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Beta Blockers in Contemporary Cardiology: Is It Better to Cast Them Out?

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AUTHOR'S SUMMARY

This review gives a detailed account of the clinical trial evidence of the use of beta blockers in heart failure (HF) with preserved ejection fraction and other common indications. As we know the use of beta blockers is very prevalent in cardiology and this review gives a critical appraisal of the available evidence for the use of beta blockers in patients with HF, coronary artery disease, hypertension and atrial fibrillation (AF). In paroxysmal AF, this article proposes that beta blockers have the potential to induce recurrent episodes of AF which needs further studies.

ABSTRACT

Beta blockers are one of the commonest prescription drugs in medicine and they have been thought to revolutionize the treatment of heart failure (HF) with reduced ejection fraction (HFrEF) in the last century. In addition to HFrEF, they are prescribed for a variety of diseases in cardiology from hypertension to HF, angina, and stable coronary artery disease (CAD). The increased prescription of beta blockers in conditions like HF with preserved ejection fraction (HFpEF), and stable CAD may be doing more harm than good as per the data we have so far. The available data shows that beta blockers are associated with increased stroke risk and atrial fibrillation (AF) in hypertension and in patients with HFpEF, they have been associated with decreased exercise capacity. In patients with stable CAD and patients with myocardial infarction with normal systolic functions, beta blockers don't offer any mortality benefit. In this article, we critically review the common indications and the uses of beta blockers in patients with HFpEF, CAD, hypertension and AF and we propose that beta blockers are over-prescribed under the shadow of their beneficial effects in patients with HFrEF.

Keywords: Coronary artery disease; Heart failure; Atrial fibrillation; Hypertension

INTRODUCTION

Ever since the discovery of propranolol, the first drug of the beta blocker family to be discovered, the therapeutics of beta blockers continued to expand in cardiology and today they are used in a myriad of conditions from hypertension, atrial fibrillation (AF), heart

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failure (HF) and coronary artery disease (CAD) with and without myocardial infarction (MI).[1] The indications of beta blockers in many of these conditions are not based on solid evidence from randomized clinical trials. In this article, we critically review the common indications of beta blockers in contemporary cardiology practice.

BETA BLOCKERS IN HEART FAILURE

The discovery of beta blockers in HF was quite enigmatic as it was contrary to the intuitive effect of beta blockers in HF due to their negative inotropic effects. The landmark trials—MERIT-HF, COPERNICUS and CIBIS II on patients with HF with reduced ejection fraction (HFrEF) conclusively showed that the selected beta blockers had mortality benefits of up to 30–35%.[2-4] However, their benefit in patients with HF with preserved ejection fraction (HFpEF) remains unknown, though in clinical practice they are still used ubiquitously in HF irrespective of left ventricular (LV) systolic functions. The recent trials of the patients with HFpEF reported beta blocker usage of 80–85% in EMPEROR-preserved and PARAGON trials.[5][6] The analysis from the TOPCAT trial also showed that beta blockers increased hospitalizations for HF in patients with HFpEF and did not offer any mortality benefit to patients with left ventricular ejection fraction (LVEF) of more than 50%.[7] In patients with HFrEF, beta blocker benefit has been correlated with heart rate lowering of up to 5–10 beats per minute as was demonstrated in a pooled patient-level analysis of 11 randomized clinical trials. In the same analysis, beta blockers demonstrated mortality benefit in patients with LVEF below 50% who were in sinus rhythm however, the patients who had LVEF more than 50% or who were in AF had no mortality benefit of beta blockers.[8] Whether this decrease in the heart rate in HFpEF is what mars these patients is what came out of a recent study by Palau et al.[9] who demonstrated that patients with HFpEF who have chronotropic incompetence improve markedly after discontinuing the beta blocker therapy with a significant improvement in functional capacity as measured with peak exercise oxygen uptake and this effect was significantly associated with an increase in the exercise heart rate. What came out of this study is that a significant proportion of the patients of HFpEF who are on beta blockers have symptomatic chronotropic incompetence which is reversed with the withdrawal of these agents. Whether there is a subgroup of patients with HFpEF fraction who do benefit from beta blockers was studied by Park et al.[10] who studied around 2 thousand patients in the STRATS-AHF registry with LVEF of more than 40% and found that patients with low global longitudinal strain (GLS) of less than 14% had significantly lower mortality than the patients with LVEF of 40% and GLS more than 14%. Pertinently, they included patients with LVEF of more than 40% in HFpEF, which is now classified separately in HF with mid-range ejection fraction. Beta blockers reverse the cardiac remodeling in patients with ventricular dysfunction and in patients with HFpEF, the primary cardiac pathology is complex and doesn't necessarily involve cardiac remodeling and that could be the possible reason for the inefficacy of beta blockers in HFpEF.

BETA BLOCKERS IN CORONARY ARTERY DISEASE

Before the revascularization era, beta blockers were frequently used in patients with any history of MI and some of the guidelines still recommend beta blockers to be given at discharge after MI irrespective of LV systolic functions for some fixed time. However, the data on this population of patients is again contradictory. In a meta-analysis of 64 randomized trials of patients on beta blockers, they have been shown to reduce mortality in the pre-reperfusion era

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(defined as 50% or less receiving reperfusion, aspirin, or statin) while as in the contemporary reperfusion era, beta blockers have been proven to have no benefit on mortality of the patients with the acute coronary syndrome (ACS) with normal LV functions. Beta blockers were in fact, found to increase HF hospitalisations (number needed to harm=79) and cardiogenic shock at the cost of a decrease in angina and recurrent MI (number needed to treat to benefit=209) in the short term without any effect on long-term mortality.[11] Dondo et al.[12] in 2017 studied a large cohort of patients of both ST-elevation myocardial infarction and non ST-elevation myocardial infarction without HF or LV systolic dysfunction with more than 163,772 person-years of observation and found that the use of beta blockers was not associated with any reduction in the risk of death at any time point up to 1 year. In a propensity-matched cohort study published in 2012, beta blockers were found to increase mortality in patients with risk factors for CAD while as those patients with CAD with or without any remote MI, beta blockers were not associated with any benefit in terms of primary outcome which was cardiovascular death, non-fatal MI or non-fatal stroke.[13] After percutaneous coronary intervention for stable CAD without any history of MI or HF, again the beta blockers were not found to be useful and were associated with increased mortality.[14][15] In another meta-analysis published in 2021, 6 studies were included, which studied beta blockers in patients with CAD after ruling out the patients with previous MI or LV dysfunction, and it was found that beta blockers had no effect in reducing major adverse cardiovascular events among patients with stable CAD without previous history of MI or LV dysfunction.[16] Contrary to these findings, Godoy et al.[17] recently reported in a large observational study of geriatric patients with age above 66 years who were newly diagnosed as stable CAD on routine coronary angiogram, that beta blocker prescription was associated with a significant reduction in MI hospitalisation with no difference in all-cause death or HF hospitalisations. How beta blockers reduce MI hospitalisation was quite enigmatic and the authors proposed some unproven mechanisms for this finding like beta blockers arresting atherosclerosis progression. Whether there was some inherent bias in this observational study is what was pointed out in the limitations of this study.

One of the main effects of beta blockers in patients with stable CAD by which they are purported to act and thereby prescribed in a clinical context is their negative chronotropy, as increased heart rate remains a major concern in many patients of CAD with angina. A heart rate of more than 70 is independently associated with increased morbidity and mortality in patients with CAD.[18][19] Park et al.[20] reported in a study of patients with ACS without any HF or ventricular dysfunction that a higher discharge heart rate of more than 75 beats per minute benefited from beta blocker therapy in terms of overall mortality reduction of 48% compared to the patients with a lower discharge heart rate of less than 75 beats per minute. Pertinently, they found that heart rate differences between patients with low and high heart rates at discharge were sustained during the 5-year follow-up. And whether it is the heart rate lowering effect of beta blockers, came into question after a randomised, double-blind, placebo-controlled clinical trial, SIGNIFY showed that patients with stable CAD without HF failed to show any long-term mortality benefit after decreasing the heart rate significantly by about 10 beats per minute with ivabradine.[21] Hence this rate-lowering effect of beta blockers is counterintuitive to the results seen in the trials of patients with CAD as almost half of the patients in those trials had increased baseline heart rate above 70 beats per minute and if at all there was a benefit of lowering the heart rate in these patients, it should have been quite clear in this randomised placebo-controlled trial.[22]

The incidence of new-onset diabetes after beta blocker therapy is also a concern. Though there are no randomized studies of beta blocker therapy with new-onset diabetes as the

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primary endpoint, however, the data from the randomized studies of hypertension trials suggest that beta blockers do increase the incidence of diabetes. In a meta-analysis of over 94000 patients with hypertension treated with beta blockers, the risk of new-onset diabetes occurred in 22%, 21%, and 19% of patients on beta blockers compared with nondiuretic antihypertensive agents, calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs), respectively.[23] And on propensity matching in ACCORD trial data, it was shown that diabetic patients who were on beta blockers had a higher incidence of adverse cardiovascular outcomes.[24]

BETA BLOCKERS IN HYPERTENSION

Regarding the use of beta blockers as antihypertensives, they don't have a favourable effect on central aortic pressure as the beta blocker induced bradycardia causes uncoupling of the forward and the reflected pulse waves and leads to an increase in the central aortic pressure. In the CAFE sub-study of the ASCOT trial, the combination of metoprolol plus thiazide versus amlodipine plus perindopril led to a higher central aortic pressure despite similar peripheral arterial pressure reduction.[25] Although the data on central aortic pressure is marred by a lack of data on this parameter compared to the peripheral blood pressure (BP), whatever limited data is there, there is a clear trend that central aortic pressure does predict cardiovascular disease and events better than the peripheral BP.[26] Further, a meta-analysis of 13 randomized controlled trials on hypertension showed that beta blockers were associated with a 16% increased risk of stroke compared to CCBs and ARBs with no difference in MI. When the effect of beta blockers was compared with that of placebo or no treatment, the relative risk of stroke was increased by 19% for all beta blockers, with no difference for MI or mortality.[27] In another meta-analysis involving more than 165,000 patients, it was found that compared with other antihypertensive agents, beta blockers appear to be substantially less protective against stroke and overall mortality. However, they exhibit a substantial risk-reducing ability for all events when prescribed to lower BP in patients with modest or more clear BP elevations and therefore can be used as additional second-line agents in hypertensive patients.[28] Law et al.[29] in a large metanalysis of 147 epidemiological studies of antihypertensives reported that beta blockers fared well compared to other anti-hypertensives except for the extra benefit of a significant reduction in coronary events in patients with previous MIs and whether this effect was seen about LV systolic dysfunction is not known. Pertinently, CCBs were found to have the extra benefit of a significant reduction in stroke rates.

BETA BLOCKERS IN ATRIAL FIBRILLATION

Finally, coming to the use of beta blockers in AF, it is generally considered to be safe to use beta blockers in AF with a fast ventricular rate and in fact, guidelines do recommend the use of beta blockers for rate control of AF without much evidence.[30] Chao et al.[31] have reported a significant reduction in mortality in patients on rate control strategy with beta blockers and CCBs compared to digoxin. However, there is some emerging data indicating that beta blockers accelerate the progression of paroxysmal AF to permanent AF compared to CCBs.[32] As is known, AF progresses by electrical and mechanical remodelling of the atrial myocardium and the rapid calcium influx during the rapid heart rates leads to electrical remodelling of the atria and non-dihydropyridine CCBs block this pathway of electrical remodelling,[33] while as beta blockers have no role in this electrical remodelling. Beta blockers decrease the

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sympathetic tone and provide a favourable substrate for vagal-mediated paroxysmal AF.[34] Low sinus rates also favour atrial extrasystoles which trigger AF. The decrease in heart rate and its role in the onset of AF was also seen in the SIGNIFY trial which showed that ivabradine in patients with angina, without any HF decreased sinus rate significantly with an attendant increase in AF which led to increased stroke rate by about 40%.[21]

The same kind of signal of increased incidence of AF with beta blockers was also found in 2 large beta blocker outcome trials in patients with hypertension with normal LV systolic functions which showed that beta blockers significantly increase the incidence of AF. In the LIFE trial, Atenolol was compared with Losartan and resulted in a 30% increase in the incidence of AF and a 3-fold increase in the rate of stroke compared to Losartan, despite a similar reduction in BP.[35] Disproportionate incidence of strokes and AF despite a similar reduction in BP with beta blockers was also seen in the ASCOT trial which compared amlodipine versus atenolol.[36] Given these landmark trials, beta blockers were downgraded to second-line drugs in the management of hypertension. To better understand the mechanism of increased incidence of AF in patients on beta blockers, physiology does point to the answers. The incipient bradycardia in the presence of normal LV functions increases the diastolic filling time which thereby increases the diastolic LV volume and pressures that are transmitted to left atrial (LA) and hence there is excessive stretching of the LA myocardium. Due to this atrial stretching, remodelling of the LA sets in which gives rise to the increased incidence of AF.[37] This hypothesis was favoured by a study that compared beta blockers with CCBs in patients with permanent AF with normal LV functions and what they found was a significant increase in the levels of brain natriuretic peptide (BNP) levels with decreased exercise tolerance in patients on beta blockers.[25] When compared to digoxin, again beta blockers fared worse in terms of increase in the levels of BNP levels and progression of the disease. In patients with paroxysmal AF, beta blockers are usually prescribed for rate control and prevention of AF progression without much evidence and, in a sub-study of the RACE 4 trial, it was found that beta blockers increase the progression of the disease to paroxysmal AF compared to the CCBs.[32] For controlling ventricular rates in AF, again CCBs were found to have a much more robust effect as compared to beta blockers as CCBs have use dependence and they control the ventricular rates with much lesser bradycardia as compared to beta blockers.[38][39]

CONCLUSION

To summarise, beta blockers have a unique round plot story in cardiology. The uses of beta blockers that over the years proved to be their boon are the ones that were once their contraindications and their common uses in contemporary clinical practice for AF rate control and progression, hypertension and CAD are at a crossroads today due to their uncertain benefit. Other than HF with ventricular systolic dysfunction, we have better drugs with many proven roles and beta blockers should be used as second-line drugs in AF, hypertension and CAD.

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