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INTERPRETING THE COMET TRIAL

In heart failure, all beta-blockers are not necessarily equal

ABSTRACT

The Carvedilol or Metoprolol European Trial (COMET; *Lancet* 2003; 362:7–13) found that in patients with heart failure, survival appears to be better with carvedilol than with immediate-release metoprolol tartrate. Whether the target doses used were equivalent (carvedilol 25 mg twice daily vs metoprolol tartrate 50 mg twice daily) has been debated, but the COMET trial shows that drugs in the same class do not necessarily have the same effects. Given the overwhelming evidence of the benefit of carvedilol, metoprolol succinate, and bisoprolol in patients with heart failure, we should all strive to increase the use of these drugs in appropriate doses.

FOR PATIENTS in chronic heart failure, all beta-blockers are not necessarily equal, according to the results of the Carvedilol or Metoprolol European Trial (COMET).[1]

In this, the largest and longest-running trial in chronic heart failure to date, the mortality rate was 17% lower in patients randomized to receive carvedilol (Coreg) than in those randomized to receive metoprolol tartrate (Lopressor and generic preparations—not to be confused with metoprolol succinate [Toprol XL], as we shall see).

However, the COMET trial has prompted debate about the equivalence of dosing between the study drugs and whether there are differences between the short-acting and long-acting versions of metoprolol.

Why COMET was needed, what it showed us, and how we should apply its findings in clinical practice are the topics of this article.

BEFORE COMET

Before COMET, several randomized, placebo-controlled studies showed that the beta-blockers metoprolol succinate,[2] bisoprolol (Zebeta, Ziac),[3] and carvedilol[4–6] all reduce the all-cause mortality rate in patients with heart failure by about 35%. But these studies did not tell us if any of these drugs is better than the others.

Carvedilol, bisoprolol, and metoprolol succinate all reduce mortality by about 35%

Particularly debated are the pros and cons of selective beta-1 adrenoceptor blockade vs nonselective alpha and beta adrenoceptor blockade.[7] Metoprolol and bisoprolol are selective for the beta-1 receptor. Carvedilol, in contrast, is nonselective: it blocks beta-1, beta-2, and alpha-1 receptors and has in vitro antioxidant properties that may have additional beneficial effects on endothelial function.[8] Yet, in the Beta-Blocker Evaluation of Survival Trial (BEST), bucindolol, another nonselective beta-blocker with possibly some intrinsic sympathomimetic activity, did not show a significant survival benefit when compared with placebo in patients with advanced heart failure.[9]

Several small studies directly compared carvedilol and metoprolol tartrate in patients with chronic heart failure.[10–15] According to a meta-analysis,[16] carvedilol improves hemodynamic measures at rest and during exercise to a greater extent than does metoprolol tartrate, although both drugs significantly improve left ventricular ejection fraction.

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TABLE 1

Inclusion and exclusion criteria in the COMET trial

Inclusion criteria

- Symptomatic congestive heart failure (New York Heart Association class II–IV) despite standard therapy
- Receiving frusemide (furosemide) > 40 mg/day or equivalent
- Receiving an angiotensin-converting enzyme inhibitor unless contraindicated
- Left ventricular ejection fraction ≤ 35% or left ventricular end-diastolic dimension > 6 cm and fractional shortening < 20% as measured by 2-dimensional transthoracic echocardiography
- At least one hospitalization for cardiovascular reasons during the last 2 years
- Written informed consent

Exclusion criteria

- Study objective-related
  - Recent change of heart failure treatment
  - Treatment with calcium channel blocker (diltiazem or verapamil)
  - Unstable angina or myocardial infarction within past 2 months
  - Heart transplantation anticipated within 2 months
  - Hemodynamically significant valvular disease
  - Arrhythmias (unless adequately treated)
- Contraindications to beta-blocker therapy
  - Heart rate < 60 beats per minute
  - Systolic blood pressure < 85 mm Hg
  - Atrioventricular block (unless treated with a pacemaker)
  - History of asthma or chronic obstructive pulmonary disease
  - Unstable insulin-dependent diabetes mellitus
- General exclusion criteria
  - Hepatic disease
  - Pregnancy or childbearing potential (unless using adequate contraception)
  - Stroke in past 2 months
  - Some specific endocrine disorders

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These results suggested that carvedilol's nonselectivity and additional properties may be important and thus set the stage for a head-to-head mortality trial.

COMET STUDY DESIGN

COMET, sponsored by Hoffmann-La Roche and GlaxoSmithKline Pharmaceuticals, was the first head-to-head trial conducted in Europe to compare the effects of different beta-blockers on mortality in heart failure.[1]

Patients

Patients were at high risk with symptomatic chronic heart failure (primarily New York Heart Association class II to IV) despite standard treatment. TABLE 1 lists the inclusion and exclusion criteria. All patients had a left ventricular ejection fraction of 35% or lower, as measured by echocardiography or radionuclide left ventriculography.

COMET enrolled a total of 3,029 patients at 317 centers in 15 European countries. TABLE 2 shows their baseline characteristics.

Treatment

Patients were randomly allocated to receive either:

- Carvedilol, starting at 3.125 mg and titrated to the target dose of 25 mg twice daily (n = 1,511) or
- Metoprolol tartrate, starting at 5 mg and titrated to the target dose of 50 mg twice daily (n = 1,518).

Why metoprolol tartrate—which is an immediate-release formulation—and not metoprolol succinate—which is an extended-release formulation and was shown to reduce mortality in the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure study)? Simply, the drugs and doses were chosen on the basis of data available in 1996, before metoprolol succinate was introduced.

End points

The primary end point was all-cause mortality; during the study a second primary end point was added: the composite of death or hospital admission for any cause (previously this was a secondary end point).

STUDY RESULTS

Primary end points

Mortality. Over a mean follow-up of 58 months, 34% of the patients in the carvedilol group died, compared with 40% in the metoprolol tartrate group—17% fewer (5-year Kaplan-Meier estimate 35.3% vs 41.0%, hazard ratio = 0.83, P = .002; FIGURE 1). A differ-

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ence in mortality first appeared at about 6 months, and carvedilol extended median survival by 1.4 years (95% confidence interval 0.5–2.3 years) compared with metoprolol.

The difference in mortality was not affected by baseline characteristics, loss to follow-up, or open-label use of beta-blockers. It did not influence the mode of death and was consistent across all predefined subgroups except for women, in whom the hazard ratio was 0.97 (FIGURE 2). The lack of a difference in women was likely due to the small sample of female subjects (20% of patients).

The combined end point of death or hospital admission, in contrast, did not differ significantly in incidence between the two groups (75.5% with carvedilol vs 78.5% with metoprolol tartrate, hazard ratio = 0.94, P = .122). Together, these results indicate that the sole advantage of carvedilol over metoprolol tartrate was a lower mortality rate, not a lower hospitalization rate. This is further supported by the rate of cardiovascular mortality, which was a solid 20% lower in the carvedilol group (29% vs 35%, hazard ratio = 0.797, P = .0004).

Secondary end points

The carvedilol group also had significantly lower rates of:

- Death from stroke (hazard ratio = 0.332, P = .006)
- New-onset diabetes (hazard ratio = 0.778, P = .04).[17]

Rates of adverse events and drug withdrawal were similar in the two groups (TABLE 3).

TABLE 2

Patient baseline characteristics in the COMET trial

	CARVEDILOL (N = 1,511)	METOPROLOL (N = 1,518)
Mean age (years)	61.1	62.3
Male (%)	79.4	80.2
Ischemic heart disease (%)	52	54
Months of heart failure (mean)	42.6	42.2
Months of heart failure (median)	22	20
Heart rate	81	81
Systolic blood pressure (mm Hg)	126	126
Diastolic blood pressure (mm Hg)	77	77
New York Heart Association class (%)		
II	48	49
III	48	47
IV	3	4
Atrial fibrillation or flutter (%)	20.5	19.2
Diabetes (%)	23.8	24.4

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CONTROVERSY: THE ISSUE OF DRUG DOSING

COMET engendered considerable discussion, particularly as to whether the doses of the two drugs were comparable. However, in clinical trials in heart failure, controversies over appropriate drug dosing are not new, particularly in the setting of polypharmacy.

Are higher doses better?

While some experts continue to push for maximal doses of neurohormonal antagonists, most clinicians are far less aggressive about increasing the dose, particularly when patients are feeling well. Furthermore, there are even concerns that overzealous antagonism of neurohormonal systems may lead to adverse outcomes.[18]

Twice-a-day dosing of metoprolol tartrate may not be enough

Therefore, any argument of an unfair comparison based on dosing differences assumes that higher doses equal lower mortality—an assumption that is yet to be proven. The answer may not be clear even in head-to-head dosing-ranging comparisons such as the Assessment of Treatment With Lisinopril and Survival (ATLAS) trial.[19]

The bottom line is that there is no agreement either on an optimal dose equivalent between different drugs, or on a strategy to titrate drugs to target doses other than those set by large mortality trials.

In COMET, the mean daily dose at entry into the maintenance phase in the carvedilol group was 41.8 mg/day, with 75% of patients taking the target dose. In contrast, the mean daily dose at entry into the maintenance phase in the metoprolol tartrate group was 85 mg/day, with 78% receiving the target dose. These figures were comparable to those reported recently in a large heart failure clinic,[20] and therefore are representative of contemporary clinical practice.

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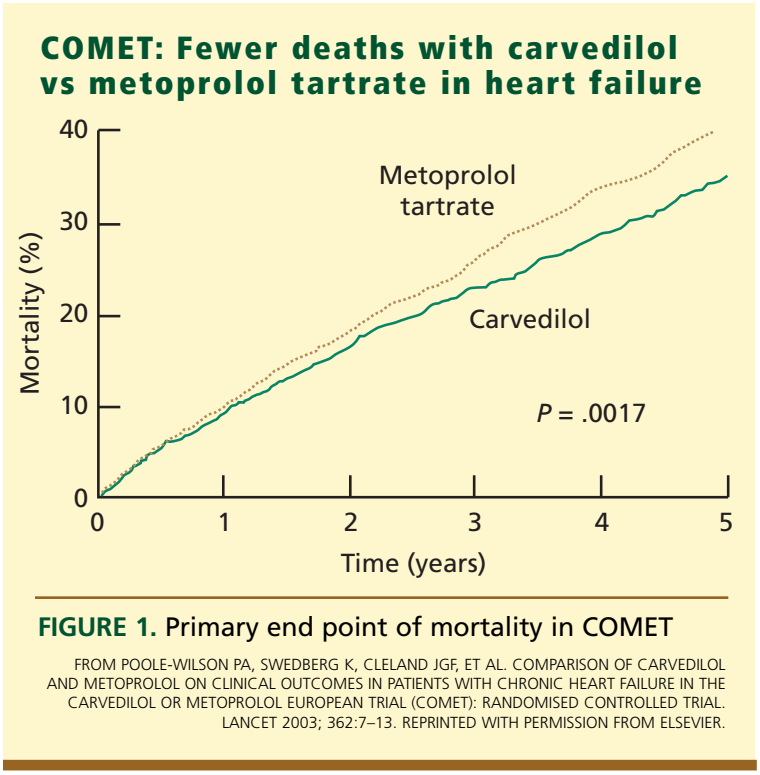

FIGURE 1. Primary end point of mortality in COMET

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Is selectivity important in beta-blockers? No one knows

Metoprolol tartrate is not the same as metoprolol succinate

The COMET trial used metoprolol tartrate, which is an immediate-release formulation, whereas the MERIT-HF trial used metoprolol succinate, which is an extended-release formulation. The difference may be important in treating patients with chronic heart failure.

The bioavailability of metoprolol tartrate tablets is 50%,[21] while that of metoprolol succinate is lower—it achieves blood levels of about 65% to 77% of those with metoprolol tartrate.[22,23] By extrapolating pharmacokinetic data, we calculate that the mean blood levels of active drug in COMET were slightly lower than those in MERIT-HF (42.5 mg/day of active drug absorbed in COMET vs 60 mg/day in MERIT-HF).

Furthermore, when given twice a day as in COMET, metoprolol tartrate may provide less consistent beta-1 blockade throughout the day, with peaks and troughs of blood levels. Indeed, resting heart rates recorded by Holter monitoring have been shown to be similar with metoprolol tartrate 50 mg three times daily vs metoprolol succinate 100 mg once daily, but lower mean 24-hour and exercise heart rates were obtained with metoprolol succinate 200 mg once daily.[24]

To date, all studies of carvedilol vs metoprolol have used metoprolol tartrate rather than metoprolol succinate, as used in the placebo-controlled MERIT-HF trial. The MERIT-HF investigators[25] have "cried foul," saying that the comparison between carvedilol and metoprolol tartrate in COMET was unfair, based on the doses used and the duration of antiadrenergic effects. They suggest that an appropriate comparison might be carvedilol 25 mg twice daily vs metoprolol tartrate 50 mg *four* times daily or metoprolol succinate 200 mg per day as used in MERIT-HF.

Metoprolol succinate may offer advantages over metoprolol tartrate,[26] being better tolerated and therefore easier to start at a higher dose, easier to up-titrate, and more convenient to take. It may even be as effective as carvedilol; when it was compared with placebo in the MERIT-HF trial, it reduced the mortality rate by 34%.[2]

Resting heart rate as a measure of beta-blockade

To determine if the beta-blockade was equivalent with carvedilol or metoprolol tartrate in terms of adrenergic blockade, the COMET investigators recorded the patients' resting heart rate throughout the study. At baseline, the mean heart rate was 81 beats per minute in both groups. After 4 months on treatment, it was lowered by 13.3 beats per minute in the carvedilol group compared with 11.7 in the metoprolol tartrate group ($P = .002$), but after 16 months it was the same in both groups, suggesting similar degrees of long-term adrenergic blockade.

Resting heart rate is less reliable than chronotropic response to exercise, however, suggesting that one cannot be absolutely sure if the degree of beta-blockade was comparable. Since the COMET patients did not undergo testing to determine their chronotropic response to exercise (nor do we perform this in clinical practice), equivalency between the two drugs will continue to be a point of contention. Nevertheless, previously published data comparing various beta-blockers would suggest that these two treatments were reasonably comparable with regard to dose.

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COMET's defenders further argue that metoprolol tartrate 50 mg twice a day reduces the heart rate to a similar degree when blood levels are at peak (–23 beats per minute) vs at trough (–20 beats per minute).[27] Some evidence also suggests that plasma levels achieved with metoprolol tartrate 50 mg twice daily produce nearly maximal beta-1 adrenergic blockade, and larger doses would not be expected to produce greater effects.[28] Of course, this discussion is valid only if the assumption that beta-blockers exert their benefits solely via their adrenergic blockade is true.

WHICH DRUG IS MORE COST-EFFECTIVE?

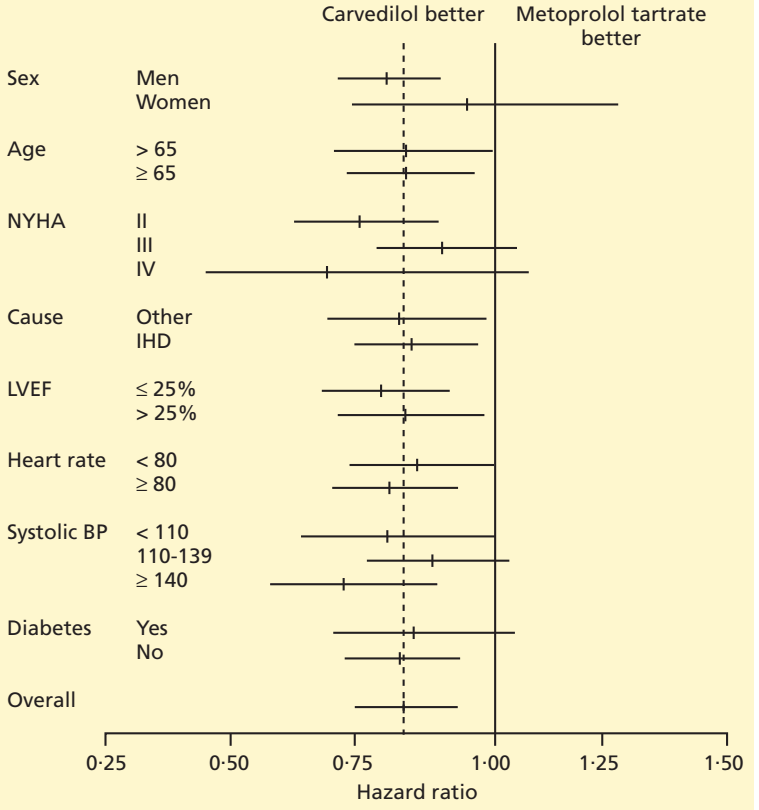
The COMET report did not address the issue of drug cost. A 1-month supply of carvedilol 25 mg twice daily costs almost $100 retail in the United States, compared with approximately $60 for metoprolol succinate 200 mg once daily and $18 for metoprolol tartrate 50 mg four times daily (the dosage suggested by the MERIT-HF investigators as equivalent to that of the target dose for metoprolol succinate,[25] but not approved by the US Food and Drug Administration).

Without any further cost-effectiveness analysis, physicians and patients will have to weigh the relative pros and cons of these agents with respect to cost, tolerability, convenience, and effectiveness. Despite concerns about cost, the relative reduction in mortality with carvedilol in COMET (17%) is impressive.

CLINICAL QUESTIONS AND MANAGEMENT

COMET, one of very few survival studies with a head-to-head comparison using an active control, provides valuable data along with a whole set of new mechanistic questions. It is an important study conducted by well-respected heart failure experts and reflects a real-life dilemma in choosing between different drugs of the same class. The sponsors took a chance by supporting this head-to-head comparison, and the investigators are to be congratulated for the rather lengthy but complete follow-up and prompt reporting.

COMET: Carvedilol beats metoprolol tartrate in all subgroups



NYHA = New York Heart Association class, LVEF = left ventricular ejection fraction, IHD = ischemic heart disease, BP = blood pressure

FIGURE 2. Mortality in subgroups

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Superiority of carvedilol

The COMET data indicate that carvedilol at a target dose of 50 mg/day is superior to metoprolol tartrate at a target dose of 100 mg/day in reducing all-cause mortality in patients with symptomatic chronic heart failure already on angiotensin-converting enzyme inhibitor therapy.

The annual mortality rate with carvedilol (8.3%) was similar to that in previous beta-blocker trials (7.2% with metoprolol succinate in MERIT-HF and 8.8% with bisoprolol in CIBIS-II).

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TABLE 3

Adverse events and withdrawals in the COMET trial

	CARVEDILOL (N = 1,511)	METOPROLOL (N = 1,518)
Patients with at least 1 adverse event	93.6%	95.8%
Patients with at least 1 cardiovascular adverse event	73.9%	75.8%
Patients with at least 1 serious adverse event	75%	77.4%
Patients with at least 1 cardiovascular serious adverse event	55.1%	57.4%
Patients withdrawn for any cause	762	827
Patients withdrawn excluding deaths	481	483
Bradycardia as an adverse event	9.5%	8.9%
Bradycardia as a serious adverse event	2.6%	2.6%
Hypotension as an adverse event	14.2%	10.5%
Hypotension as a serious adverse event	3.2%	1.9%

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What we don't know

Is metoprolol succinate better? On the basis of COMET and the placebo-controlled trials of carvedilol and metoprolol succinate, it would be compelling to consider metoprolol tartrate as a second-line agent for the treatment of chronic heart failure—a drug that remains in common use in clinical practice because of its low cost. However, as pointed out in an editorial accompanying the COMET report, the definitive head-to-head comparison of carvedilol and metoprolol succinate at doses proven to reduce mortality remains to be done.[29]

Patients doing well on metoprolol or bisoprolol probably need not switch to carvedilol

The debate over COMET also points out our lack of understanding of the pharmacokinetics, pharmacodynamics, and optimal dosing for different beta-blockers. Some critics may insist that the COMET results cannot imply differences in pharmacological properties between carvedilol and metoprolol.

Regardless of these criticisms, the results of the COMET trial highlight the notion that drugs in the same class cannot necessarily be judged as having the same beneficial effects. By the same token, the superiority of carvedilol over metoprolol tartrate cannot be simply extrapolated to imply advantages over metoprolol succinate, especially in the light of solid evidence of mortality and morbidity benefits from MERIT-HF.[2]

Why should carvedilol be better than metoprolol tartrate? Large trials such as COMET seldom provide mechanistic data. However, there is no question that the adrenergic blockade provided by carvedilol (alpha-1, beta-1, and beta-2) is more complete than that of metoprolol (selective beta-1) in any formulation. The results suggest, but do not prove, that more complete beta-blockade may be desirable in patients with chronic heart failure.

Implications for management

Given the overwhelming evidence of the benefit of either carvedilol, metoprolol succinate, or bisoprolol in patients with chronic heart failure, we should all strive to increase their use in appropriate doses until we have a better understanding of what optimal beta-adrenergic blocker therapy in chronic heart failure entails.

On balance, there may be an advantage to the more complete adrenergic blockade afforded by carvedilol. Some will continue to challenge the dosing differences and ignore the findings, while others may question the true cost-effectiveness. Nevertheless, some heart failure experts have already embraced these new data and will be giving more weight to considering carvedilol (at a target dose of 50 mg/day) instead of more selective beta-1 adrenergic agents in treating new patients. On the other hand, the use of metoprolol succinate at the target dose of 200 mg/day should

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still be justified based on the MERIT-HF data.[2]

Patients who are receiving beta-1-selective blockers (particularly metoprolol succinate or bisoprolol) and are clinically stable and doing well should probably not be switched to carvedilol, but one should ensure that they are receiving adequate doses.

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