Effect of β-blocker therapy in diabetic patients with stable coronary heart disease: a meta-analysis

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Abstract

Background β-blocker (BB) therapy is a cornerstone for the treatment of coronary heart disease (CHD). The evidence of the benefit from long-term BB therapy in diabetic patients with stable CHD is scarce. This meta-analysis summarizes the evidence relating to the BB therapy in diabetic patients with stable CHD.

Methods A meta-analysis was performed according to PRISMA and MOOSE guidelines for reporting of systematic reviews of observational studies. PubMed, Embase, and Cochrane central were searched and two authors independently screened studies for eligibility. The quality of studies was assessed with the Newcastle Ottawa scale. The primary outcome of interest was all-cause mortality, cardiovascular (CV) mortality and major adverse cardiovascular events (MACE) in diabetic patients with and without BB therapy. A generic inverse variance model was used to pool odds ratio or hazards ratio from included studies to calculate the overall effect estimate. The significance threshold was set at $P$-value < 0.05. Heterogeneity was assessed by $I^2$.

Results Four non-randomized studies with 9515 participants were selected for the analyses. Four studies were post-hoc analyses of randomized controlled trials, and one article was an analysis of a nationally representative survey. In a fixed effects model, BB therapy in diabetic patients with stable CHD was found to be associated with increased risk of CV mortality, and MACE (27% and 32% respectively; $P$-value < 0.05) and was not associated with a reduction in all-cause mortality (HR 1.12; 95% CI: 0.94–1.33; $P$-value = 0.22).

Conclusion BB therapy in diabetic patients with stable CHD appears to be linked to higher mortality. Large randomized trials are needed in this population to confirm these findings.

Keywords: β-blockers; Cardiovascular mortality; Diabetes; MACE

1 Introduction

Atherosclerotic cardiovascular heart disease (ASCVD) is frequently associated with diabetes. β-blockers (BBs) are extensively prescribed and are used by 4 out of 5 diabetic patients with ASCVD.[1] BBs render a wide therapeutic window as they are useful for a variety of clinical indications including angina, hypertension, and prevention of postoperative arrhythmias including atrial fibrillation.[2–4] Accordingly, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommends BBs for the treatment of ST-elevation myocardial infarction (STEMI),[5] non-ST elevation myocardial infarction (NSTEMI),[6] and systolic heart failure.[7] Furthermore, ACC/AHA guidelines advocate for the use of BBs to be continued for 3-years in patients with myocardial infarction (MI) and normal left ventricular systolic function, and long-term in those with left ventricular dysfunction (Class I). The same guidelines also endorse BBs as long-term therapy in patients with stable coronary or vascular disease (Class IIb). These recommendations are based on the trials that predate the contemporary reperfusion strategies and medical therapies including statins, antiplatelets and angiotensin-converting enzyme inhibitors (ACEi). There is a paucity of evidence in the reperfusion era for the additional benefit of β-blockers in patients with heart disease. A large meta-analysis performed in 2014 found no evidence of long-term mortality benefit from BB therapy in the patients after MI despite showing improvement in secondary outcomes such as recurrent MI, angina, heart failure, and cardiogenic shock.[8]

No trial to date has assessed the benefits of BBs in diabetic patients with stable chronic heart disease (CHD). Systolic blood Pressure Intervention Trial (SPRINT) showed a 27% risk reduction in mortality with intensive blood pressure (BP) control (systolic BP < 120 mmHg).[9] However, the Action to Control Cardiovascular Risk in Diabetes...
Blood Pressure (ACCORD BP) trial failed to show the cardiovascular benefits of similarly intensive BP control in diabetic patients suggesting that the benefits of improved cardiovascular outcomes due to a stringent blood pressure control cannot be extended to diabetic patients.\textsuperscript{10,11} Therein lies the knowledge gap where we need more evidence on the proven therapies for cardiovascular outcomes risk reduction in diabetic patients.

The objective of this meta-analysis is to evaluate the effects of BB in diabetics with a stable CHD in the absence of other significant comorbidities such as left ventricular dysfunction or arrhythmias according to PRISMA and MOOSE guidelines (appendix Tables).

2 Methods

We performed a comprehensive literature search in PubMed, Cochrane library, and Embase through November 4, 2018. The keywords utilized were ‘diabetes’ AND ‘β-blocker’ AND ‘heart disease’ AND ‘mortality,’ with no limits activated. Figure 1 depicts the search methodology. After the initial search, the studies were screened against pre-specified selection criteria of β blockers in diabetic patients with stable CHD. Twenty-eight full manuscripts of potentially relevant studies were extracted and reviewed for the outcomes of interest of all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (MACE). Throughout this process, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for all stages of the design and implementation. Finally, relevant data of outcomes was extracted along with other pertinent information regarding the author’s name, publication year, study design, population characteristics, and the length of follow-up.

The software R version 3.5.1 (R Development Core Team, 2010) was used to perform the meta-analysis. The relative hazard ratios (HR) with their confidence intervals were extracted to calculate treatment effects with standard errors. We used a logarithmic approach to limit the variation and used generic inverse variance to perform the meta-analysis utilizing both Mantel-Haenszel fixed effects and DerSimonian-Laird random effects estimator for $\tau^2$ to generate the pooled HR with its 95% confidence interval (CI).\textsuperscript{12} The Hartung-Knapp modification was used to adjust the standard errors of the estimated coefficients.\textsuperscript{13} A two-sided \(P < 0.05\) was considered to represent statistical signifi-
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Heterogeneity was assessed by calculating \( \tau^2 \) and \( I^2 \) and was considered none, low, moderate and high for \( I^2 \) values of 0, 25%–50%, 50%–75%, and > 75%. Funnel plots were formed to assess the publication bias. This was also confirmed by a trim-and-fill method to adjust for funnel plot asymmetry as explained by Duval and Tweedie. Sensitivity and influential analysis were performed as described by Cooper, et al. by utilizing the leave-one-out method to identify whether any individual study was driving the observed results. Finally, Baujat plots were created for graphical assessment to explore heterogeneity. Quality assessment of the studies was conducted by using the Newcastle-Ottawa Scale (NOS) for observational studies as a guide. The quality of the studies was further evaluated for selection, attrition, performance, detection, and reporting biases. A final quality grade from A to C was assigned to each study. Studies with <5 stars were considered low quality (grade C), 5–7 stars moderate quality (grade B), and >7 stars high quality (grade A).

3 Results

Our initial search yielded 653 articles. One hundred duplicate articles were removed, and 553 studies underwent title and abstract screening. A total of 4 studies with 9,515 participants met the inclusion criteria and were selected for quantitative review. The quality of the studies was further evaluated for selection, attrition, performance, detection, and reporting biases. A final quality grade from A to C was assigned to each study. Studies with <5 stars were considered low quality (grade C), 5–7 stars moderate quality (grade B), and >7 stars high quality (grade A).

Table 1. Baseline characteristics of the patients in the included studies.

| Publication Year | ACCORD | TOPCAT | BARI 2D | CORONOR |
|------------------|---------|--------|---------|---------|
| Journal          | 2017    | 2018   | 2017    | 2014    |
| Hypertension     |         |        |         |         |
| Number of patients | 5054   | 2530   | 1477    | 454     |
| Mean age, yrs    | 62.9    | 69.1   | 62.1    | 69.2    |
| Male             |         |        |         |         |
| Hypertension     |         |        |         |         |
| Hyperlipidemia   |         |        |         |         |
| Smokers          |         |        |         |         |
| On insulin       |         |        |         |         |
| Follow up, yrs   | 4.7     | 3.3    | 6       | 2       |
| Statistical model to match populations | Propensity score | Propensity score | Propensity score | Propensity score |
| Study Grade      | B       | B      | B       | C       |

NA: Not available.

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BBs in these patients. Funnel plots in appendix Figure 3 shows reasonable spread and the Baujat plot in appendix Figure 2 in suggests an overall lack of heterogeneity between the studies.

4 Discussion

The significant finding of this study is that the use of BBs in diabetic patients with stable CHD does not seem to be associated with a mortality benefit in the contemporary era. Furthermore, in a fixed effect model, BBs were found to be associated with higher risk of cardiovascular mortality, and MACE in diabetic patients with stable CHD (27%, and 32% respectively; \( P \)-values < 0.05) and was not associated with a reduction in all-cause mortality (HR 1.12; 95% CI 0.94–1.33; \( P \)-value = 0.22).

Our findings are concordant with those from the United States National Health and Nutrition Examination Survey (NHANES) that also showed an increase risk in all-cause mortality with the use of BB therapy.[25] BBs are thought to improve left ventricular (LV) remodeling by a relative reduction in myocardial ischemia, left ventricular wall stress, and arrhythmias because of their negative inotropic and chronotropic properties. These effects have been extrapolated to cause similar potential benefits in the patients with stable CHD. The evidence for this practice is scarce, especially in patients with diabetes mellitus who are relatively at a higher risk of developing complications secondary to BB therapy.[26]

Majority of the data for the cardiovascular (CV) mortality benefit of BB therapy comes from studies performed in pre-reperfusion era showing up to a 25% risk reduction.[27–32] In the reperfusion era, BB therapy was found to reduce mortality by 23% in the patients who underwent fibrinolysis.[33] The evidence for the long-term benefit of BB therapy in the patients undergoing reperfusion via percutaneous
coronary intervention (PCI) is inconclusive especially in the contemporary era, where we have higher usage of statins, newer antiplatelets, and ACE inhibitors. Multiple observational studies and meta-analyses have concluded that the mortality benefit of BB therapy is driven by the improved survival seen in subgroups of patients with preserved ejection fraction (LVEF) or multivessel coronary artery disease. The most convincing evidence of a lack of benefit from BB therapy in low-risk groups came from a 2017 study of a cohort of 179,810 post-MI patients. The results showed that in the patients without evidence of reduced LVEF, BB therapy did not improve mortality in both NSTEMI and STEMI cohorts (P-value = 0.82 and 0.64, respectively). Diabetic patients comprised only 13.5% of the whole cohort. There remains a need for further studies assessing the benefit of BB therapy in diabetic patients with stable CHD. The only mortality benefit of BB therapy in diabetic patients comes from a study performed in a pre-reperfusion era without the optimal use of statins, antiplatelet agents (aspirin 74%), and ACE inhibitors (27%). This was an observational study that showed a significant benefit of BB on mortality but lacked any mortality benefit in diabetic patients who were not on insulin therapy.

Current ACC/AHA recommendations strongly support the use of BB especially in patients with a history of MI or heart failure. The guidelines do not have any specific recommendations for diabetic patients. In addition to the lack of any proven mortality benefit, BB therapy in diabetics may lead to severe hypoglycemic episodes because it can dampen the symptoms of hypoglycemia. It can also worsen diabetes and dyslipidemia by inhibiting the release of insulin and increasing weight gain. A recent study has shown that in patients with hypertension, BBs can increase the risk of developing diabetes by 22% compared to other antihypertensives, except diuretics. The same study showed a 15% increased risk of stroke with BB in hypertensive patients.

As mentioned previously, the present analysis comprises of post-hoc analyses of the four RCTs. The patients included in all the studies were matched according to their propensity score, which adds to the credibility of the findings. Notwithstanding, this analysis suggests that BB, at the very least, are not beneficial in diabetic patients with stable CHD. This finding, in addition to the potential side effects of BBs and increased cost and pill-burden for the patients with heart disease, makes a strong case for careful reassessment and potentially discontinuation of BB therapy. Patients should instead be encouraged to adhere to the proven therapies of statins, antiplatelets, and ACEi in addition to improving lifestyle choices.

This study has several limitations. First, it is important to note that the data included is observational and it should be interpreted with caution as it cannot confer causality because of the lack of randomization. Despite propensity score matching and covariate adjustment, there may be some unmeasurable residual confounding variables that might have attributed higher mortality risk to the patients on BBs. Additionally, we are not sure why the patients with stable CHD were prescribed β-blockers and whether it was because they were deemed to be at a higher risk for adverse cardiovascular events, such as arrhythmias. However, in all the trials we used the adjusted effects estimate to account for the confounding. Second, the patient population is widely different in each post-hoc analysis including some patients with risk factors for coronary artery disease (ACCORD) to those who have undergone coronary revascularization (BARI2D, CORONOR) and those with patients with heart failure and preserved ejection fraction (TOPCAT). Additionally, the definition of stable CHD is somewhat subjective and is different in each included study. Some studies included patients with MI and/or heart failure in their population, whereas some studies excluded those patients. To counter this, we performed jackknife influential analyses, as shown in the appendix, and the results generally held robust. Furthermore, including higher risk patients, such as patients with left ventricular dysfunction, would cause BB therapy to be more efficacious and this fact further strengthens our findings. Third, these analyses lack the information regarding BB blockade dosage and adherence. Fourth, we did not have information regarding individual BBs and we have pooled different BBs together assuming a class effect. Finally, the risk of publication bias remains important as studies showing significant findings are more likely to get published.

The use of BB in diabetic patients with stable CHD needs to be carefully reassessed. Based on the evidence from observational data of post-hoc analyses, diabetic patients who have stable CHD and are without any further compelling indications for BB therapy, may need be considered for possible discontinuation of BB therapy, especially if they are experiencing adverse effects. Future RCTs are required to confirm these findings.

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