IS **CARVEDILOL** SUPERIOR TO **METOPROLOL** IN HEART FAILURE?

KEY POINTS

- *Carvedilol may be an option if metoprolol succinate is poorly tolerated.*

- *In patients with heart failure who have not previously used a beta-blocker, carvedilol may be considered as the first choice agent.*

- *Strategies for initiating carvedilol are discussed in the following article.*

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BACKGROUND

There has been much debate concerning the relative effectiveness of different types of beta-blockers, particularly carvedilol and metoprolol. Several large clinical trials have been conducted comparing these drugs.

Carvedilol is a non-selective beta-blocker with α_1, β_1 and β_2 adrenergic receptor blockade properties. It has shown to be effective in the treatment of hypertension, coronary heart disease (anti-ischaemic and anti-anginal properties), chronic heart failure and left ventricular dysfunction following acute myocardial infarction.[1]

Metoprolol is a cardioselective beta-blocker, that is it blocks β_1 adrenergic receptors (mainly cardiac in origin) at lower doses than those needed to block β_2 adrenergic receptors (mainly located in the bronchi and peripheral vessels). There are two chemical forms of metoprolol. They are different salts of the same drug; metoprolol succinate (Betaloc CR) and metoprolol tartrate (Lopressor, Slow Lopressor). In New Zealand, the succinate is only available as a slow release preparation designed for once daily dosing. The tartrate is available as an immediate release (twice or three times daily dosing) or a once daily slow release preparation. Metoprolol tartrate is indicated for the treatment of hypertension, angina, disturbances of cardiac rhythm, functional heart disorder with palpitation, hyperthyroidism and migraine prophylaxis.[2] In addition, metoprolol succinate is also indicated for maintenance treatment after myocardial infarction and for chronic heart failure, as an adjunct to other heart failure therapy.[3]
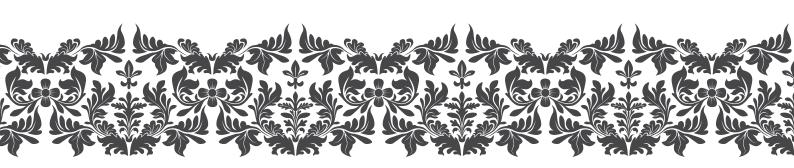
COMPARING CARVEDILOL AND METOPROLOL: RESULTS OF THE COMET TRIAL

The Carvedilol or Metoprolol European Trial (COMET) compared overall mortality in patients with heart failure, randomised to receive either carvedilol or metoprolol tartrate.[4] The doses used were carvedilol 25 mg twice daily and metoprolol tartrate 50 mg twice daily. The results of the trial showed that carvedilol was associated with a 15% relative risk reduction in all cause mortality, compared to metoprolol tartrate.[5] Carvedilol extended median survival by 1.4 years (95% CI: 0.5–2.3 years) compared with metoprolol and was associated with significantly lower rates of death from stroke and new-onset diabetes. There were no observed differences between carvedilol and metoprolol tartrate in rate of hospitalisation, adverse events or drug withdrawal.[6]

Based on the results of the COMET trial, the authors concluded that carvedilol, at a dose of 25 mg twice daily, provides superior morbidity and mortality benefit compared to metoprolol tartrate at a dose of 50 mg twice daily. However there is some controversy surrounding the conclusions drawn from this study, with debate focusing on whether the doses of the two drugs were comparable. It has been suggested that metoprolol tartrate should have been titrated to a higher dose (up to 200 mg per day). However, there is no agreement on what the optimal dose equivalence between the two drugs should be and in addition it is unproven whether higher doses of metoprolol tartrate confer lower mortality.[6]

It is important to note that in the COMET trial, carvedilol was compared with metoprolol tartrate. The MERIT-HF trial compared metoprolol succinate to placebo and it was found that metoprolol succinate reduced the mortality rate by 34% in patients with heart failure.[7] This is comparable to carvedilol.[6]

While carvedilol appears to be preferable to metoprolol tartrate for patients with heart failure, there is currently no evidence to demonstrate that it is superior to higher doses of metoprolol tartrate (e.g. 200 mg per day) or metoprolol succinate. Carvedilol is a more complex, non-selective beta-blocker and may represent a more comprehensive antagonism of the characteristics of heart failure than a cardioselective beta-blocker such as metoprolol.[5] However, these characteristics also mean that carvedilol is not an appropriate medication for people with respiratory disease due to risk of bronchoconstriction (*see BPJ Issue 1 page 38, and BPJ Issue 7 page 48 for more information*).

CARVEDILOL MAY BE AN OPTION IF METOPROLOL SUCCINATE IS POORLY TOLERATED.[1]

There is no advantage in changing to carvedilol for people who are already taking metoprolol succinate at effective doses. However, carvedilol may be an option if metoprolol succinate is poorly tolerated. In patients with heart failure who have not previously used a beta-blocker, carvedilol may be considered as the first choice agent.

If a decision is made to switch from metoprolol succinate to carvedilol there are some important considerations:[8]

1. Adequate beta-blockade must be maintained to avoid precipitating ischaemia or arrhythmia.
2. Initial dosing must be low enough to avoid hypotension resulting from vasodilation.
3. A stable heart failure regimen (e.g. ACE inhibitor, diuretic, etc) must be in place.
4. The patient must not be acutely decompensated.

STRATEGIES FOR CHANGING TO CARVEDILOL

Two strategies have been suggested for changing from metoprolol succinate to carvedilol; either a *non-overlapping protocol* where a straight switch is made, or an *over-lapping protocol* where the dose of metoprolol succinate is gradually reduced whilst simultaneously up-titrating carvedilol.[8] Whichever method is used, co-existing heart failure medication should be stable and the patient should be relatively euvolaemic.
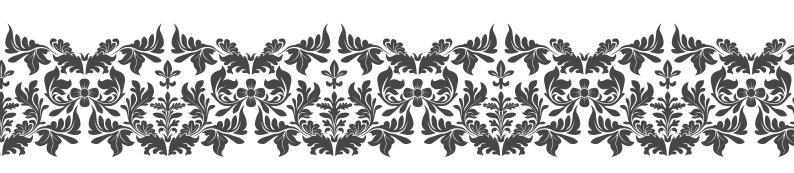
An overlapping method may be considered if the patient is taking high doses of metoprolol. In this method, the dose of metoprolol is gradually reduced while the dose of carvedilol is increased. Most patients seem to tolerate a simple approach without an overlap period, particularly if they are taking relatively low doses (i.e. <95 mg daily) of metoprolol.[8] In this method, the metoprolol is stopped upon initiation of the carvedilol, which is titrated to the target or maximum tolerated dose (Table 1).

Table 1: Non-overlapping method for switching from metoprolol succinate to carvedilol

Adapted from Abraham et al. [8]

Previous daily metoprolol succinate dose	Carvedilol (twice daily)			
	Initiate	week 2	week 4	week 6*
≤47.5 mg	6.25 mg	12.5 mg	25 mg	25 mg
>47.5 mg	12.5 mg	25 mg	25 mg	25 mg

At week 6, the dose of carvedilol can be increased to 50 mg twice daily, in patients >85 kg, unless congestive heart failure (CHF) is severe.

INITIATING CARVEDILOL IN PATIENTS WITH STABLE CHRONIC HEART FAILURE[1]

-   All other medication (e.g. digoxin, diuretics, ACE inhibitors) should be stabilised prior to starting carvedilol

-   Carvedilol should be given twice daily

-   Recommended starting dose is 3.125 mg, twice daily, for two weeks

-   Increase dose at intervals of at least two weeks, to 6.25 mg, 12.5 mg then 25 mg, twice daily, as tolerated

-   Maximum dose for patients with severe CHF, or weighing less than 85 kg, is 25 mg twice daily. In patients with mild to moderate CHF and over 85 kg, the maximum recommended dose is 50 mg twice daily

-   Signs of intolerance to carvedilol include bradycardia (<50 bpm), systolic BP <80 mmHg or fluid retention

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