta-blockers usage in post-myocardial infarction patients with COPD

Of 1573 MI survivors with COPD that we selected for our analysis, 822 patients (52.2%) were on beta-blockers, similarly to the 2390 COPD patients available in the entire high-risk database, where 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 underuse 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 to14 days after MI admission in EPHESUS [18] and up to 10 days in VALIANT [20]); it cannot be excluded that proportion of patients with beta-blockers was higher at discharge. We cannot make a direct comparison with other similar studies [14,15,27] as they assessed beta-blockers intake at discharge [14,27] or also according to different stages (before or throughout MI hospitalisation) [15]; however also in these studies beta-blockers usage varied widely, with discharge percentage even lower than that we observed in our cohort [15].

Firstly, such an apparent reluctance by physicians in prescribing beta-blockers in this subset of MI patients is due to the fact that COPD patients are more likely to be older, with more cardiovascular comorbidities (previous stroke or peripheral artery disease) [8] and especially with more previous HF or MI, which is problematic considering that the diseases represent the main indications for beta-blocker treatment. Secondly, a marked geographic variability[14,28] persists in the use of evidence-based therapy

recommended by guidelines for MI [2] as beta-blockers, both overall among MI patients [28] and also specifically in the subset with COPD [14].

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

After adjustments for confounders, the HR for all-cause mortality between groups was about 0.70, both in the whole cohort as in the PS matched-cohort, confirming previous findings in a high-risk setting. 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 the hospital admission (fully adjusted HR=0.50, 0.36 to 0.69; P<0.001) or before (HR=0.59, 0.44 to 0.79;P<0.001); similar results were obtained with propensity scores. Compared to these findings, our results showed higher hazards for all-cause death. 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 HF hospitalization, about 40% with a previous MI and all had symptomatic HF and/or depressed EF. Additionally, we considered also strong predictors of MI survivors' prognosis as age, blood pressure, creatinine and Killip class, all included in the updated version of GRACE score, which showed to be highly discriminative in predicting death at long-term [29]. Additionally, we adjusted for LVEF, a well-known predictor of both sudden and non-sudden death after MI [30]. However, similarly for baseline characteristics, we are not able to make a direct comparison in terms of benefit from beta-blockers with previous published studies [14,15,27] as they assessed beta-blockers use at discharge.

Data on beta-blocker use at discharge are not available in high-risk MI database and we don't know exactly how many patients stopped the treatment during hospitalization or started it after randomization; nevertheless, we can get some information from a post-hoc analysis of VALIANT [31] which evaluated prognostic value of beta-blocker according to their usage at randomization or at discharge. Overall, among

all 14703 VALIANT patients, only the subgroup with a persistent use of beta-blockers had a significant survival benefit at long-term; indeed, patients with beta-blockers only at randomization or at discharge had rates of death not significantly different from those of not treated patients [31]. Thus, we can take very clearly from this observational study that beta-blockers can be used in the early post-MI period in most patients, even in a high-risk setting. In VALIANT study, there were 1254 with COPD, of which 732 patients with beta-blockers at randomization and 522 without. At discharge, beta-blockers were stopped in 139 patients (18.9%) and started in 55 patients (11.7%) [31]. Thus, beta-blockers intake didn't change in the large majority of patients of VALIANT study. 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 our study may be mainly due to 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 line with previously published studies using International Classification of Diseases codes [7] or medical records [27]. Our findings seems to be comparable to those of HF patients with COPD [32]; to this purpose a recent study by Staszewsky et al [32] showed that beta-blocker intake at baseline was associated with a lower total mortality risk in a in a cohort of 2837 acute HF patients with COPD derived from administrative health databases (adjusted HR=0.74); as reported by the editorial accompanying the paper [33], even though the use of pulmonary function testing as spirometry may result in over-diagnosing 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

The main limitation of our study is its the post-hoc nature. Furthermore, there may be unknown or unmeasured confounders which were not considered, We don't have precise information on the timing of beta-blocker treatment initiation as it was evaluated at randomization (occurred up to about two weeks after MI admission); thus, some patients might have already been on a beta-blocker before their MI hospitalization and other might have started treatment during MI hospitalization. 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 time. Similarly, data on the specific beta-blocker agent and dose were not available and could not be adjusted for; further studies are needed to better define whether the mortality benefit of beta blockers in this setting is observed with cardioselective agents, non-cardioselective agents, or both (i.e. beta-1-selective versus 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 our study.

Another limitation is that diagnosis of COPD was investigator-derived, obtained from hospital records or pulmonary function if available, and questioning the patient; additionally, no pre-specified criteria were defined in the investigator brochure. We did not have data on COPD severity as we did not have measurements of pulmonary function test. In the absence of such information, we could not verify the diagnosis and severity of COPD. Therefore we were not able to further adjust for this potential confounder as in other previous studies [15]. Additionally COPD severity might 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 COPD or asthma MI patients [27]. Overall, we cannot ascertain the absence of residual confounding due to the aforementioned limitations. Of note, study investigators were likely to have the same level of information than treating physicians in "real life", making the lack of precise data

regarding COPD diagnosis less relevant. In addition, it is likely that the High-Risk MI database included patients with well-established COPD diagnosis, probably those with advanced degrees of COPD. Therefore, this might strengthen our results, confirming that beta-blocker mortality benefit in patients with more severe airflow obstruction. Additionally, the study has several methodological strengths. In order to address the issue of confounding by indication, we adjusted for an extensive number of clinical variables (24 clinical covariates) in a multivariate Cox model, and, secondly, we performed 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 for all-cause and cardiovascular death at long-term follow-up. However, due to the above limitations, one cannot make any firm conclusions about a causal relationship between the use of beta-blockers and reduced total and cardiovascular mortality; however, beta-blocker prescription in this specific high-risk setting is to be encouraged and if possible, shortly after admission.

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Conflict of interest:

Dr. Pitt reports personal fees from Novartis, personal fees from Pfizer, personal fees from Takeda, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from GE Healthcare, personal fees from Relypsa, personal fees from BG Medicine, personal fees from Nile Therapeutics, personal fees from Merck, personal fees from Forest Laboratories, personal fees from Novartis, grants from Forest Laboratories , grants from Novartis, other from Relypsa, other from BG Medicine, other from Nile Therapeutics, other from Aurasenc, outside the submitted work. Prof. Dickstein has received honoraria and research support from numerous pharmaceutical and device companies. Dr. Maggioni reports grants from Novartis, Cardiorentis, Abbott Vascular, and Bayer, outside the submitted work. Dr Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. Dr Zannad is co-founders of CardioRenal diagnosticS. Prof. Ambrosio has received Advisory board fees and speakers bureau fees from Menarini, Merck and Angelini. Dr. Girerd reports that he has received Board Membership Fees from Novartis. Dr. Rossignol has received Board Membership fees from Novartis, Relypsa and Steathpeptides; he is co-founder of CardioRenal diagnosticS. All the other authors have nothing to disclose.

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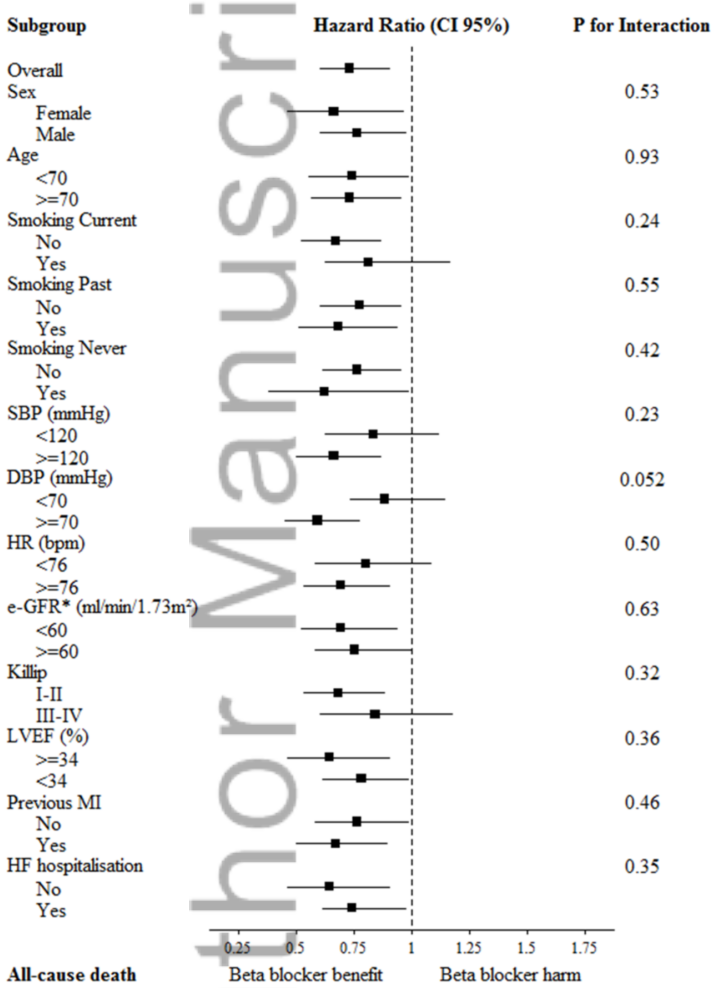
Figure Legends

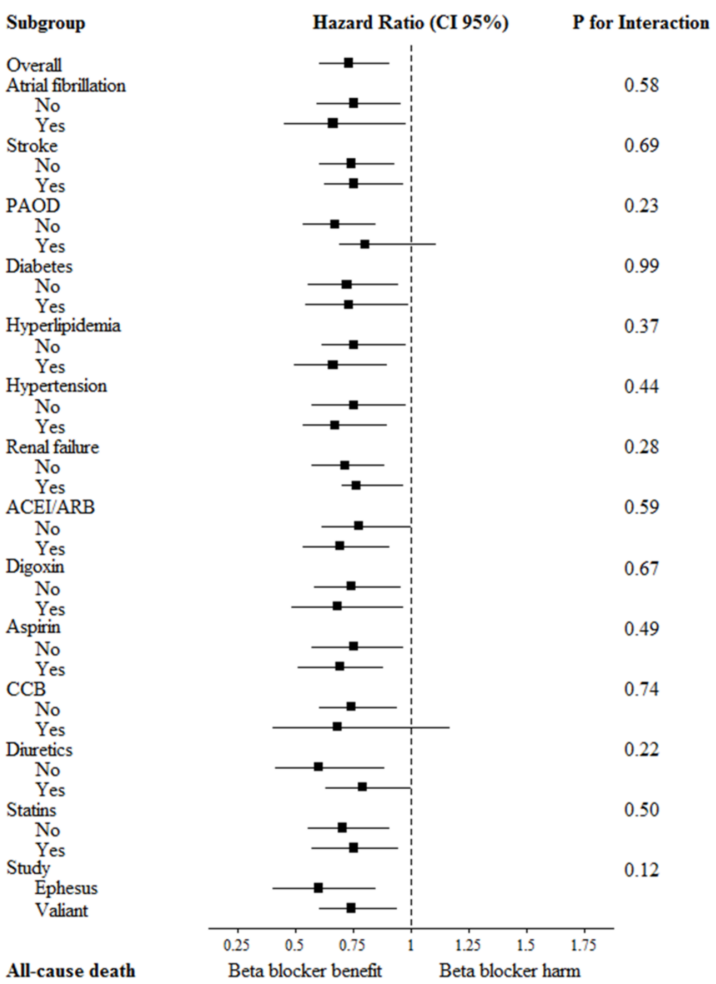
Figure 1 Forest Plot (all-cause death): consistency of beta-blocker treatment effects across subgroups according to baseline characteristics for all-cause death.

Figure 2 Forest Plot (Cardiovascular death): consistency of beta-blocker treatment effects across subgroups according to baseline characteristics for cardiovascular death.

Figure 3 Kaplan-Meier: restricted cohort, matched case (561 pairs): Kaplan–Meier plots for all-cause mortality (panel A) and cardiovascular death (panel B) in propensity-matched patients receiving and not receiving beta-blockers as initial therapy at baseline. HR, hazard ratio; 95%CI, 95% confidence interval

Figure S1 (supplementary material) Love plot: Love plot displaying absolute standardized differences for 24 baseline characteristics between patients with chronic obstructive pulmonary disease receiving and not receiving beta-blockers as initial baseline therapy, before and after propensity score matching





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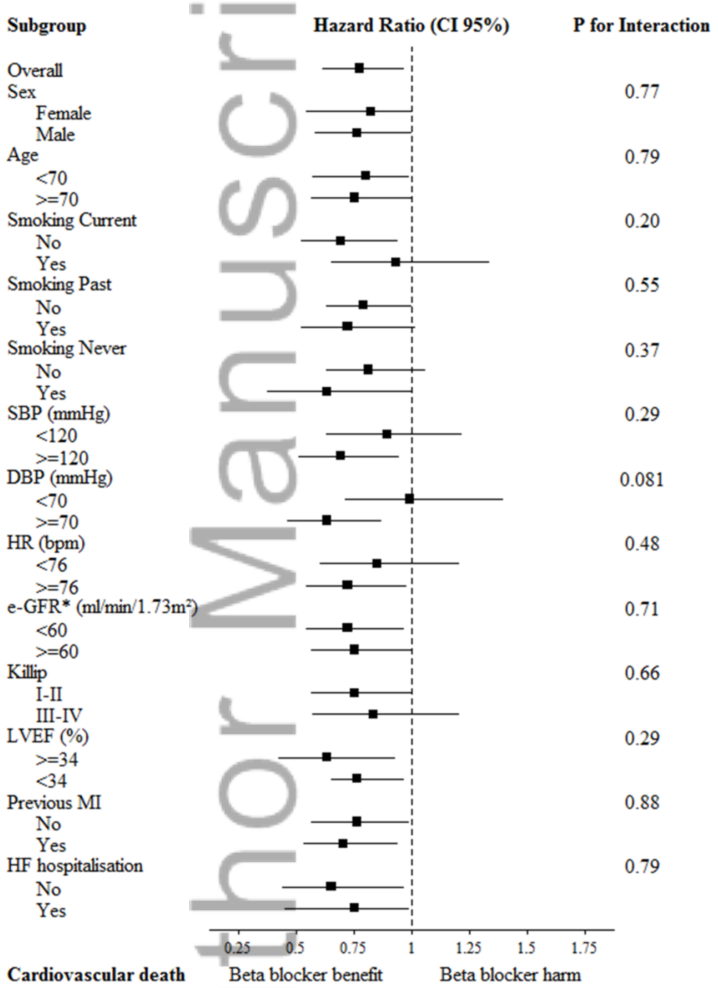


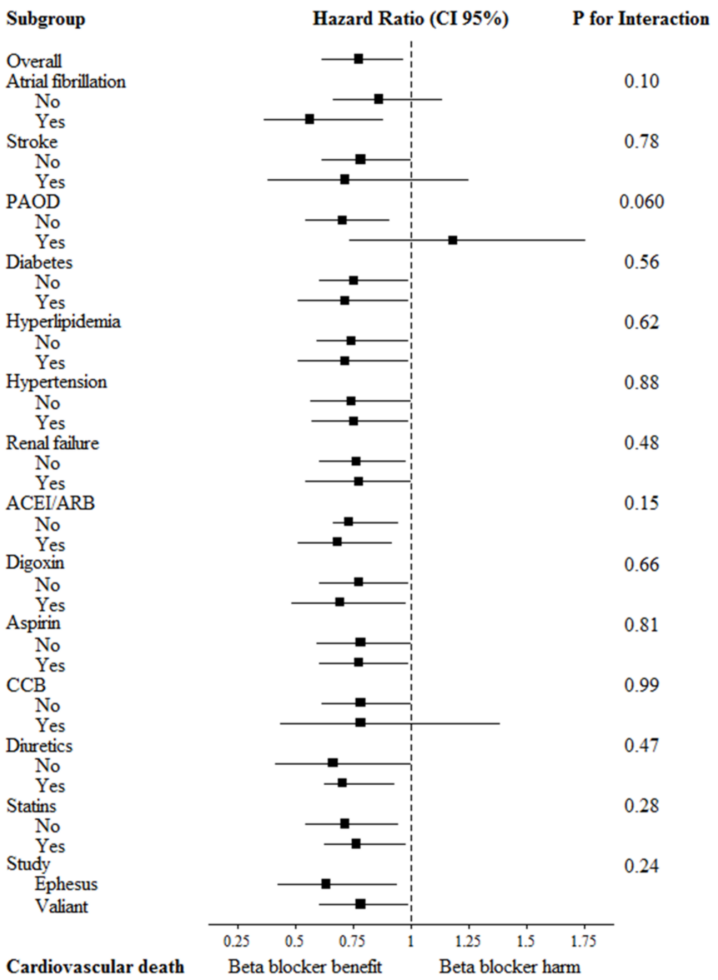
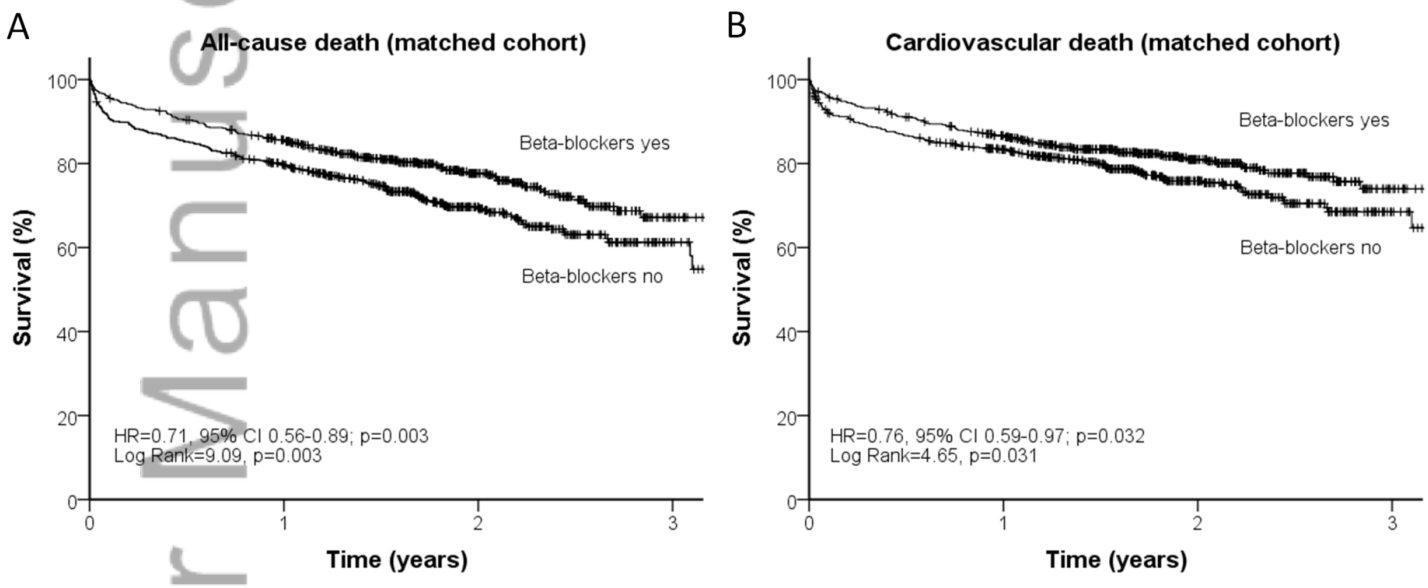


Figure 2.TIF



Subjects at risk								
Beta-blockers								
No	561	428	404	387	561	469	439	427
Yes	561	481	447	431	561	487	463	454

Figure 3.tif

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Table 1
Patients' characteristics

	Before matching				After matching			
Observed frequency	Beta-blockers use No n=751	Yes n=822	Standardized difference	P value	Beta-blockers use No n=561	Yes n=561	Standardized difference	P value
Anthropometry- life style								
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								
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 (bpm)	80 ± 13	75 ± 12	37.6%	< 0.0001	78 ± 13	77 ± 13	6,4%	0.306
e-GFR*	66 ± 21	73 ± 54	13.1%	0.001	67 ± 21	69 ± 23	2,9%	0.226
Killip class e 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 hospitalisation	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
Hyperlipidemia	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

Baseline characteristics according to beta-blockers intake in patients with chronic obstructive pulmonary disease (before and after propensity-matching).

Standardized difference: expressed as % of the difference standard deviation (SD); p-value from Chi-Square or Student T test. Figures are percents or means ± SD.BP: blood pressure; *eGFR: estimated glomerular filtration rate according to the MDRD formula; MI myocardial infarction; HF heart failure; PAOD: peripheral artery obstructive disease;; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers

Table 2

Association of beta-blockers use as initial therapy at baseline with outcomes using Cox proportional hazard models in the whole cohort (adjusted according to clinical models and on PS) and in the PS-matched cohort

	All-cause mortality HR (95%CI)	**p-value**	**Cardiovascular death HR (95%CI)**	**p-value**
Whole cohort				
Model adjusted on 24 covariates*	0.73 (0,60-0.90)	0.002	0.77 (0.61-0.97)	0.025
Model adjusted on PS	0.73 (0.60-0.90)	0.003	0.77 (0.61-0.96)	0.022
Matched cohort				
Crude analysis	0.71 (0.56-0.89)	0.003	0.76 (0.59-0.97)	0.032

HR, hazard ratio; 95%CI, 95% confidence interval; PS, propensity score.

***Model** is adjusted on age, gender, smoking habits, Killip classe3, 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),LVEF and treatment at baseline (digoxin, ACE-I/ARB, diuretics, aspirin, calcium channel blockers, statin).