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Carvedilol is not superior to metoprolol for heart failure patients when given at equivalent doses

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ABSTRACT   A critical appraisal and clinical application of Lazarus DL, Jackevicius CA, Behlouli H, et al. Population-Based Analysis of Class Effect of β Blockers in Heart Failure. *The American Journal of Cardiology* 2011;107(8):1196-1202. doi: 10.1016/j.amjcard.2010.12.017.

Keywords: *heart failure, beta blocker, carvedilol, metoprolol*

Clinical Context

Mary Garcia (pseudonym) was a 91-year-old woman with a history significant for congestive heart failure with reduced ejection fraction of 20%, hypertension, CABG procedure with drug eluting stent placement, and biventricular ICD placement. She presented to the emergency room due to an exacerbation of shortness of breath that she had been experiencing over the last month. She described this issue as inhibiting acts of daily living, such as ambulating around her apartment and cooking for herself, which she was able to do at her baseline. She mentioned that recently taking food out of the oven caused her to need to hold onto the counter to catch her breath. This was concerning for her because she was very proud to live independently in her own apartment with only some help from a grandson who visited a few times a week.

There was an interest from the hospital teams taking care of her to change her medication regimen to better control her symptoms, reduce her mortality risk associated with her heart failure, and lower her blood pressure from the elevated 181/82 it was on admission. Her daily cardiovascular medications were aspirin 81 mg, atorvastatin 20 mg, furosemide 40 mg, losartan 25 mg, spironolactone 12.5 mg, and metoprolol 50 mg. Everyone agreed that part of her therapy should continue to include a beta blocker, as this has been shown to decrease mortality in heart failure patients according to AHA/ACC guidelines.[1] However, there was disagreement about which one to use. One consulting team wanted to try to increase her metoprolol dose she was on at home from 50 mg daily to 200 mg daily, and the other consulting team wanted to switch her metoprolol to carvedilol 12.5 mg twice a day. Ms. Garcia was interested in trying any treatment that would help her be more independent again and give her more time alive to spend with her grandchildren.

Clinical Question

Is there a difference between carvedilol or metoprolol effects on all-cause mortality in heart failure patients when the medications are given at equivalent doses?

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Research Article

Lazarus DL, Jackevicius CA, Behlouli H, et al. Population-Based Analysis of Class Effect of β Blockers in Heart Failure. *The American Journal of Cardiology* 2011;107(8):1196-1202. doi: 10.1016/j.amjcard.2010.12.017

Related Literature

A general search of PubMed was done looking for the terms "carvedilol," "metoprolol," "Heart Failure," and "Mortality" for randomized control trials and retrospective or prospective cohort studies. Systemic reviews were analyzed to seek the most relevant studies. Publications that focused on subsets of heart failure with additional co-morbidities, like patients on hemodialysis, were excluded.

The most recent review found was a 2015 meta-analysis, published by Briasoulis et al.[2], directly investigated the clinical question for our patient of a potential advantage between carvedilol or metoprolol effects on all-cause mortality with heart failure patients. This review was very well designed with comprehensive study searches done and use of the Cochrane risk-of-bias tool to eliminate studies with a high risk of bias. The Briasoulis review also incorporated an exclusion criteria that included elimination of studies that tested low doses of the beta blockers in question, which they set to carvedilol <= 12.5 mg/day and metoprolol <= 100 mg/day. That review found four articles that met the criteria of comparing both medications at high doses and not having a high risk of bias: Shore et al.[3], Pasternak et al.[4], Bolling et al.[5], and Lazarus et al.[6]. Its conclusion was that there was no significant difference between the two drugs.

The most substantial study that was excluded was the "Carvedilol Or Metoprolol European Trial" (COMET) of 2003.[7] This was a double-blind randomized parallel group trial of 1,511 patients with chronic heart failure treated with either 50 mg of carvedilol daily or 100 mg of metoprolol daily. This article found that the patients taking carvedilol had a lower all-cause mortality rate than the patients taking metoprolol. However, as was discussed in the most recent meta-analysis, this trial was comparing a metoprolol given at a low dose to carvedilol given at a high dose, so it was not included in this literature search. While a randomized control trial would have been ideal to have been analyzed for this appraisal, this one did not compare equivalent doses of medications.

Shore et al. evaluated 3,716 patients with heart failure NYHA class 3 or worse. It compared patients on carvedilol and metoprolol succinate over the course of 10 years. This study did find any significant different between the two drugs in all-cause mortality, baseline ejection fraction, or repeat hospitalizations in both patients with ischemic and non-ischemic heart failure.[3]

Pasternak et al. conducted a cohort study that evaluated 11,664 patients with heart failure with reduced ejection fraction on guideline determined medical treatment. 6,026 of them received carvedilol and 5638 received metoprolol succinate. The results did not show a significant absolute risk difference between the two treatments, and this was true across all different NYHA classifications. However, only 52% of patients on carvedilol and 12% of metoprolol users reached the recommended daily target doses of 50 mg and 200 mg daily respectively.[4]

Bolling et al. conducted a retrospective cohort study that investigated 58,634 patients who initiated beta-blocker treatment within 60 days of discharge from admission due to heart failure. This paper showed that carvedilol was associated with lower mortality rates than metoprolol at the higher doses. However, the article also stated that the patients receiving carvedilol were younger, had less co-morbidities, and were receiving more concomitant treatments, like angiotensin-converting enzyme (ACE)-inhibitors and statins. All three of those differences could potentially explain the difference in mortality.[5]

Lazarus et al. investigated 26,787 patients with congestive heart failure. It is a study that adjusted for age, initial beta-blocker dose, co-morbidities, drugs prescribed at discharge, interval to the filling of the first prescription, and other factors. Because this study took into account these factors and utilized such a large sample size, it was chosen for critical appraisal. A double-blinded, placebo-controlled trial could not have been chosen in this case because none were available that tested high doses of both medications and had a low risk of bias according to the Briasoulis et al. analysis.[6] There are newer studies, such as Perreault et al.[8], that have similar findings and similar study designs, but they included less patients than this one did.

Critical Appraisal

This study was an observational cohort study that used data from the Quebec government administrative and prescription claims databases. The investigators collected their data from patients admitted to the hospital with a primary diagnosis of heart failure as described by ICD codes. They only included patients who were at least 65 years old who had not been admitted to the hospital within 3 years of the study period and who filled their prescription for a beta blocker within 90 days after discharge. Patients were categorized based on the beta blocker they were prescribed, which were metoprolol, atenolol, carvedilol, and acebutolol. Adherence to therapy was measured by recording percentage of days that a patient was covered by a beta blocker prescription during the year after discharge or until death if that came first.

The primary outcome that the researchers were interested in was mortality at any point during the follow up period. A secondary outcome that was also tracked was readmissions because of heart failure, which was also checked using ICD codes. For each patient, prescriptions of non-over-the-counter medications, co-morbidity information, length of hospital stay, medical procedures received between admission and first beta blocker prescription filling (e.g. catheterization), and the specialty of the admitting physician were also collected.

Once the data was collected, it was analyzed using various statistical techniques. The Kaplan-Meier method was used to calculate the unadjusted mortalities for the patients on each of the different beta blockers. The investigators used a multivariable Cox proportional hazards model to allow them to account for differences in patient characteristics, like patient age and dosage of beta blocker, as described in the previous section. Their target dosage for beta blockers included 200 mg/day for metoprolol and 50 mg/day for carvedilol, which are both higher doses.

This study had a large number of various results, but the most relevant for our clinical question was the comparison between the metoprolol and carvedilol groups. Patients prescribed metoprolol accounted for ~54% of the patients in the study and patients prescribed carvedilol accounted for only ~8%. There was similar adherence to therapy across both groups of patients with the carvedilol patients being at 83% and the metoprolol patients being at 81%. The patients on carvedilol had similar use of most heart failure medications like ACE inhibitors and statins to those on metoprolol, although that cohort did have higher use of spironolactone and digoxin.

The final results after analysis showed no significant difference in mortality or readmission outcomes, although the carvedilol group had slightly lower rates. These results did not change after stratifying patients according to hypertension of myocardial infarction co-morbidities. Interestingly, the study did find an advantage when prescribing patients low-lipid soluble beta blockers like atenolol and acebutolol. For example, atenelol when compared to metoprolol had lower mortality rates (HR 0.82, 95% CI 0.77 to 0.87, $p < 0.001$) and combined mortality-readmission rates (HR 0.84, 95% CI 0.79 to 0.89, $p < 0.001$), however this result was not as relevant to our clinical question.

Since this was a cohort study, this study is somewhat limited in its ability to create clinical recommendations. The authors did acknowledge some selection bias with the absence of randomization among the groups. They also had no way of differentiating patients depending on severity of their heart failure, which could either be measured through determining its stage or class or by comparing ejection fractions, as they only were able to look at the ICD code for heart failure. A randomized-control, double-blinded trial would give the best evidence to support the authors' conclusion that, when given at a high dose, there is no significant difference between carvedilol and metoprolol. This paper was determined to be at a 2b level of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.

Clinical Application

In the case of Ms. Garcia, the 91-year-old lady with a history of congestive heart failure on low-dose metoprolol in addition to other medications, there was no advantage in switching to carvedilol instead of just raising the metoprolol dose. The literature on this topic showed that there is not a significant decrease in all-cause mortality between the two treatments assuming that both are prescribed in a high dose. In the case of this patient specifically, Ms. Garcia stated that she would also be more comfortable taking a higher dose of a medication that she is used to taking instead of switching to a different one. For those reasons, the best course of action was to increase her metoprolol dose to 200 mg per day.

Learning points:

1. There is no significant difference between metoprolol and carvedilol in decreasing mortality in patients with congestive heart failure.

2. Beta blockers should be given at high doses instead of low doses for equal reduction in mortality risk.

3. Medications can be more or less efficacious depending on dosing and that should be taken into account along with their drug class.

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