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Betablockers in Heart Failure Treatment

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Betablockers are one of the main drug classes used in heart failure treatment, for improving survival and slowing the progression of the disease. Patients with symptomatic heart failure present neurohumoral activation, with increased activity of the sympathetic nervous system. A number of trials have demonstrated that patients with heart failure with reduced ejection fraction benefit from treatment with betablockers in terms of reduced mortality, reduced hospitalization rates and symptomatic improvement. The most studied betablockers in patients with heart failure were metoprolol succinate, carvedilol and bisoprolol.

The MERIT-HF trial included almost 4000 patients with heart failure NYHA class II to IV and left ventricular ejection fraction ≤ 40%, already treated with digoxin, and ACE inhibitor and a diuretic [1,2]. These patients were randomized to receive either extended-release metoprolol (starting with 12.5 mg or 25 mg daily and uptitrated to 200 mg/day) or placebo. The study was prematurely terminated due to significant benefits observed in the subgroup treated with metoprolol: 34% relative risk reduction in all-cause mortality at 12 months versus 11% for placebo, reduction of hospitalization rate for cardiovascular causes (20% versus 25%) or for heart failure (10% versus 15%). Another trial with metoprolol, MDC trial (Metoprolol in Dilated Cardiomyopathy), randomized 383 patients to placebo or metoprolol tartrate (starting dose 10 mg and slowly uptitrated to 150 mg/day) [3]. The inclusion criteria were the diagnosis of dilated cardiomyopathy with left ventricle ejection fraction less than 40% and systolic pressure >90 mm Hg. The patients were compared after 12 months and 18 months. Patients treated with metoprolol demonstrated a greater increase in ejection fraction (12% versus 6%) and tolerance to effort and also improvement in the quality of life.

Bisoprolol was studied in CIBIS and CIBIS II trials. CIBIS II trial randomized 2647 patients with heart failure NYHA class III or IV (already on treatment with diuretics and ACE inhibitors) and ejection fraction <35%, to bisoprolol or placebo [4,5]. This trial has been also prematurely terminated due to significant reduction of all-cause mortality (11.8% versus 17.3%), significant reduction by 15% in hospital admissions for any cause and 30% in admissions for heart failure.

Carvedilol was studied in COPERNICUS study, which included 2289 patients with symptoms of heart failure and ejection fraction less than 25%, randomly assigned to placebo or carvedilol for an average 10.4 months [6,7]. Carvedilol decreased the combined risk of death or hospitalization for cardiovascular reasons by 27% and the combined risk of death or hospitalization for heart failure by 31%. The mean duration of hospitalization was also shorter in patients treated with carvedilol. The COPERNICUS trial concluded that in euvolemic patients symptomatic at rest or on minimal exertion the addition of carvedilol to standard heart failure treatment improves the symptoms of heart failure and reduces the risk of hospitalization.

There have been a number of trials that tried to compare the effects of different betablockers in heart failure patients. COMET trial compared the effects of carvedilol with those of metoprolol tartrate on 3029 patients with heart failure NYHA class II to IV, with at least one hospitalization for cardiovascular disease during previous two years and ejection fraction ≤ 35% [8]. Patients randomly received either carvedilol 25 mg twice/day either metoprolol tartrate 50 mg twice/day. The patients were followed five years. The subgroup treated with carvedilol had a lower rate of all-cause mortality (34% versus 40%) and cardiovascular mortality (29% versus 35%). The median survival was significantly longer in patients treated with carvedilol (8.0 versus 6.6 years).

Carvedilol (vasodilator) was compared with bisoprolol (non-vasodilator) in a meta-analysis of different trials that compared betablockers to placebo [9]. Patients treated with carvedilol had a longer survival compared to those treated with bisoprolol (45% versus 27%).

In conclusion, the reduced mortality and amelioration of symptoms of heart failure are class effects of betablockers. The 2013 heart failure guidelines of the American College of Cardiology Foundation/American Heart Association recommend treatment with one of the three betablockers (bisoprolol, carvedilol, metoprolol succinate) in order to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction.

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