

## Alternatives for Metoprolol Succinate

### Background

Metoprolol tartrate (*Lopressor*) is a regular, immediate-release tablet, while metoprolol succinate (*Toprol XL*) is an extended-release tablet.<sup>1,2</sup> A shortage of generic metoprolol succinate has necessitated switching some patients to alternative therapy. An option for some patients is metoprolol tartrate (*Lopressor* and its generics). This article reviews the differences between metoprolol tartrate and metoprolol succinate, and offers practical information on switching patients taking metoprolol succinate to alternate therapy.

### Indications

Metoprolol tartrate is FDA-approved for hypertension, angina, and post-MI.<sup>1</sup> Metoprolol succinate is approved for hypertension, angina, and heart failure.<sup>2</sup>

### Pharmacokinetics, Pharmacodynamics, and Dosing

Metoprolol tartrate is usually dosed twice daily. It can be effective for hypertension when dosed once daily, but low doses (e.g., 100 mg) given once daily may not control blood pressure for a full 24 hours.<sup>1</sup> Metoprolol succinate is dosed once daily. Metoprolol succinate produces more level metoprolol concentrations than the immediate-release tablets (i.e., lower peaks and less peak-to-trough variation).<sup>2</sup> Metoprolol tartrate is at least 30% more bioavailable than metoprolol succinate (i.e., more drug is absorbed).<sup>2,3</sup> However, overall 24 hour beta-blockade is comparable at the same dose.<sup>2</sup>

### Heart Failure

As noted above, metoprolol succinate is indicated for heart failure, while metoprolol tartrate is not. Metoprolol succinate was compared to placebo in heart failure patients in the MERIT-HF study. Patients with Class II through IV heart failure with an ejection fraction of 40% or less received metoprolol succinate

titrated to a target of 200 mg daily. Patients also continued ACE inhibitors, digoxin, and diuretics. The main outcome measures were total mortality and a combined endpoint of total mortality or all-cause hospitalization. MERIT-HF was stopped after the second interim analysis of the data because predetermined criteria for termination had been met (i.e., there was a significant difference between treated patients and those receiving placebo). After a mean follow-up of one year, total mortality was 7.4% in the metoprolol succinate group and 11% in the placebo group ( $p=0.0062$ ). The combined endpoint (total mortality plus hospitalization) occurred in 38.3% of the placebo patients vs 32.2% of the metoprolol patients ( $p<0.001$ ).<sup>4,5</sup>

In the COMET trial, carvedilol (*Coreg*) immediate-release (target dose 25 mg twice daily) was compared to metoprolol tartrate (target dose 50 mg twice daily) in patients with Class II through IV heart failure and an ejection fraction less than 35%. Mortality was lower in the carvedilol group (34% vs 40%,  $p=0.0017$ ).<sup>3</sup>

The clinical applicability of COMET's findings have been questioned because of the low metoprolol target dose used.<sup>6</sup> Indeed, a recent epidemiologic study of heart failure patients found mortality rates per 100 person-years of 17.7 for carvedilol, 20.1 for atenolol, and 22.8 for metoprolol tartrate. Only the difference between atenolol and metoprolol tartrate was significant ( $p=0.04$ ). (Carvedilol and metoprolol tartrate were not directly compared).<sup>7</sup> There was also no difference in the rate of rehospitalization among the three agents.<sup>8</sup> These results must be interpreted with caution because these studies were not randomized, and differences among patients (e.g., age, severity of heart failure, comorbidities) may have affected the results.

### Commentary

When shortages or other circumstances necessitate alternate therapy for patients taking

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metoprolol succinate, indication must be considered. For hypertension or angina, stable patients can be switched to the same total daily dose of metoprolol tartrate divided twice daily.<sup>2,9</sup> Because metoprolol tartrate produces a higher peak and is better absorbed than metoprolol succinate, some patients might not tolerate it.<sup>13</sup> Watch for side effects beginning within one hour after the dose.<sup>1</sup> Also monitor pulse and blood pressure. A lower dose may be necessary, or some patients might be better able to tolerate a longer acting beta-blocker such as bisoprolol (*Zebeta*).

For heart failure, some clinicians use metoprolol tartrate, but it is best to stick with agents with proven outcomes in heart failure (e.g., carvedilol, bisoprolol, metoprolol succinate) [Evidence level C; consensus].<sup>10</sup>

It has been suggested that patients can be switched from metoprolol succinate to an alternate beta-blocker starting 24 hours after their last dose. The dose of the alternate beta-blocker is based on dose equivalencies and clinical judgment.<sup>11</sup>

In the open-label portion of COMET, to maximize safety, it was determined that patients should be switched to one-half the equivalent dose of an evidence-based beta-blocker. For example, patients receiving metoprolol tartrate 50 mg twice daily were to be switched to carvedilol 12.5 mg twice daily or bisoprolol 2.5 mg daily. The dose was then doubled every one to two weeks, if tolerated, to carvedilol 50 mg twice daily or 10 mg of bisoprolol once daily. Slower titration could be done per the investigator's clinical judgment. Patients who were tolerating only a low beta-blocker dose, and patients with Class III or IV heart failure, pulse <50 beats per minute, or systolic blood pressure  $\leq$ 90 mm Hg, were considered at higher risk of decompensation during the switch. Despite the planned protocol, many patients were switched to an equivalent dose, rather than half the equivalent dose, of the new beta-blocker. Serious adverse effects (e.g., serious bradycardia or hypotension) occurred in 3.1% of patients switching from metoprolol tartrate to carvedilol, and 2.3% experienced worsening heart failure. In the metoprolol to bisoprolol group, worsening heart failure occurred in about 2% of patients. Serious adverse effects also occurred in about 2% of the metoprolol to bisoprolol patients. Adverse effects were higher

in patients switched to the equivalent dose rather than half the equivalent dose.<sup>12</sup>

### Conclusion

Whenever a medication becomes unavailable, it is an opportunity to evaluate the patient's medication regimen. You may find that the patient does not need the medication at all, or that a substitute from another therapeutic class would be more appropriate. When switching beta-blockers, start with a conservative dose and consider the patient's clinical status (e.g., vitals, disease control) [Evidence level A; high-quality RCT].<sup>12</sup> No matter what alternate medication is chosen, educate the patient about possible side effects and what to do if they occur.

Suggested Beta-blocker switch, based on COMET <sup>12</sup>	
Metoprolol succinate daily dose	Consider switch to:
25 mg	Carvedilol 3.125 mg BID or bisoprolol 0.625 mg daily
50 mg	Carvedilol 6.25 mg BID or bisoprolol 1.25 mg daily
100 mg	Carvedilol 12.5 mg BID or bisoprolol 2.5 mg daily
200 mg	Carvedilol 25 mg BID or bisoprolol 5 mg daily

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A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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