CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-962/S-013

Medical Review(s)

dup
DF

JUN 22 2000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Memorandum

To: Dr. Robert Temple, Office Director, ODEI

From: Norman Stockbridge, Medical Officer, HFD-110

N. Stockbridge 6/22/00

Re: MERIT study.

Distribution: NDA 19-962
HFD-100/Temple
HFD-110/Lipicky
HFD-110/Project Manager
HFD-110/Duarte
HFD-710/Cui
HFD-110/Fredd
HFD-110/Stockbridge

Background

This memo is in response to your memo of 12 June 2000, regarding the metoprolol MERIT heart failure study. The first part of this memo addresses the deaths in the US that were, according to the end point committee, either non-cardiovascular or non-sudden and non-CHF. The second part of this memo addresses your questions about other potential US-vs.-non-US comparisons among studies of beta-blockers in heart failure. Final comments propose a framework for interpreting these results and making a regulatory decision.

Protocol

No constraints were placed upon the end point committee determinations about a specific cause of death. The committee also categorized deaths according to a system of 14 protocol-specified bins. These bins were grouped as cardiac, cardiovascular, or non-cardiovascular. The breakdown of events by bin, region, and treatment group is shown in Table 1.

Table 1. Deaths in MERIT, by category, region and treatment group[1].

		Non-US		US	
		Pcbo	Metop	Pcbo	Metop
Non-cardiovascular	Suicide	1	0	0	0
	Other injury or violence	0	1	0	0
	Cancer	6	6	2	2
	Other non-cardiovascular	4	3	1	5
	Total non-cardiovascular	11	10	3	7
Non-cardiac cardiovascular	Ischemic stroke	1	3	1	0
	Hemorrhagic stroke	0	1	0	1
	Unclassifiable stroke	0	4	0	1
	Aortic aneurysm	1	0	0	0
	Other non-cardiac cardiovascular	0	1	0	0
	Total non-cardiac cardiovascular	2	9	1	2
Cardiac	Heart failure	49	19	9	11
	Sudden death	97	51	35	28
	Acute myocardial infarction	6	5	1	2
	Other cardiac	3	0	0	1
	Total cardiac	155	75	45	42
Total cardiovascular		157	84	46	44
Total deaths		168	94	49	51

Non-cardiovascular deaths (US)

There were 7 non-cardiovascular deaths on metoprolol and 3 on placebo, in the US. These events are described below, based upon a review of the case report forms.

Subject E5050 (center 504, randomization 321) was a 75 year old American Indian male, NYHA III, with a 23-year history of ischemic heart disease, myocardial infarction 19 years prior to enrollment, angina, stroke, hypertension, diabetes mellitus, hyperuricemia, polyarthritis, atrial fibrillation, and hypothyroidism. He was on furosemide, losartan, digoxin, long-acting nitrates, allopurinol, levothyroxin, and potassium. His baseline EF was 0.36 and heart rate was 72. Progress through the study was as follows:

3/19/97: Randomized to metoprolol, starting dose 25 mg, HR 71.
4/2/97: Visit; dose increased to 50 mg; HR 58.
4/16/97: Visit; no changes; HR 60.
4/28/97: Visit; no changes; HR 66.
5/14/97: Visit; no changes; HR 64.
5/28/97: Visit; dose increased to 100 mg; HR 60.
8/27/97: Visit; no changes; HR 60.
11/25/97: Unscheduled event; dose decreased to 50 mg.
11/29/97: Unscheduled event; dose decreased to 25 mg.
12/10/97: Visit; worsening valvulopathy, valve surgery planned; HR 56.
1/8/98: Visit?; no vital signs recorded; dose increased to 50 mg.
2/12/98: Hospitalization for myocardial infarction; study drug discontinued for bifascicular block; underwent aortic and mitral valve replacement; discharged 2/22/98; on aspirin.
3/18/98: Visit; now NYHA II; HR 76 (remains off study drug).
7/8/98: Hospitalized for "emboli" or "GI bleed".
8/12/98: Death on same hospitalization (6 months after last dose of study

[1] *Analysis by Dr. Cui. One bin, pulmonary embolism, had no events.*

drug). End point committee ruled cause to be non-cardiovascular, attributable to hepatic and renal failure.

Subject E5065 (center 543, randomization 345) was a 63-year old obese Black female, NYHA II, with a 4-year history of idiopathic dilated cardiomyopathy, angina, hypertension, and insulin-dependent diabetes. She was on furosemide, benazepril, long-acting nitrates, and aspirin. Baseline EF was 0.38, HR 76. Progress through the study was as follows:

4/17/97 Randomized to metoprolol, starting dose 25 mg; HR 64.
5/1/97: Visit; dose increased to 50 mg; HR 68.
5/24/97: Visit; dose increased to 100 mg; HR 52.
5/29/97: Visit; dose increased to 200 mg; HR 58.
6/12/97 - 1/8/98: 4 visits; no events or changes reported; HR 54-60.
3/13/98: Hospitalized for large cell carcinoma metastatic to liver. Discharged to home hospice care on 3/26/98.
4/10/98: Death at home, one day after last dose of study drug.

Subject E6721 (center 599, randomization 389) was a 47-year old Caucasian male with less than a one-month history of idiopathic dilated cardiomyopathy. History positive only for peptic ulcer. He was taking furosemide, fosinopril, digoxin, and aspirin. Baseline EF was 0.28, HR 98. Progress through the study was as follows:

5/5/97: Randomized to metoprolol, starting dose 12.5 mg; HR 110.
5/16/97: Visit; improvement to NYHA II; dose increased to 25 mg; HR 76.
5/30/97: Visit; dose increased to 50 mg; HR 84.
6/16/97: Visit; dose decreased to 25 mg; HR 80.
7/10?/97: Visit; dose increased to 50 mg; HR 80.
7/14/97: Visit; dose increased to 100 mg; HR 64.
7/28/97: Visit; dose increased to 200 mg; HR 70.
10/27/97: Visit; no changes; HR 66.
1/26/98: Visit; no changes; HR 78.
4/27/98: Visit; NYHA III; dose decreased to 100 mg; HR 64.
6/1/98: Visit; no changes; HR 80.
6/18/98: Visit; serious adverse event (not described); study drug discontinued; subject not hospitalized.
6/20/98: Death in ER from GI bleed.

Subject E5265 (center 536, randomization 709) was a 74-year old Black male with less than a one-year history of NYHA IV heart failure attributed to ischemic heart disease. History of MI 15 years previously, angina, hypertension, diabetes mellitus, prostate cancer, arthritis, gout, atrial fibrillation. Treated with furosemide, quinapril, digitalis, long-acting nitrates, anticoagulant, clonidine, and colchicine. Baseline EF 0.33, HR 74. Progress through the study was as follows:

6/16/97: Randomized to metoprolol; starting dose 12.5 mg; HR 70.
7/3/97: Visit; dose increased to 25 mg; HR 73.
7/17/97: Visit; NYHA III; dose increased to 50 mg; HR 72.
7/30/97: Visit; NYHA IV; HR 92.
8/5/97: Hospitalized for cellulitis of knee.
8/20/97: Hospitalized for laparoscopic cholecystectomy. Post-op cardiac arrest led to comatose state with do-not-resuscitate order.
11/25/97: Death from anoxic encephalopathy.

Subject E6700 (center 579, randomization 363) was a 69-year old Caucasian female with a 4-year history of NYHA III heart failure attributed to ischemic heart disease. History included angina, intermittent claudication, rheumatic fever, and atrial fibrillation. Treated with furosemide, enalapril, digitalis, anticoagulant, and potassium. Baseline EF was 0.25, HR 84. Progress through the study was as follows:

6/17/97: Randomized to metoprolol; started at 12.5 mg; HR 80.

7/3/97: Visit; dose increased to 25 mg; HR 80.
7/22/97: Visit; dose increased to 50 mg; HR 80.
8/4/97: Visit; dose increased to 100 mg; HR 80.
8/20/97: Visit; dose increased to 200 mg; HR 80[2].
9/17/97: Visit; no changes; HR 60.
12/15/97: Visit; no changes; HR 64.
2/19/98: Treatment discontinued when subject moved out-of-area.
5/8/98: Death in nursing home, metastatic renal cell carcinoma.

Subject E6795 (center 608, randomization 509) was a 65-year old Caucasian male, with less than 6-month history of NYHA II ischemic heart failure. Other history includes MI 6 years previous, angina, intermittent claudication, hypertension, CABG, diabetes mellitus, hyperlipidemia, and peptic ulcer disease. Treated with furosemide, lisinopril, aspirin, simvastatin, pentoxifylline, potassium, and nortryptyline. Baseline EF 0.38, HR 80. Progress through the study was as follows:

6/19/97: Randomized to placebo; started on (25) mg; HR 100.
7/1/97: Visit; dose increased to (50) mg; HR 92.
7/16/97: Visit; dose increased to (100) mg; HR 100.
7/28/97: Visit; dose increased to (200) mg; HR 94.
8/11/97: Visit; no changes; HR 96.
8/25/97: Visit; no changes; HR 84.
11/13/97: Visit; no changes; HR 74.
2/11/98: Visit; now NYHA IV; HR 72.
3/8/98: Hospitalized for heart failure and pleural effusion, apparently lung tumor.
6/1/98: Death, attributed to cancer.

Subject E5034 (center 583, randomization 554) was a 77-year old, obese Caucasian male with a 4-year history of ischemic heart failure NYHA II. Other history includes angina, hypertension, CABG, thrombocytopenia, degenerative joint disease, inguinal hernia, hypercholesterolemia, aortic valvular stenosis, and ventricular arrhythmia. Treated with spironolactone, benazepril, aspirin, and simvastatin. Baseline EF was 0.35, HR 70. Progress through the study was as follow:

7/3/97: Randomized to placebo; started at (25) mg; HR 82.
7/15/97: Visit; dose increased to 50 (mg); HR 74.
7/29/97: Visit; dose increased to (100) mg; HR 70.
8/12/97: Visit; dose increased to (200) mg; HR 70.
8/28/97: Visit; no changes; HR 76.
9/22/97: Visit; no changes; HR 76.
11/26/97: Hospitalized for lung cancer, manifest by multiple bone metastases.
12/16/97: Death at home, attributed to cancer.

Subject E7056 (center 633, randomization 909) was a 72-year old Caucasian male with NYHA III ischemic heart failure, and history of valvulopathy, angina, CABG, abdominal aortic aneurysm repair, recurrent bacteremia from aneurysm surgery, esophageal reflux, and renal insufficiency. Treated with torsemide, quinapril, long-acting nitrates, alprazolam, and clarithromycin. Baseline EF was 0.14, HR 98. He was hospitalized twice during placebo run-in for septicemia. Subsequent progress through the study was as follows:

9/24/97: Randomization to metoprolol; started on 12.5 mg; HR 86.
10/8/97: Visit; dose increased to 25 mg; HR 80.
10/16/97: Visit; dose decreased to 12.5 mg; HR 72.
10/30/97: Visit; no changes; HR 70.

---

[2] *Five consecutive measurements of 80 bpm seem implausible.*

11/10/97: Visit; dose increased to 25 mg; HR 72.
11/24/97: Visit; dose increased to 50 mg; HR 76.
12/9/97: Visit; NYHA II; dose increased to 100 mg; HR 80.
12/23/97: Visit; no changes; HR 76.
2/17/98: no changes; HR 60.
2/23/98: ER visit for bacteremia.
3/14/98: Hospitalized for MI.
3/31/98: Visit; NYHA III; HR 82.
4/2/98: Hospitalized briefly for spinal stenosis.
4/5/98: Hospitalized for shortness of breath.
4/12/98: Hospitalized for heart failure, renal failure.
4/14/98: Subject discharged to hospice care; study drug discontinued.
5/12/98: Hospitalized for renal failure.
5/17/98: Death attributed to renal failure.

Subject E7191 (center 564, randomization 3843) was a 72-year old Caucasian female with a 2-year history of NYHA II heart failure attributed to idiopathic dilated cardiomyopathy. Other history includes bronchitis, TIA, and hypothyroidism. Treated with ramipril, digoxin, levothyroxin, HRT, and nabumetone. Baseline EF was 0.23, HR 88. Progress through the study was as follows:

10/29/97: Randomized to placebo; started at (25) mg; HR 88.
11/13/97: Visit; dose increased to (50) mg; HR 90.
11/26/97: Visit; dose increased to (100) mg; HR 88.
12/10/97: Visit; dose decreased to (50) mg; HR 76.
12/29/97: Visit; now NYHA III; dose decreased to (25) mg; HR 100.
1/7/98: Visit; now NYHA II; dose increased to (50) mg; HR 92.
3/2/98 - 3/5/98: Hospitalized for CHF.
4/10/98: Visit; now NYHA III; study drug discontinued; HR 92.
5/1/98: Visit; no changes; HR 88.
5/9/98 - 5/19/98: Hospitalized for CHF.
5/27/98: Death attributed to urosepsis, end-stage heart failure.

Subject E5242 (center 524, randomization 644) was a 59-year old Caucasian male with a 4-year history of NYHA II ischemic heart failure. Other history includes MI 22 years previously, and diabetes mellitus. Treated with furosemide, captopril, digoxin, ISDN, simvastatin, and potassium. Baseline EF was 0.17, HR 72. Progress through the study was as follows:

12/18/97: Randomized to metoprolol 25 mg; HR 78.
12/30/97: Visit; dose increased to 50; HR 68.
1/13/98: Visit; dose increased to 100; HR 66.
1/27/98: Visit; dose increased to 150 mg; HR 58.
2/12/98: Visit; dose increased to 200 mg; HR 58.
2/27/98: Visit; now NYHA III; HR 48.
3/19/98: Visit; dose decreased to 100 mg; HR 48.
3/31/98: Visit; dose decreased to 50 mg; HR 40.
6/18/98: Visit; atrial fibrillation; HR 60.
8/16/98: ER visit; shortness of breath. Hospitalized with pneumonia (Legionnaires' disease).
8/23/98: Death, attributed to pneumonia.

Selected cardiovascular deaths (US)

There were 5 non-sudden, non-CHF cardiovascular deaths on metoprolol and 2 on placebo, in the US. These events are described below, based upon a review of the case report forms.

Subject E5213 (center 536, randomization 707) was a 54-year old Black male with NYHA III heart failure attributed to a 7-year history of ischemic heart disease. Other

history includes MI, angina, hypertension, diabetes, and PTCA. Treated with furosemide, quinapril, digoxin, long-acting nitrates, and anticoagulants. Baseline EF was 0.25, HR 84. Progress through the study was as follows:

6/6/97: Randomized to placebo; started at (12.5) mg; HR 104.
6/19/97: Visit; no changes; HR 104.
7/3/97: Visit; dose increased to (25) mg; HR 78.
7/17/97: Visit; dose increased to (50) mg; HR 88.
8/1/97: Visit; dose increased to (100) mg; HR 100.
8/4/97: Hospitalized for peri-rectal abscess.
8/15/97: Hospitalized for peri-rectal abscess.
8/29/97: Visit; dose increased to (200) mg; HR 84.
11/21/97: Visit; no changes; HR 96.
1/15/98: Hospitalized for ethanol intoxication and motor vehicle accident.
2/25/98: Visit; no changes; HR 100.
5/15/98: ER visit for atypical chest pain.
5/22/98: Visit; no changes; HR 76.
9/9/98: Visit; no changes; HR 88.
10/26/98: Hospitalized for seizures.
10/30/98: Death attributed to ischemic stroke.

Subject E7096 (center 626, randomization 933) was a 70-year old Caucasian male, with NYHA III heart failure attributed to 2-year history of ischemic heart disease. Other history includes MI 2 years previously, angina, intermittent claudication, hypertension, insulin-dependent diabetes, CABG, bronchitis, osteoarthritis, and nephrolithiasis. Treated with furosemide, losartan, digoxin, nifedipine (replaced with amlodipine), long- and short-acting nitrates, aspirin, and potassium. Baseline EF was 0.22, HR 84. Progress through the study was as follows:

9/9/97: Randomized to placebo; starting dose (12.5) mg; HR 88.
9/23/97: Visit; dose increased to (25) mg; HR 84.
10/8/97: Visit; dose increased to (50) mg; HR 84.
10/21/97: Visit; dose increased to (100) mg; HR 88.
10/24-25/97: Hospitalized for chest pain and heart failure.
11/4/97: Visit; no changes; HR 88.
12/4/97: Visit; no changes; HR 100.
1/2-6/98: Hospitalized for pneumonia; dose decreased to (25)?
1/23/98: Visit; dose increased to (50) mg; HR 100.
2/10/98: Visit; dose increased to (100) mg; HR 92.
3/10/98: Visit; no changes; HR 96.
6/16/98: Visit; no changes; HR 92.
7/12/98: Hospitalized for gangrenous foot.
8/9/98: Hospitalized for chest pain.
8/10/98: Death, A-V dissociation, asystole, ventricular fibrillation.

Subject E6687 (center 544, randomization 331) was a 75-year old Black male with NYHA II heart failure attributed to a 2-year history of ischemic heart disease. Other history includes MI 2 years previously, hypertension, diabetes, CABG, peripheral vascular disease, anemia, diabetic retinopathy, and paroxysmal atrial fibrillation. Treated with furosemide, digoxin, quinidine, hydralazine, long-acting nitrates, anticoagulant, and potassium. Baseline EF was 0.33, HR 72. Progress through the study was as follows:

5/12/97: Randomized to metoprolol; starting dose 12.5 mg; HR 80.
5/13/98: Hospitalized with near-syncopal episode, diagnosed as cerebral hemorrhage; died the same day.

Subject E6948 (center 559, randomization 714) was a 76-year old Caucasian female with NYHA II heart failure, attributed to a 2-year history of hypertensive

cardiomyopathy. Other history included intermittent claudication. Treated with furosemide, lisinopril, amlodipine, aspirin, short-acting nitrates, and simvastatin. Baseline EF was 0.20, HR 89. Progress through the study was as follows:

6/18/97: Randomized to metoprolol; starting dose 25 mg; HR 68.
7/3/97: Visit; no changes; HR 55.
7/21/97: Visit; dose increased to 50 mg; HR 66.
8/12/97: Visit; dose increased to 100 mg; HR 56.
9/2/97: Visit; dose increased to 200 mg; HR 60.
9/15/97: Visit; no changes; HR 55.
12/3/97: Visit; no changes; HR 60.
12/28/97: Hospitalized for myocardial infarction; died the following day.

Subject E5146 (center 567, randomization 488) was a massively obese Black male with NYHA II heart failure attributed to an 8-year history of ischemic heart disease. History included MI and PTCA. Treated with furosemide, spironolactone, indoline, digoxin, hydralazine, aspirin, short-acting nitrates, potassium. Baseline EF was 0.22. Progress through the study was as follows:

7/15/97: Randomized to metoprolol; started on 25 mg.
7/26/97: CVA attributed to emboli from chronic atrial fibrillation (although AF is not noted in medical history). Subject died from aspiration pneumonia on 8/9/97.

Subject E6708 (center 618, randomization 4085) was a 72-year old Caucasian male with NYHA II heart failure attributed to a 5-year history of ischemic heart disease. Other history included hypertension, MI, stroke, intermittent claudication, peripheral vascular disease, hyperlipidemia, and hiatal hernia. Treated with furosemide, enalapril, digoxin, amlodipine, short- and long-acting nitrates, and alprazolam. Baseline EF was 0.18, HR 68. Progress through the study was as follows:

10/11/97: Randomized to metoprolol; started on 12.5 mg; HR 60.
10/29/97: Study drug discontinued for hypotension and bradycardia.
11/27/97: Hospitalized for aorto-femoral bypass.
11/30/97: Death from myocardial infarction.

Subject E7120 (center 572, randomization 962) was a 60-year old Caucasian male with NYHA II heart failure from a <1-year history of idiopathic dilated cardiomyopathy. History included COPD, hiatal hernia, renal stone, pneumonia, and prostatitis. Treated with ramipril, digoxin, aspirin, and omeprazole. Baseline EF was 0.28, HR 77. Progress through the study was as follows:

11/7/97: Randomized to metoprolol; started on 25 mg; HR 73.
11/20/97: Visit; dose increased to 50 mg; HR 74.
12/2/97: Visit; dose increased to 100 mg; HR 66.
12/17/97: Visit; dose decreased to 75 mg; HR 67. Later that evening, subject hospitalized after having cardiac arrest at home. Diagnosed with anterior wall MI. Immediate sequela was anoxic encephalopathy, from which he died 12/24/97.

Other development programs

Your memo mentions several major studies of beta-blockers in heart failure. Recent reviews[3] of such studies were consulted to look for other multinational trials with a US component.

MDC was a comparison of metoprolol and placebo in 383 subjects with idiopathic dilated cardiomyopathy, NYHA II or III. It was conducted in Europe and North America[4],

---

[3] *Bristow MR. 2000. Beta-adrenergic receptor blockade in chronic heart failure.* Circulation *101:55-569 and Teerlink JR & Massie BM. 1999. Beta-adrenergic blocker mortality trials in congestive heart failure.* Am J Cardiol *84:94R-102R.*

but the distribution of subjects is not known. There was a statistically non-significant trend in reducing the number of deaths or cardiac transplants.

The carvedilol heart failure development program consisted of 5 multi-center studies of reasonable size. Four of these, including study 240, which was pivotal for defining the ultimate indication, were conducted at US centers only. The other multi-center study, 223, was conducted in Australia and New Zealand. Thus, there is no carvedilol trial with both US and non-US centers. Given differences in the subject selection criteria among these studies, a US-vs.-non-US cross-study comparison does not seem interpretable.

Bisoprolol was the subject of two published multi-center studies, CIBIS (I) and CIBIS II. Both studies were conducted in Europe only. CIBIS II was stopped early with a highly statistically significant reduction in its primary end point of total mortality among 2647 subjects with NYHA III or IV heart failure.

Bucindolol was the subject of a multi-center study (BEST) in 2708 NYHA III and IV subjects. Its results are known only through unpublished material in the IND. This study was conducted solely in the US, and the study demonstrated a statistically non-significant trend in reducing its primary end point of total mortality.

Comments

Per your request, brief descriptions of the non-cardiovascular, non-heart failure, and non-sudden deaths are presented. Note that exclusion of committee-categorized non-cardiovascular events changes the picture very little, from a two-subject excess in the metoprolol group to a two-subject excess on placebo.

These cases illustrate the subjectivity of such categorizations. Ignoring the social/legal convention of defining alive/dead by heartbeat, many of the deaths described above as non-cardiovascular are related to underlying cardiovascular disease.

Deaths from hepatic failure, renal failure, anoxic encephalopathy, and multiple organ failure all are likely the end stage of cardiac failure; they are not independent processes.

Even when the immediate cause of death is an independent process, the death may not be independent of cardiovascular status. For example, a death from pneumonia is rendered more likely by cardiovascular disease, because of the culture medium of pulmonary edema, interference with normal defense mechanisms, opportunities to encounter antibiotic-resistant organisms through frequent hospitalizations, and the general lack of reserve that would make a given burden more lethal.

Some of these concerns apply as well to deaths from a uniformly-fatal but not causally-related cancer, because cardiovascular state may influence how long one survives with the additional insult.

There appears to be no disagreement that the MERIT supplement should result in a new indication for metoprolol. The controversy centers around whether the new indication should encompass mortality distinct from the combination of mortality plus hospitalization.

The mortality effect was at least much smaller in the US than in Europe, but the numbers suggest it may be absent or even adverse. Was this a statistical anomaly or is such a difference a plausibly reproducible result? To answer this question there are purely statistical considerations, considerations related to the nature of the disease process and its management, and considerations pertaining to the experience with other beta-blockers in heart failure.

---

[4] Fourteen centers in US, 8 in Austria, 4 in Sweden, 2 in Germany and Netherlands, 1 in Canada and Italy.

For granting an indication, we expect the equivalent of least two studies with $p<0.05$, but generally the supporting data from other studies and secondary end points increases our confidence in the reproducibility of an indication beyond this level. Dr. Peto (letter included in fax to Agency of 6 June 2000) treats the interpretation of regional heterogeneity from this perspective.

The position of the reviewers is not that this subgroup finding establishes the truth, nor even that the precise p-value is characterizable or important. This is what Dr. Fenichel means when he shows a difficult-to-ignore funnel plot and says Dr. Cui's assigned p-value seems about right. They, and I, are thinking about this finding the way we think about safety findings, or like a discordant model-related secondary end point; i.e., it raises reasonable doubt.

So, no analysis proves the expected mortality reduction in the US is less than that in Europe, but the burden of proof is not on the Agency to show this. It is on the sponsor to show that the overall effects apply to the US. The statistical analyses appropriate to the Agency's regulatory mission suggests that the overall effect size does not apply to the US.

Is it silly to suppose US-vs.-non-US effects are reproducible? The nature of the heart failure disease process, its treatment in the US and elsewhere, and characteristics of the clinical trial impact our interpretation of this result.

Drs. Cui and Fenichel noted a quantitative difference in the effect size for mortality in the US compared with other countries. They explored possible biological bases for the observed differences, but failed to find a compelling correlate. The failure to identify factors related to region that might underlie this difference weakens the case that this phenomenon is apt to be reproducible, in much the same way that failure to find supporting secondary end points undermines, to some extent, one's confidence in a primary end point. Models carry considerable weight, but how much weight is appropriate borders on being a theological issue. On the other hand, heart failure management is much an art; witness, for example, highly statistically significant improvements in NYHA class in single-center carvedilol studies and generally no effect in the multi-center studies. So, even in the absence of biases caused by the incomplete blinding of a beta-blocker trial, it is plausible that there are important regional variations in monitoring and treatment which affect the magnitude (or possibly the sign) of benefit of an additional therapy.

Indeed, there is the additional problem of biases in supporting care made possible by imperfect blinding. This problem was discussed at length in the carvedilol reviews, and in the primary reviews of MERIT. The general ease with which the treatment groups can be distinguished can be appreciated in the small sample of clinical courses you asked to see.

Thus, on its face, it is not silly to suppose that the observed US-vs.-non-US differences are reproducible. Is there precedent among the other development programs for beta-blockers in heart failure?

The best data would come from a study like MERIT, with stratification within US and non-US centers. Unfortunately, there is no comparable US-vs.-non-US experience within a study among development programs for other beta-blockers for heart failure. However, the comparison between CIBIS II (bisoprolol) and BEST (bucindolol) is pretty interesting. These were similar studies of similar size. The results were highly positive in CIBIS II and non-significant in BEST, a difference one might describe in terms of effect size. The difference may be attributable to receptor selectivity, but how is one to exclude the possibility that the difference is related to where the studies were performed?

Metoprolol should be approved for the indication not tainted by the US-vs.-non-US heterogeneity. Were that not a primary end point, such a move would be as supportable as it was for SOLVD-Prevention. It is easier to support this action, since mortality plus hospitalization was a primary end point.

The clinical trials section should contain a description of the mortality results overall and of the discrepant US findings. Advertising of the mortality data should contain fair balance by showing the US results as well.

Where regulatory decisions are made in the absence of data in the US population, in children, in the elderly, in Blacks, or in other subgroups comprising a reasonable fraction of the US population or the population at risk from some disease, the label should accurately describe the state of our agnosticism. The decision to be explicit in our agnosticism ought not depend upon a model. When data obviate complete subgroup agnosticism, those results deserve attention, too. As circumstances dictate, this might be through a requirement to replicate a finding or, as in this case, to describe it in the label.

APPEARS THIS WAY
ON ORIGINAL

Z McDonald
FEB 9 2000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA Number: 19-962/S-013

Name of Drug: Metoprolol Succinate

Test Product and Dosage: Metoprolol CR/XL 12.5-200 mg

Sponsor: Astra-Zeneca

Type of Submission: Supplemental New Drug Application

Drug Category: Beta Blocker

Proposed Indication: Chronic Congestive Heart Failure

Date of Submission: September 10, 1999

Date Review Completed: December 22, 1999-Revised February 9, 2000

Reviewer: Cristobal G. Duarte, MD

1.0. Background.

Metoprolol controlled release/extended release Tablets (CR/XL), marketed as Toprol^{R} (metoprolol succinate), has been approved for once-a-day treatment for hypertension and angina pectoris in the US. In addition, metoprolol CR/XL has been approved in other countries for the following indications: hypertension, angina pectoris, post-myocardial infarction, cardiac arrhythmias, functional heart disorders, migraine and hyperthyroidism.

Lately there has been increasing awareness of the beneficial effects that can be obtained by adding adrenergic blocking agents in the treatment of congestive heart failure. The rationale is to limit the deleterious effect of increased sympathetic nervous activity and other $beta_1$ mediated disturbances that are associated with this condition. Numerous experimental and clinical studies have shown beneficial effects with beta-blockade in heart failure. Meta-analysis of these studies suggests that beta-blockers reduce all cause mortality in patients with congestive heart failure. However, until recently, there was a need for a single controlled study to confirm this hypothesis. The Merit Trial (SH-MET-0024), the pivotal study of this submission, was planned to fulfill this need. In addition, protocols S-996 and SH-AHS-001 (RESOLVD) were carried to provide additional support for efficacy, tolerability and safety. Protocol SH-MET-0022 deals with pharmacokinetics and pharmacodynamics.

This submission consists of 101 hard copy archival volumes and 4 electronic discs 3 of which contain the patients' report forms and the fourth the statistical report.

2.0. Study SH-MET-0024 (Volumes 10 through 35 0f 101). In the review of this protocol, not only the material submitted by the sponsor was considered, but also results contained in a publication by the investigators (1), and in the process of being published (2) and editorial and other comments (3-9).

2.1. Title of Study: "Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. Merit HF. A Double-Blind, Placebo Controlled Survival Study with Metoprolol CR/XL in Patients with Decreased Ejection Fraction and Symptoms of Heart Failure".

2.2. Principal Investigators and Sites of Investigation

Dr. C Berthe
Clinique des Bruyeres
Chenee, Belgium

Dr. J-M Boutefeu
Hopital Princess
Paola,Aye,Belgium

Dr. G. Boxho
CHR La Tourelle
Verviers, Belgium

Dr. P. Decroly
Clinique Louis Caty
Baudour, Belgium

Dr. J.P. Derbaudrenghien
Clinique Dr. Leon Neuens
Chatelet, Belgium

Dr. D. El Allaf
Centre Hospitaliere Hutois
Huy, Belgium

Dr. J. Pirlet
Centre Hospitalier du
Grand Hornu
Bossu, Belgium

Dr. P. Henry
Clinique Ste-Elizabeth
Namur, Belgium

Prof. G. Heyndrickx
O.L.V. Ziekenhuis
Aalst, Belgium

Dr. L. Missault
A.Z. Saint-Jan OCMW
Brugge, Belgium

Dr. M. Nannan
Clinique N.D. de la Misericorde
Libramont, Belgium

Dr. P. Timmermans
Centre Hospitalier Reine Fabiola
Sambreville, Belgium

Dr. J-L. Vachiery
Hopital Universitaire Erasme
Bruxelles, Belgium

Prof. W. Van Mieghem
ZOL Andre Dumont
Genk, Belgium

Prof J.L. Vandenbosche
Hopital Universitaire St. Pierre
Bruxelles, Belgium

Dr. J. Vitovec
Hospital St. Ann
Brno, Czech Republic

Dr. J. Toman
Faculty Hospital
Brno, Czech Republic

Dr. P. Svitil
Hospital St. Ann
Jihlava, Czech Republic

Prof. J. Rybka
ILF Batova nemocnice
Zlin, Czech Republic

Dr. K. Dvorak
Municipal Hospital
Ostrava 1, Czech Republic

Dr. A. Kana
Interna Klinika FN Ostrava Poruba
Ostrava-Poruba, Czech Republic

Dr. P. Petr
1st Dept Medicine Pharmacotherapy
Budejovice, Czech Republic

Dr. J. Smid
Military Hospital
Pzlen, Czech Republic

Dr. J. Hradec
Charles University
Praha, Czech Republic

Dr. M. Herold
Charles University
Praha, Czech Republic

Prof. J. Aldershvile
Righospitalet
Kobenhavn, Denmark

Dr. H. Nielsen
Sundby Hospital
Kobenhavn S, Denmark

Dr. P. Hildebrandt
Fredriksberg Hospital
Fredriksberg, Denmark

Dr. K. Skagen
Herlev Amtssygehus
Denmark

Dr. O. Amtorp
Gentofte Amtssygehus
Hellerup, Denmark

Dr. A. Johannessen
Kalundborg Sugehus
Kalundborg, Denmark

P. Eliasen
Stagelse Centralsygehus
Slagelse, Denmark

Dr. F. Pedersen
Hillerod Sygehus
Hillerod, Denmark

Dr. P. Kaiser-Nielson
Horsholm Sygejus
Horsholm, Denmark

Dr. P.E. Nielsen
Frederikssund Sygehus
Glostrup, Denmark

Dr. J.R. Nielsen
GlostrupAmtssygehus
Glostrup, Denmark

Dr. E. Agner
Helsingor Sygehus
Helsingor, Denmark

Dr. C-O Gotzche
Viborg Sygehus
Viborg, Denmark

Dr. K. Egstrup
M. Sygehus Fyn
Svendborg, Denmark

Dr. M. Halinen
Kuopio University
Hospital
Kuopio, Finland

Dr. T. Honkanen
Paijat-Hame Central Hospital
Lahti, Finland

Dr. H. Jaaskelainen
Mikkeli Central Hospital
Mikkeli, Finland

Dr. H. Koskivirta
Satakunta Central Hospital
Pori, Finland

Dr. J. Rinne
Lansi-Uusimaa District Hospital
Tammisaari, Finland

Dr. E. Hussi
Heinola City Hospital
Heinola, Finland

Dr. J. Juvonen
Kainuu Central
Hospital
Kajaani, Finland

Dr. T. Salonen
Lohja District Hospital
Lohja, Finland

Prof. R. Dietz
Univ. Klinikum Charite
Franz-Volhard
Berlin, Germany

Dr. H. Voller
Klinikum am See-Reha-
Zentrum fur Herz und
Kresilauf
Rudersdorf, Germany

Dr. H. Dingerkus
Geneinschaftspraxis
Berlin, germany

Prof. M. Sigmund
Medizinische Klinik 1
Wiesbaden, Germany

Dr. Wunderlich
Gemeinschaftpraxis
Berlin, Germany

Dr. B. Eichsler
Havel, Germany

Dr. K. Schmaizl
Ruppiner Klinikum
Neuroppin, Germany

Dr. T. Pomykaf
Stadt. Klinikum Braunschweig
Braunschweig, Germany

Prof H. Uwe Janka
Zentral-Krakenhaus Bremen
Bremen, Germany

Dr. H. Bethge
Stadisches Krankenhaus Verden
Verden, Germany

Prof. J. Schrader
St. Josefs-Hospital
Cloppenberg, Germany

Dr. K-H Depping
Kreiskrankenhaus
Hameln
Hameln, Germany

Prof. K-L. Neuhaus
Stadisches Klinik Kassel
Kassel, Germany

Dr. R. Obst
Burgfeld-Krakenhaus Kardiologie
Kasel, Germany

Dr. K-H Konz
Krakenhaus Maria
Hilf
Monchengladbach
Germany

Dr. K. Melchior
Geneinschaftspraxis
Ruhr, Germany

Prof. H. Simon
Krakenhaus Duren
Duren, Germany

Dr. L. Drude
Marburg, Germany

Dr. P. Wirtz
Kreiskrankenhaus
Mechernich
Mechernig, Germany

Prof. Bundschu
Caritas-Krankenhaus
Bad Mergebtheim, Germany

Dr. Darius
Johannes Gutenberg-
Universistat
Mainz, Germany

Dr. Christ, Prof. Daniel
Herz-Kreislauf Zentrum Dresden
Dresden, Germany

Prof. Nast
Ketteler Krankenhaus
Offenbach am Main,
Germany

Dr. Fach
Bethanien –Krakenhaus
Frankfurt, Germany

Prof. Delius
Stadt. Krakenhaus
Bogenhausen
Munchen, Germany

Dr. Gross
Kardiologische Praxis
Munchen, Germany

Dr. Beythien
St. Sixtus Hospital
Haltern, Germany

Dr. Maier
Puttlingen, Germany

Dr. Hepp
Vinzenzkrankenhaus
Hannover, Germany

Prof. Roskamm
Herz-Zentrum Bad Krozingen
Krozingen, Germany

Dr. Berwing
Klinikum hoyerswerda
Hoyerswerda, Germany

Dr. Kuhlkamp
Eberhard-Karls-Universitat
Tubingen, Germany

Dr. Krosse
Dresden, Germany

Prof Maurer
Bayreuth, Germany

Dr. Hambrecht
Leipsig, Germany

Dr. Duck
Erfurt, Germany

Dr. Forster
Berlin, Germany

Prof von Olshausen
Hamburg, Germany

Prof. Schwimmbeck
Berlin, Germany

Prof. Strasser
Heidelberg, Germany

Prof. Laderitz
Bonn, Germany

Dr. Heinemann
Halle, Germany

Dr. Odemar
Dernburg, Germany

Dr. Thilo
Burgwedel, Germany

Dr. Bischoff
Waldbrof, Germany

Dr. Lobe
Leipsig, Germany

Dr. Hahn
Eisenach, Germany

Dr. Schroeder
Hamburg, Germany

Dr. Lewek Halle, Germany	Prof. Vohringer Berlin, Germany	Prof. Andresen Berlin, Germany	Dr. C. Istvan Moricz, Hungary
Dr. Hetey Szechenyi, Hungary	Prof. A. Janosi Diosarok, Hungary	Dr. A. Katona Semmelweis, Hungary	Dr. M. Lengyel Haller, Hungary
Dr. A. Nyaradi Tallian Gy, Hungary	Dr. B. Oze Torteli, Hungary	Dr. A. Rednik Korhaz, Hungary	Dr. K. Sandori Varisi, Hungary
Dr.P. Szabo Sergelyesi, Hungary	Prof. J. Tarjan Markusovsky, Hungary	Prof. J. Tenczer Telenyi, Hungary	Dr. S. Tinar Nyfri, Hungary
Dr. P. Valyi Soproni, Hungary	Dr. G. Veress Gyvogy, Hungary	Dr. J. Zamolyi Maglodi, Hungary	Dr. G. porgeirsson Reykjavic, Iceland
Dr. G. Porgeirsson Reykjavik, Iceland	Dr. G. Porgeirsson Reykjavik, Iceland	Dr. PJL Bernink Netherlands	Dr. AC Bredero Netherlands
Dr. RW Breedveld Netherlands	Dr. JJJ Bux Netherlands	Dr. PAR Milliano Netherlands	Dr. FR den Hartog Netherlands
Dr. PHJM Netherlands	Dr. BJB Hamer Netherlands	Dr. NJ Holwerda Netherlands	Dr. JCA Hoornje Netherlands
Dr. JA Kragten Netherlands	Dr. AH Lien Ntherlands	Dr. RJT Taverne Netherlands	Dr. AR Misier Ntherlands	Dr. JH Cornel Netherlands
Dr. P. Sijbring Ntherlands	Dr. J Hoogsteen Netherlands	Dr. LHJ Kempen Netherlands	Dr. R. van Stralen Netherlands
Dr. DJ van Veldhuisen Netherlands	Dr AR Willems Netherlands	Dr. AJAM Withagen Netherlands	Dr. HR Michels Netherlands
Dr. PNWM Breuls Netherlands	Dr. A. Schelling Netherlands	Dr. GCM Linssen Netherlands	Dr. Chr Verter Netherlands
Dr. JCL Wesdorp Netherlands	Dr. PAG Zwart Netherlands	Dr. K Waage Norway	Dr. HA Tjonndal Norway
Dr. O Vikesdal Norway	Dr. T Johansen Norway	Dr. C Sjodin Norway	Dr. L Gullestad Norway	Dr. M Dahle Norway
Dr. P Nesje Norway	Dr. R Bjornerheim Norway	Dr. G Froland Norway	Dr. T Gundersen Norway	Dr. T Hole Norway

Dr. TM Omland Norway	Dr. J Mannsverk Norway	Dr. P Smith Norway	Dr. K Dickstein Norway
Dr. K Hofsoy Norway	Prof J Kuch Warszawa, Poland	Prof. J Adamus Warsaw, Poland	Dr. K Jaworska Torun, Poland
Dr. P Kolodziej Siedlce, Poland	Prof. Z Kornacewicz-Jach Szczecin, Poland	Prof. M Krzeminska-Pakula Lodz, Poland	
Dr. W Piotrowski Krakow, Poland	Prof. W Piwowarska Krakow, Poland	Dr. A Stogowski Bialystok, Poland	Prof. J Wodniecki Zabrze, Poland
Prof. K Wrabec Wroclaw, Poland	Dr. J Herlitz Goteborg, Sweden	Dr. B Lernfelt Goteborg, Sweden	Dr. V Widgren Goteborg, Sweden
Dr. P Ahlstrom Motala, Sweden	Dr. K Angman Hudiksvall, Sweden	Dr. S Ekdahl Eksjo, Sweden	Dr. LO Hemmingston Harnosand, Sweden
Dr. L Holmberg Stockholm, Sweden	Dr. H Nilsson Fagersta, Sweden	Dr. P Rickenbacher Basel, Switzerland	Dr. P Mohacsi Bern, Switzerland
Dr. H Schlapfer Biel, Switzerland	Dr. R Polikar Nyon, Switzerland	Dr. P Erne Luzern, Switzerland	Dr. M Maltz London, UK
Dr. A Cowley Nottomgham, UK	Dr. G Reynolds Leeds, UK	Dr. J Swan Manchester, UK	Dr. TS Callaghan Angus, UK
Prof. A Struthers Dundee, UK	Dr. RA Greenbaum Middlesex, UK	Dr. J Stephens Dr. Romford, UK	DR. G Tildesley Hertlepool, UK
Dr. P Batin Wakefield, UK	Prof. M Frenmeaux Cradiff, UK	Dr. KE Berkin Leeds, UK	Dr. J Forfar Oxford, UK
Dr. DL Murdoch Glasgow, UK	Dr. P Alagona Tampa,FL,USA USA	Dr. J Alderman Framingham,Mass, USA	Dr. J Anderson Oklahoma City,OK USA
Dr. MR Berk Dallas,TX,USA	Dr. RK Bhalla Nassau Bay,TX,USA	Dr. SD Bilazarian Havehill,MA,USA	
Dr. KF Browne Lakeland,FL,USA	Dr. CM Butcher Cleveland,OH,USA	Dr. RJ Carlson Syracuse,NY,USA	Dr. CJ Carlson Fremont,CA,USA
Dr.K Dansia Muskigee,OK,USA	Dr.I Dauber Denver,CO,USA	Dr. MA De Wood Spokane,WA,USA	Dr. P Deedwana Fresno,CA,USA

Dr. G Deenish III Encinitas,CA,USA	Dr. R DiBianco Takoma Park,MD,USA	Dr. M Dunlap Cleveland,OH,USA	Dr. K Dowd Linwood,NJ, USA
Dr. WA Edmiston Psadena,CA,USA	Dr. M El Shahawy Sarasota,FL,USA	Dr. U Elkayan Los Angeles,CA,USA	Dr. J Farnham Madison,WI, USA
Dr. P Fernster Tucson,AZ,USA	Dr. SD Friedman Easton,MD,USA	Dr. JTJ Heywood Loma Linda,CA,USA	Dr. JP Galichia Wichita,KS,USA
Dr. M Geller Pittsburgh,PA,USA	Dr. JK Ghali Shreveport,LA,USA	Dr. M Gheorghiade Chicago,ILL,USA	Dr. TD Giles New Orleans,LA, USA
Dr. AD Goldberg Detroit,MI,USA	Dr. DA Goldscher Baltimore,MD,USA	Dr. GP Gooden Winter Haven,FL, USA	Dr. MC Goodman Garden City,NY,USA
Dr. LS Goodman Savannah,GA,USA	Dr. JI Gorwit Escondido,CA,USA	Dr. SS Gottlieb Baltimore,MD,USA	Dr. AH Gradman Pittsburgh,PA,USA
Dr. D Grech Elyria,OH,USA	Dr. TC Hack Ayer,MA,USA	Dr. JH Hall Indianapolis,IN,USA	Dr. MT Hatenhauer Tualatin,OR,USA
Dr. MB Higginbotham Durham,NC,USA	Dr. S Hutchins Little Rock,AR,USA	Dr. RL Gillespie San Diego,CA.USA	Dr. BC Iteld Chalmette,LA,USA
Dr. BK Jackson Redondo Beach,CA, USA	Dr. SM Jafri Detroit,MI,USA	Dr. W Jauch South Bend,IN,USA	Dr. BH Kahn Baltimore,MD,USA
Dr. W Kao Chicago,Ill,USA	Dr. KJ Kaplan Safety Harbor,FL, USA	Dr. RP Karlsberg Beverly Hill,CA, USA	Dr. HL Kennedy Taos,NM,USA
Dr. LW Kirkegaard Tacoma,WA,USA	Dr. LD Lalonde Whitefish,MT,USA	Dr. MF Lesser Melbourne,FL,USA	Dr. M Levy Los Angeles,CA,USA
Dr. M Levy Los Angeles,CA,USA	Dr. RL Lewis Daytona Beach,FL, USA	Dr. IK Loh Thousand Oaks,VA, USA	Dr. FR Maislos Houston,TX,USA
Dr. D Mann Houston,TX,USA	Dr. GL Maurice Portland,OR,USA	Dr. CJ Weaver Orlando,FL,USA	Mr. M Rotman Austin,TX,USA

Dr. MA O'Shaughnessy Fort Wayne,IN,USA	Dr. WD Old Norfolk,VA,USA	Dr. JD Pappas Corpus Christi, TX,USA	Dr. SN Promisloff Hillsboro,OR,USA
Dr. AM Rashkow Derby,CT,USA	Dr. B Reeves Charleston,NC,USA	Dr. JH Rosen Fort Myers,FL,USA	Dr. R Shah Levittown,PA,USA
Dr. Y Shalev Milwaukee,WI,USA	Dr. B Silverman Atlanta,GA,USA	Dr. RM Steingart Mineola,NY,USA	Dr. L Swenson St. Paul, MN,USA
Dr. U Thadam Oklahoma City,OK, USA	Dr. RD Thorsen Stillwater,MN,USA	Dr. MJ Tonkon Anaheim,CA.USA	Dr. RC Touchon Huntington,WVA, USA
Dr. GS Uhl Las Vegas,NV,USA	Dr. KJ Vaska Sioux Falls,SD,USA	Dr. SG Wagner Louisville,KY,USA	Dr. RJ Weiss Auburn,ME,USA
Dr. WJ Wickemeyer Des Moines,IA,USA	Dr. JR Wilson Nashville, TN,USA	Dr. R Wright Santa Monica,CA,USA	Dr. L Yellen San Diego,CA.USA
Dr. DH Kraus Memphis,TN,USA	Dr. BT Beamblossom Louisville,KY,USA	Dr. H Madyoon Manteca,CA,USA	Dr. JG Shanes Melros Park,Ill,USA
Dr. PM Diller Cincinnati,OH,USA	Dr. HJ Willens Petosky,MI,USA	Dr. M Ashraf Madera,CA,USA	Dr. D Benvenuti Newport Beach,CA, USA
Dr. R Levites Trenton,NJ,USA	Dr. A Nisar Elgin,Ill,USA	Dr. EM Gross Westlake,OH,USA	Dr. K Phadke Syracuse,NY,USA
Dr. K LaBresh Pawtucket,RI,USA	Dr. DM Denny Jeffersonville,IN,USA	Dr. Z Ansari Fulton,NY.USA	Dr. MS Alipour Newport Beach.CA USA
Dr. TM Saleem Stow,OH,USA	Dr.SK Bennett Washington,DC,USA	Dr. MC Goldberg Tucson,AZ,USA	Dr. M Imburgia Louisville,KY,USA
Dr. JJ Kennedy Annapolis,MD,USA	Dr. AS Abbasi Long Beach,CA,USA	Dr. SV Savran Nevada,USA	

2.3. Objectives. The objectives of this study were to investigate the effect of metoprolol CR/XL od added to standard therapy in patients with decreased ejection fraction and symptoms of heart failure. The study had two primary objectives ranked in order of importance.

2.3.1. Primary Objectives: Primary objectives were:

- The first primary objective was to determine whether metoprolol CR/XL reduced total mortality.
- The second primary objective was to determine whether metoprolol CR/XL reduced the combined endpoint of all cause mortality and all cause hospitalization.

2.3.2. Secondary Objectives. Secondary objectives were to evaluate the effects of metoprolol CR/XL on:

- The combined endpoints of all cause mortality and hospitalization due to heart failure
- The combined endpoints of all cause mortality and heart transplantation.
- Death from cardiovascular causes with cause-specific mortality for heart failure
- The pooled incidence of cardiac death and non-fatal acute myocardial infarction
- Number of hospitalizations due to heart failure and other cardiovascular causes.

2.3.3. Tertiary Objectives. Tertiary objectives were to evaluate the effects of metoprolol CR/XL on:

- The combined endpoint of all cause mortality, hospitalization due to heart failure and emergency room visit due to heart failure.
- Tolerability defined as overall permanently early discontinuation of treatment and permanent early discontinuation due to worsening of heart failure.
- Functional state as evaluated by New York Heart Association (NYHA) classification
- Quality of life substudy
- Health economics substudy

2.4. Inclusion Criteria. Eligible patients were men and women , 40-80 years old who had symptomatic heart failure, New York Heart Association (NYHA) functional class II-IV for 3 months or more before randomization and who were receiving optimal standard therapy at enrollment (2 weeks before randomization), defined as any combination of diuretics and an ACE inhibitor. If an ACE inhibitor was not well tolerated, hydralazine, a long acting nitrate or an angiotensin II receptor-antagonist could be used. Digitalis could also be prescribed.

Other inclusion criteria were: a stable clinical condition during the two-week run-in phase between enrollment and randomization and a left ventricular ejection fraction (LVEF) of 0.40 or lower within 3 months before enrollment. Patients with LVEF between 0.36-0.40 were included only if their maximum walking distance was 45 m or less in a 6 min walk test. Supine heart rate had to be 60 beats per minute or more before enrollment (1).

2.5. Exclusion Criteria. Women of childbearing potential without a reliable method of contraception. Acute myocardial infarction or unstable angina pectoris within 28 days before randomization. Medical condition that in the opinion of the investigator required treatment with a beta blocker making potential randomization to placebo medically unacceptable. Any condition that in the opinion of the investigator would have precluded the use of beta blocker such as obstructive lung disease. Chronic beta-adrenergic blockade within the last six weeks prior to enrollment.

Heart failure secondary to any of the following conditions:

- Clinically significant, uncorrected, primary valvular disease.
- Obstructive, hypertrophic, cardiomyopathy
- Malfunctioning artificial heart valve
- Acute endo-or myocarditis or pericardial disease
- Systemic disease such as uncorrected thyroid disease or amyloidosis

The following invasive procedures:

- Planned coronary artery- bypass surgery, or angioplasty, or any of these procedures performed within the last four months prior to enrollment
- Implanted cardioversion defibrillator (ICD); or ICD expected to be implanted within the study period
- Heart transplant patient; or heart transplantation expected to be performed within the study period
- Performed cardioplasty; or cardioplasty expected to be performed within the study period

Second or third degree of atrioventricular block or sick sinus syndrome except for those patients with intrinsic cardiac activity at enrollment and randomization using an on-demand pacemaker. Patients with unstable, decompensated heart failure (pulmonary edema, hypoperfusion) at enrollment or randomization, or hypotension defined as a supine systolic blood pressure <100 mmHg at optimal treatment for heart failure at enrollment. Patients in need of continuous or intermittent inotropic therapy (excluding digitalis) should not be enrolled or randomized.

Any other serious disease or condition at enrollment or randomization which may affect life expectancy or make it difficult to successfully manage and follow the patient according to the protocol such as:

- Human immnunodeficiency virus infection
- Malignancy, except patients who have been in remission for at

least five years with no signs of recurrence

- Clinically significant primary hepatic or renal disease
- Known or suspected alcohol or drug abuse
- Suspected or confirmed poor compliance
- Calcium antagonists other than vascular-selective dihydropiridines, such as amlodipine and felodipine. Heart rate reducing calcium antagonists such as diltiazem and verapamil were not permitted.
- Patients receiving amiodarone within six months before enrollment
- Participation in a clinical study during the last 30 days.

2.6. Withdrawal of Patients. Patients were free to discontinue their participation in the study at any time. Patient's participation in the study could be also terminated at the discretion of the investigator. However, all patients randomized were evaluated even if wrongly included from the beginning or if exclusion criteria had developed after randomization.

If a decision of withdrawal had been taken, medication had to be down-titrated over a period of time not shorter than two weeks.

2.7. Period of Study, Organization of the Study and Statistics. It was assumed that 3200 patients, 1600 randomized to metoprolol CR/XL, and 1600 randomized to placebo, would be recruited in 14 months with a significant α=0.04 for the first primary endpoint, all cause mortality, and α=0.01 for the second primary endpoint, all cause mortality and all cause hospitalization, and a power of at least 80%. A mean annual risk of approximately 9.4% for the first primary endpoint (when continuing double-blind treatment with placebo) and a risk-reducing effect of metoprolol CR/XL of 30% (when continuing double-blind treatment with 200 mg metoprolol CR/XL) were assumed from start to completion of the study. During the titration period, risk reduction was assumed to be half that assumed above. The withdrawal rate from study medication was assumed to be 5% during titration period, 15% during the first year (20% after 12 months) and thereafter 5% annually. The mean follow-up period was assumed to be 2.4 years. With the expected number of deaths, the observed risk-reduction on an intention-to-treat basis would be 21%; with treatment the risk reduction would approach 30%. The stopping rule for efficacy was to be based o all cause mortality analyzed on an intention to treat basis done when 25%, 50% and 75% of expected total deaths had occurred.

An International Executive Committee had the main responsibility for the study between International Steering Committee meetings. The Independent Safety Committee monitored safety issues during the study. An Independent Endpoint Committee, whose members were unaware of treatment status, classified all deaths according to prespecified definitions from medical records and other documents. Each event was classified by two members and agreement between the two constituted a final classification.

The predefined endpoints were: vital status, which was verified with the patient, a close relative or through valid documentation. Cardiovascular death which included deaths for which a non-cardiovascular death had not been identified. Death from heart failure which

was any of cardiogenic shock, pulmonary edema, heart failure symptoms or signs requiring intravenous therapy or oxygen, confinement because of heart failure symptoms or sudden death during hospital stay for aggravated heart failure. Sudden death which was any of witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 minutes or more, unwitnessed death in the absence of pre-existing progressive circulatory failure or any other causes of death, or death within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, death during attempted resuscitation, or death within 60 min from onset of new symptoms, unless a cause other than cardiac was obvious.

The randomization began on February 14, 1997 and the last patient was randomized on April 14, 1998. The International Steering Committee stopped the study on October 31, 1998 on the recommendation of the Independent Safety Committee. The second pre-planned interim analysis (50% point) showed that the predicted criterion for ending the study had been met and exceeded (Z=3.807 vs a boundery value of 2.98). 3981 patient-years, 2004 in the metoprolol CR/XL group and 1977 in the placebo group (total mortality) had accumulated. The corresponding patient years for the combined endpoint of total mortality or all cause hospitalization was 1650 vs 1600 patient years, and for total mortality or hospitalization for worsening heart failure 1880 vs 1840 patient years respectively. The mean follow-up time was one year. The mean daily dose of study drug at end of study was 159 mg once daily in the metoprolol CR/XL group with 87% of patients receiving 100 mg or more and 65% receiving the target dose of 200 mg once daily. In the placebo group the corresponding values were 179 mg, 91% and 82% respectively. 1990 patients had been randomized to the metoprolol CR/XL group and 2001 patients to placebo.

There were five protocol amendments submitted during the study. None of the amendments meant any major changes during the study although the number of patients was increased from the planned of 3200 to 3991 since the inclusion during the 14-month recruitment period went better than originally planned. None of the amendments affected the conclusions of this study.

2.8. Study Design. This was a randomized, double-blind, placebo-controlled, parallel-group, international, multicenter survival study.

The two primary objectives were to determine the effects of metoprolol CR/XL od on total mortality and the combined endpoint of all cause mortality and all cause hospitalization in patients with symptomatic congestive heart failure with NYHA classes II-IV and decreased ejection fraction.

Patients fulfilling the admission criteria were to receive single-blind treatment with placebo once daily for two weeks. Patients who subsequently fulfilled all the admission criteria and none of the exclusion criteria were to be allocated to a starting dose of 12.5 mg metoprolol CR/XL or placebo at a ratio 1:1. Half the 25 mg metoprolol CR/XL/placebo tablet was recommended as the starting dose in patients with NYHA class III-IV. This dose was increased in a stepwise fashion to 50, 100 and 200 mg

metoprolol CR/XL/placebo od every second week. The dose titration schedule is given in the following Table:

Table 2.8.1

Dose Titration Schedule

Time (Weeks)	Trial Drug Dose
1-2 (from randomization)	12.5-25.0 mg (half or one 25 mg metoprolol CR/XL/placebo Tablet)
3-4	50 mg (one 50 mg metoprolol CR/XL/placebo Tablet)
5-6	100 mg (one 100 mg metoprolol CR/XL/placebo Tablet)
7	200 mg (one 200 mg metoprolol CR/XL/placebo Tablet)

In patients with severe heart failure (unable to carry any physical activity without marked discomfort) the first dose may have to be given at the investigator site with monitoring of symptoms, blood pressure and heart rate. Clinical improvement may not be noted until the second or third month of therapy. Persistence with therapy was to be encouraged .

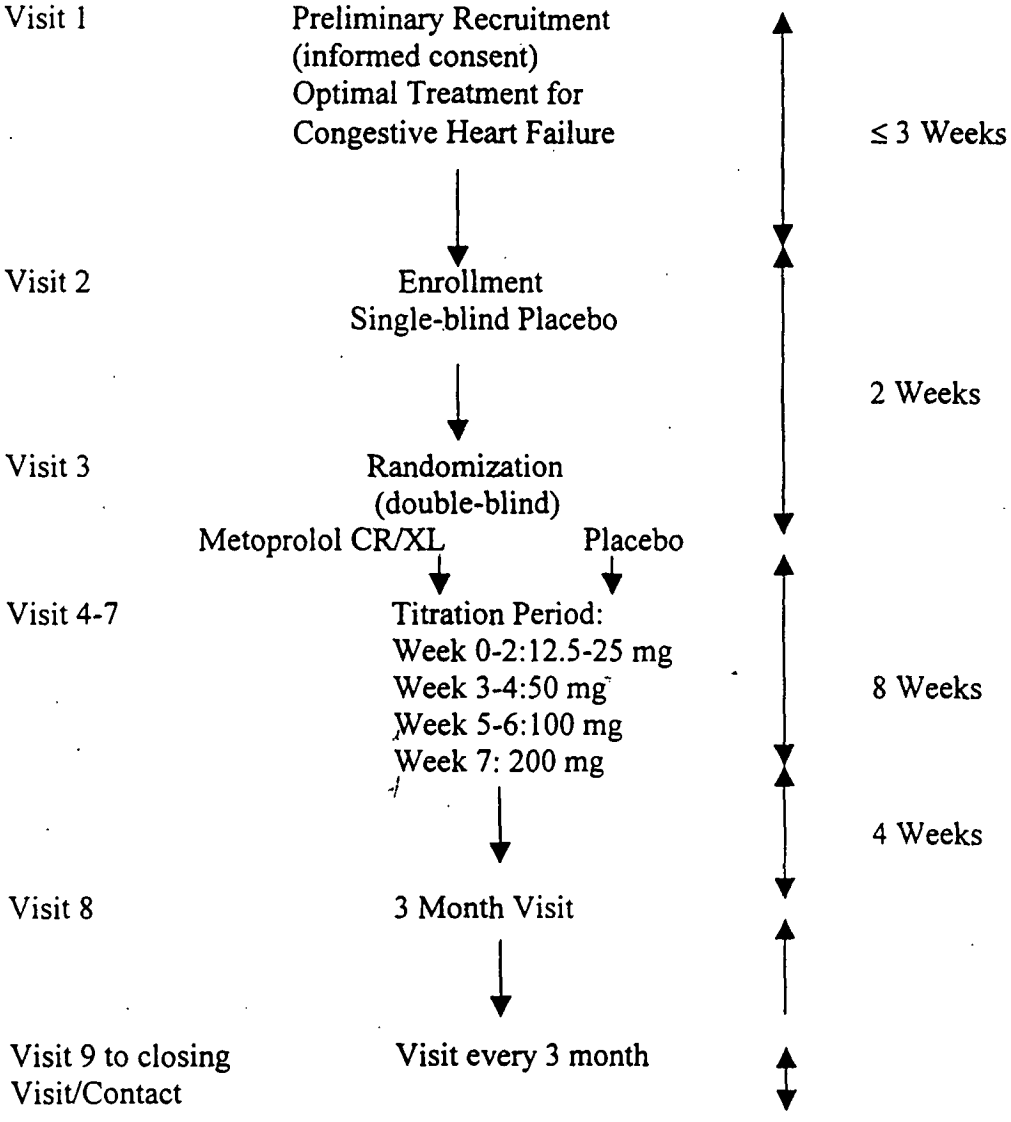
A worsening clinical picture with shortness of breath, increase in weight, edema, and pulmonary rales was to be treated with diuretics. If hypotension without increased congestion was a major problem during titration temporary reduction of the dose of ACE inhibitor and/or diuretics was to be considered.

In cases of hospitalization for worsening heart failure and/if diuretics failed to improve the patient heart failure or in cases of severe hypotension, study medication may have to be reduced or discontinued. Efforts to restart treatment with the study drug should have to be made. In cases of worsening heart failure, not responding to diuretic treatment or reduction in dose of study drug, trial medication was to be withdrawn.

The overall study design is given in the following Table:

Table 2.8.2

Study Design



The Study Schedule is given in the following Table:

Table 2.8.3

Study Schedule

	1 Preliminary Recruitment	2 Enrollment	3 Randomization	4-7 Titration Period	8-14 Follow-up Contact	20 Closing Visit/ Visit	Post trial
Visit (time)[1]	–5 week	-2 week	0	2-8 week	Every 3 Months	Fixed date for all	Within 4 week after closing visit/contact or later
Informed Consent	X						
Medical history		X					
Vital signs		X	X	X	X	X	X
NYHA class		X	X	X	X	X	X
Current therapy		X	X	X	X	X	X
Body weight		X	X	X	X	X	X
ECG[2]			X		X	X	
Walk test		X					
Lab test[3]		X					
Single-blind treatment		X					
Trial treatment:							
Up-titration[4]			X	X			
Blood sample[5]					X		
Trial treatment: Down titration						X	X
Tolerability			X	X	X	X	X
Compliance			X	X	X	X	X
Adverse and Clinical Events			X	X	X	X	X
Health economics[6]			X	X	X	X	
Quality of Life[7]			X	X	X	X	

1. For patients already on optimal treatment preliminary recruitment and enrollment could be combined in one visit 2.
2. An electrocardiogram was recorded at randomization and the twelve-month follow-up and when deemed necessary by the investigator.
3. Laboratory tests included serum concentrations of creatinine, sodium and potassium at entry.
4. In some patients the up-titration was prolonged
5. A blood sample (whole blood) for metoprolol assay was drawn at the 3-month visit
6. Health economic parameters were recorded at randomization and at applicable follow-up visits in the USA study
7. Quality of life questionnaires were recorded at visits 2, 3, 9, 11, 13 and 14
8. Some patients were treated with open-label metoprolol CR/XL after study closure.

2.9. Results

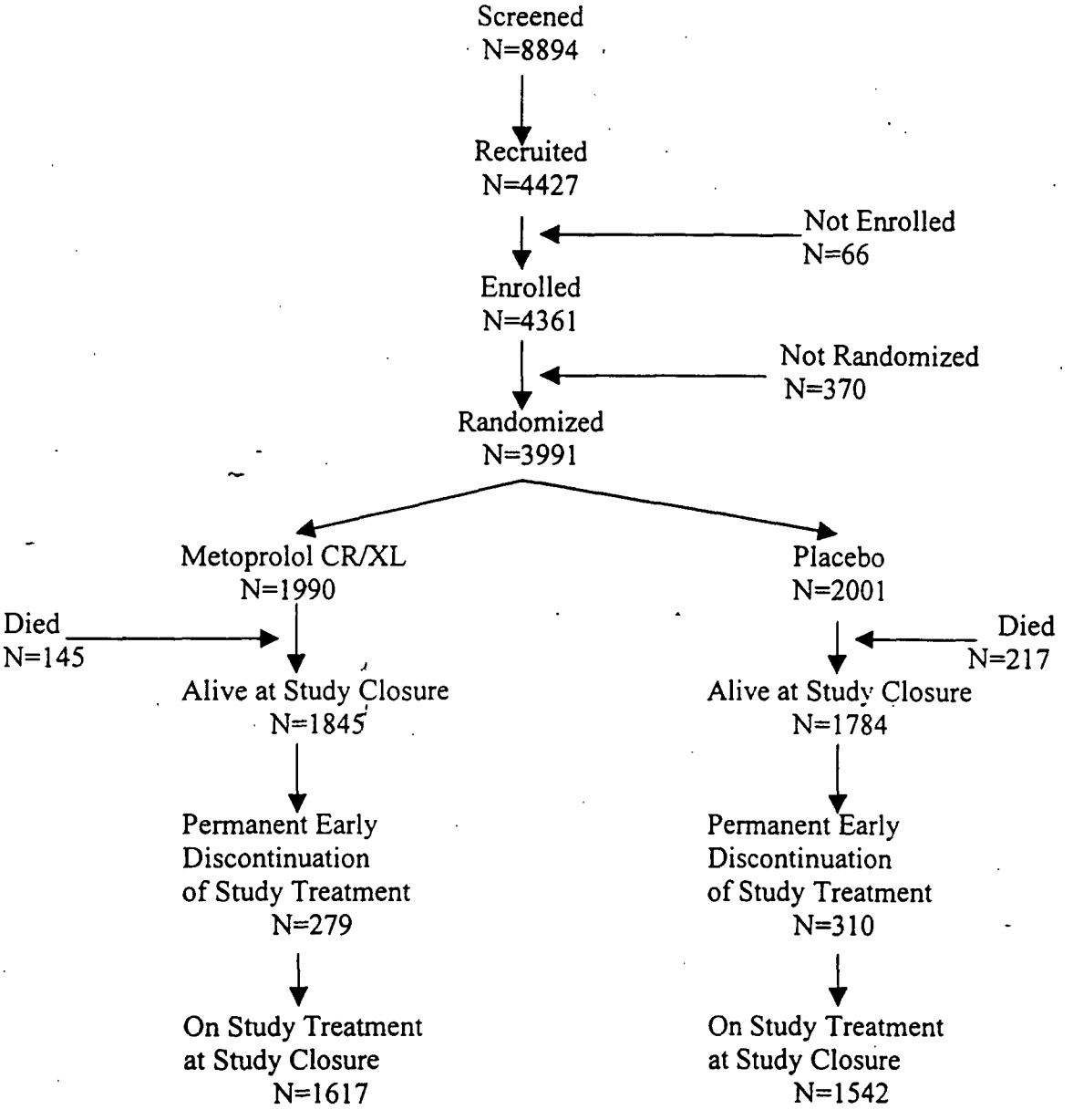
2.9.1. Disposition of Patients. Eight thousand eight hundred and ninety four (8894) patients were screened for inclusion. There were 255 sites in 11 of the 14 participating countries using the screening program. In total 4432 patients were recruited and 4364 outpatients from 313 study sites in Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Iceland, the Netherlands, Norway, Poland, Sweden, Switzerland, United Kingdom and the United States were enrolled into the study. Of these patients, 3991 were randomized during the planned recruitment time. There were 436 patients who discontinued this study before randomization: 66 patients before enrollment and 370 patients before randomization.

There were 609 patients who discontinued the study after being randomized. Twenty (20) of these discontinuations occurred during five days before the date of death and are not counted as permanent early discontinuation. Adverse experience was the main reason for permanent early discontinuation in 430 cases, 196 on active treatment and 234 on placebo. During the double-blind treatment period 362 patients died: 145 on the metoprolol and 217 in the placebo group. The number of patients alive at study closure in the metoprolol group was 1845 of which 1617 were on study treatment. At study closure, 1784 patients were in placebo group were alive, of which 1542 were on study treatment. All patients randomized were included in the data analysis according to intention to treat. A flow chart is given in the following figure:

APPEARS THIS WAY
ON ORIGINAL

Figure 1.

Disposition of Patients



The main reasons for permanent early discontinuation are given in the following Table:

Table 2.9.1.

Main Reasons for Permanent Early Discontinuation

	Metoprolol CR/XL	Placebo	Total
All Discontinuations (Randomized Patients)	279	310	589
Discontinuations due to any Adverse Reaction (Including Worsening of Heart Failure)	196	234	430
Discontinuation due to Worsening of Heart Failure	64	85	149
Discontinuation due to other Reason than Adverse Reaction	83	76	159

2.9.2. Demographic Characteristics. Results of demographic characteristics at baseline is given with figures representing the number of subjects in each group and the percentage in each group within parenthesis.

Table 2.9.2.1

Demographics. Overall Summary at Baseline

Variable	Group	Metoprolol CR/CL N=1990	Placebo N=2001	Total N=3991
Gender	Male	1539 (77.3)	1554 (77.7)	3093 (77.5)
	Female	451 (22.7)	447 (22.3)	898 (22.5)
Race	Caucasian	1870 (94)	1885 (94.2)	3755 (94.1)
	Black	106 (5.3)	101 (5.0)	207 (5.2)
	Asian	7 (0.4)	11 (0.5)	18 (0.5)
	Other	7 (0.4)	4 (0.2)	11 (0.)
Age	40-49	208 (10.5)	218 (10.9)	426 (10.7)
	50-59	448 (22.5)	464 (23.2)	912 (22.9)
	60-69	706 (35.5)	702 (35.1)	1408 (35.3)
	70-79	617 (31)	603 (30.1)	1220 (30.6)
	80-81	11 (0.6)	14 (0.7)	25 (0.6)

There were not enough patients in the age range 80 years old and older.

Table 2.9.2.2

Demographics of Medical History

Variable	Group	Metoprolol CR/XL N=1990	Placebo N=2001	Total N=3991
NYHA class visit 2	II	804 (40.4)	821 (41)	1625 (40.7)
	III	1119 (56.2)	1099 (54.9)	2218 (55.6)
	IV	67 (3.4)	81 (4.0)	148 (3.7)
NHHA class visit 3	II	810 (40.7)	825 (41.2)	1635 (41.0)
	III	1111 (55.8)	1100 (55.0)	2211 (55.4)
	IV	69 (3.5)	76 (3.8)	145 (3.6)
Etiology	Non Ischemic	696 (35.0)	688 (34.4)	1384 (34.7)
	Ischemic	1294 (65.0)	1313 (65.6)	2607 (65.3)
History of Hypertension	No	1119 (56.2)	1125 (56.2)	2244 (56.2)
	Yes	871 (43.8)	876 (43.8)	1747 (43.8)
History of Diabetes	No	1495 (75.1)	1511 (75.5)	3006 (75.3)
	Yes	495 (24.9)	490 (24.5)	985 (24.7)
History of MI	No	1040 (52.3)	1025 (51.2)	2065 (51.7)
	Yes	950 (47.7)	976 (48.8)	1926 (48.3)
Years since previous MI	< 1	150 (7.5)	136 (6.9)	289 (7.2)
	1-5	342 (17.2)	368 (18.4)	710 (17.8)
	> 5	457 (23,0)	468 (23.4)	925 (23.2)
Diuretics %		91	90	
ACE Inhibitor %		89	90	
AII Blocker		7	6	
ACE Inhibitor or AII Blocker %		95	96	
Digitalis %		63	64	
Spironolactone %		7	8	

There were not enough patients in NYHA Class IV.

Concomitant Medications. There were no significant differences between active treatment and placebo groups in reference to concomitant medication taken at baseline and consisting of diuretic, ACE inhibitor, angiotensin II blocker, ACE blocker, digoxin, digitoxin, digitalis, class I antiarrhythmics, calcium channel blocker, hydralazine, long acting nitrate, other vasodilator, aspirin, oral anticoagulant, oral antiplatelet aggregatory, short-acting nitrates, statin resin, fibrate, other lipid lowering, any lipid lowering, other cardiovascular drug, open beta-blocker, insulin or oral antidiabetic.

The dose of furosemide was similar at baseline and during follow-up in the two randomized groups: in the metoprolol CR/XL group 66 mg vs 70 mg and in the placebo group 65 mg vs 73 mg respectively. For the most commonly used ACE inhibitors corresponding doses were for enalapril similar in the two randomized groups at baseline

14 mg and at follow-up 15 mg; captopril 68 mg vs 70 mg and 60 vs 64 mg; and for lisinopril 17 mg vs 17 mg and 16 mg vs 16 mg at baseline and follow-up in the metoprolol CR/XL and placebo group respectively.

Physical Examination at Baseline. There were no significant differences between active treatment and placebo groups in physical examination at baseline in reference to peripheral pitting edema, jugular venous distension, pulmonary rales, hepatomegaly, irregular heart beat, atrial fibrillation, third heart sound or heart murmur.

Laboratory Variables. There were no significant differences in laboratory variables referent to creatinine, sodium and potassium determinations between active treatment and placebo groups.

Table 2.9.2.3

Other Significant Demographic Characteristics at Baseline [Mean(SD)]

Variable	Metroprolol CR/XL N=1990	Placebo N=2001	Total 3991
Ejection Fraction	0.28 (0.07)	0.28 (0.07)	0.28 (0.07)
Systolic Blood Pressure	130 (17)	129.5 (17.3)	129.7 (17.2)
Diastolic Blood Pressure	78.4 (9.2)	78.1 (9.1)	78.3 (9.2)
Heart Rate	82.4 (10.1)	82.7 (10.3)	82.5 (10.2)
ECG Heart Rate	82.1 (13.9)	82.5 (13.7)	82.3 (13.8)

2.9.3 Efficacy Evaluation.

2.9.3.1. Endpoints. For definitions of endpoints, see sections 2.3.1, 2.3.2 and 2.3.3, objectives of this review.

2.9.3.2 Results of all endpoint evaluation. Results of analysis of all endpoints estimated from times to events are given in the following Table:

Table 2.9.3.2.

All Endpoints Evaluation

Variable	N	Events	Relative Risk	Lower 95% CI	Upper 95% CI	p Value
All cause mortality	3991	362	0.6588	0.5338	0.8129	0.0001
All cause mortality and all cause hospitalization	3991	1408	0.8146	0.7335	0.9047	0.0001
All cause mortality and hospitalization due to CHF	3991	750	0.6944	0.6005	0.8030	<0.0001
Death and heart transplantation	3991	368	0.6796	0.5520	0.8367	0.0002
Death from CV causes	3991	331	0.6222	0.4987	0.7762	<0.0001
Mortality from CHF	3991	88	0.5101	0.3283	0.7927	0.0023
Mortality from sudden death	3991	211	0.5905	0.4468	0.7804	0.0002
Cardiac death and non-fatal acute MI	3991	364	0.6096	0.4934	0.7531	<0.0001
All cause mortality and hospitalization due to CHF and emergency room visit due to CHF	3991	773	0.6844	0.5931	0.7899	<0.0001

2.9.3.3. Distribution of Clinical Events by Treatment Groups. The distribution of clinical events by treatment groups is given in the following Table:

TABLE 2.9.3.3.

Clinical Events by Treatment Groups

Variable	Treatment	Events
All cause mortality	Placebo	217
	Metoprolol CR/XL	145
All cause mortality and all cause hospitalization	Placebo	767
	Metoprolol CR/XL	641
All cause mortality and hospitalization due to heart failure	Placebo	439
	Metoprolol CR/XL	311
Death and heart transplantation	Placebo	218
	Metoprolol CR/XL	150
Death from cardiovascular causes	Placebo	203
	Metoprolol CR/XL	128

TABLE 2.9.3.3. (Continued)

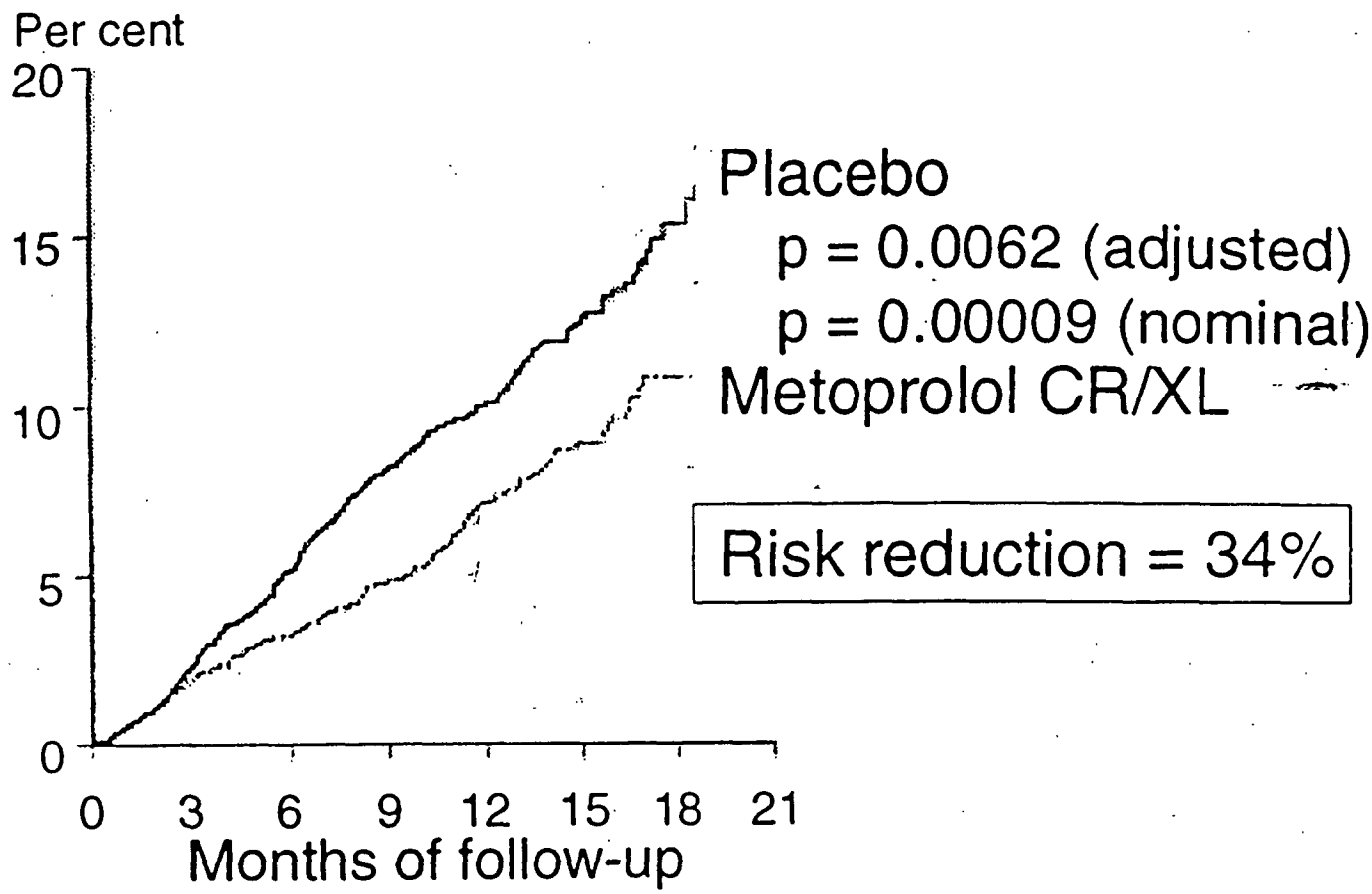
Clinical Events by Treatment Groups

Variable	Treatment	Events
Mortality from sudden death	Placebo	132
	Metoprolol CR/XL	79
Mortality from heart failure	Placebo	58
	Metoprolol CR/XL	30
Cardiac death and non-fatal acute MI	Placebo	225
	Metoprolol CR/XL	139
All cause mortality and hospitalization due to CHF and Emergency Room visit due to CHF	Placebo	455
	Metoprolol CR/HL	318

The cumulative percentages for primary and other endpoints are given in the following graphs:

Figure 2.

Total Mortality

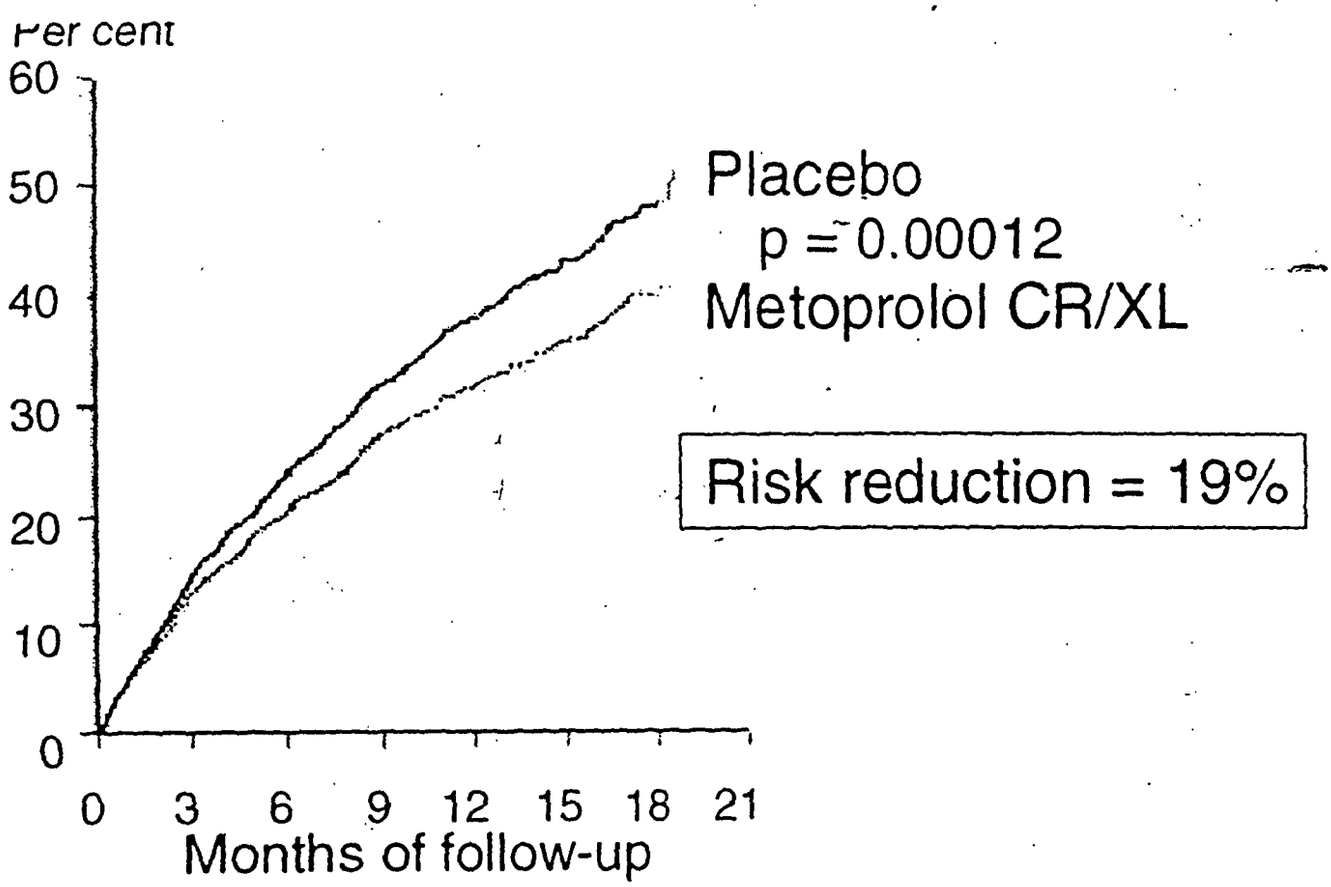


Cumulative percentage for total mortality obtained from Kaplan-Meier estimates for the two randomized groups

Figure 3.

All Cause Mortality and all Cause Hospitalization

(Time to First Event)

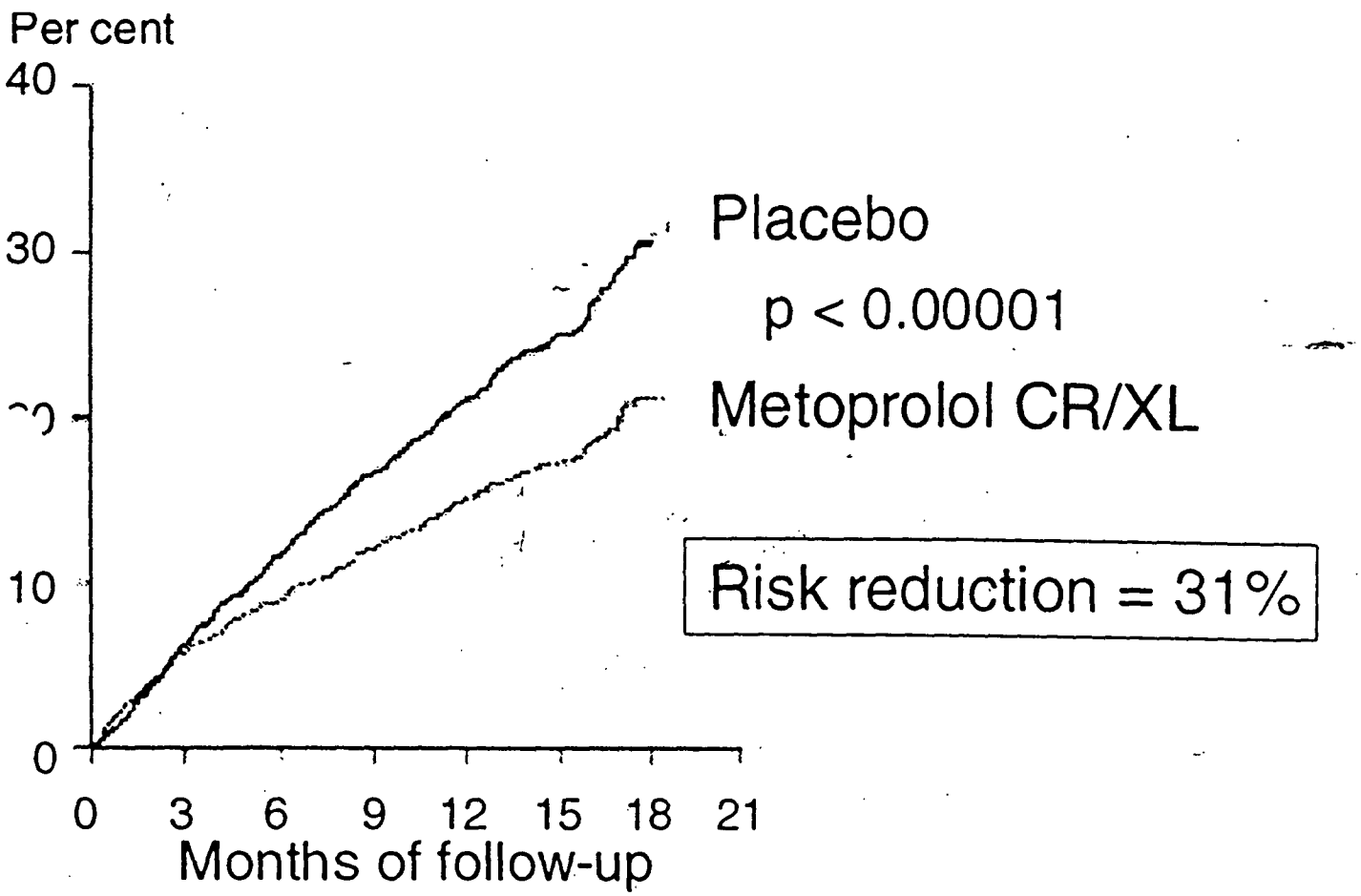


Cumulative percentages for the combined endpoint of all cause mortality and all cause hospitalization (time to first event) obtained from Kaplan-Meier estimates in the two randomization groups.

Figure 4.

All Cause Mortality and Hospitalization for Congestive Heart Failure

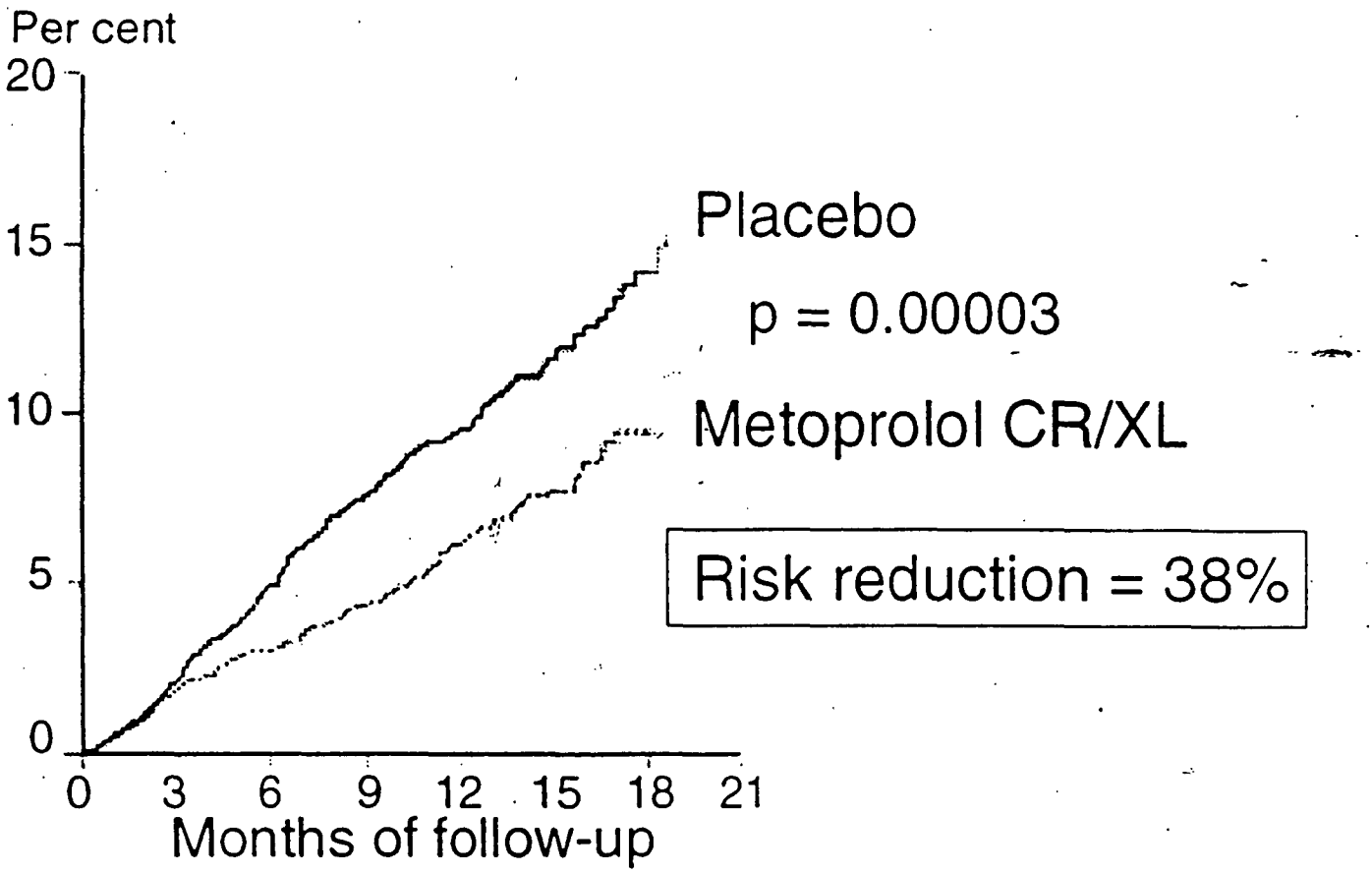
(Time to First Event)



Cumulative percentages for the combined endpoint of all cause mortality and hospitalization for heart failure (time to first event) obtained from Kaplan-Meier estimates in the two randomized groups.

Figure 5.

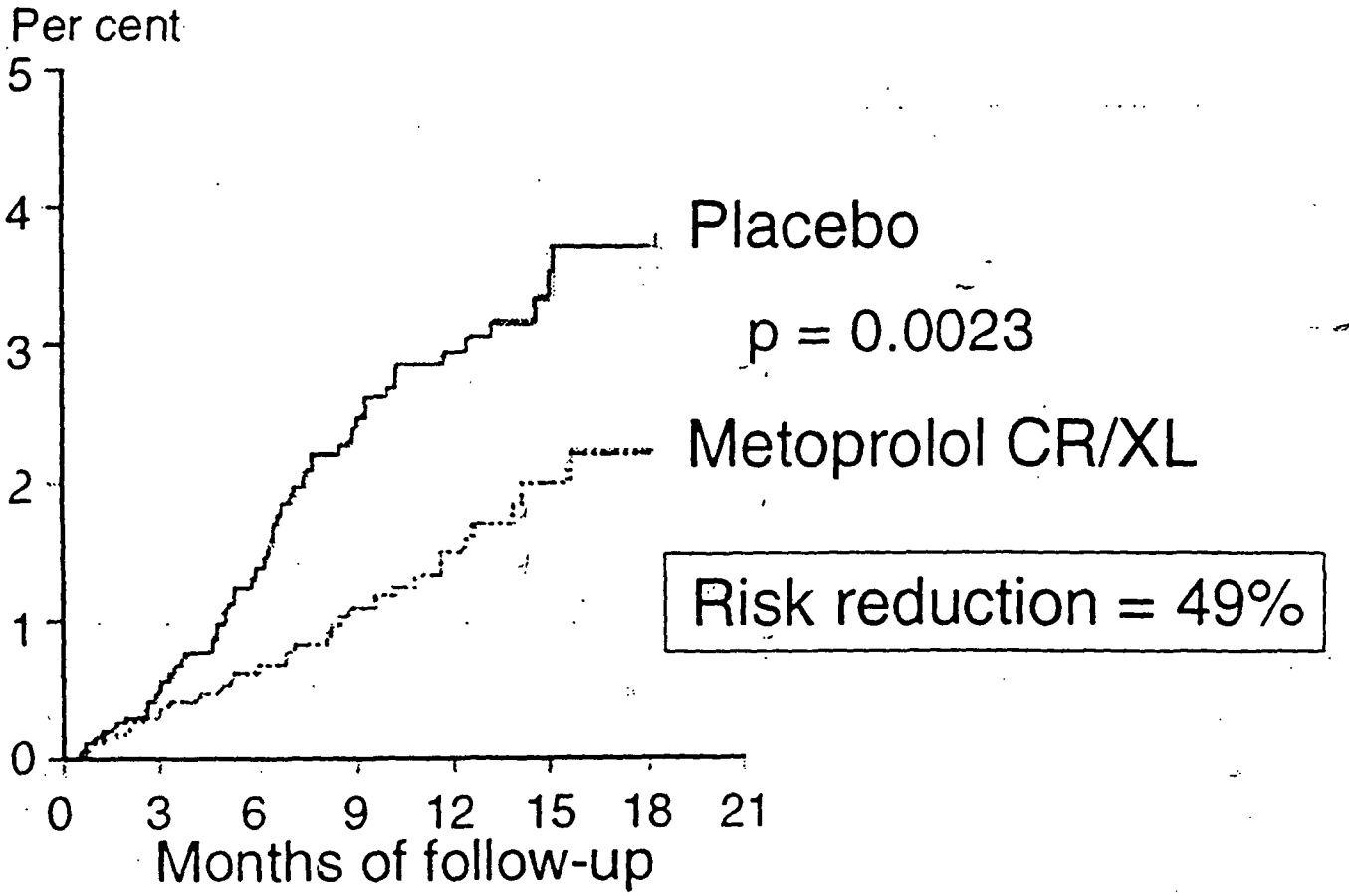
Cardiovascular Mortality



Cumulative percentages for cardiovascular mortality obtained from Kaplan-Meier estimates in the two randomization groups

Figure 6.

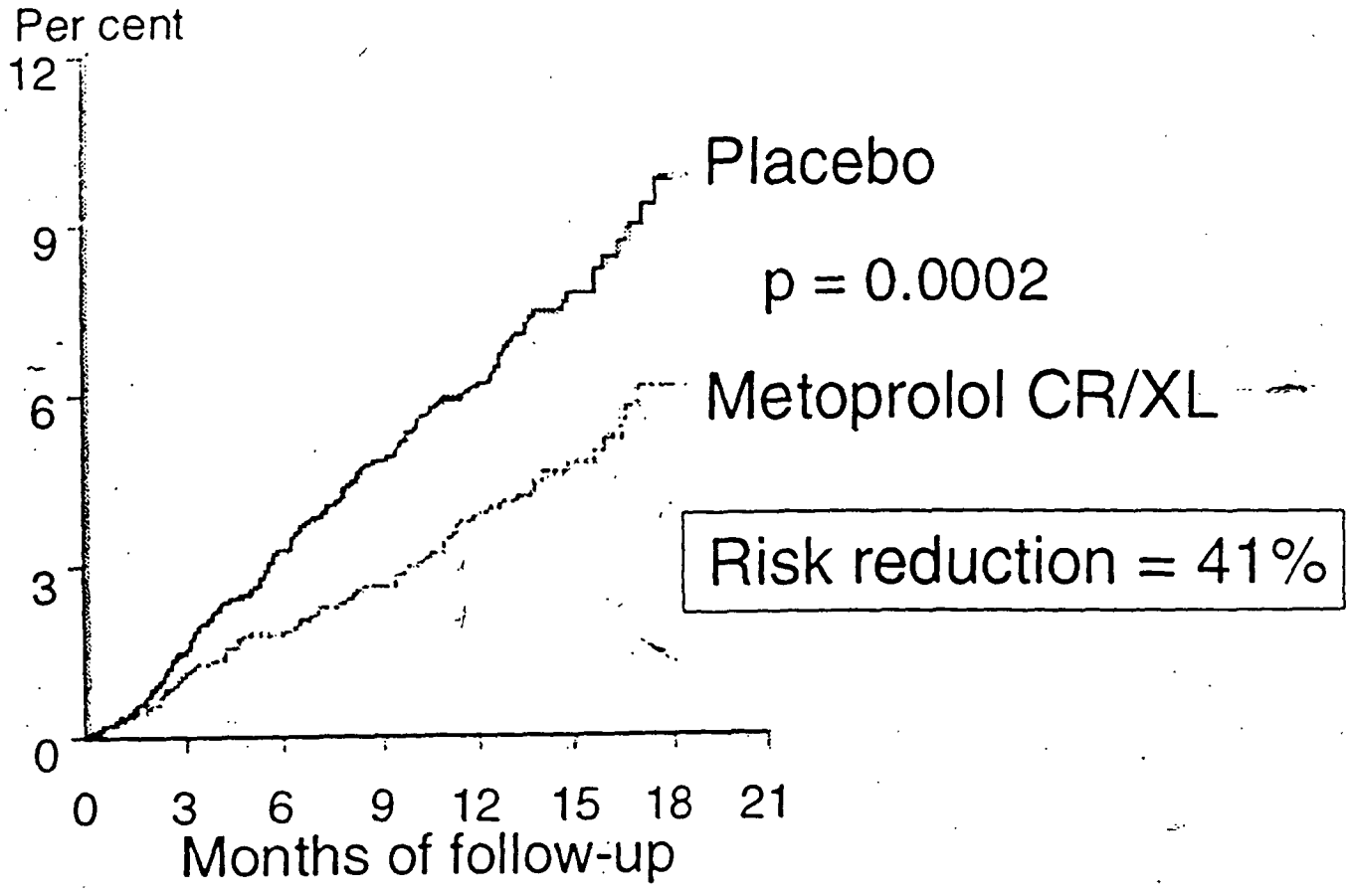
Deaths from Worsening Heart Failure



Cumulative percentages for death from worsening heart failure obtained from Kaplan-Meier estimates in the two randomization groups.

Figure 7.

Sudden Deaths



Cumulative percentages for sudden death obtained from Kaplan-Meier estimates in the two randomization groups.

2.9.3.4. Total Number of Hospitalizations, Hospitalizations due to Cardiovascular Causes and Worsening Heart Failure. The cause-specific data for number of patients hospitalized at least once, total number of hospitalizations and total number of days spent in the hospital in the two randomized groups are given in the following Table (2):

Table 2.9.3.4.

Hospitalizations

	Metoprolol CR/XL N=1990	Placebo N=2001	p-Values
Hospitalizations			
Due to all causes			
Number of patients with any hospitalization [number (%)]	581 (29.1%)	668 (33.3.%)	0.0043
Total number of hospitalizations	1021	1149	0.0050
Total number of days in the hospital	10172	12262	0.0042
Due to cardiovascular causes			
Number of patients with any hospitalization [number (%)]	394 (19.8%)	494 (24.7$)	0.00021
Total number of hospitalizations	649	773	0.00028
Total number of days in the hospital	6584	8403	0.00018
Due to worsening heart failure			
Number of patients with any hospitalization [number (%)]	200 (10%)	294 (14.7%)	<0.00001
Total number of hospitalizations	317	451	<0.00001
Total number of days in the hospital	3401	5303	<0.00001

In comparison to placebo, metoprolol CR/XL reduced the number of patients with any hospitalization, the total number of hospitalizations, and the total number of days in hospital due to all causes to cardiovascular causes and worsening heart failure.

Although not included with this submission, upon request, the sponsor submitted the following additional information:

Table 2.9.3.4.2.

Additional Information

Number of Patients and Number of Emergency Room Visits Due to Heart Failure

	Treatment	# of Patients	Total Number
Emergency Room Visits	Metoprolol CR/XL	24	28
	Placebo	30	33

Number of Patients who had Transplants due to Heart Failure

	Treatment	# Patients	Total Number
Cardiac Transplants	Metoprolol CR/XL	5	5
	Placebo	1	1

Number of Patients with Non-Fatal MI

	Treatment	# of Patients
Non-Fatal MI	Metoprolol CR/XL	31
	Placebo	37

The number of emergency room visits and the number of patients in need of heart transplantation was small and there was no significant difference between both groups.

2.9.3.5. Tolerability. Tolerability is defined as early discontinuation of study drug and was analyzed both for all cause of discontinuation and for discontinuation due to worsening heart failure. In the analysis of times to discontinuation, time to death was a censored time. In the analysis of discontinuation due to worsening heart failure, time to death and time to due to other causes were censored time.

A comparison of metoprolol CR/XL versus placebo: permanent early discontinuation is given in the following Table:

Table 2.9.3.5.1.

Comparison of metoprolol CR/XL versus placebo:

Permanent Early Discontinuations of Study Drug

Variable	N	Events	Relative Risk	95% CI Lower	Upper	p-value
Permanent Early Discontinuation	3991	589	0.8963	0.7624	1.0536	0.1842

A comparison of discontinuation of metoprolol CR/XL versus placebo due to worsening of congestive heart failure is given in the following Table:

Table 2.9.3.5.2.

Comparison of metoprolol CR/XL versus placebo:

Discontinuation of Study Drug due to Worsening Heart Failure

Variable	N	Events	Relative Risk	95% CI Lower	Upper	p-value
Worsening Heart Failure	3991	149	0.7501	0.5423	1.0376	0.0813

The distribution of permanent early discontinuation by treatment group is given in the following Table:

Table 2.9.3.5.3.

Distribution of Permanent Early Discontinuation by Treatment Group

Variable	Treatment	Events
All Discontinuation	Placebo	310
	Metoprolol CR/XL	279
Discontinuation due to worsening heart failure	Placebo	85
	Metoprolol CR/XL	64
Discontinuation due to any adverse event	Placebo	234
	Metoprolol CR/XL	196
Discontinuation not due to an adverse event	Placebo	76
	Metoprolol CR/XL	83

Metoprolol CR/XL was well tolerated. Withdrawal of study medication from all causes was 10% lower and withdrawal due to worsening heart failure was 25% lower in the metoprolol CR/XL group compared with the placebo group. For the most common adverse reactions leading to withdrawals of study medication, including worsening heart failure, atrial fibrillation and angina pectoris, withdrawal was more common in the placebo group. Less than 1 out of 100 patients treated for one year withdrew metoprolol CR/XL treatment for bradycardia, dizziness or hypotension.

2.9.3.6.Changes in NYHA Functional Class. The change in NYHA functional class from baseline to last available visit is shown in the following Table:

Table 2.9.3.6.

Comparison of Changes in NYHA Functional Classes

Variable	Missing	N	p-value		99 %CI	
			Asymptotic	Estimated	Lower	Upper
NYHA Class	39	3952	0.0026	0.0027	0.0026	0.0028

The distribution of changes in NYHA functional classes is shown in the following Table

Table 2.9.3.6..2.

Distribution of changes in NYHA classes

NYHA Class last visit	Metoprolol CR/XL N=1970	Placebo N=1982
Improved by 2 classes	51 (2.6)	30 (1.5)
Improved by 1 class	513 (26.0)	482 (24.3)
Same as baseline	1288 (65.4)	1322 (66.7)
Deteriorated by 1 class	113 (5.7)	134 (6.8)
Deteriorated by 2 classes	5 (0.3)	14 (0.7)

Although most patients remained at the same NYHA class at end of the study as in baseline, more patients in the treatment group showed some improvement, while more in the placebo group experienced deterioration.

Total mortality and mode of death was analyzed in relation to NYHA Functional Class at randomization. In NYHA Class II 44 deaths occurred in the metoprolol CR/XL group and 59 in the placebo group. In NYHA Class III 90 deaths occurred in the metoprolol CR/XL group and 142 in the placebo group. In NYHA Class IV 11 deaths occurred in the metoprolol CR/XL group and 16 in the placebo group. The proportion of sudden deaths decreased with increasing severity of heart failure according to NYHA functional Class. Conversely, the proportion who died from worsening heart failure increased with increasing severity of heart failure (1).

Of the 362 patients who died, 217 had been randomized to placebo and 145 to metoprolol CR/XL. Most deaths occurred in patients in NYHA Class III (145 patients randomized to placebo and 87 to metoprolol CR/XL). Most causes of death were due to

sudden death (85 patients randomized to placebo and 52 to metoprolol CR/XL) and to heart failure (43 patients in the placebo group and 18 in the metoprolol CR/XL group).

2.9.3.7. Quality of Life. A study of Quality of Life was performed in a subset of sites in Norway, the Netherlands, Sweden, the United Kingdom and the United States. The objective was to determine whether the addition of metoprolol CR/XL od to standard therapy for heart failure improved Quality of Life as compared to placebo. Quality of life was assessed using two validated questionnaires: the Minnesota Living with Heart Failure Questionnaire (LihFE) and the Overall Treatment Evaluation (OTE) Questionnaire. The change in total score of answers to the last available visit was calculated for all complete questionnaires. The number of patients who returned a questionnaire at visit 3 was 824 while observations at last follow-up visit was 670 patients.

The overall treatment evaluation questionnaire had three items addressing the overall effect of treatment. The first item was an assessment of the effect of treatment as better, same as before or worse. In case of improvement or deterioration responders were asked to grade that evaluation on a seven point ordered scale by answering the second question if better or the third question if worse. The evaluation scale was constructed by giving the midpoint value to the "same as before" answers, while answers on the "better" or "worse" parts of the scale are given the grading chosen in the answer to question two or three with the "worse" grades below the midpoint and the "better" ones above the midpoint. The number of reliable answers from the last overall treatment evaluation questionnaire was 741.

Some results of the Quality of Life Questionnaire are given in the following Tables:

Table 2.9.3.7.1.

LihFE Questionnaire

Treatment Comparison of Changes in Sum Scores from Baseline to Last Available Visit

Treatment Comparison	Adjusted Mean	95% CI Lower	95% CI Upper	p Value
Metoprolol CR/XL Vs Placebo	-0.9	-3.4	1.6	>0.200

According to this questionnaire, the difference was not statistically significant.

The overall treatment evaluation scale analysis is shown in the following Tables:

Table 2.9.3.7.2.

Overall Treatment Evaluation Scale Analysis:

Analysis of the difference in Overall Treatment Evaluation scores Between Treatment Groups at last Visit

Variable	N (Missing)	p-value		99 % CI	
		Asymptotic	Estimated	Lower	Upper
Overall Treatment Evaluation Questionnaire	741 (18)	0.0086	0.0087	0.0085	0.0089

The distribution of answers in the scale resulting from answers to the overall treatment evaluation questionnaire is shown in the following Table. Percentages are calculated for the non-missing scale.

Table 2.9.3.7.3.

Overall Treatment Evaluation Questionnaire Distribution of Answers

Overall Treatment Evaluation scale last visit	Metoprolol CR/XL N=371	Placebo N=370
A very great deal worse	0 (0)	7 (1.9)
A great deal worse	4 (1.1.)	3 (0.8)
A good deal worse	8 (2.2)	6 (1.6)
Moderately worse	7 (1.9)	5 (1.4
Somewhat worse	7 (1.9)	6 (1.6)
A little worse	7 (1.9)	9 (2.4)
Hardly worse at all	3 (0.8)	1 (0.3)
About the same	150 (40.4)	185 (50.0)
Hardly better at all	6 (1.6)	2 (0.5)
A little better	17 (4.6)	20 (5.4)
Somewhat better	33 (8.9)	28 (7.6)
Moderately better	37 (10.0)	31 (8.4)
A good deal better	47 (12.7)	38 (10.3)
A great deal better	26 (7.0)	21 (5.7)
A very great deal better	19 (5.1)	8 (2.2)

Although most patients in both groups felt about the same, a small number of those receiving active treatment felt better.

The importance of the changes experienced as expressed in the answers to the overall treatment evaluation shown in the Table above is given below. Those who experienced improvement or worsening were instructed to answer the fourth question.

Table 2.9.3.7.4.

Overall Treatment Evaluation Questionnaire

Last Question Responders Deteriorated

Variable	Metoprolol CR/XL	Placebo
N	35	36
Missing	1	1
Not important	2 (5.7)	4 (11.1)
Slightly important	2 (5.7)	4 (11.1)
Somewhat important	5 (14.3)	3 (8.3)
Moderately important	3 (8.6)	9 (25.0)
Important	7 (20.0)	5 (13.9)
Very important	9 (25.7)	7 (19.4)
Extremely important	7 (20.0)	7 (19.4)

Table 2.9.3.7.5.

Overall Treatment Evaluation Questionnaire

Last Question Responders Improved

Variable	Metoprolol CR/XL	Placebo
N	185	148
Missing	2	6
Not important	3 (1.6)	2 (1.4)
Slightly important	9 (4.9)	7 (4.8)
Moderately important	27 (14.7)	14 (9.7)
Important	57 (31)	34 (23.4)
Very important	37 (20.1)	33 (22.8)
Extremely important	38 (20.7)	40 (27.6)

These questionnaires indicate that most patients considered the deterioration or improvement of their clinical condition to be important, very important or extremely important.

Proportion of answers yielding scale values reflecting a beneficial effect of treatment are larger for the group treated with metoprolol CR/XL than they are for the placebo group.

2.9.3.8. Dose of Study Drug at Last Available Visit. At last available visit, 63 % of patients in the treatment group were on the 200 mg dose of metoprolol CR/HL as compared to 78 % in the placebo group. Eighty six percent (86 %) were on the ≥ 100 mg dose of metoprolol CR/XL as compared to 92 % on placebo.

2.9.3.9. Symptoms Reported in the Case Report Form. There were no great differences in the symptoms of fatigue and chest pain between treatment and placebo groups at the last visit.

2.9.3.10. Physical Examination. There were not great differences in the findings of peripheral pitting edema, irregular heart beat and breathlessness between both groups at the last visit.

2.9.3.11. Blood Pressure and Pulse Rate. There was a smaller decrease in systolic blood pressure in patients treated with metoprolol CR/XL than with placebo (systolic blood pressure: metoprolol CR/XL at baseline 129.99±17 mmHg,127.76±20 mmHg at last visit; placebo at baseline 129.50±17 mmHg and at last visit 125.89±19). There were no significant differences in diastolic blood pressures. Heart rate was reduced more in the metoprolol CR/XL group [-10.9 (-11.6 to –10.2) bpm $p<0.0001$].

2.9.3.12. Creatinine, Sodium and Potassium. Chemistry determinations were not performed at the end of the study.

2.9.3.13. Heart Transplantation. According to the sponsor, combined endpoints of all death and heart transplantation were significantly significant ($p=0.0002$) (see Table 2.9.3.2.1., page 21). However, when information was requested on heart transplantation as single endpoint, it was reported that there were 6 heart transplantation in subjects that participated in this study: 5 were being treated with metoprolol CR/XL and one was on placebo (Table 2.93.4.5. , page 30). The difference was not statistically significant. Therefore it cannot be claimed that treatment with metoprolol CR/XL reduced the need for heart transplantation in these patients with congestive heart failure.

2.9.3.14. Efficacy Assessment. This review of protocol 0024 consists not only of the data submitted by the sponsor (volumes 10 through 35 of 101), but also of publications of the results (1,2) and editorial comments (3-9).

The results of this study support the conclusion that the sponsor succeeded in demonstrating that metoprolol CR/XL od had a significant beneficial effect when added to optimum treatment with primarily ACE inhibitors and diuretics to patients with moderate to severe chronic congestive heart failure. Because a trend in this direction became evident in the course of the study the international steering committee stopped the study after an accumulated follow-up time of one year.

These beneficial effects are supported by the findings that treatment with metoprolol CR/XL od caused a lessening in total mortality of 34 %, in all cause mortality and all cause hospitalization of 19 %, all cause mortality and hospitalization for congestive heart

failure of 31 %, cardiovascular mortality of 38 %, death from worsening heart failure of 49 % and sudden death of 41%.

There were 145 deaths in the metoprolol CR/XL group and 217 in the placebo group (p=0.0062). The mortality rates were 7.2% and 11% respectively per patient-year of follow-up with a relative risk of 0.66 (95% confidence indices of 0.53-0.81).

There were 128 cardiovascular deaths in the metoprolol CR/XL group and 203 in the placebo group [0.62(0.50-0.78), p=0.00003].

There were 79 sudden deaths in the metoprolol CR/XL group and 132 in the placebo group [0.59(0.45-0.78), p=0.0002]

Thirty (30) patients died from worsening congestive heart failure in the metoprolol CR/XL group versus 58 in the placebo group [0.51(0.33-0.79), p=0.0023].

Metoprolol CR/XL od reduced significantly the number of hospitalizations due to worsening congestive heart failure by 30% [317 vs 451 hospitalizations (p=0.0013)] and the number of hospitalizations due to cardiovascular causes by 16% (649 vs 773 hospitalizations (p=0.029)].

The metoprolol CR/XL group had a slightly lower risk of permanently early discontinuation of study drug due to all causes and due to worsening heart failure.

Treatment with metoprolol CR/XL improved congestive heart failure when compared to placebo. However, only 3.6% of all patients randomized were in NYHA Class IV (Table 2.9.2.2., page 19) and, therefore, no conclusion can be drawn from this study on the efficacy of metoprolol treatment in patients with advanced congestive heart failure. There is reluctance from the part of physicians to treat patients with advanced congestive heart failure with beta blockers because of concerns regarding adverse effects. However, there is a partial report in the literature of a meta-analysis of all studies (published plus unpublished metoprolol CR/XL data and results of treatment with bisoprolol and carvedilol) in which beta blockers were given to NYHA Class IV patients (10). Criteria for inclusion were similar for those listed in this protocol. For all NYHA Class IV patients, there was a pooled relative reduction in mortality of 29% with beta blocker vs placebo with a point estimate of 0.67 and 95% CI of 0.59-0.65. Because this is a partial report, it cannot be used to support an indication of metoprolol CR/XL for NYHA Class IV patients until the manuscript is published.

Only a 0.6 % of patients randomized in this study were 80 years of age or older. Therefore, more studies are needed in this category of patients.

There were more patients in the metoprolol CR/XL group in need of cardiac transplantation, the number was small and the difference was not significant. Therefore it cannot be claimed that treatment with metoprolol CR/XL reduced the need for cardiac transplantation.

Most patients reached the goal of being titrated at the highest dose of metoprolol CR/XL at last available visit (63 % metoprolol CR/XL 200 mg od, 86 % metoprolol CR/XL 100 mg od or higher). The mean daily dose of study drug at the end of the study in the metoprolol CR/XL was 159 mg od and 179 mg in the placebo group.

Metoprolol CR/XL treated patients tended to enjoy a better quality of life.

Patients treated with metoprolol CR/XL had a slightly lower risk of permanent early discontinuation of study drug due to all causes and for worsening heart failure.

There were deficiencies in laboratory determinations. Few chemistry measurements were done at baseline (sodium, potassium and creatinine) and they were not repeated at the end of the study. Determinations of liver and renal function were not done systematically. Left ventricular ejection fraction was measured only at baseline thus depriving of the opportunity to evaluate another potentially valuable endpoint.

Probably because most studies were done in Europe, a preponderant number of patients were white (94%). Blacks were 5 % of the total population, Asians 0.4 % and others 0.4 %. These numbers do not represent the typical distribution of the American population.

2.9.4. Safety Evaluation. 2.9.4.1. Adverse Events.

2.9.4.1.1. Summary of Adverse Events. Adverse events were reported for 785 of 1990 patients (39.4 %) randomized to metoprolol CR/XL and for 886 of 2001 patients (44.3 %) randomized to placebo. A summary of adverse events is shown in the following Table:

Table 2.9.4.1.1.

Summary of Adverse Events

Summary of Adverse Events	Metoprolol CR/XL N=1990	Placebo N=2001
Number (%) of patients with:		
Adverse Event	785 (39.4)	886 (44.3)
Fatal Adverse Event	145 (7.3)	217 (10.8)
Non-fatal Adverse Event	664 (33.4)	751 (37.5)
Non-clinical Serious Adverse Event	133 (6.9)	149 (7.4)
Drug stopped due to Adverse Event	205 (10.3)	245 (12.2)

2.9.4.1.2. Most Common Adverse Events. Number (%) of patients with the most commonly reported adverse event (at least 1% of the patients in any of the treatment groups) are shown in the following Table. The adverse events are ordered by descending frequency by column metoprolol CR/XL.

Table 2.9.4.1.2.

Most Commonly Reported Adverse Events [N(%)]

Adverse Events (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Cardiac failure/cardiac failure aggravated	279 (14)	379 (19)
Sudden death	79 (4)	132 (6)
Angina pectoris/angina pectoris aggravated	71 (3.6)	90 (4.5)
Myocardial infraction	46 (2.3)	48 (2.4)
Pneumonia	40 (2)	38 (1.9)
Cerebrovascular disorder	37 (1.9)	41 (2)
Chest pain	36 (1.8)	45 (1.2)
Dizziness/vertigo	35 (1.8)	21 (1)
Fibrillation atrial[1]	38 (1.7)	54 (2.7)
Dyspnea/dyspnea aggravated	30 (1.5)	27 (1.3)
Syncope	30 (1.5)	25 (1.2)
Bradycardia	29 (1.5)	9 (0.4)
Accident and/or injury	27 (1.4)	16 (0.8)
Coronary artery disorder	26 (1.3)	22 (1.1)
Tachycardia ventricular/arrhythmia aggravated	26 (1.3)	35 (1.7)
Hypotension	22 (1.1)	13 (0.6)
Diabetes mellitus/diabetes mellitus aggravated	21 (1.1)	12 (0.6)
Abdominal pain	20 (1)	22 (1.1)
Fatigue	20 (1)	14 (0.7)
Bronchitis/bronchitis aggravated	15 (0.8)	20 (1)
Fibrillation ventricular	12 (0.6)	22 (1.1)

[1] Newly developed atrial fibrillation as compared to medical history at baseline was reported for 22 patients in the metoprolol CR/XL group and for 45 patients in the placebo group.

2.9.4.1.3. Patients with Adverse Events by System Organs. The sponsor submits an extensive Table in which the number (%) of patients with adverse events by system organ are listed. From this Table, events with an incidence of 0.5 % or higher were selected and presented in the following Table:

Table 2.9.4.1.3.

Adverse Events by System Organ

System Organ Class Adverse Event (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Total number (%) of patients with Adverse Events	785 (39.4)	886 (44.3)
Muscle-Skeletal System Disorders		
Fracture	16 (0.8)	16 (0.8)
Hernia	7 (0.4)	14 (0.7)
Central and Peripheral Nervous System Disorders		
Dizziness	22 (1.1)	16 (0.8)
Vertigo	13 (0.7)	6 (0.3)
Gastrointestinal System Disorders		
Abdominal pain	20 (1.0)	22 (1.1)
Diarrhea	11 (0.6)	9 (0.4)
Metabolic and Nutritional Disorders		
Dehydration	13 (0.7)	10 (0.5)
Diabetes Mellitus[1]	15 (0.8)	7 (0.3)
Gout	9 (0.5)	7 (0.3)
Cardiovascular Disorders		
Cardiac Failure	166 (8.3)	231 (11.5)
Cardiac Failure Aggravated	153 (7.7)	211 (10.5)
Hypotension	22 (1.1)	13 (0.6)
Syncope	30 (1.5)	25 (1.2)
Myo Endo Pericardial and Valve Disorders		
Angina Pectoris	71 (3.6)	86 (4.3)
Myocardial Infarction	46 (2.3)	48 (2.4)
Heart Rate and Rhythm Disorders		
Bradycardia	29 (1.5)	9 (0.4)
Fibrillation Atrial	33 (1.7)	54 (2.7)
Fibrillation Ventricular	12 (0.6)	22 (1.1)
Tachycardia	3 (0.2)	11 (0.5)
Tachycardia Ventricular	22 (1.1)	32 (1.6)
Vascular (Extracardiac) Disorders		
Cerebrovascular Disorder	37 (1.9)	41 (2.0)
Peripheral Ischemia	18 (0.9)	10 (0.9)
Respiratory System Disorders		
Bronchitis	13 (0.7)	19 (0.9)
Dyspnea	29 (1.5)	26 (1.3)
Pneumonia	40 (2.0)	38 (1.9)
Respiratory Infection	4 (0.2)	12 (0.6)

Table 2.9.4.1.3. (Continued)

Adverse Events by System Organ

System Organ Class Adverse Event (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Red Blood Cell Disorders		
Anemia	10 (0.5)	9 (0.4)
Urinary System Disorders		
Renal Failure Acute	14 (0.7)	5 (0.2)
Renal Failure NOS	11 (0.6)	9 (0.4)
Reproductive Disorders Male		
Prostate Disorder	11 (0.6)	6 (0.3)
Body as a Whole-General Disorders		
Accident and/or Injury	27 (1.4)	16 (0.8)
Chest Pain	36 (1.8)	45 (2.2)
Fatigue	20 (1.0)	14 (0.7)
Sudden Death	79 (4.0)	132 (6.6)

[1] A new diagnosis of diabetes mellitus was reported for four patients in each randomization group as compared to medical history recorded at baseline.

2.9.4.1.4. Serious Adverse Events. Among serious adverse events, those not leading to death, those leading to death, and those leading to discontinuation can be considered.

2.9.4.1.5. Adverse Events Leading to Death. The number (%) of adverse events leading to death, ordered by descending frequency by column metoprolol CR/XL is shown in the following Table:

Table 2.9.4.1.5.

Adverse Events Leading to Death

Adverse Events (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Sudden death	79 (4.0)	132 (6.6.)
Cardiac failure/cardiac failure aggravated	30 (1.5)	58 (2.9)
Cerebrovascular disorder	7 (0.4)	2 (0.1)
Myocardial infarction	7 (0.4)	7 (0.3)
Cerebral hemorrhage	3 (0.2)	0
Pulmonary carcinoma	2 (0.1)	4 (0.2)
Accident and/or injury	1 (0.1)	0
Cardiac arrest	1 (0.1)	1 (<0.1)

Table 2.9.4.1.5 (Continued)

Adverse Events Leading to Death

Adverse Events (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Cholecystitis	1 (0.1)	0
Colon carcinoma	1 (0.1)	2 (0.1)
Gastric carcinoma	1 (0.1)	1 (<0.1)
GI hemorrhage	1 (0.1)	0
Hepatic neoplasm, malignant	1 (0.1)	0
Intestinal gangrene	1 (0.1)	0
Leukemia acute	1 (0.1)	0
Multiorgan failure	1 (01)	0
Pancreas neoplasm	1 (01)	0
Pancreatitis	1 (0.1)	0
Peritonitis	1 (0.1)	0
Pneumonia	1 (0.1)	0
Renal carcinoma	1 (0.1)	0
Renal failure NOS	1 (0.1)	0
Sepsis	1 (0.1)	2 (0.1)
Aortic aneurysm	0	1 (<0.1)
Fibrillation ventricular	0	2 (0.1)
Ileus	0	2 (0.1)
Larynx carcinoma	0	1 (<0.1)
Suicide attempt	0	1 (<0.1)
Urosepsis	0	1 (<0.1)

2.9.4.1.6. Serious Adverse Events other than Deaths. The number (%) of patients by the most commonly reported serious adverse events other than those leading to death (at least 1 % of patients in any of the treatment groups) are given in the following Table. The adverse events are ordered by descending frequency by column metoprolol CR/XL.

Table 2.9.4.1.6.

Serious Adverse Events other than those Leading to Death

Adverse Event (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Cardiac failure/cardiac failure aggravated	244 (12.3)	343 (17.1)
Angina pectoris/angina pectoris aggravated	71 (3.6)	88 (4.4)
Myocardial infarction	39 (2.0)	41 (2.0)
Pneumonia	39 (2.0)	38 (1.9)
Fibrillation atrial	33 (1.7)	52 (2.6)
Cerebrovascular disorder	30 (1.5)	39 (1.9

Table 2.9.4.1.6. (Continued)

Serious Adverse Events other than those Leading to Death

Adverse Event (preferred term)	Metoprolol CR/XL	Placebo
Chest pain	30 (1.5)	44 (2.2)
Syncope	30 (1.5)	25 (1.2)
Accident and/or injury	26 (1.3)	16 (0.8)
Coronary artery disorder	26 (1.3)	22 (1.1)
Tachycardia ventricular/arrhythmia aggravated	26 (1.3)	35 (1.7)
Diabetes mellitus/diabetes mellitus aggravated	21 (1.1)	12 (0.6)
Abdominal pain	15 (0.8)	22 (1.1)
Fibrillation ventricular	12 (0.6)	20 (1.0)

2.9.4.1.7. Adverse Events Leading to Discontinuation. The number (%) of patients with the most commonly reported adverse event leading to discontinuation of study drug (at least 0.5 % of the patients in any of the treatment groups) is given in the following Table.

Twenty (20) patients that stopped intake of study drug during the 5 days prior to date of death are included although the clinical event criteria for permanent early discontinuation was not fulfilled.

Table 2.9.4.1.7.

Adverse Events Leading to Discontinuation

Adverse Event (preferred term)	Metoprolol CR/XL N=1990	Placebo N=2001
Cardiac failure/cardiac failure aggravated	82 (4.1)	121 (6.0)
Bradycardia	16 (0.8)	5 (0.2)
Dyspnea/dyspnea aggravated	15 (0.8)	12 (0.6)
Fatigue	14 (0.7)	9 (0.4)
Dizziness	13 (0.7)	6 (0.3)
Myocardial infarction	13 (0.7)	17 (0.8)
Hypotension	12 (0.6)	5 (0.2)
Angina pectoris/angina pectoris aggravated	9 (0.5)	20 (1.0)
Sudden death	7 (0.4)	9 (0.5)
Cerebrovascular disorder	6 (0.3)	11 (0.5)
Fibrillation atrial[1]	2 (0.1)	17 (0.8)

[1] Newly developed atrial fibrillation as compared to medical history at baseline was reported as an adverse reaction leading to discontinuation for one patient in the metoprolol CR/XL group and for 14 patients in the placebo group.

2.9.4.2. Assessment of Safety. The total number of all adverse events, the number of fatal adverse events, non-fatal serious adverse events, non-clinical serious adverse events and the number of patients who had to stop medication due to adverse events was lower in those treated with metoprolol CR/XL than in placebo controls.

The symptoms of fatigue, dizziness, shortness of breath, bradycardia, syncope, hypotension, dyspnea, etc. occurred more frequently in metoprolol CR/XL treated patients than in placebo and are known to be related to the administration of beta blockers.

Cardiac failure/worsening of cardiac failure, sudden death, angina pectoris/worsening of angina pectoris, chest pain, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, were reported more frequently in the placebo group than in metoprolol CR/XL treated patients.

It is noteworthy that 14 (0.7 %) patients in the metoprolol CR/XL group were listed as having developed acute renal failure versus only 5 (0.2 %) in the placebo group (Table 2.9.4.1.3, Page 41). One patient in the active treatment group died with the diagnosis of renal failure versus none in the placebo group (Table 2.9.4.1.5, page 42). It may be possible that congestive heart failure makes patients susceptible to the nephrotoxic effects of this beta-blocker.

3.0. Study S-996 (Volumes 36 through 43 of 101).

3.1. Title of Study: "A Study to Compare the Tolerability of Metoprolol Succinate Extended Release Tablets versus Placebo in Patients with Moderate to Severe Chronic Heart Failure".

3.2. Principal Investigators and Sites of Investigation:	J Anderson, MD LDS Hospital Salt Lake City, UT	M Georghiade , MD Northwestern Memorial H Chicago, Ill

S Goldstein, MD Henry Ford Hospital Detroit, MI	S Gottlieb, MD U Maryland Medical Center Baltimore, MD	M Jessup, MD Hahnemann Hospital Philadelphia, PA	R Karlsberg. MD Cardiovascular Research Institute Beverly Hills, CA

HL Kennedy, MD
St. John's Medical Center
St. Louis, MO

3.3 Objectives. 3.3.1. The primary objectives of this study were:

- To compare the tolerability and safety of metoprolol CR/XL to placebo in patients with clinically stable moderate to severe chronic heart failure. The primary

variable to assess tolerance was the need to permanently discontinue study medication due to worsening heart failure.

The incidence of worsening heart failure resulting in unscheduled clinic visits, emergency room visits, or hospitalization was also determined.

3.3.2. Secondary objectives of this study were:

- To assess the effects of metoprolol CR/XL on changes in ventricular function, as measured by changes in left ventricular ejection fraction, changes in norepinephrine, neuropeptide-Y and n-terminal atrial natriuretic factor, to monitor digoxin levels and to determine metoprolol CR/XL trough blood plasma concentration at steady state.

- Twenty-four hour Holter monitoring data was obtained in all patients for the purpose of evaluating changes in mean heart rate, heart rate variability, incidence and frequency of cardiac arrhythmias, and alterations of the signal average electrocardiogram.

  Changes in clinical status and signs and symptoms in quality of life were also recorded at each time point in the study.

- Safety data including the incidence of adverse events and monitoring of vital signs, congestive heart failure signs and symptoms, weight, electrocardiogram, hematology, blood chemistry, and urinalysis were evaluated in this patient population.

3.4. Inclusion Criteria. Male and female patients, 18 years of age or older, were eligible to enter this study. Female patients had to be either post-menopausal for two years, surgically sterile, or to be using an acceptable method of contraception. All women who were not post-menopausal were required to have a negative pregnancy test.

Patients had to have a history of NYHA Class III or IV of ischemic or non-ischemic etiology. At enrollment, patients could have been NYHA Class II, III, or IV. The left ventricular ejection fraction was required to be less than 40% within 30 days of randomization.

For a minimum of four weeks prior to enrollment, medication for congestive heart failure must have included a stable daily dose of an angiotensine converting enzyme inhibitor or, if not tolerated, stable daily doses of hydralazine and isosorbide dinitrate. Diuretics and/or digoxin may also have been administered as warranted by the patient clinical condition. Patients receiving digoxin must have been on a stable condition for four weeks previous to study enrollment. The dose of diuretics could have been varied as long as it stayed within a given stable range for the patient, as determined by the investigator.

The patient must have signed a written informed consent.

3.5. Exclusion Criteria. Exclusion criteria were: congestive heart failure due to or associated with uncorrected primary valvular disease, primary pericardial disease, known amyloidosis, active myocarditis, malfunctioning artificial valve; acute myocardial infarction, coronary angioplasty, or other invasive intervention in the coronary arteries, exertional or unstable angina, or cardiac surgery within 60 days of study; patients requiring hospitalization for congestive heart failure within 30 days of study medication; patients with I° heart block with a PR interval greater than 0.24 seconds, heart block greater than I°, sinus bradycardia defined as heart rate of less than 60 beats/minute unless they have an implanted pacemaker; patients with clinically obstructive lung disease requiring bronchodilator therapy; patients with brittle diabetes mellitus.

Patients receiving calcium channel antagonists, propafenone or intravenous inotropic agents, MAO inhibitors or tricyclic antidepressant agents within 30 days of study enrollment, or patients receiving beta adrenergic antagonists (including sotalol) or amiodarone within 6 months of study enrollment; the presence of recent history of any significant medical condition which in the judgement of the investigator would likely prevent the patient from participating or completing the study including primary renal disease or a serum creatinine greater than 3.0 mg/dl or primary liver disease or a serum bilirubin greater than 2.0 mg/dl.

Patients with a history of carcinoma except basal cell carcinoma or documented cancer in complete remission five years or more; patients participating in another investigational drug study within the previous 30 days; patients with a history of drug or alcohol abuse within the previous year; patients previously enrolled in this study; patients with known intolerance to metoprolol; women who were pregnant or lactating; patients with a planned hospitalization during the study; patients with an implanted defibrillator; history of cardiac arrest; patients on a list for heart transplantation.

3.6. Treatment Discontinuation. Patients were free to discontinue their participation in the study at any time. Patients participating in the study could have been discontinued at any time at the discretion of the investigator.

3.7. Period of Study. The first participant was enrolled into the study on February 1994. The last patient completed the study on September 1996. Duration of treatment was 26 weeks with an optional extension period of up to 18 months.

3.8. Number of patients planned. Approximately 60 patients were to be randomized into the study at 7 centers.

3.9. Drug Dosage and Mode of Administration. Metoprolol CR/XL : 12.5 mg. 25 mg, 50 mg, 100 mg and 150 mg once daily was administered in multiples of 25 and 50 mg (extended release) oral tablets. The 12.5 mg tablet was achieved by dividing the 25 mg tablet.

3.10. Study Design. This was a multi-center, randomized, double-blind, placebo-controlled study. Ascending doses of metoprolol CR/XL were 12.5, 25, 50, 100 and 150 mg once daily. The study consisted of a screening phase, a dose titration phase, a maintenance phase and an optional extension period. The study design is shown in Figure 9 and the schedule of procedures in Table 3.10:1.

3.10.1. Screening. At screening an informed consent was reviewed by the patient and witnessed. Patients had a medical history, physical examination, laboratory tests, 12-lead electrocardiogram, Holter monitor, congestive heart failure assessment, vital signs and quality of life assessment. Chest x-ray and radionuclide ventriculography were performed if they had not been done in he last 30 days.

3.10.2. Dose Titration Phase. The dose titration period was eight weeks in duration (week 0 through 7). Patients with a confirmed left ventricular ejection fraction less than 40 % who met the inclusion and exclusion criteria were subsequently randomized to initially receive at week 0 either metoprolol CR/XL 12.5 mg once daily in the morning (half a 25 mg tablet) or placebo at approximately the same time with or immediately following the morning meal. Patients were instructed to swallow the tablets whole and not to chew or crash them. Patients were instructed not to take their dose of study medication on the morning of study visits until after collection of a blood sample to determine trough drug concentration. Randomization was 2:1 metoprolol CR/XL and placebo respectively.

Patients returned to the clinic at weekly intervals from week 1 through 5 for dose titration. Patients may have returned during weeks 6 and 7 if further dose titration was needed.

The dose of metoprolol CR/XL or matching placebo was to be increased 25, 50, 100 or 150 mg (each administered once daily) at weekly visits. Dose escalation was to proceed to the maximum dose of 150 mg unless, in the judgement of the investigator, dose-limiting clinical signs and/or symptoms developed. If by the week 4 visit the maximally tolerated dose was less than 25 mg (if the patient had not tolerated 25 mg for one week) the patient was discontinued from the study.

3.10.3. Maintenance Period. The maintenance period was of 18 weeks duration (weeks 8 through 26). From week 8 to 16 dose increases above the week 7 level were not permitted. At week 16 the patient, if stable, might have the dose increased to the next higher level if the 150 mg dose had not yet been reached. Patients continue to receive blinded study medication at the maximally tolerated dose obtained by week 16 (25 to 150 mg/day) for the remaining of the 26 week treatment period.

From weeks 1 through 8, and at week 17, a blood sample was obtained one week after all dose increases to determine the trough metoprolol CR/XL plasma concentration. Only one metoprolol CR/XL plasma concentration was required for each study medication dose level. At these visits, assessments of adverse events, vital signs, and congestive heart failure assessment were also performed. Patients were seen at the clinic at treatment

post-menopausal) and a 12-lead electrocardiogram were repeated at weeks 8 and 26. At treatment week 26 a physical examination, quality of life assessment, chest x-ray and a radionucleide ventriculogram to measure left ventricular ejection fraction were performed.

3.10.4. Extension Period. Patients who successfully completed the 26-week double-blind phase were eligible to enter an optional extension period of up to 18 months to assess the long term safety of metoprolol CR/XL.

Figure 8.

Study Design

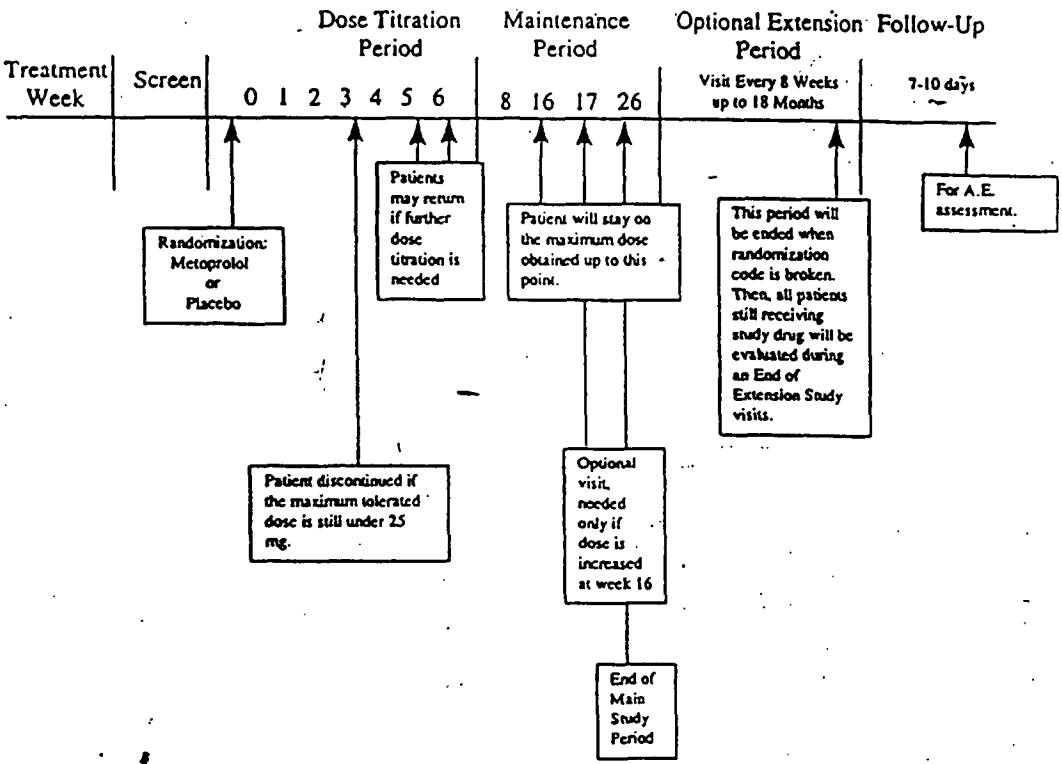


Table 3. 10.1.

Schedule of Procedures

		Dose Titration Period								Maintenance Period				Optional Extension Period	End of Extension Visit	Follow-Up
Treatment Week	Screen	0	1	2	3	4	5	6	7	8	16	17	26[c]	Every 8 weeks		7-10 days[f]
Procedures																
Consent Signed	X															
Medical History	X															
Physical Examination	X												X		X	
Clinical Laboratory Tests[g]	X									X			X		X[d]	
12-Lead ECG	X									X			X		X	
Chest X-Ray[a]	X												X			
RVG[e]	X												X			
Holter Monitor	X									X	X		X		X	
Randomization		X														
Dose Titration			X	X	X	X	X[b]	X[b]	X[b]		X[c]					
Drug Blood Levels			X	X	X	X	X	X[d]	X[d]	X		X[d]				
CHF Assessment	X		X	X	X	X	X	X[d]	X[d]	X	X	X[d]	X	X	X	
Vital Signs/Weight	X		X	X	X	X	X	X[d]	X[d]	X	X	X[d]	X	X	X	
Quality of Life Assessment	X												X	X	X	
Adverse Event Assessment			X	X	X	X	X	X[d]	X[d]	X	X	X[d]	X	X	X	X

[a] To be performed if one was not done in the past 30 days.
[b] Dose could be increased to next Level if not already at Level 5 (150 mg).
[c] To be performed if patient came in for this optional visit which was required after study medication dose increase.
[d] Pro-ANF, Norepinephrine and NPY were not to be done at this visit.
[e] To be performed at early termination. RVG to be repeated only if 8 weeks elapsed since the last one was performed.
[f] A telephone call or clinic visit to assess adverse events was to be made 7 to 10 days after discontinuation of study medication.
[g] A serum pregnancy test was to be done on all females less than two years post-menopausal

3.10.5. Laboratory Determinations. Venous blood samples and urine samples were collected at the screening visit and treatment weeks 8, 26 and at the extension period.

The following laboratory tests were performed:

Blood Chemistry
- Creatinine mg/dl
- Blood urea nitrogen mg/L
- Sodium mEq/L
- Chloride mEq/L
- Carbon dioxide mEq/L
- Potassium mEq/L
- Total bilirubin mg/dl
- Alkaline phosphatase U/L
- Serum Glutamic Oxaloacetic Transaminase (SGOT/ST) U/L
- Serum Glutamic Pyruvic Transaminase (SGPT/ALT) U/L
- Glucose mg/dl
- Digoxin mcg/dl
- Pro-ANF pmol/L*
- Norepinephrine mg/ml*
- Neuropeptide-Y*

* Not required for end of extension study visit

Hematology
- Complete blood count and differential
- Platelet count per μL

Urinalysis
- pH
- Specific gravity
- Albumin (protein)
- Glucose

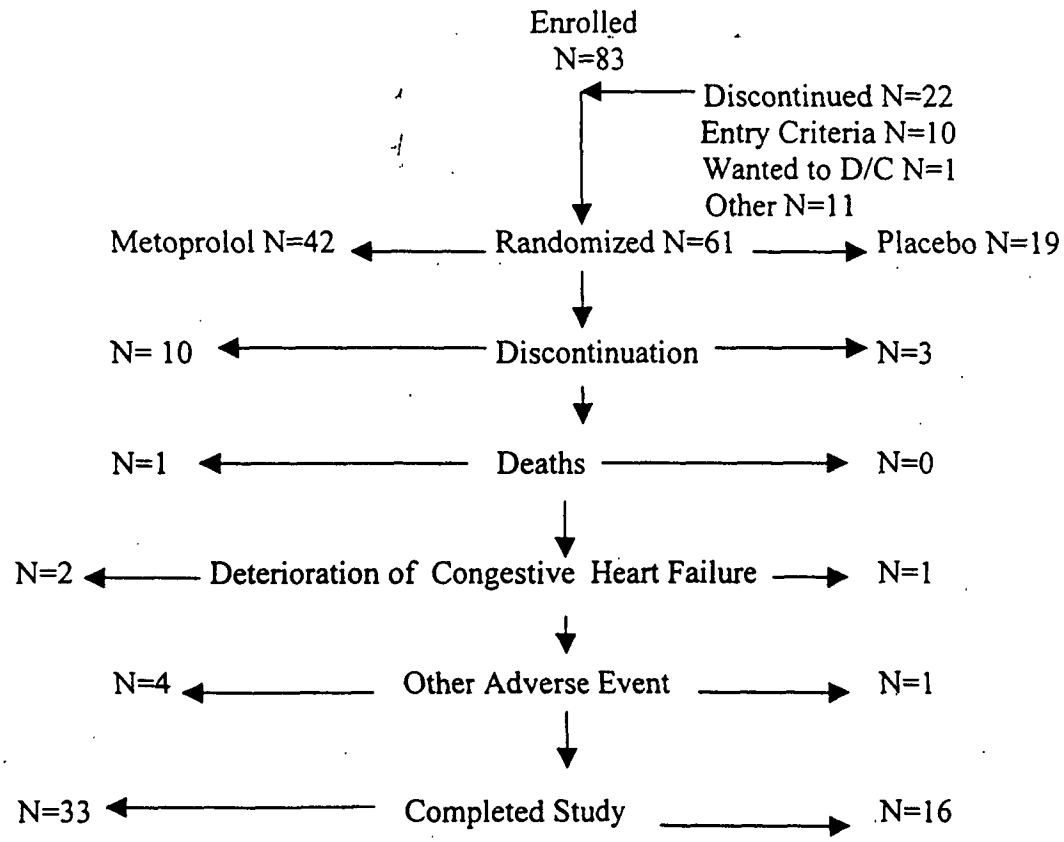
Serum pregnancy (only for women who were less than two years menopausal)

Serum metoprolol levels.

3.11. Results. 3.11.1. Disposition of Patients. The disposition of patients is given in the following Graph:

Figure 9.

Disposition of Patients



Of the 83 patients enrolled in the study, 22 were not randomized. Ten of them failed to meet the inclusion criteria of a left ventricular ejection fraction of < 40 % within 30 days on enrollment. Two patients expired, one patient had bradycardia, one patient had a first degree atrial-ventricular block, one had unstable angina, one had a complete heart block, two were on excluded medication, two decided not to participate in the study, one had a persisting elevation in bilirubin, one was hospitalized for worsening congestive heart failure, and one had surgery for abdominal aneurysm.

All the 61 randomized patients received at least one dose of study medication and had at least one observation after baseline. These patients were included in the All Patients Treated analysis. Of the 61 randomized patients, 49 completed the study through week 26.

Thirteen randomized patients did not complete the study. One patient randomized to metoprolol CR/XL treatment died. Two patients treated with metoprolol CR/XL and one patient on placebo had worsening of congestive heart failure. One patient on metoprolol CR/XL had initiation of amiodarone therapy, one withdrew consent, and one had scheduling difficulties. One patient in the placebo group had difficulties with transportation.

3.11.2. Demographic Characteristics at Baseline. The demographic characteristics are given in the following Table:

Table 3.11.2.

Demographic Characteristics.

Treatment Groups
All Patients Randomized

Variable	Metroprolol CR/XL N=42	Placebo N=19	All Patients N=61
Gender N (%)			
Male	30 (71%)	16 (84%)	46 (75%)
Female	12 (29 %)	3 (16 %)	15 (25%)
Race N (%)			
Caucasian	23 (55%)	12 (63%)	35 (57%0
Black	17 (41%)	7 (37%)	24 (39%)
Asian	1 (2%)	0 (0%)	1 (2%)
Other	1 (2%)	0 (0%)	1 (2%)
Age (years)			
Range	23-83	42-92	23-92
Mean	60	63	61
Weight (Kg)			
Mean	81	91	81
Height (cm)			
Mean	171	174	172

Table 3.11.2.(continued)

Demographic Characteristics

Treatment Groups
All Patients Randomized

Variable	Metroprolol CR/XL N=42	Placebo N=19	All Patients N=61
Tobacco Use			
Nonsmokers	14 (33%	2 (11%)	16 (26%)
Past Smokers	23 (55%)	13 (68%)	36 (59%)
Current Smokers	5 (12%)	4 (21%)	9 (15%)
Alcohol Use			
Non-alcohol users	17 (41%)	4 (21%)	21 (34%)
Past alcohol users	14 (33%)	6 (32%)	20 (33%)
Current alcohol users	11 (26%)	9 (47%)	20 (33%)
Mean Baseline LVEF	0.27	0.20	0.27
Range	0.11-039	0.09-0.39	0.09-0.39
Duration Left Ventricular Failure (at baseline)			
< 1 year	10 (24%)	5 (26%)	15 (25%)
1-5-years	25 (60%)	9 (47%)	34 (56%)
> 5 years	7 (17%)	5 (26%)	12 (20%)
Primary cause of Left Ventricular Failure N(%)			
Coronary artery disease	13 (31%)	9 (47%)	
Dilated cardiomyopathy	25 (59%0	7 (37%)	
Arterial hypertension	2 (5%)	1 (11%)	
Valvular heart disease	1 (2%)	1 (5%)	
Other	1 (2%)	0 (0%)	
Concomitant Right Ventricular Failure (baseline)	14 (33%)	3 (16%)	17 (28%)
Concomitant Valvular Heart Disease (baseline)	19 (46%)	9 (47%)	8 (46%)
Mitral regurgitation (baseline)	17 (41%)	9 (47%)	26 (43%)
Arrhythmia (baseline)	15 (36%)	7 (40%)	22 (36%)

Statistical calculations were not performed by the sponsor who considered that there were no apparent differences between the two groups.

3.11.3. Efficacy Results

3.11.3.1. Dose Tolerance. Dose tolerance was assessed in terms of the proportion of patients who were maintained on a stable regimen of study treatment of at least 25 mg

once daily without experiencing dose-limiting symptoms of heart failure. The number of patients who achieved the maximum dose is given in the following Table:

Table 3.11.3.1.

Maximum Dose Level Achieved by all Treated Patients [N (%)]

Treatment (mg)	12.5	25	50	100	150	Total
Metoprolol CR/XL	3 (7)	1 (2)	4 (10)	12 (29)	22 (52)	42
Placebo	0	0	1 (5)	3 (16)	15 (79)	19

The majority of patients in the metoprolol CR/XL group (52 %) and in the placebo group (79 %) achieved dose of 150 mg, the maximum allowable dose in this study.

3.11.3.2. Health Care Visits Related to Heart Failure. The incidence of worsening heart failure resulting in unscheduled visits, emergency room visits, or hospitalization is summarized in the following Table:

Table 3.11.3.2.

Number of Patients with Healthcare Visits Related to Heart Failure

Type of Visit		Metoprolol CR/XL N=42	Placebo N=19
Visits to Hospital			
	No	38 (90.5%)	17 (89.5%)
	Yes	2 (4.8%)	2 (10.5%)
	Number of Visits [b]	2	4
Visits to Emergency Room			
	No	40 (95.2%)	19 (100%)
	Yes	0	0
	Number of Visits [b]	----------	----------
Unscheduled Visits to Clinic			
	No	34 (81%)	17 (89.5%)
	Yes	6 (14.3%)	2 (10.5%)
	Number of Visits [b]	17	4

[b]. A patient may have more than one visit. Thus, in the metoprolol CR/XL treatment group there was a total of 17 unscheduled visits to the clinic attributable to only 6 patients.

In each of the two groups there were 2 patients who had hospital admissions. Patients in the metoprolol CR/XL groups had more unscheduled visits that patients receiving placebo.

3.11.3.3. Left Ventricular Ejection Fraction Left ventricular ejection fraction (LVEF). by radionuclide ventricular including all treated patients [last value carried forward (LVCF) and observed cases] is shown in the following Table

Table 3.11.3.3.

Left Ventricular Ejection Fraction

LVEF	Metoprolol CR/XL			Placebo		
	N	Mean	Mean Change	N	Mean	Mean Change
LCCF						
Baseline	35	0.28	--------	16	0.26	----
Week 26	35	0.36	0.09 [a]	16	0.28	0.02
Observed Cases						
Baseline	33	0.28	---------	16	0.26	------
Week 26	33	0.37	0.09 [b]	16	0.28	0.02

a. p=0.015 for comparison of metoprolol CR/XL vs placebo
b. p=0.0014 for comparison of metoprolol CR/XL vs placebo

These results indicate that the metoprolol CR/XL group experienced a statistically significant improvement in LVEF compared with the placebo group.

3.11.3.4. Neurohormonal and Pro.ANF Levels. After discarding a single patient in the metoprolol CR/XL group with hor-epinephrine levels significantly elevated and outside accepted levels at week 26 the metoprolol CR/XL change from baseline became 0.03±292.36 pg/ml and –6.43±135.40 for the placebo group.

An analysis of Pro-ANF is not included in this report.

3.11.3.5. Digoxin Levels. The changes in digoxin levels (mcg/L) [M(std)] from baseline values by daily total dose of metoprolol CR/XL in all randomized patients is given in the following Table

Table 3.11.3.5.

Digoxin levels

Digoxin Level Change from Baseline	Treatment Group: Metoprolol CR/XL 12.5mg	25 mg	50 mg	100 mg	150 mg	Total		Placebo	
Week 8 N	0	0	5	9	12	26		11	
	Mean (std)		0	0	-0.05	0.07	-0.02	0	-0.04
	(0)	(0)	(0.52)	(0.32)	(0.36)	(0.37)		(0.31)	
Week 26 N	0	3	2	8	9	22		11	
Mean (std)	0	0.32	-0.15	-0.06	0.27	0.12		0.03	
	(0)	(0.73)	(0.07)	(0.52)	(0.50)	(0.52)		0.52	

3.11.3.6. Metoprolol CR/XL Trough Plasma Concentrations. Blood samples for trough levels of metoprolol CR/XL were drawn 20-28 hours after a dose, one week after upwards titration. A summary of the trough levels at each week are shown in the following Table:

Table 3.11.3.6.

Mean Metoprolol CR/XL Trough Plasma Concentration (mmol/L)

	Metoprolol CR/XL Dose				
	12.5 mg	25 mg	50 mg	100 mg	150 mg
Week 1					
N	15	0	0	0	0
Mean (SD)	23.89(31.63)				
Week 2					
N	2	18	0	0	0
Mean (SD)	29.15(26.52)	25.56(36.65)	0	0	0
Week 3					
N	2	3	18	0	0
Mean (SD)	71.10(88.95)	83.30(66.26)	49.64(81.16)	0	0
Week 4					
N	0	1	3	15	0
Mean (SD)		15.90(0)	91.10(74.73)	83.65(142.56)	0
Week 5					
N	0	1	2	6	8
Mean (SD)		5.80 (0)	18.20(9.33)	148.92(201.83)	204.06(287.5)
Week 6					
N	0	0	2	4	4
Mean (SD)	0	0	17.10(10.89)	52.23(36,52)	250(188)
Week 7					
N	0	0	0	4	2
Mean (SD)				79.13(66.55)	146(140)
Week 8					
N	0	0	2	3	11
Mean (SD)			26.85 (24.25)	85(71)	148(201)
Week 17					
N	0	0	0	1	0
Mean (SD)				14.40 (0)	

These results indicate that plasma concentrations of metoprolol CR/XL were dependent on the administered dose.

3.11.3.7. Clinical Symptoms. The mean change from baseline for the continuous clinical symptom scores (shortness of breath, fatigue, peripheral edema) were calculated for all treated patients and were as follows.

3.11.3.7.1. Shortness of Breath. At week 16, 24% of metoprolol CR/XL patients had improved as compared with 44% of placebo patients. By week 26, 30% of metoprolol CR/XL patients reported improvement compared with 38% of placebo patients.

3.11.3.7.2 Fatigue. At week 16, 41% of metoprolol CR/XL patients reported decreases in fatigue compared with 19% of placebo patients. At week 26, the proportion was almost equal: 33% of metoprolol CR/XL reported improvement compared with 31% of placebo patients.

3.11.3.7.3. Peripheral Edema. Throughout the study the majority of patients in both groups experienced no changes in degree of peripheral edema. Fewer improvements were seen at each time point in patients treated with metoprolol CR/XL.

3.11.3.7.4. Orthopnea and Paroxysmal Nocturnal Dyspnea. The percentage of patients complaining of orthopnea and paroxysmal nocturnal dyspnea tended to decrease from baseline to week 26 in both groups of patients.

3.11.3.8. New York Heart Association Categorization. Of the 33 patients in the metoprolol CR/XL group who completed the study, 14 (42%) experienced an improvement from baseline in the NYHA functional status at week 26. Of the 16 patients in the placebo treatment group who completed the study 8 (50%) experienced an improvement from base line in the functional status rating at week 26.

.3.11.3.9. Global Evaluation. The scale used for analysis of physician's and patient's global evaluation of overall status of heart failure was as follows: 0=much improved; 1=improved; 2=no change; 3=worse; 4= much worse.

Metoprolol CR/XL patients rated a mean improvement of 1.33 and placebo patients of 1.22. Physicians assessed a mean improvement for metoprolol CR/XL of 1.33 and for placebo of 1.28. These results indicate a general slight improvement.

3.11.3.10. Quality of Life. For each of the 21 items on the quality of life questionnaire a patient was asked to choose a rating from a six point Likert Scale from 0 (no), 1 (very little), to 5 (very much). The rating indicated how much a patient's heart condition had interfered with his or her lifestyle during the previous month. The lower the score, the better the quality of life. Negative values indicate an improvement in quality of life. Results are shown in the following Table:

Table 3.11.3.10.

Mean Quality of Life Scores. All Patient's Treated

Category	Metoprolol CR/XL N	Mean (SD)	Mean Change	Placebo N	Mean (SD)	Mean Change
Total Score						
Baseline	41	39.85	-----	19	30.37	-------
Week 26	38	29.97	-8.87 (28.26)	15	26.16	-4.84 (20.65)
Physical Score						
Baseline	41	17.20	------	19	13.63	------
Week 26	38	12,55	-4.30 (11.15)	15	10.78	-3.42 (9.62)
Emotional Score						
Baseline	41	8.51	-----	19	5.95	-------
Week 26	38	5.69	-2.53 (6.38)	14	6.29	0.43 (4.67)

In total score and in physical score, there was improvement in both groups, was larger in total score for metoprolol CR/XL and almost the same for both groups for physical score. In emotional score, there was improvement for metoprolol CR/XL and almost no change for placebo.

3.11.3.11. Cardiovascular Specific Clinical Signs. The number and percentage of patients with cardiovascular specific clinical signs is shown in the following Table:

Table 3.11.3.11.

Number (%) of Patients with Cardiovascular Specific Clinical Signs

Variable	Metoprolol, CR/XL N (%)	Placebo N (%)
S3 gallop		
Baseline	17/42 (41%)	7/19 (37%)
Week 26	10/33 (30%)	3/16 (19%)
S4 gallop		
Baseline	14/42 (33%)	9/19 (47%)
Week 26	10/33 (30%)	4/16 (25%)
Pericardial friction rub		
Baseline	0/42 (0%)	0/19 (0%)
Week 26	0/33 (0%)	0/19 (0%)

Table 3.11.3.11. (Continued)

Number (%) of Patients with Cardiovascular Specific Clinical Signs

Variable	Metoprolol, CR/XL N (%)	Placebo N (%)
Rales		
Week 26	3/33 (9%)	0/16 (0%)
Jugular vein distension		
Baseline	2/42 (5%)	0/19 (0%)
Week 26	3/33 (9%)	0/16 (0%)
Murmur		
Baseline	21/42 (50%)	8/19 (42%)
Week 26	12/33 (36%)	5/16 (31%)
Hepatomegaly		
Baseline	6/42 (14%)	3/19 (16%)
Week 26	2/33 (6%)	0/16 (0%)
Splenomegaly		
Baseline	0/42 (0%)	0/19 (0%)
Week 26	0/33 (0%)	0/16 (0%)
Hepatojugular reflex		
Baseline	2/42 (5%0	1/19 (5%)
Week 26	4/33 (12%)	0/16 (0%)

In both parameters, occurrences for both treatment groups were similar at baseline and week 26.

3.11.3.12. Holter Measurements. Measurements obtained by Holter monitoring are shown in the following Table:

Table 3.11.3.12.

Summary of Holter Data

		Metoprolol CR/XL			Placebo	
Holter Heart Rate) (bpm)	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change From Baseline (SD)
Average Heart Rate						
Baseline	40	78 (8.7)	----------	18	85 (10.3)	----------
Week 8	34	67 (9.7)	-11 (6.6)	16	84 (10.3)	-1.1 (6.4)
Week 16	31	66 (9.5)	-11 (6.9)	13	80 (9.2)	-5.4 (6.3)
Week 26	31	67 (9.1)	-10 (7.2)	13	81 (8.1)	-5.2 (7.9)

Table 3.11.3.12. (Continued).

Summary of Holter Data

Holter Heart Rate) (bpm)	N	Metoprolol CR/XL Mean (SD)	Mean Change from Baseline (SD)	N	Placebo Mean (SD)	Mean Change From Baseline (SD)
Holter Ventricular Arrhythmias						
Total Number Ectopic Beats						
Baseline	40	2713 (4371)	----------	19	2640 (3417)	----------
Week 8	34	1414 (2073)	-983 (4816)	17	2437 (3729)	-193 (3218)
Week 16	31	2081 (3690)	-318 (4816)	14	1985 (4027)	-562 (1984)
Week 26	31	1702 (3024)	-768 (3951)	14	1886 (2797)	-433 (2730)
Average Number Ectopic Beats						
Baseline	40	128 (196)	----------	19	115 (149)	----------
Week 8	34	61 (87)	-56 (130)	17	103 (157)	-11 (132)
Week 16	31	91 (165)	-27 (186)	14	84 (167)	-23 (82)
Week 26	31	74 (129)	-48 (150)	14	87 (133)	-16 (117)
Non-Sustained Tachycardia						
Baseline	40	6.2 (18.9)	----------	19	4.7 (7.9)	----------
Week 8	34	1.0 (2.8)	-2.7 (5.6)	17	5.8 (16)	1.3 (9.2)
Week 16	31	1.4 (3.9)	-2.7 (7.7)	14	8.2 (28.2)	3.9 (20.9)
Week 26	31	1.4 (2.6)	-2.7 (6.7)	14	4.1 (7.9)	-0.9 (8.0)
Couplets						
Baseline	40	132 (336)	----------	19	117 (174)	----------
Week 8	34	44 (119)	-54 (144)	17	108 (255)	-6 (223)
Week 16	31	61 (153)	-44 (208)	14	124 (312)	15 (162)
Week 2631	331	39 (92)	-67 (150)	14	59 (133)	-34 (112)

The mean change in average heart rate from baseline was more pronounced in the metoprolol CR/XL group which is consistent with the effect of this beta blocker. There were arrhythmias in both groups at baseline, but a greater tendency in general to the control of arrhythmias in patients treated with metoprolol CR/XL.

3.11.3.13. Clinical Assessment. The small number of patients enrolled in this study did not provide enough power to allow for meaningful statistical evaluation in some instances.

Two patients (5%) in the metoprolol CR/XL group had one hospital admission each and two patients (11%) in the placebo group had a total of four hospitalizations. Three patients in the metoprolol CR/XL group and on placebo patient had to withdraw from the study because of worsening congestive heart failure. There were no visits to the emergency

room but 14% of patients in the metoprolol CR/XL group and 10% in the placebo group made unscheduled clinic visits because of worsening congestive heart failure. Thus, this study was only marginally successful in achieving the primary endpoints of the protocol.

Patients on metoprolol CR/XL had a 30% improvement in left ventricular ejection fraction as compared with 10% of placebo patients (p=0.015). Measurements of plasma levels of metoprolol CR/XL indicated that they were dose dependent.

Holter measurements were done to determine heart rate and detect cardiac arrhythmias. At week 26, heart rate was slower in metoprolol CR/XL treated patients, which is consistent with the effect of this beta blocker. There was a tendency to a decrease in arrhythmias in patients treated with metoprolol CR/XL.

At week 26, patients on placebo showed a greater improvement in shortness of breath and peripheral edema but improvement in fatigue was almost the same in both groups. At week 26, more patients on metoprolol CR/XL had symptoms of orthopnea than placebo patients (18% vs 6%) and paroxysmal nocturnal dyspnea (6% vs 0%).

Fifty percent (50%) of patients on placebo experienced improvement in NYHA status as compared to metoprolol CR/XL patients (42%) at week 26.

There was not a clear trend between both groups in cardiovascular clinical signs but a greater improvement in quality of life was detected in patients receiving metoprolol CR/XL.

3.11.3.14.Conclusion. In some instances, superiority of metoprolol CR/XL could not be established in this study of tolerability and safety. This may be due to the relatively small number of patients enrolled in the study.

3.11.4. Safety Evaluation.

3.11.4.1.Extent of Exposure. Thirty three patients (79%) in the metoprolol CR/XL group and 16 (84%) in the placebo group completed 26 weeks of treatment. The summary of of the extent of exposure is given in the following Table:

Table 3.11.4.1.

Extent of Exposure

Number of Patients Returning	Metoprolol CR/XL	Placebo
Week 1	40 (95%)	19 (100%)
Week 2	39 (93%)	19 (100%)
Week 3	39 (93%)	19 (100%)
Week 4	36 (86%)	18 (95%)
Week 5	31 (74%)	16 (84%)

Table 3.11.4.1.(Continued).

Extent of Exposure

Number of Patients Returning	Metoprolol CR/XL	Placebo
Week 8	37 (88%)	16 (84%)
Week 16	34 (81%)	16 (84%)
Week 26	33 (79%)	16 (84%)

Percentage-wise, more patients in the metoprolol CR/XL group dropped-out from the study.

3. 11.4.2. Adverse Events. The number of patients reporting adverse events including withdrawals due to adverse events is given in the following Table:

Table 3.11.4.2.1.

Brief Summary of Adverse Events.

Adverse Event Variable	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
≥ 1 Adverse event	40 (95%)	18 (95%)
Adverse events leading to death*	1 (2.4%)	0
Serious adverse events	9 (21%)	3 (16%)
Withdrawals due to adverse events	3 (7%)	0
Non-serious adverse events	31 (74%)	15 (79%)
Withdrawals due to no-serious adverse events	3 (7%)	2 (10%)

* Patient with an adverse event leading to death is also included in the serious adverse events leading to withdrawal.

Almost the same percentage (95%) in the metoprolol CR/XL and placebo groups had one or more adverse event.

Nine patients (21%) in the metoprolol CR/XL group had serious adverse events, leading to 3 (7%) withdrawals and one death (2.4%). Three patients (16%) in the placebo group had serious adverse events, but there were no withdrawals or deaths.

Thirty one patients (81%) in the metoprolol CR/XL group had non-serious adverse events leading to 3 (7%) withdrawals. Fifteen patients (79%) in the placebo group had non-serious adverse events leading to 2 (10%) withdrawals.

The number (%) of patients reporting adverse events by body system and treatment (> 6% of patients in a treatment group) are given in the following Table:

Table 3.11.4.2.2.

Adverse Events by Body System

Adverse Event	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
Body System		
Respiratory System		
Dyspnea	11 (26%)	3 (16%)
Coughing	11 (26%)	3 (16%)
Rales	5 (12%)	2 (11%)
Body as a Whole		
Fatigue	12 (29%)	2 (11%)
Chest pain	6 (14%)	4 (21%)
Pain	4 (10%)	0
Accident and/or injury	3 (7%)	0
Asthenia	3 (7%)	1 (5%)
Ascitis	0	2 (11%)
Peripheral edema	3 (7%)	0
Gastrointestinal System		
Diarrhea	4 (10%)	0
Constipation	0	3 (16%)
Abdominal pain	3 (7%)	2 (11%)
Central and Peripheral Nervous System		
Dizziness	6 (14%)	6 (31%)
Headache	4 (10%)	2 (11%)
Autonomic Nervous System		
Hypertension	4 (10%)	0
Bradycardia	3 (7%)	0
Metabolic and Nutritional		
Hyperglycemia	3 (7%)	1 (5%)
Weight Increase	3 (7%)	1 (5%)
Cardiovascular Disorders		
Cardiac failure aggravated	5 (11%)	1 (5%)
Heart Rate and Rhythm		
Bradycardia	4 (10%)	0
Resistance Mechanisms		
Viral Infection	3 (7%)	0
Skin and Appendages		
Rash	1 (2%)	2 (11%)

Table 3.11.4.2.2. (Continued)

Adverse Events by Body System

Adverse Event	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
Myo-Endo-Pericardial & Valve		
Heart sounds abnormal	3(7%)	0
Urinary System		
Micturation frequency	3(7%)	0

The most common adverse events (≥15%) for patients treated with metoprolol CR/XL were: dyspnea (26%), coughing (26%), and fatigue (29%). The most common adverse events (≥15%) for patients on placebo treatment were: dizziness (32%), chest pain (21%), constipation (16%), dyspnea (15%) and coughing (15%). Bradycardia was observed in the metoprolol CR/XL group, and not in the placebo group.

Thirty three percent (14/42) of metoprolol CR/XL patients and 26% (5/19) of placebo patients had at least one severe event. The most frequent severe events were aggravated cardiac failure (metoprolol CR/XL treated patients 12%, placebo patients 5%) , pulmonary edema and/or edema (metoprolol CR/XL patients 7%, placebo patients 0) and dyspnea (metoprolol CR/XL patients 26%, placebo patients 16%). Severe adverse events led to discontinuation in 3 metoprolol CR/XL patients and death to one. Severe adverse events not leading to withdrawals were also serious events in four metoprolol CR/XL patients and three placebo patients.

The number (%) of patients reporting adverse events considered to be probably or possibly related to treatment are listed in the following Table:

Table 3.11.4.2.3

Adverse Events Possibly or Probably Related to Treatment

Body System	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
No Treatment-Related Adverse Event	21 (50%)	9 (47%)
At least One Treatment-Related Adverse Event	21 (50%)	10 (52%)
Body as Whole	12 (29%)	1 (11%)
Fatigue	8 (19%)	0
Asthenia	2 (5%)	1 (5%)
Chest pain	2 (5%)	1 (5%)

Table 3.11.4.2.3 (Continued)

Adverse Events Possibly or Probably Related to Treatment

Body System	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
At least One Treatment-Related Adverse Event		
Body as a Whole		
Peripheral edema	2 (5%)	0
Abnormal laboratory tests	1 (2%)	0
Malaise	1 (2%)	0
Edema	1 (2%)	0
Edema legs	1 (2%)	0
Chills	1 (2%)	0
Psychiatric	6 (14%)	1 (5%)
Apathy	2 (5%)	0
Depression	2 (5%)	1 (5%)
Insomnia	1 (2%)	0
Increased libido	1 (2%)	0
Nervousness	1 (2%)	0
Respiratory System	6 (14%)	2 (10%)
Dyspnea	5 (12%)	0
Coughing	2 (5%)	0
Dyspnea (aggravated)	1 (2%)	0
Pulmonary edema	1 (2%)	0
Pneumonia	0	1 (5%)
Rales	0	1 (5%)
Heart Rate and Rhythm	5 (11%)	0
Bradycardia	4 (10%)	0
Tachycardia	1 (2%)	0
Cardiovascular General	4 (10%)	0
Cardiac failure aggravated	3 (7%)	0
Hypotension	1 (2%)	0
Syncope	1 (2%)	0
Central, Peripheral Nervous System	4 (10%)	5 (26%)
Dizziness	4 (10%)	5 (26%)
Hypokinesis	1 (2%)	1 (5%)
Autonomic Nervous System	2 (5%)	1 (5%)
Bradycardia	2 (5%)	0
Postural hypotension	0	1 (5%)
Gastrointestinal System	2 (5%)	1 (5%)
Diarrhea	1 (2%)	0
Vomiting	1 (2%)	0
Constipation	0	1 (5%)

Table 3.11.4.2.3 (Continued)

Adverse Events Possibly or Probably Related to Treatment

Body System	Treatment Group	
	Metoprolol CR/XL N=42	Placebo N=19
At least One Treatment-Related Adverse Event		
Hearing and Vestibular	1 (2%)	0
Tinnitus	1 (2%)	0
Metabolic and Nutritional	1 (2%)	1 (5%)
Hyperphosphatemia	1 (2%)	0
Edema	0	1 (5%)
Skin and Appendages	1 (2%)	0
Increased sweating	1 (2%)	0
Vision	0	1 (5%0
Vision abnormal	0	1 (5%)

Most frequently reported treatment-related adverse events (>6%) for metoprolol CR/XL-treated patients were: fatigue, bradycardia (as rhythm disorder and autonomic nervous system disorder), dyspnea and aggravated cardiac failure. The only treatment-related adverse event in placebo patients was dizziness (26%), (metoprolol CR/XL patients 10%).

3.11.4.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events. Twenty-one percent (9/42) of patients in the metoprolol CR/XL group and 16% (3/19) of patients in the placebo group experienced at least one serious adverse event. Three of the patients in the metoprolol CR/XL group and one of the patients in the placebo group had a serious adverse event that was considered to be possibly related to treatment. The remaining patients experienced adverse events that were unlikely related to treatment. There was one death in a patient treated with metoprolol CR/XL Three patients in the metoprolol CR/XL group and one patient in the placebo group had a serious adverse event that was considered to be possibly related to treatment.

3.11.4.3.1. Deaths. A 57 year-old black male with a history of congestive heart failure died after 174 days of blinded medication (metoprolol succinate 100 mg). A death certificate listed massive pulmonary embolism as cause of death. No autopsy was performed. Relationship of this adverse event to study medication was considered unlikely by the investigator.

3.11.4.3.2. Serious Adverse Events Possible Related to Treatment.

A 76-year-old male caucasian with a history of congestive heart failure after 34 days on blinded study medication (metoprolol succinate 100 mg) was seen for routine evaluation with complaints of shortness of breath and insomnia for two to three days. A chest X-ray showed a pleural effusion. He was started on hydralazine and admitted to the hospital for

monitoring and observation with the diagnosis of worsening heart failure. The dose of hydralazine was increased and he was given lasix iv. Three days after admission he was discharged fully recovered. Study medication was not discontinued but reduced to 50 mg od.

A 77-year-old caucasian male with history of congestive heart failure, myocardial infarction and stent placement was admitted to the hospital after 3 days of blinded medication (metoprolol succinate 12.5 mg) with increased weakness, lightheadedness, dizziness and severe dyspnea on exertion and mild chest tightness. He was diagnosed with severe pulmonary edema and his metoprolol medication was permanently discontinued. His BUN and plasma creatinine were elevated at admission. Treated with dopamine, oxygen, morphine lasix and nitroglycerine, he had a good diuresis and recovered, being discharged four days later.

A 61-yer-old female patient with a 6 month history of congestive heart failure, after 58 days of blinded study medication (metoprolol succinate 50 mg) had increased dyspnea for three days progressing to severe shortness of breath and sharp chest pain. She was hospitalized for worsening congestive heart failure. She had laboratory results consisting with a myocardial infarction. She underwent coronary artery bypass surgery for triple vessel disease. Study medication was discontinued on day 62 and the patient was considered completely recovered two days later.

A 72-year-old black male was started on metoprolol CR/XL 12.5 mg od, the dose increased to 25 mg of after one week and to 50 mg seven days later. One week later the dose was reduced to 25 mg od, One week later the patient experienced vomiting and dyspnea. The patient was discontinued from the study that day.

A 64-year-old Asiatic female was started on metoprolol CR/XL 12.5 mg od the dose being increased to 25 mg od one week later and to 50 mg after a month. Ten days later the patient complained of fatigue and hypokinesia. The dose was reduced to 25 mg/day and as the patient did not improve, she was discontinued from the study.

A 55-year-old black female was started on placebo and approximately two months later experienced chest pain. The medication was stopped and the patient withdrew from the study.

A 52-year-old white male was started on placebo and approximately one week later developed severe edema. The dose of study drug was reduced and finally the patient was discontinued from the study.

3.11.4.4. Laboratory. 3.11.4.4.1.Hematology. The hematology results are summarized in the following Table:

Table 3.11.4.4.1.

Number (%) of Patients with Relevant Abnormalities in Hematology

Hematology Parameters	Metoprolol CR/XL N (%)	Placebo N (%)
Any Hematology	31 (74%)	15 (79%)
Hematocrit	24 (57%)	7 (37%)
Hemoglobin	22 (52%)	7 (37%)
Eosinophils	9 (21%)	1 (5%)
MCH	9 (21%)	3 (16%)
MCV	7 (17%)	1 (5%)
WBC	6 (14%)	1 (5%)
Platelet Count	2 (5%)	2 (11%)

There was a greater incidence of clinically relevant abnormalities in all parameters considered, except platelets count, in metoprolol CR/XL patients.

3.11.4.4.2. Serum Chemistry. A summary of clinically important abnormalities in serum chemistry is shown in the following Table.

Table 3.11.4.4.2.

Number (%) of Patients with Clinically Relevant Abnormalities in Serum Chemistry

Serum Chemistry Parameters	Metoprolol CR/XL N (%)	Placebo N (%)
Any Serum Chemistry	35 (83%)	17 (90%)
Glucose	16 (38%)	14 (74%)
Norepinphrine	12 (29%)	7 (37%)
Creatinine	11 (26%)	4 (21%)
Alkaline phosphatase	7 (17%)	5 (26%)
Sodium	6 (14%)	4 (21%)
CO_2	6 (14%)	0
Chloride	4 (10%)	8 (42%)

3.11.4.4.3. Urinalysis. A summary of results of clinically relevant urinalysis by treatment group is shown in the following Table.

Table 3.11.4.4.3.

Number (%) of Patients with Clinically Relevant Abnormal Urinalysis

Urinalysis Parameters	Metoprolol CR/XL N (%)	Placebo N (%)
Any urinalysis	14 (33%)	9 (47%)
Protein	9 (21%)	8 (42%)

3.11.4 5. Vital Signs, Physical Findings, etc. There were no clinically relevant changes from baseline in PR interval, QRS duration, QTc or rhythm by electrocardiogram in the metoprolol CR/XL group at week 26.

There were no clinically significant differences between both treatment groups by chest X-ray evaluations.

The following Table summarizes the mean change from baseline for vital signs:

Table 3.11.4.5.

Vital Signs: Mean Changes from Baseline to Week 26

Vital Signs	Metoprolol CR/XL N=33	Placebo N=19
Weigh (Kg)	0.9	-1.1
Systolic blood pressure (mmHg)	1.8	-4.6
Diastolic blood pressure (mmHg)	-2.1	0.4
Heart rate (beats/minute)	-5.0	-2.6
Respiratory rate (breath/minute)	0.3	0.9

Patients in the placebo group lost more weight than patients in the metoprolol CR/XL group. Patients in the placebo group had a greater reduction in systolic blood pressure and patients in the metoprolol CR/XL a greater reduction in diastolic blood pressure. The reduction in heart rate was greater in patients in the metoprolol CR/XL group.

3.11.4.6 Safety Assessment. An equal proportion of patients in both groups (95%) had one or more adverse events. More frequently reported adverse evens (>15%) were fatigue, dyspnea, respiratory infection, bradycardia, dizziness, chest pain and constipation.

The rate of serious adverse events was 21% in patients being treated with metoprolol CR/XL and 16% in the placebo group. Three patients in the active treatment group and one patient in the placebo group had serious adverse events possibly related to treatment. The rate of adverse events that caused withdrawal of the patient from treatment was 14%

in the metoprolol CR/XL group and 11% in the placebo group. Three patients, one receiving placebo and two receiving metoprolol CR/XL were discontinued because of worsening congestive heart failure.

There was one death, a patient in the metoprolol CR/XL group due to pulmonary embolism that was considered not to be related to study drug.

It is difficult to determine laboratory results as related to treatment groups when considering that these patients were on multiple combination therapy and the clinical pathological processes they were undergoing.

3.114.7. Conclusion. The primary objective of this study was to compare the tolerability and safety of metoprolol CR/XL to placebo in patients with moderate to severe chronic congestive heart failure. The primary variable to assess tolerance was the need to permanently discontinue study medication due to worsening heart failure and worsening heart failure resulting in unscheduled clinic visits, emergency room visits or hospitalizations. In those scores, treatment with metoprolol CR/XL was not strikingly superior to placebo. Therefore it has to be concluded that the endpoints of this study have not been reached.

4.0. Study SH-AHS-0001. The RESOLVD Pilot Study (Volumes 44 through 50 of 101).

Background. Stage I of this study was aimed at evaluating the efficacy, safety and tolerability of candesartan, enalapril and the combination of both. Stage II was aimed at evaluating the efficacy, safety and tolerability of the addition of metoprolol CR/XL to the above regimens. The optimum dose found in this study was used in a large scale study which determined the effects of mortality and hospitalization in these patients

4.1. Title of Study: " The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study. Stage II".

4.2. Principal Investigators and Sites of Investigation:

Dr. O Rizzi Coelho
Hospital das Clinicas da Unicamp
Campinas, Brazil

Dr. A Averum
Dante Pazzanese
Cardiology Institute
Sao Paulo, Brazil

Dr. AC Carvalho
Hospital Sao Paulo
Sao Paulo, Brazil

Dr. R Pavanelo
Hospital do Coracao
da Asociacao do
Sanatorio Sirio
Sao Paulo, Brazil

Dr. K Woo
North Shore Cardiology
Laboratory
North Vancouver, BC
Canada

Dr. V Bernstein
Vancouver Hospital and
Health Sciences Centre
Vancouver, BC, Canada

Dr. DW Rupka
Royal Columbian Hospital
Westminster, BS, Canada

Dr. P Polazek
Surrey Memorial Hospital
Surrey, BC, Canada

Dr. P Greenwood
Misericordia Hospital
Calgary, AB, Canada

Dr. D Humen
University of Alberta
Hospitals
Calgary, AB, Canada

Dr. C Lai
Thunder Bay Regional
Hospital
Winnipeg, MB, Canada

Dr. CD Morgan
Sunnybrook Health
Science Centre
Toronto, ON, Canada

Dr. A Panju
Mc Master University
Medical Centre
Hamilton, ON, Canada

Dr. JMO Arnold
London Health Science
Centre
Niagara Falls, ON, Canada

Dr. S Lepage
Centre Universitaire
Se Sante de l'Estrie
Ottawa, ON, Canada

Dr. M White
Institut de Cardiology
de Montreal
Montreal, PQ, Canada

Dr. D Isaac
Foothills Hospital
University of Calgary
Calgary, AB, Canada

Dr. W Hui
Royal Alexandra Hospital
Calgary, AB, Canada

Dr. N Habib
Plains Health Centre
Calgary, AB, Canada

Dr. S Nawaz
Sudbury Cardiac
Research
Sudbury, ON, Canada

Dr. AJ Ricci
Centenary Health Centre
Scarborough, ON, Canada

Dr. AD Kitching
St Joseph's Hospital
Hamilton, ON, Canada

Dr. S Smith
University of Ottawa
Heart Institute
Ottawa, ON, Canada

Dr. D Fitchett
Royal Victoria Hospital
Montreal, PQ, Canada

Dr. SM Kouz
Center Hospitalier
Regional de Lanaudier
Joliette, PQ, Canada

Dr. D Roch
Calgary General Hospital
Calgary, AB, Canada

Dr. M Seratne
Grey Nuns Community
Health Centre
Calgary, AB, Canada

Dr. A Morris
St. BonifaceGeneral Hospital
Winnipeg, MB, Canada

Dr. G Moe
St. Michel's Hospital
Toronto, ON, Canada

Dr. T Boyne
Hamilton Health
Sciences Corporation
Hamilton, ON, Canada

Dr. YK Chan
Niagara Medical
Centre
Niagara Falls, ON, Canada

Dr. J Bedard
London Clinical Research
Ottawa, ON, Canada

Dr. F Sestier
Hopital Notre Dame
Montreal, PQ, Canada

Dr. J Lenis
INVASCOR
Joliette, PQ Canada

Dr. P Auger
Hotel Dieu de Levis
Levis, PQ, Canada

Dr. C Kolpillai
Queen Elizabeth II
Health Science Centre
Quebec, PQ, Canada

Dr. E Paciaroni
Ospedale INRCA
Ancona, Italy

Dr. A Gavazzi
Ospedale Policlinico
San Matteo
Pavia, Italy

Dr. P Giannuzzi
Ospedale Fondazione
Clinica del Lavoro
Veruno, Italy

Dr. T Moccerti
Ospedale Civico
Lugano, Switzerland

Dr. D Fishbein
University of Washington,
Cardiology
Seattle, Wa, USA

Dr. RM Kohn
Buffalo General Hospital
Buffalo, NY, USA

Dr. A Naftilan
St. Thomas Medical
Group
Nashville, TN, USA

Dr. R Dupuis
Centre Hospitalier
Therford Mines, Canada

Dr. B Sussex
General Hospital
Health Sciences Centre
Quebec, PQ, Canada

Dr. R Belluschi
Ospedale Sant'Anna
Como, Italy

Dr. V Cirrincione
Ospedale Villa Sofia
Palermo, Italy

Dr. A Sanna
Ospedale San Michele
Brozu
Veruno, Italy

Dr. J Grover
Kaiser Center for
Health Research
Portland, OR, USA

Dr. P Pande
Rochester General Hospital
Rochester, NY, USA

Dr. A Miller
University of Florida
Health Science Center
Jacksonville, FL, USA

Dr, NM Robitaille
Hopital Laval
Quebec, PQ, Canada

Dr. J Cobelli
Ospedale Fondazione Clinica
del Lavoro
Monrescano, Italy

Dr. A Boccanelli
Ospedale San Camilo
Roma, Italy

Dr. C de Vita
Ospedale Niguarda-
Ca Granda
Milano, Italy

Dr. BN Singh
West Los Angeles
VA Medical Center

Dr. J Young
The Cleveland Clinic
Foundation
Cleveland, Ohio, US

4.3. Objectives. 4.3.1. The primary objective of this study was:

- To determine the efficacy of administered metoprolol CR/XL in addition to the study medication of candesartan, enalapril or the combination of candesartan and enalapril in patients from stage I in terms of submaximal exercise capacity and neurohormonal parameters.

4.3.2. The secondary objective of this study was :

- To determine the safety and tolerability of the above combinations and to determine the efficacy of the above combinations on quality of life, New York Heart Association Class and ventricular volumes and function.

4.4. Inclusion Criteria (for entry into Stage I).

- Patients with congestive heart failure (NYHA II-IV), 6 minute walk distance of ≤ 500 m and with an ejection fraction <0.40 were eligible for the study.

  The diagnosis of congestive heart failure was based upon:

  - Current or past evidence of low output (such as limitation of activity)
  - Congestion (edema, elevation of jugular vein pressure, rales or radiological evidence of pulmonary congestion)

  For the purposes of screening any method of ventricular function evaluation was acceptable (echocardiography, angiography or MUGA)

  The ejection fraction to be considered at screening was not to have been performed within 5 days of acute myocardial infarction, cardiac surgery or prior to any revascularization procedure, and must have been performed within 1 year of visit 1.

4.5. Exclusion Criteria (for entry into Stage I).

- Age < 21 years
- Unstable refractory angina, cardiac surgery, or PTCA within 4 weeks
- Cor pulmonale
- Advanced pulmonary disease which precluded accurate assessment of symptoms of congestive heart failure
- Constrictive pericarditis
- Acute myocarditis
- Amyloid cardiomyopathy
- Complex congenital heart disease
- Current continuous treatment with intravenous inotropic drugs

- Clinically unstable congestive heart failure
- Serum potassium > 5.5 mmol/L
- Significant renal insufficiency
- Significant renal artery stenosis
- Severe liver disease
- Need for cardiac surgery
- Need of urgent heart transplant
- Non-cardiac cause of congestive heart failure
- Non-cardiac disease that which might have shortened life expectancy to less than I year
- Patients unlikely to comply with protocol
- Pregnancy or women of child-bearing potential who were not protected by an accepted method of contraception
- Intolerance to ACE inhibitors or A-II antagonists
- Hemodynamically significant primary valvular or outflow tract obstruction
- Recurrent syncopal episodes
- Uncontrolled hypertension
- Symptomatic hypotension
- Failure to give consent.

Additional Exclusion Criteria (for entry into Stage II)

- Participant already on beta blocker unable or unwilling to discontinue it
- Bradycardia with a heart rate < 50 beats/minute
- Second or third degree AV block without a pacemaker
- Chronic obstructive pulmonary disease or asthma
- Brittle insulin-dependent diabetes
- Symptomatic peripheral vascular disease
- Any contraindication considered significant by the investigator
- Medication with verapamil and unwillingness to discontinue this medication

4.6. Duration of Treatment: 24 weeks.

4.7. Period of Study: First enrollment was in January 1996 and last enrollment on July 1997. The study was prematurely stopped 6 weeks early.

4.8. Results

4.8.1. Number of Patients. Of 768 patients randomized into Stage I, 426 patients were randomized to Stage II.

4.8.2. Distribution of Patients and Study Design. The RESOLVD pilot study was a randomized double-blind trial of various therapeutic options consisting of a 3 X 2 factorial design with a two-stage randomization.

4.8.2.1. Stage I. Patients with congestive heart failure NYHA functional Class II-IV, six-minute walking distance < 500 m and ejection fraction < 0.40 were eligible to enter the study.

In stage I seven hundred sixty eight (768) patients, after completion of a run-in period,were randomized to one of three treatment groups for 43 weeks: Group A: candesartan alone; Group B: candesartan plus enalapril combination; or Group 3: enalapril alone.

Patients were further randomized to candesartan at low dose: Group AI, 4 mg once daily; medium dose: Group A2, 8 mg once daily or high dose, Group A3, 16 mg once daily.

Group B patients were further randomized to combination treatment with low dose candesartan 4 mg once daily, with enalapril 10 mg bid (Group BI) or medium dose candesartan 8 mg once daily plus enalapril 10 mg bid.

Group C patients received enalapril 10 mg bid alone.

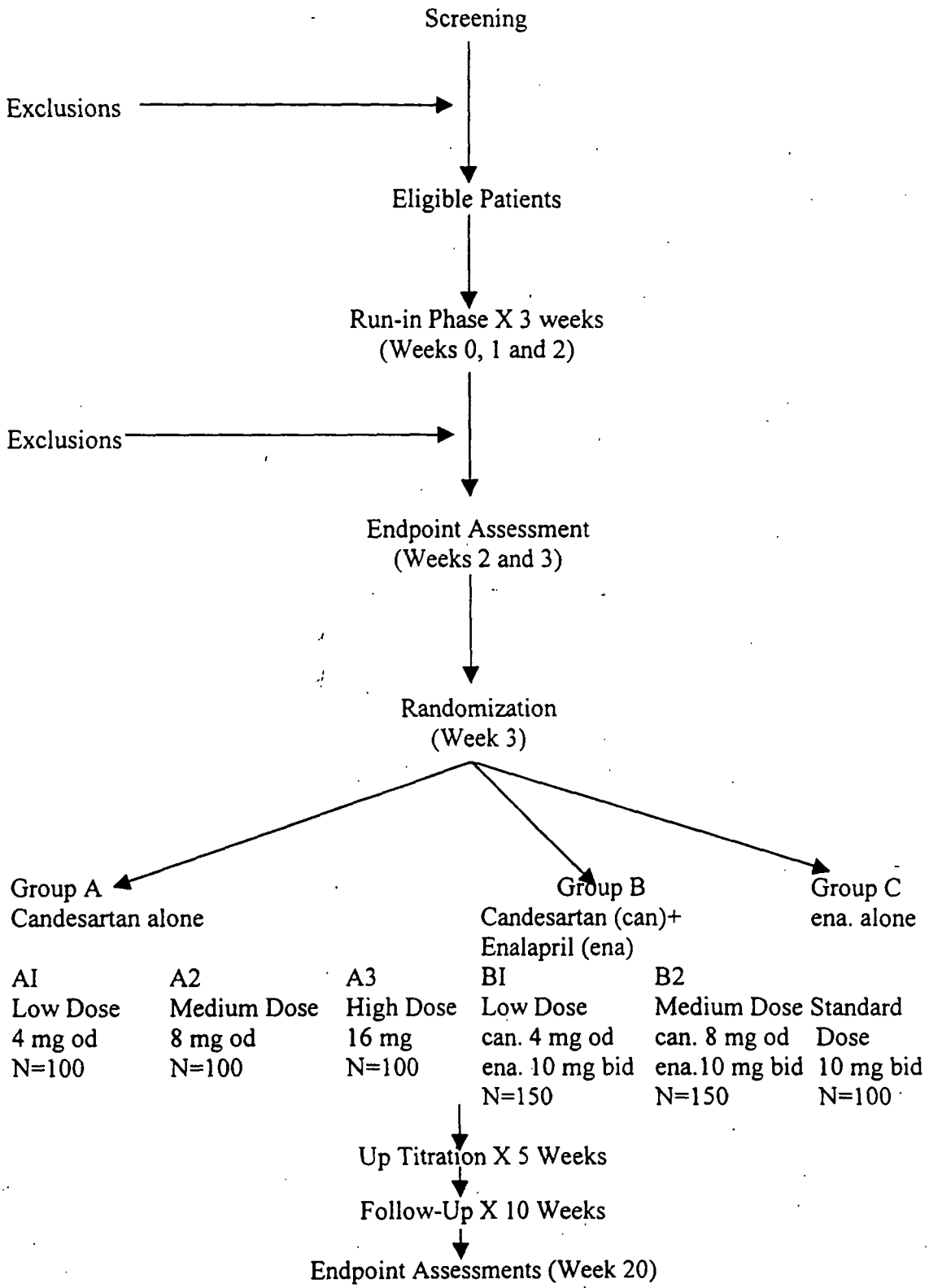
Medication was blindly titrated upward over 4 to 6 weeks.

At the end of the study there was no difference in the 6-minute walk distance, NYHA functional class, or quality of life among the groups. Ejection fraction increased more with candesartan plus enalapril therapy. End-diastolic and end-systolic volumes increased less with the combination therapy. Blood pressure decreased with the combination therapy. Aldosterone and brain natriuretic therapy decreased with the combination therapy.

The study design of Stage I is given in the following graph:

Figure 10

Distribution of Patients and Study Design Stage I

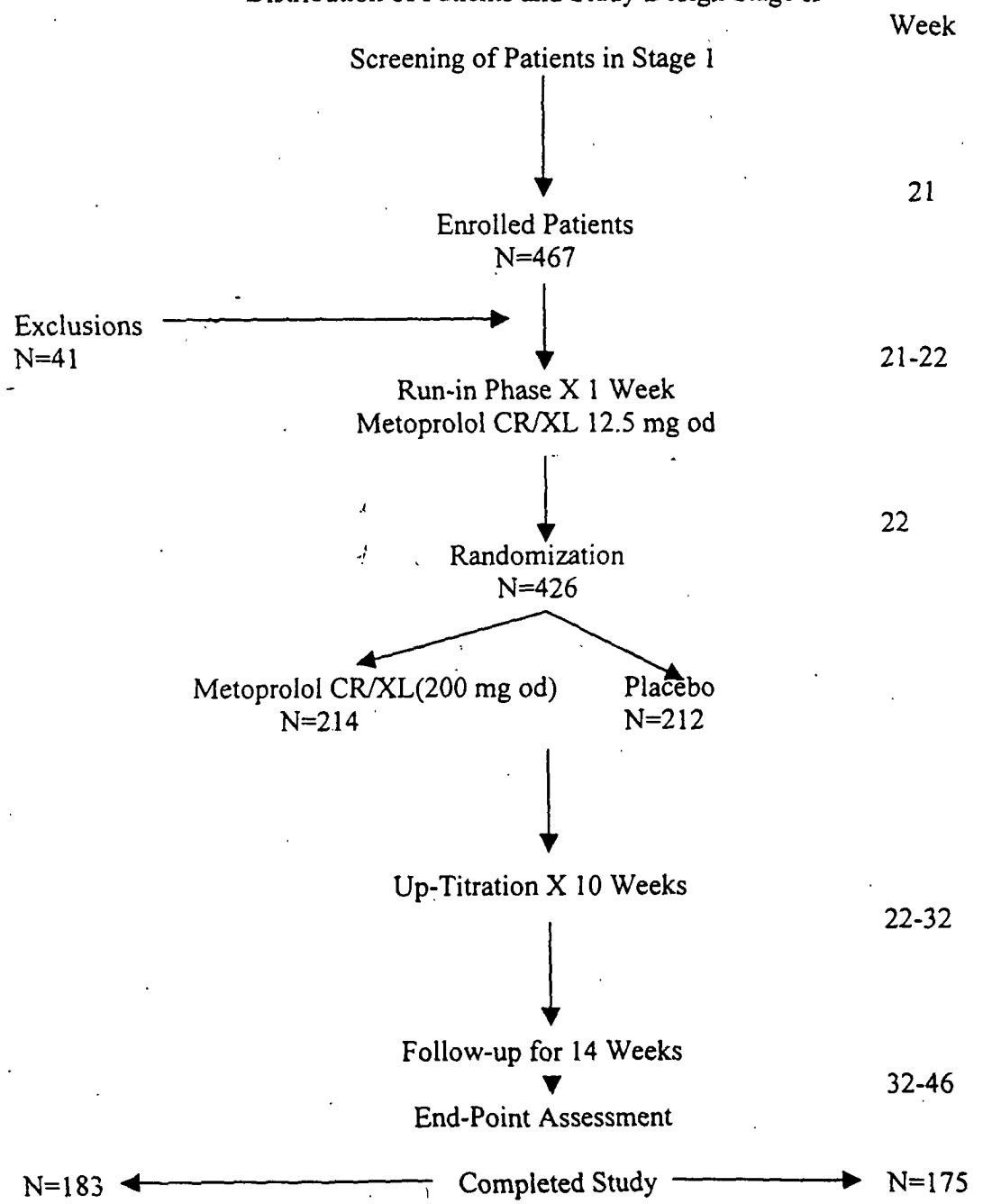


4.8.2.2. Stage 2. In stage II eligible patients were randomized to receive metoprolol CR/XL up-titrated to 200 mg daily or placebo and followed for an additional 25 weeks. Patients in stage II also continued to take the study medications that were assigned in Stage I.

The study design of Stage II is shown in the following graph:

Figure 11

Distribution of Patients and Study Design Stage II



4.8.3. Demographics. The clinical characteristics of patients randomized into Stage II are given in the following Table:

Table 4.8.3.

Demographic Characteristics. (N=426)

Variable		Metoprolol CR/XL N=214	Placebo N=212
Age years (M±SD)		62±12	61±11
Sex	Male	169 (79%)	181 (85%)
	Female	45 (21%)	31 (15%)
Race	White	188 (87%)	183 (87%)
	Black, other	26 (13%)	29 (13%)
Time with Congestive Heart Failure			
	7-12 months	27 (13%)	26 (12%)
	> 12 months	189 (87%)	186 (88%)
Previous myocardial infarction		139 (65%)	132 (63%)
Hypertension		80 (37%)	73 (34%)
Diabetes		58 (27%)	50 (24%)
Smoker	Former	133 (62%)	127 (60%)
	Never	50 (23%)	52 (25%)
	Current	31 (14%)	33 (16%)
New York Heart Association Class	I	10 (5%)	19 (9%)
	II	157 (73%)	138 (65%)
	III	46 (21%)	54 (26%)
	IV	2 (1%)	0 (0%)
Left Ventricular Ejection Fraction		0.28±0.11	0.29±0.11
Six-minute walk m		397±84	400±85
Digoxin		139 (65%)	146 (69%)
Diuretics		180 (84%)	176 (83%)
Nitrates		82 (38%)	67 (32%)
On candesartan		96 (45%)	84 (40%)
On enalapril		30 (14%)	41 (19%)
On combination		89 (41%)	86 (41%)

Comment. Both groups were in general well matched. It is of note, however, that although a condition for admission to this study was to belong to NYHA Class II-IV, 5% of patients randomized to the metoprolol CR/XL group and 9% to placebo were NYHA Class I.

4.8.4. Efficacy. 4.8.4.1. Submaximal Exercise Capacity, 6-Minutes Walk Test. This was one of the primary objectives of this study. Results are shown in the following Table:

Table 4.8.4.1.

Six-Minute Walk Test. Stage II All Patients.

Visit	Metoprolol CR/XL		Placebo	
	N	Mean (SD) m	N	Mean (SD) m
20 Weeks (Baseline)	214	397 (84)	211	400 (85)
46 Weeks	200	396 (94)	192	397 (103)

Comment. Chronic administration of metoprolol CR/XL did not result in any improvement in the 6-minute walk test distance.

4.8.4.2. Neurohormones. This was the other primary objective of this research. Chronic treatment with metoprolol CR/XL provided additional reduction in activation in the renin-angiotensin system and ANP but did not decrease the aldosterone, catecholamines or endothelin levels.

4.8.4.3. NYHA Functional Class. This was one of the secondary objectives of this research. Chronic administration of metoprolol CR/XL caused no significant change in NYHA Class.

4.8.4.4. Hemodynamics. Chronic therapy with metoprolol CR/XL caused no significant change in systolic or diastolic blood pressure, but caused a decrease in heart rate of about 6 to 8 beats per minute.

4.8.4.5. Ventricular Function. Chronic administration of metoprolol CR/XL caused a greater increase in left ventricular ejection fraction as compared to placebo (metoprolol CR/XL +0.025±0.06 vs placebo –0.0005±0.06, $p<0.05$), a lower increase in left ventricular end diastolic volume (metoprolol CR/XL +6±60, placebo +22±64, $p<0.05$) and a decrease in left ventricular end systolic volume (metoprolol CR/XL -2±51, placebo +19±55).

4.8.4.6. Quality of Life. As determined by the Minnesota Living with Heart Failure questionnaire, metoprolol CR/XL caused no significant change in the quality of life score.

4.8.4.7. Compliance. Only 7% of patients on metoprolol CR/XL took less than 80% of study medication a rate that was similar to the 8% of placebo patients. The mean dose of metoprolol CR/XL was 154±71 mg and 69% of patients were receiving the maximal dose of metoprolol CR/XL (200 mg od).

4.8.4.8. Assessment of Efficacy. This study failed to demonstrate that metoprolol CR/XL administered chronically to patients with moderate to advanced congestive heart failure elicited an improvement in a 6-minute walk distance test as compared to baseline or to placebo. Metoprolol CR/XL caused a decrease in the renin-angiotensin and ANP but no change in aldosterone, catecholamines or endothelin.

Metoprolol CR/XL induced an improvement in left ventricular ejection fraction but no beneficial effects were achieved in NYHA Class, blood pressure or quality of life

4.8.5. Safety. 4.8.5.1. Adverse Events. A summary of adverse events is shown in the following Table

Table 4.8.5.1.1

Summary of Patients with Adverse Events [N(%)]

	Metoprolol CR/XL N=214	Placebo N=212
Number of patients with:		
Adverse events	175 (82%)	174 (82%)
Fatal serious AE	8 (3.8)	17 (8)
Non-fatal serious AE	41 (19)	40 (19)
Total number of adverse Events recorded.	1226	1141

Percentage of fatal serious adverse events and total number of adverse events were higher in the placebo group.

The number of all adverse events [N(%) with an incidence ≥10% is shown in the following Table:

Table 4.8.5.1.2

Display of Adverse Events.

Drug: Number of Patients	Metoprolol CR/XL N=214	Placebo N=12	Total N=426
Dyspnea	92 (43)	81 (38)	173 (41)
Fatigue	94 (44)	72 (34)	166 (39)
Dizziness/vertigo	61 (29)	54 (25)	115 (27)
Cough	52 (24)	42 (20)	94 (22)
Chest pain	41 (19)	47 (22)	88 (21)
Increased weight	42 (20)	34 (16)	76 (18)
Flu-like disorder	29 (14)	33 (15)	62 (15)

Table 4.8.5.1.2 (Continued)

Display of Adverse Events.

Drug: Number of Patients	Metoprolol CR/XL N=214	Placebo N=12	Total N=426
Edema	32 (15)	21 (10)	53 (12)
Arthralgia	23 (11)	21 (10)	44 (10)
Headache	22 (10)	22 (10)	44 (10)
Heart sound abnormal	25 (12)	16 (8)	41 (10)
Rales	24 (11)	17 (8)	41 (10)
Decrease in weight	20 (9)	21 (10)	41 (10)
Abdominal pain	18 (8)	21 (10)	39 (9)
Nausea	17 (7)	21 (10)	36 (9)

Comment. The number of patients with adverse events as well as the number of adverse events were similar in both groups.

The sponsor submits a narrative of serious adverse events, dividing them into two groups: fatal and non-fatal. Some patients had more than one diagnosis.

4.8.5.2. Serious Fatal Adverse Events. There were 18 serious fatal adverse events in the placebo group. Diagnosis were sudden death or cardiac arrest in 11, aggravated cardiac failure in 3, cardiac arrhythmias in 3 unstable angina pectoris in 1 and miscellaneous causes the rest.

There were 8 reported cases of serious fatal adverse events in the metoprolol CR/XL group. Diagnosis was sudden death or cardiac arrest in 4, aggravated cardiac failure in 2, arrhythmia in 2, myocardial infarction and coronary ischemia in 2.

Number (%) of fatal serious adverse events related to death are shown in the following Table:

Table 4.8.5.2

Serious Fatal Adverse Events

Drug:	Metoprolol CR/XL N=214	Placebo N=212	Total N=426
Sudden death	3 (1.4)	10 (4.7)	13 (3.1)
Cardiac failure/aggravated Cardiac failure	2 (0.9)	3 (1.4)	5 (1.2)
Tachycardia ventricular/ Arrhythmia aggravated	2 (0.9)	2 (0.9)	4 (0.9)
Cardiac arrest	1 (0.5)	1 (0.5)	2 (0.5)
Cerebrovascular disorder	1 (0.5)	1 90.5)	2 (0.5)

Table 4.8.5.2 (Continued)

Fatal Serious Adverse Events

Drug:	Metoprolol CR/XL N=214	Placebo N=212	Total N=426
Angina pectoris/aggravated	0	1 (0.5)	1 (0.2)
Atrial fibrillation	1 (0.5)	0	1 (0.2)
Ventricular fibrillation	0	1 (0.5)	1 (0.2)
Myocardial infarction	1 (0.5)	0	1 (0.2)
Myocardial ischemia	1 (0.5)	0	1 (0.2)
Pleural mesothelioma	0	1 (0.5)	1 (0.2)
Pneumonia	0	1 (0.5)	1 (0.2)

Comment. The incidence of sudden death was higher in the placebo group. Otherwise there were no significant differences between both groups.

There were 40 cases of non-fatal serious adverse events in the placebo group. Diagnosis was aggravated cardiac failure in 10, cardiac arrhythmias in 7, unstable angina pectoris in 2 and the rest miscellaneous causes.

4.8.5.3. Serious Nonfatal Adverse Events. There were 47 cases of non-fatal serious adverse events in the metoprolol CR/XL group. Diagnosis was aggravated cardiac failure in 28, cardiac arrhythmia in 6, abnormal renal function in 5, unstable angina pectoris in 3, myocardial infarction in 2 and the rest miscellaneous causes.

In reviewing the narrative of serious adverse events it is striking the number of cases listed of patients who developed renal failure while being treated with metoprolol CR/XL.

The summary of those cases of serious, non-fatal adverse reactions, follows:

Patients on metoprolol CR/XL.

Patient 3462. After 5 ½ months on candesartan, medium dose and one month on metoprolol CR/XL the patient was admitted to the Hospital with the diagnosis of pulmonary embolism, deep vein thrombosis and abnormal renal function. Values of renal function were not given. Study drugs were stopped, the patient was discharge after 11 days but was readmitted 14 days later. Causal assessment was considered unlikely as related to study drugs.

Patient 3077. After 10 months on candesartan, medium dose, and six months on metoprolol CR/XL a 52-tears old male patient was admitted to the Hospital with diagnosis of hypoglycemia, chronic renal failure, aggravated cardiac failure and myocardial infarction. His plasma creatinine rose from 149 μmoles/L to 179 μmoles/L.

The event was considered to be "possible" as related to, but unlikely as related to metoprolol CR/XL.

Patient 3832. A 79-year-old male on candesartan-enalapril low dose for 6 months and metoprolol CR/XL for two months had worsening of congestive heart failure with the diagnosis of anemia, abnormal renal function, hiatal hernia, blood in stools, bacterial infection and renal cyst. Values of renal function were not given. Causal assessment was considered unlikely to all drugs.

Patient 3205. A 56-year-old male had elevated creatinine levels to 159 μmoles/L (baseline levels not given) 189 days after randomization to candesartan and 53 days after starting metoprolol CR/XL. The drugs were temporarily stopped but when restarted the patient had hypotension, elevation in plasma creatinine and diarrhea. Causal assessment was considered unlikely to study drugs.

Patient 3211. A 54-year-old male patient after 9 months of randomization to candesartan-enalapril low dose and five months on metoprolol CR/XL was hospitalized for abnormal renal function manifested by an elevation in plasma creatinine from 124 μmole/L to 194 μmoles/L and hyperkalemia. Concomitant medications were spironolactone, potassium chloride, digoxin, furosemide and chlorthalidone. Assessment for abnormal renal function was considered possible as related to candesartan and metoprolol CR/XL

Patients on Placebo. No diagnosis of renal failure or abnormal renal function could be found in this group of patients.

4.9. Laboratory Evaluation. There were no clinically relevant changes in laboratory values between both groups and in the same groups between baseline values and after treatment.

4.10. Assessment. This study has been the subject of some preliminary publications (11-13).

In patients with moderate or advanced congestive heart failure and primed with candesartan, enalapril, or the combination of both, the addition of metoprolol CR/XL failed to elicit an improvement in the 6-minute walk test distance. Furthermore, in evaluating the response of neurohormones to metoprolol CR/XL administration, although activation of the renin-angiotensin system was reduced, plasma aldosterone was not reduced, levels of catecholamines and endothelin did not change, but ANP rose. Therefore, this protocol was not very successful in fulfilling its stated primary endpoints.

Chromic administration of metoprolol CR/XL did not improve NYHA Class, the quality of life, or the symptoms. Most patients (69%) tolerated titration to the maximal target dose of 200 mg od.

Left ventricular ejection fraction improved and the increase in end diastolic and end systolic ventricular volumes did not change in patients treated with metoprolol CR/XL

while those parameters deteriorated in the placebo group. Therefore metoprolol CR/XL provided some protection to cardiac function.

There were more deaths in the placebo group and the main cause of death was sudden death. Main causes of death in the metoprolol CR/XL group was also sudden death followed by aggravated cardiac failure.

Main diagnosis for non-fatal serious adverse events was worsening od cardiac failure followed by cardiac arrhythmia. It is interesting to note that these diagnosis were followed by abnormality of renal function that was reported only in the metoprolol CR/XL group and was absent in the placebo group.

Conclusion. Although primary endpoints were not reached in this protocol, the study provided further relative evidence of a protective effect of metoprolol CR/XL for patients with moderate to advanced congestive heart failure.

5.0. Protocol SH-MET-0022 (Volumes 8 and 9 of 101).

5.1. Title of Study: "A Pharmacokinetic and Pharmacodynamic Study Comparing Metoprolol Immediate Release and Metoprolol CR/XL in Patients with Congestive Heart Failure".

5.2. Principal Investigator and Site of Investigation:	Dr. Bert Anderson Division of Cardiology Sahlgrenska University Hospital Goteborg, Sweden

5.3. Objectives. 5.3.1. Primary Objective. The primary objective of this study was to compare peak and trough plasma concentrations after repeated dosing to steady state with metoprolol immediate release 50 mg tid with that of 100 mg and 200 mg metoprolol succinate CR/XL od in patients with congestive heart failure.

Other objectives were to compare the effect of the three formulations on exercise induced tachycardia, heart rate recorded by Holter over 24 hours and heart rate recorded at rest by electrocardiograph.

5.3.2. Secondary Objective. The secondary objective was to compare the effect of the three formulations on tolerability.

5.4. Inclusion Criteria. Patients fulfilling the following criteria were selected for inclusion into this study: patients with congestive heart failure due to primary cardiopathy or ischemic heart disease in the stable phase of the disease; treatment with metoprolol immediate release or metoprolol CR/XL, maintenance 100-200 mg/day for at least 6 months prior to entry; the candidate must have been able to perform moderate bicycle testing and be able to sign a consent form; an ejection fraction < 0.40 prior to treatment with metoprolol and/or an ACE inhibitor.

5.5. Exclusion Criteria. Patients with the following conditions were excluded from the study: patients in the waiting list for heart transplantation; expected revascularization within three months; signs of other serious diseases that might interfere with the study; atrial fibrillation or frequent arrhythmias that might interfere with heart rate.

5.6. Number of Patients. Fifteen patients were enrolled and completed the study.

5.7. Duration of Study. The patients were enrolled and randomized into the study on February 19, 1999 and the last patient completed the study on May 31, 1999.

5.8. Study Design. This was a randomized, open, three way, cross-over single center study where each treatment period lasted seven days.

Fifteen patients of either sex with stable congestive heart failure who fulfilled the admission criteria were entered into an open two-week run-in period where all patients were started on metoprolol CR/XL 200 mg od during the first week and continued on metoprolol CR/XL 100 mg od during the second week.

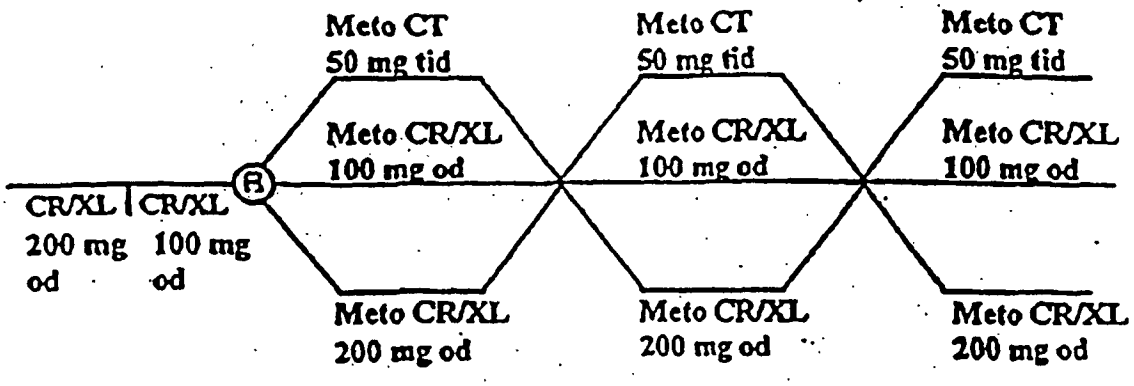
At the end of this period patients were allocated to receive each of the three regimens in random order for one week period.

On the last day (day 7) of each treatment period the patients arrived to the laboratory around 7.30 am without having taken the morning dose of study medication. Blood samples over 24 hours for steady pharmacokinetics were drawn and a Holter recorder was connected to obtain 24-hour ambulatory heart rate. Systolic and diastolic blood pressures were measured and a resting electrocardiogram was performed. Four minutes of bicycle exercise testing was performed four times over 24-hours. The patient stayed in the laboratory for 9 hours and arrived again the following morning for the 24 hour measurement.

The overall study design is given in the following graph:

Figure 12.

Study Design



The time schedule for the study period is given in the following Table:

Table 5.8.1.

Time Schedule for the Study Period

Week	-2	-1	0	1	2	3
Visit	1	2	3	4	5	6
Informed Consent	X					
Medical History	X					
Supine BP-HR	X	X	X	X	X	X
Resting EKG	X	X	X	X	X	X
Randomization			X			
Blood Sampling		X		X	X	X
24 Hour ambulatory Heart rate		X		X	X	X
Physical examination	X					
Exercise		X		X	X	X
Adverse Events		X	X	X	X	X

The time schedule for blood sampling, tablet administration, exercise testing and standardized meals at visits 2, 4, 5 are given in the following Table:

Table 5.8.2.

Time Schedule for the Investigational Day

Time (h)	0	0.5	1	1.5	2	3	4.5	6.5	7	7.5	8	8.5	9	14.5	24
Blood sampling	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tablet Administration															
CT 50 mg tid	x							x						x	
CR/XL 100/200 Mg od	x														
Exercise testing				x			x				x				x
Connection to Holter	X														
Disconnection of Holter	x														

5.9. Results. 5.9.1. Efficacy

5.9.1.1. Demographic Characteristics. The demographic characteristics are given in the following Table:

Table 5.9.1.1

Demographic Characteristics

Gender	Male	13
	Female	2
Age	44-51	2
	54-59	3
	60-69	4
	70-79	6
NYHA Class	II	3
	III	12
History of		
Diabetes		2
Hyperlipidemia		1
MI		1
Concomitant		
Therapy	Yes	14
	No	1
Previous		
Metoprolol		
Therapy		
CR/XL	100 mg	6
	150 mg	7
	200 mg	2

5.9.1.2. Pharmacokinetics. The C_{max} for metoprolol CR?XL 200 mg od and metoprolol immediate release 50 mg tid were close while the level for metoprolol CR/XL 100 mg od was lower. The average plasma concentration for metoprolol CR/XL 200 mg od was higher than that for metoprolol immediate release 50 mg tid while the average plasma concentration for metoprolol CR/XL 100 mg od was much lower.

The plasma concentration versus time curve of metoprolol immediate release formulation gave larger variations, as expected.

The plasma metoprolol levels following oral administration of metoprolol CR/XL as compared to conventional metoprolol were characterized by lower peaks, longer time to peak, and significantly lower peak to trough variations. At steady state, the average bioavailability following administration of metoprolol CR/XL across he dose range of 50 to 400 mg od was 77% relative to the corresponding single or divided conventional metoprolol.

In man, absorption of metoprolol is rapid and complete. Approximately 12% is bound to plasma proteins and plasma half life ranges from 3 to 7 hours. Plasma levels following oral administration of conventional metoprolol tablets approximate 50% of intravenous administration. Elimination is mainly by biotransformation in the liver and elimination in

the urine is less than 5% after an oral dose, the rest being excreted as metabolites. The dose does not need to be reduced in renal failure and gastrointestinal absorption is not affected by food.

See also review by HFD-860, Biopharmaceutics.

5.9.1.3. Pharmacodynamics. Metoprolol CR/XL 200 mg od was associated with a more effective suppression of heart rate as compared to metoprolol immediate release 50 mg tid as determined by Holter monitoring and at rests by electrocardiogram. Metoprolol CR/XL caused a more significant reduction in systolic and diastolic blood pressure as determined in supine position after a 5-minute rest. Metoprolol CR/XL also elicited a more significant reduction in heart rate, systolic and diastolic blood pressure during exercise that metoprolol immediate release 50 mg tid.

5.9.2. Safety. 5.9.2.1. Summary of Adverse Events. A summary of adverse events is given in the following Table:

Table 5.9.2.1.

Summary of Adverse Events (AE)

Drug	Run-in	Metoprolol CT 50 mg tid	Metoprolol CR/XL 100 mg od	Metoprolol CR/XL 200 mg od
# Patients	15	15	15	15
With AE	5	8	4	6
With Serious AE	0	0	0	0
Drug stopped due to AE	0	0	0	0
Drug reduced due to AE	0	0	0	0
AE of severe Intensity	0	0	0	0

5.9.2.2. Number of Patients with Adverse Events. The number of patients with adverse events is given in the following Table:

Table 5.9.2.2.

Number of Patients with Adverse Events

Drug	Run-in	Metoprolol CT 50 mg tid	Metoprolol CR/XL 100 mg od	Metoprolol CR/XL 200 mg od
# Patients	15	15	15	15
Fatigue	1	3	1	1
Chest pain	3	1	0	1
Dizziness	1	0	2	2
Flue-like Disorder	0	1	0	1
Vomiting	0	1	0	1
Diarrhea	0	0	0	1
Heart sound abnormal	0	1	0	0
Nausea	0	1	0	1
Respiratory infection	0	1	0	0
Arrhythmia	1	0	0	1

Adverse events reported were few and of mild to moderate intensity. There were no significant differences among the groups. There were no deaths or serious adverse events. There were no discontinuations due to adverse events. One patient developed a carcinoma 39 days after the end of the study.

5.10. Assessment. 5.10.1. Efficacy. Pharmacokinetics showed a better correlation between metoprolol CR/XL 200 mg and metoprolol immediate release 50 mg tid than with metoprolol CR/XL 100 mg od.

A more even and pronounced beta blocking effect was achieved with metoprolol CR/XL than with the immediate release preparation.

5.10.2. Safety. Metoprolol CR/XL was safe and well tolerated.

6.0. Case Reports. Case reports forms for patients that died or discontinued due to an adverse event are provided in [illegible]s 1-3 for studies SH-MET-0024 (MERIT-HF), S-996 and SH-MET –001 (RESOLVD). The distribution of reports is as follows:

Table 6.1

Distribution of Case Reports

	Metoprolol CR/XL	Placebo	N/A	Blank
S-996	11	4	2	1
SH-AHS-0001	32	41		1
SH-MET-0024	359	429		

The quality of the reports is in general good although on occasions it is difficult to read. No gross errors were detected in a perfunctory review of the forms.

7.0. Total Assessment. Protocol SH-MET-0024, the only pivotal study of this submission (pp.2-44), provided substantial evidence of the benefits than can be attained by treating patients with moderate to advanced congestive heart failure with metoprolol CR/XL.

When administered to patients with chronic congestive heart failure in stable condition by previous treatment with a diuretic and an ACE inhibitor, metoprolol CR/XL reduced significantly total mortality and the combined endpoints of all cause mortality and all cause hospitalization as compared to placebo (Tables 2.9.3.2 and 2.9.3.3, page 21, Figures 2 and 3, pp. 23 and 24) (1, 2). These were the first and second primary endpoints of this submission.

Metoprolol also provided benefits to the combined endpoints of all cause mortality and hospitalization due to congestive heart failure, death and heart transplantation, death from cardiovascular causes, death from congestive heart failure, mortality from sudden death, cardiac death and non-fatal acute myocardial infarction and all cause mortality and hospitalization due to congestive heart failure and emergency room visit due to congestive heart failure (Tables 2.9.3.2 and 2.9.3.3, page 21 and Figures 2-7, pp. 23-28).

Metoprolol CR/XL also decreased the number of patients with congestive heart failure with any hospitalization, the total number of hospitalizations and the total number of days in the hospital when hospitalizations were due to all causes, to cardiovascular causes or to worsening heart failure (Table 2.9.3.4.1, page 29) (2).

It is relevant to know the incidence of those clinical occurrences given by the sponsor as combined endpoints, when considered as single events. The combined endpoints of death and heart transplantation were very significant in favor of metoprolol CR/XL (Tables 2.9.3.2 and 2.9.3.3, page 21) but when the need for heart transplantation was considered as a single event, more patients in the metoprolol CR/XL group than placebo patients received a heart transplant in the course of the study, and the difference was not statistically significant (Table 2.9.3.4.2, page 30). Also, there was no great difference between both groups in the number of patients making emergency room visits or suffering a non-fatal myocardial infarction (Table 2.9.3.4.2, page 30). Therefore, it cannot be inferred that treatment with metoprolol CR/XL had a significant effect in

reducing the need for heart transplantation or decreasing the number of visits to the emergency room or in the incidence of non-fatal myocardial infraction in this study in patients with congestive heart failure.

Metoprolol CR/XL was well tolerated (2.9.3.5, pages 30-31, 3.11.3.1, page 52, 4, 8.4, 7, page 78). It provided some improvement in NYHA Functional Class classification (2.9.3.6, page 31, 3.11.3.8, page 56) although there were not enough patients with very severe (NYHA Class IV) congestive heart failure (Table 2.9.2.2, page 19). Therefore, more studies are needed in this category of patients.

Metoprolol CR/XL provided some improvement in the quality of life in patients with congestive heart failure (2.9.3.7, pp. 33-35, 3.11.3.10, page 56).

Additional support for efficacy and safety for metoprolol CR/XL in the treatment of congestive heart failure was provided by protocols S-996 (pp. 44-69) and SH-AHS-0001 (pp. 69-83).

Metoprolol CR/XL improved left ventricular ejection fraction (Table 3.11.3.3, page 54 and 4.8.4.5, page 78), caused a lesser increase in left ventricular end diastolic volume and a decrease in left ventricular end systolic volume (4.8.4.5, page 78) in patients with congestive heart failure. It also lowered the heart rate and decreased the incidence of arrhythmias (Tables 2.9.4.1.3, page 40, 3.11.3.12, page 58, 4.8.4.4., page 78).

It is striking in reviewing the incidence of adverse events that the diagnosis of acute renal failure was mentioned in repeated occasions in patients in congestive heart failure being treated with metoprolol CR/XL. In the MERIT protocol, acute renal failure occurred in a disproportionate number of patients treated with metoprolol CR/XL (0.7% in metoprolol CR/XL treated patients vs 0.2% in placebo patients, $p<0.05$) (Table 2.9.4.1.3., page 41). Acute renal failure was mentioned as diagnosis in one patient treated with metoprolol CR/XLthat died and none in the placebo group (Table 2.9.4.1.5, page 42). In the RESOLVD protocol, in the section dealing with serious non-fatal adverse events, there were 5 patients who developed abnormalities in renal function in the metoprolol CR/XL group while there were none in the placebo group (4.8.5.1.2, pp.81-82).

In demographics, there was not enough number of patients in the $\geq$ 80 years of age category.

8.0. Recommendations. After submission of the supplement for NDA 19-962, the sponsor submitted on January 2000, an amendment to the package inserts for Toprol-XL in which changes for the indication for treatment of congestive heart failure were inserted. Therefore, these recommendations will refer to the proposed package insert label.

The following amendments are recommended:

In page 5, in the section. Heart Failure, Clinical Trials, it is recommended that in the last paragraph at the bottom of the page, the following be added to the last line:

DRAFT LABELING

In the same section, Heart Failure, Clinical Trials, page 6, fourth paragraph, subsection Slowing Progression of Heart Failure, it is recommended that a paragraph be added at the end of this subsection stating:

DRAFT LABELING

In page 12, in the section Adverse Reactions, subsection Miscellaneous a line should be added to the last paragraph stating:

DRAFT LABELING

Finally, it is recommended that Toprol-XL be approved for the treatment for congestive heart failure based on the claims stated in page 8, Indications and Usage subsection Heart Failure that states that treatment of patients with congestive heart failure with Toprol-XL:

DRAFT LABELING

/S/

Cristobal G. Duarte, MD – HFD-110

CC.
ORIG. NDA 19-962
HFD-110
HFD-110/CSO/Ms.McDonald
HFD-110/Dr. Fenichel
HFD-860/Dr. Marroum
HFD-710/Dr. Cui
HFD-110/CGD/22Dec99-Revised-09Feb00

References

1. The MERIT-HF Study Group. Effects of metoprolol CR/XL in chronic heart failure Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). Lancet 1999:353:2001-2007.

2. The MERIT-HF Study Group. Total mortality, hospitalizations, and well being in the Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). J Am Med Assoc. Accepted for publication.

3. Sharpe N. Benefit of β-blockers for heart failure: proven in 1999. Editorial. Lancet 1999:353:1988-1989.

4. Krum H. Beta blockers in heart failure. The 'new wave" of clinical trials Drugs 1999:58:203-210

5. Goldstein S. Clinical studies of beta blockers and heart failure preceding the MERIT-HF trial. Am J Cardiol 1997:80:50J-53J.

6. The International Steering Committee and Organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). Am J Cardiol 1997:80:54J-58J.

7. Goldstein S, Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure. Results of the MERIT-HF Trial. Clin Cardiol 1999:Suppl V:V30-V35.

8. Eichorn EJ. Experience with beta blockers in heart failure mortality trials. Clin Cardiol 1999:22Suppl 5:V21-29.

9. Carson PE. β-blocker therapy in heart failure: Pathophysiology and clinical results. Curr Probl Cardiol 1999:24:423-460.

10. Krum H, Whorlow S. Meta-analysis of effects of beta-blocker therapy. Circulation 1999:100 Suppl:I:203

11. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effect of converting enzyme inhibitor Enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD investigators. Circulation 1992:86:431-438.

12. The RESOLVD Pilot Study Investigators. Combination neurohormonal blockade with ACE inhibitors, angiotensin II antagonists and beta-blockers in patients with congestive heart failure. Design of the Randomized Evaluation of Strategies on Left Ventricular Dysfunction (RESOLVD) pilot study. Can J Cardiol 1997:13:1166-1174.

13. The RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure. Circulation 1999:100:1056-1064.

APPEARS THIS WAY
ON ORIGINAL

NDA 19-962 Index

Tables

Figures

dup NDA 19-962/S-013

MAY 16 2000 McDowa

Memo to: Raymond J. Lipicky

From: Robert R. Fenichel /S/

Subject: metoprolol succinate (TOPROL-XL®, Astra-Zeneca LP) for CHF

Date: 16 May 2000

With this application, the sponsor proposes to market sustained-release metoprolol succinate ("metoprolol") as adjunctive therapy for patients with systolic dysfunction and symptomatic congestive heart failure. There is extensive experience with this product in its approved uses for the treatment of angina and hypertension.

Essentially all of the new data come from a single trial, the MEtoprolol Randomized Intervention Trial (MERIT). This was a 14-country, 3991-patient, double-blind, randomized, parallel-group trial comparing metoprolol to placebo in stable patients

- who had had symptomatic congestive failure for at least 3 months, despite "optimal" standard therapy with diuretics and ACE inhibitors;[1]
- who had objective systolic dysfunction, as shown by a measured left-ventricular ejection fraction (LVEF) less than 0.4.[2]

Women at risk of pregnancy were excluded, as was any other otherwise-qualified patient

- who had an implanted cardiac defibrillator, or in whom implantation of a defibrillator was planned for the study period;
- who had received a heart transplant or cardioplasty, or in whom one of these procedures was planned for the study period;
- who had received amiodarone within 6 months;
- who had had coronary revascularization within 4 months, or in whom revascularization was planned;
- who had received chronic beta-blocker therapy within 6 weeks;
- who had had acute myocardial infarction or acute coronary syndrome within 4 weeks;
- who was receiving diltiazem, verapamil, or inotropic therapy other than digitalis;
- whose supine heart rate was less than 60 beats per minute;

---

[1] Patients who did not tolerate ACE inhibitors could be recruited if they were instead receiving angiotensin-II antagonists or treatment with a hydralazine/nitrate combination.

[2] If the LVEF were greater than 0.35, then the patient could be included only if the 6-minute walking distance was less than 45m.

- whose supine systolic blood pressure was less than 100 mm Hg;
- for whom therapy with beta-blockers was required or contraindicated;
- whose heart failure was attributable to uncorrected valvular disease, obstructive cardiomyopathy, endocarditis, myocarditis, pericardial disease, infiltrative myocardial disease, or systemic conditions (*e.g.*, thyroid disease);
- who had second- or third-degree atrioventricular block or sick sinus syndrome (unless he or she had intrinsic cardiac activity and a demand pacemaker); or
- who had another serious disease that the investigators thought might interfere with the study, or might plausibly lead to death during the study period.

Randomization and dosing

Enrolled patients were randomized 1:1 between metoprolol and placebo. Those randomized to metoprolol initially received 25 mg daily (12.5 mg daily for patients with NYHA class III or class IV), but this was titrated upward over the next few weeks toward a target dose of 200 mg. The intended duration of the trial was 36 months.

Endpoints

The primary endpoints of the trial were

- all-cause mortality and
- an endpoint ("the Composite Endpoint") that combined all-cause mortality with all-cause hospitalization.

The secondary endpoints included various combinations of cardiovascular mortality, heart transplantation, myocardial infarction, hospitalization due to heart failure, emergency-room visit due to heart failure, and NYHA class.

Analysis

The proposed analyses were log-rank tests of time-to-event. The power analysis derived from the mortality endpoint, and contemplated a 21% risk reduction in the active-therapy group. For 80% power to achieve an overall significance level of 0.05 (with approximately 0.04 allocated to all-cause mortality and 0.01 allocated to the Composite Endpoint[3]), the anticipated sample size was 1600 patients in each group. Interim analyses for all-cause mortality were planned after 25%, 50%, and 75% of the total number of expected deaths, with small fractions of the total significance level allocated to each of these analyses.

---

[3] The two primary endpoints were positively correlated (all-cause mortality was a component of the Composite Endpoint), so the proper allocation of the overall 0.05 significance should give allocations that sum to more than 0.05. On the basis of the observed overall data, the sponsor's analysis later adjusted the allocations to 0.043 and 0.01.

Course of the trial

The first patient was randomized in January 1997, and recruitment continued for about 14 months, with a total enrollment of 3991. The enrolled patients were 78% male and overwhelmingly white, their average age was 64, and their average ejection fraction was 28%. About half had had acute myocardial infarctions. Their baseline NYHA classes were 41% II, 55% III, and 4% IV.

About one quarter of the patients were recruited in the United States, and the remainder came from 13 countries of Europe.

The second interim analysis indicated that treatment with metoprolol was associated with a 34% reduction in all-cause mortality (nominal $P = 0.0001$, adjusted $P = 0.0062$), and the trial was stopped on 31 October 1998.

Results

When the trial was stopped, the overall results were as shown in the table below (reproduced from Table 1.3 of Dr. Cui's careful review). As is apparent from the

...	placebo	metoprolol	relative risk (95% CI)	nominal *P*-value
patients	2001	1990		
all-cause mortality (1°)	217	145	0.66 (0.53, 0.81)	0.0001
and hospitalization (1°)	767	641	0.81 (0.73, 0.90)	0.0001
and CHF hospitalization	439	311	0.69 (0.60, 0.83)	<0.0001
and ED visits	455	318	0.68 (0.59, 0.79)	<0.0001
cardiovascular mortality	203	128	0.62 (0.50, 0.78)	<0.0001
and non-fatal MI	225	139	0.61 (0.49, 0.75)	<0.0001
CHF mortality	58	30	0.51 (0.33, 0.79)	0.0023
sudden death	132	79	0.59 (0.45, 0.78)	0.0002

table, metoprolol was significantly superior to placebo by every metric, including the two primary endpoints (all-cause mortality[4] and the Composite Endpoint[5]). As shown in Dr. Cui's Table 1.4 (not reproduced here), these favorable findings were more-or-less

---

[4] To take account of the "multiple looks" intrinsic to the chosen strategy of interim analyses, the sponsor's calculations show that the p-value for all-cause mortality should be adjusted to 0.0062.

[5] Because all-cause mortality (the metric examined in the interim analyses) was a component of the Composite Endpoint, the p-value for the Composite adjustment also needs to be adjusted. The necessary adjustment has no closed-form expression, but Dr. Cui has estimated that the adjusted value would be about 0.0002.

uniform across a variety of plausible subgroups, including groups selected on the basis of age, sex, ejection fraction, baseline blood pressure, NYHA classification, and history of myocardial infarction. What could be wrong with this picture?

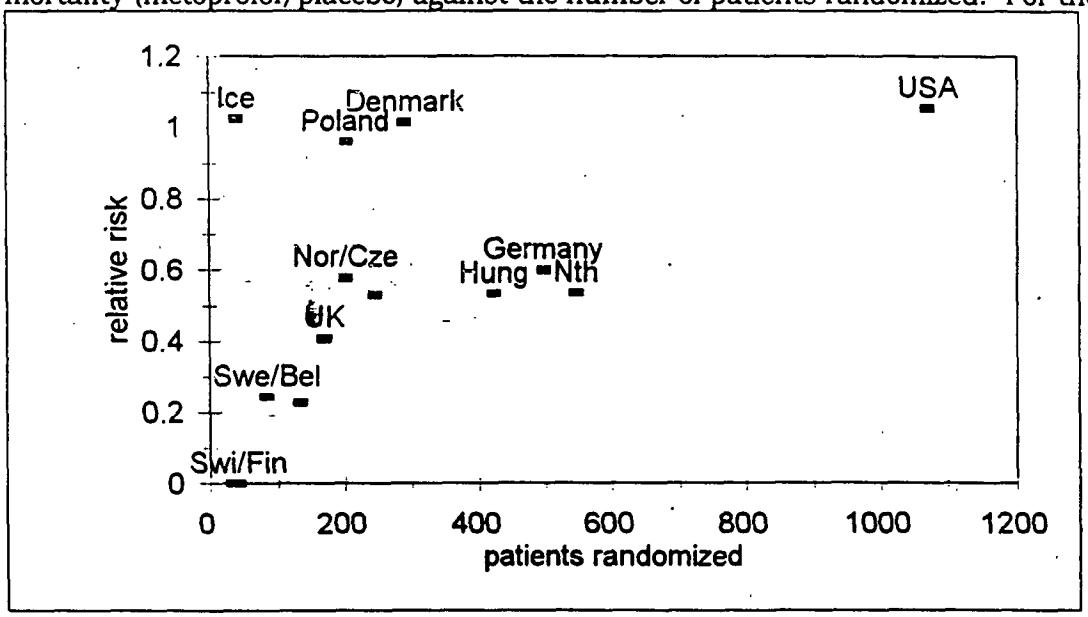
Mortality Effect in the U.S. Subpopulation

Because of demographic differences or differences in concomitant care, a treatment might be beneficial overall but neutral or detrimental in some subpopulations. In particular, even though studies in U.S. patients are not required for approval, evidence that a treatment is non-beneficial in U.S. patients (or even in some identifiable subpopulation among U.S. patients) must not be ignored. The observed mortality among U.S. patients receiving metoprolol was ***105%*** of that seen in those receiving placebo.

How should this finding be interpreted? The finding of adverse U.S. mortality effects could of course be attributable to chance, but it could alternatively be a genuine finding, the result of U.S.-European differences in demographics or concomitant therapy.

Dr. Cui has argued that the result should not be attributed to **chance**, and I agree. Dr. Cui's argument (page 8 of his review dated 7 May) relies on a test comparing the U.S. and non-U.S. hazard ratios, and he rejects the null hypothesis of homogeneity with $P = 0.00297$. This is an impressive P-value, but I initially had some uneasiness about accepting it at face value. The test was applied only *because* the U.S. seemed to be an outlier, and one should never be surprised that the testing of outliers confirms that they are outliers.

In the figure below[6], I have plotted for each country the observed relative risk of mortality (metoprolol/placebo) against the number of patients randomized. For the



[6] This figure is similar to several others that will appear below. In each, the relative risk of all-cause mortality is plotted on the ordinate, while the abscissa varies from figure to figure. A

most part, the results are what one might expect. That is, the observed ratios varied widely among the countries that contributed small numbers of patients to the trial, but as one moves to larger and larger subpopulations, the separate estimates converge toward a value close to the reported overall risk ratio (0.66). ***The United States is a striking exception.*** I cannot assign a *P*-value to the message of this figure, but Dr. Cui's 0.00297 does not seem so far-fetched after all.

Because the results in the U.S. patients do not seem at first blush to be attributable to random variation, it may be useful to search for one or more cofactors to which the anomalous results might be attributed. Suppose, for example, that it were true in every country that metoprolol increased mortality in women, and that much of the inter-country variation (including the U.S. result) could be explained by taking the per-country differences in sex distribution into account. Such a result would add to the credibility of the U.S. mortality result and of the trial as a whole. If, on the other hand, the U.S. mortality were not plausibly explained by any known cofactors, one would be forced to reconsider the possibility that – unlikely as it seems – it was a chance finding.

Could the anomalous U.S. results be the result of **demographic differences**? The table below (taken from Dr. Cui's table 2.2) shows that the U.S. and non-U.S.

	U.S.	Non-U.S.
patients	1071	2920
male	71%	80%
white	80%	99%
NYHA II	40%	41%
III	55%	56%
IV	5%	3%
history of MI	46%	49%
age	63	64
LVEF	27%	28%
BP	126/75	131/79
heart rate	81	83

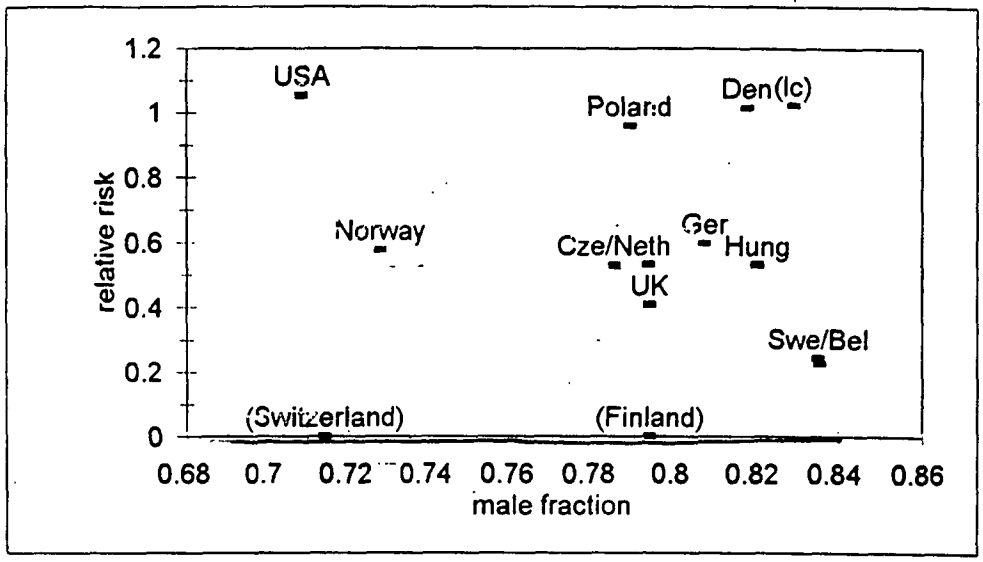
populations were similar in some demographic respects, but different in others. Of the demographic characteristics listed, the most prominent are the differences in the distributions by race and sex.

The most obvious difference between the U.S. and non-U.S. populations was in racial composition. Of the 236 non-white patients studied, all but 21 came from the U.S. When the U.S. relative risk of mortality is recalculated with non-white patients excluded, however, the result goes from bad (1.05) to worse (1.21).

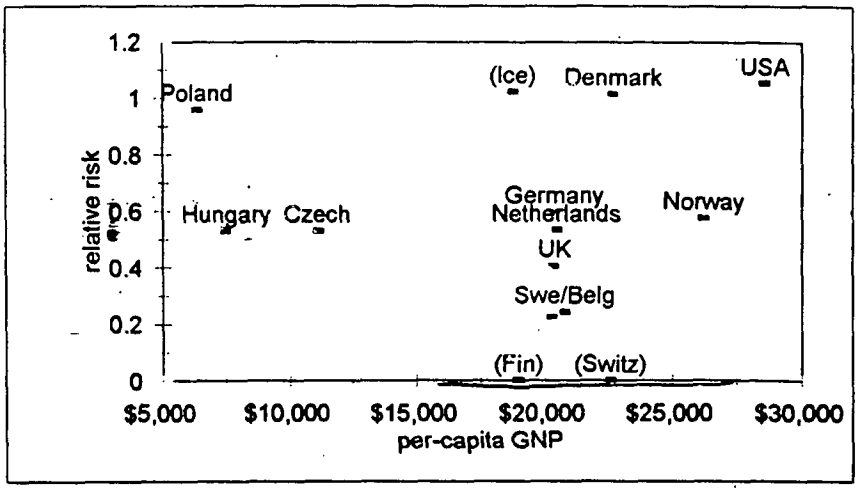
---

point is shown for each of the 14 countries, and each point is labeled with the name (sometimes abbreviated) of the country. When two or more points are very close, they share a label.

In contrast, the relative risk of mortality in women (0.92) was significantly different (nominal $P < 0.025$) from the relative risk in men (0.61), and the difference was even more marked (1.45 *vs.* 0.95) in the U.S. Also, the fraction of patients who were women (29%) was higher in the U.S. than in any other country. This sounds promising, but the sex ratio was, overall, only a fair predictor. As seen in the figure below[7], the observed inter-country variations in relative risk of mortality were only moderately linked to the per-country sex distribution.



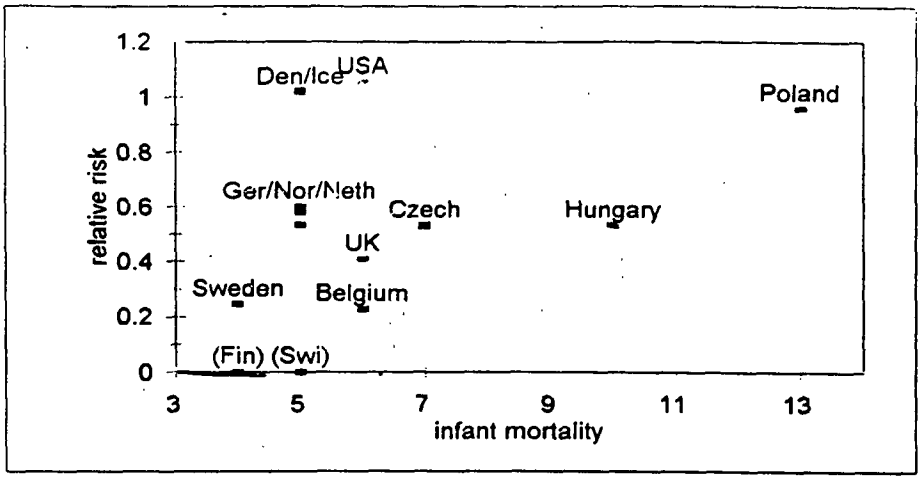
Some other inter-country differences are known to be dramatic, and they need not be gathered on a per-patient basis. For example, the several countries are moderately different economically, and these differences might lead to differences in patient or physician behavior and thereby to differences in the effects of metoprolol. No such effect is readily apparent, however, in the figure below.[8]



[7] In this figure and others below, the names of Finland, Iceland, and Switzerland are parenthesized to remind the reader that each of these countries contributed fewer than 50 patients to the trial.

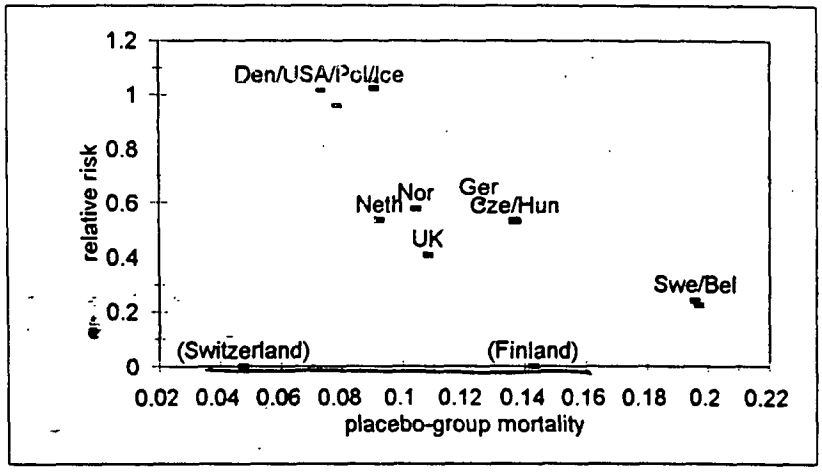
[8] The per-capita GNP data are taken from the 1999 *World Almanac*.

Similarly, one might speculate that the efficacy of a specific therapy (in this case, metoprolol) might be affected by the general level of public health. Using infant mortality[9] as a measure of public health, the figure below is suggestive of a relationship



(better public health leads to better efficacy of metoprolol), but the pattern is not compelling, and in any event the datum of interest (that representing the U.S.) is again an outlier.

Inter-country differences in outcome might be more the result of differences in specific **concomitant medical care** than in demography. For example, one can compare the participant countries with respect to variations in placebo-group mortality, which presumably integrates demographic differences with local differences in medical practice. As shown in the figure below, there may well be a negative association

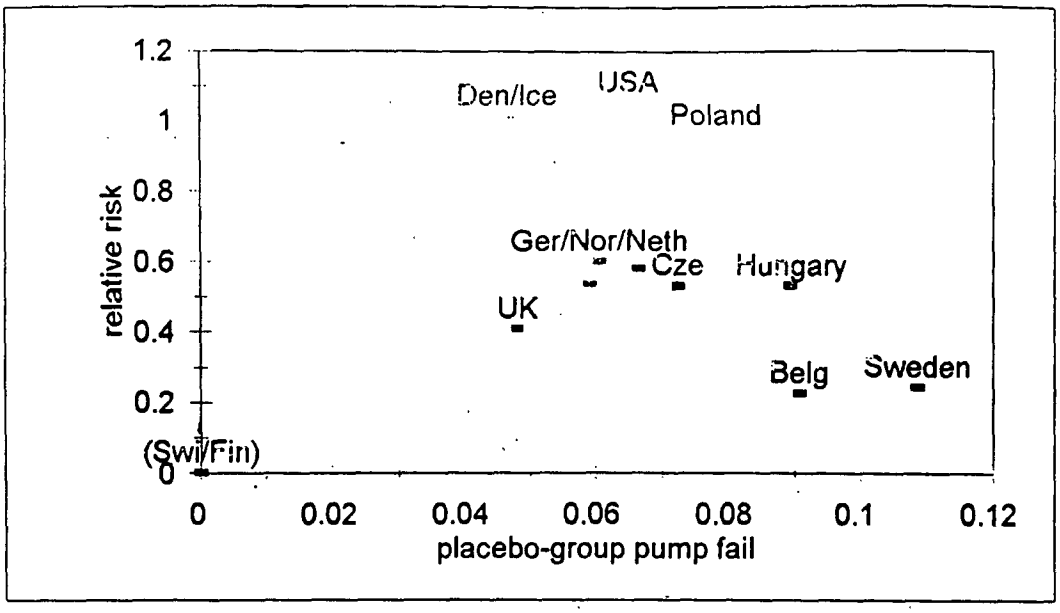


between placebo-group mortality and the relative risk, as if metoprolol's survival benefit were achieved through a reduction in a particular variety of death, and that variety of death were more common in some places than in others.

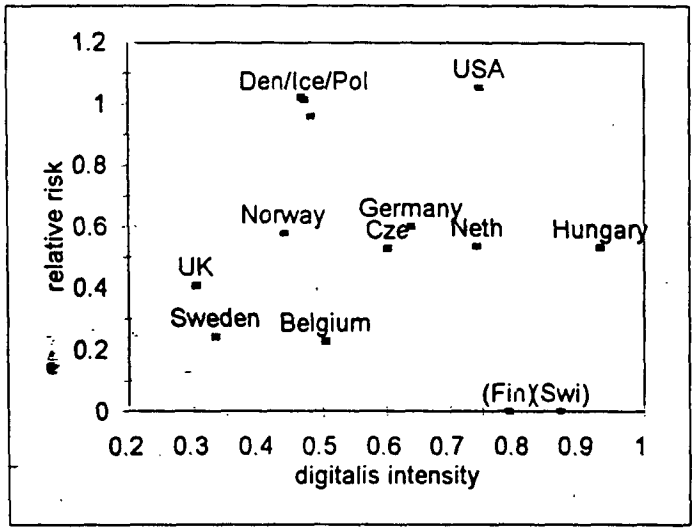
I have no idea what form of death that might be. For example, the frequency of death attributed to pump failure varied at least as much as the overall death rate, but

---

[9] From the 1999 *World Almanac*.

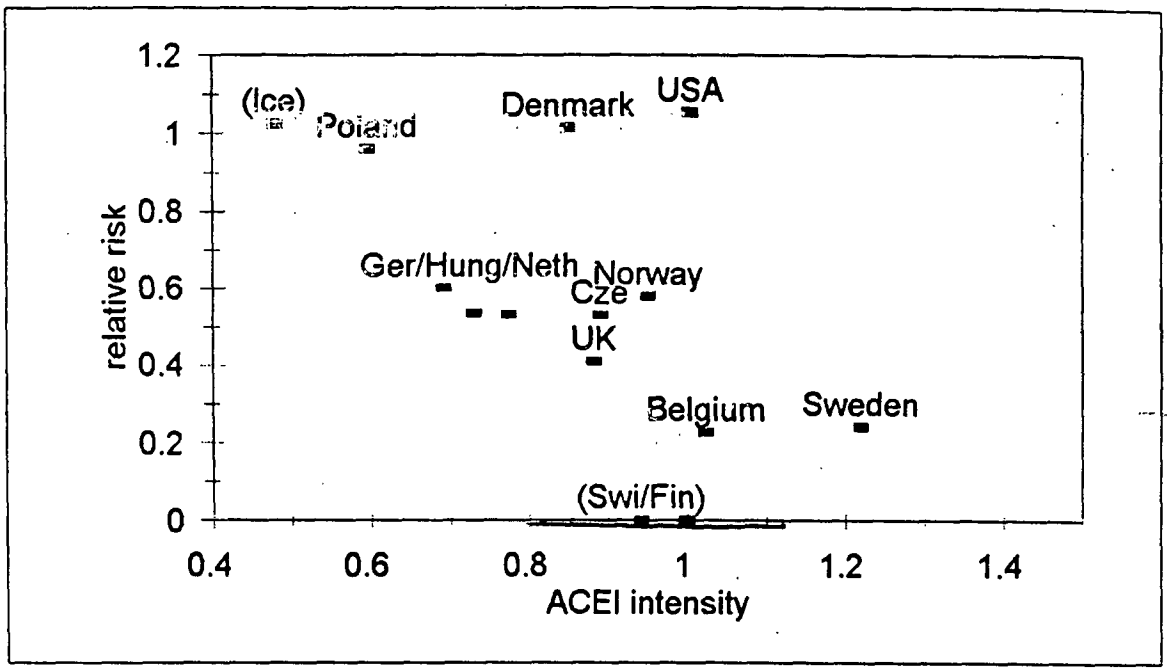


the relationship to the trial results was not especially stronger. Nor can I find any more specific cofactor that might explain the U.S. mortality result. For example, looking only at patients who were randomized to placebo, digitalis preparations were received by 18% of British patients, but by 48% of the Swiss patients. Among patients receiving digoxin, the average daily dose was almost twice as high in the Netherlands as in Norway. There is plenty of inter-country variation here, but when the relative risk of mortality is plotted against an index of digitalis dose,[10] there is no clear pattern to the data.



[10] The index was derived from Dr. Cui's data showing for each country and for each drug (digoxin and digitoxin) the average dose of each drug that was received by the average patient who received that drug. Grand per-drug averages were computed by averaging across countries, *not* weighting by the number of patients per country. Then, each per-country average dose of each drug was normalized by dividing by the grand average for that drug, and finally the per-country intensity index was computed by combining the normalized average doses, weighted by the number of patients receiving each drug, and dividing by the number of patients from that country in the trial.

There may be more of a signal in an analogous index of ACE-inhibitor intensity, but the easily-available data are not those that one would like to have. The protocol specified that all patients were to be treated with ACE inhibitors, except that patients who could not tolerate ACE inhibitors could be treated with angiotensin-II receptor inhibitors or with hydralazine and nitrates. The data most readily available describes the dosing of only captopril, enalapril, lisinopril, and ramipril. About ¾ of all of the patients received one or another of these, and an intensity index was computed using the dosing data from these (but also using the per-country rates of overall ACE-inhibitor use). As shown in the figure below, there appears to be a strong relation between



increasing use of ACE inhibitors and increasing efficacy of metoprolol. This relation is extraordinarily interesting (if it is real), but for all that, it is one in which the U.S. does not seem to participate, so it is unhelpful to this review.

Combined Endpoint in the U.S. Subpopulation

The favorable effect of metoprolol on the combined endpoint was more-or-less uniform over the studied population. In particular, the relative risk (metoprolol/placebo) was not different in the U.S. subpopulation (0.84) from what it was in the non-U.S. population (0.81).

Conclusions

As used in the MERIT study, the sponsor's sustained-release metoprolol was associated with a significant reduction in all-cause mortality. The statistical significance of this result was much smaller than the protocol-allocated risk of type-I error (nominal $P = 0.0001$, adjusted $P = 0.0062$, allocated $\alpha = 0.043$).

The mortality benefit was not observed in the U.S. subpopulation, perhaps because of the play of chance but more likely because of inter-country differences in the

sex ratio of randomized patients, differences in the causes of death in congestive heart failure, and/or other differences in demographics or medical practice. The point estimate of the mortality effect in the U.S. patients was actually adverse (RR ≈ 1.05), but the data are not convincing that it was worse than neutral.

The survival benefit of metoprolol appeared to be greater in men than in women, and it appeared to increase with increasing intensity of ACE-inhibitor therapy.

As used in the MERIT study, the sponsor's sustained-release metoprolol was associated with a significant reduction in the Combined Endpoint of all-cause mortality plus all-cause hospitalizations. The statistical significance of this result was much smaller than the protocol-allocated risk of type-I error (nominal $P = 0.0001$, adjusted $P \approx 0.0002$, allocated $\alpha = 0.01$). The effect on the Combined Endpoint was approximately uniform across demographic subgroups and geographic regions.

Discussion

Can it be proper to believe that a trial result is well established, but that it somehow does not apply to the U.S. population? The idea at first seems to be scientifically unsound, not to mention impolitic. One answer to the question might be implicit in the fact that trials in U.S. patients have never been required for drug approval by FDA.

Suppose, though, that the MERIT study had been performed entirely in Argentina, with the same findings of significant benefit with respect to both survival and the Combined Endpoint. Further, suppose that the mortality benefit had been found only in patients whose congestive heart failure was attributable to Chagas' disease, while the benefit with respect to the Combined Endpoint had been etiology-independent. In this hypothetical case, one might doubt that the mortality finding applied to the United States.

The actual MERIT study is different, because no reduviid bug has yet been identified in the ointment. Still, if one rejects the notion that the anomalous U.S. mortality results should be attributable to chance, one must believe that they reflect some biological reality, and that the overall mortality benefit found in MERIT might *not* apply to the U.S. population.

Recommendations

TOPROL-XL should be approved for use in the treatment of congestive heart failure, with the indication that when it is so used in patients who are receiving optimal therapy with ACE inhibitors and diuretics, it reduces the combined incidence of death and hospitalization.

The labeling of TOPROL-XL should describe the MERIT study, including the fact that the overall effect of active treatment was a reduction in all-cause mortality. This description should include language to the effect

DRAFT LABELING

DRAFT LABELING

Results of beta-blocker congestive-heart-failure trials abroad should no longer be assumed to provide compelling evidence regarding mortality effects that might be seen in U.S. patients.

dup Z. McDonald

JUN 2 6 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service
Division or Cardio-Renal Drug Products — **Memorandum**

Date : 26 June 2000
From : Director, Division of Cardio-Renal Drug Products, HF0-110 /S/
Subject : NDA 19-962/S013, Metoprolol for CHF, Astra-Zeneca LP.
To : Director, Office of Drug Evalutaion I, HFD-101

There is no doubt that the controlled release dosage form of metoprolol succinate, marketed under the Trade Name Toprol-XL, is approvable for the treatment of chronic systolic heart failure. The results of the single trial, MERIT (also known as study SH-MET-0024 and titled "Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. MERIT-HF. A Double Blind, Placbo controlled Survival Study with Metoprolol CR/XL in Patients with Decreased Ejection Fraction and Symptoms of Heart Failure") provide data that amply support such an action. The trial was stopped early because of a 34% reduction of total mortality in the metoprolol group observed in the second (planned) interim analysis of the data.

The results of three other trials (2 of which were conducted in patients with chronic heart failure) were also submitted to this NDA supplement. One was a US trial that randomized 42 patients to metoprolol and 23 to placebo. There were no pertinent findings that came from this study. A second was the RESOLVD Pilot Study, involving a host of centers worldwide that randomized 214 patients to metoprolol and 212 to placebo after 20 weeks of randomized treatment with candesartan, enalapril, or a combination of candesartan and enalapril. This was an exercise tolerance trial, and it did not distinguish metoprolol from placebo as add-on therapy to candesartan, enalapril or the combination. There were 9 fatal adverse effects in the metoprolol group and 17 fatal adverse events in the placebo group. This was a pretty big difference, and all deaths were related to the cardiovascular system. The third was a pharmacokinetic study that involved 15 subjects. None of these 3 trials needs close inspection; they contribute little, although the results of RESOLVD are consistent with the results of MERIT.

The MERIT study had 2 primary end points, the first being total all-cause mortality, and the second being a combined endpoint of total all-cause mortality plus all-cause hospitalization. There were 2001 patients randomized to placebo and 1990 patients randomized to metoprolol, worldwide. For total mortality there were 217 deaths in the placebo group and 145 deaths in the metoprolol group, the results favoring metoprolol, relative risk being 0.66 with a nominal p value of 0.0001, (p = 0.0062 corrected for multiple looks). For the combined end-point there were 767 events in the placebo group and 641 events in the metoprolol group, the result favoring metolprolol, relative risk being 0.81, nominal p value of 0.0001, corrected p = 0.0002 (a guess since there no way to explicitly calculate it). So, the intent-to-treat, overall study result is pretty striking and with no debate nor contrary points of view. Based on all historical standards that we have applied in making any past decision, metoprolol is approvable. This was an adequate and well controlled trial, there were no flaws in its execution nor in the approaches to statistical analysis, and the p values for the 2 prospective end-points were close to (for total mortality) or an order of magnitude less (the combined endpoint) than the 0.00125 number that the Division has been currently urging as the standard for one-trial acceptance. There is no question related to the approvability of metoprolol.

There is question with respect to how to express the indication and how to describe the results of the trial. The question arises because of an analysis done by Dr. Lu Cui. In this analysis he compared the results of MERIT in the United States with the results in Europe and found what appears to be a major difference with respect to total mortality (total mortality was decreased in Europe and not in the United States).

Subgroups

Prospective and retrospective analyses of subgroups are not just routine, they are required by our review policies. Moreover, without dividing the study up into smaller groups (based upon something like age, country), the components of the primary end point are frequently examined individually. For example, for MERIT there were 12 different analyses of the primary end point and/or its components. We also, by

policy, encourage such analyses. So it is not surprising that such endeavors are undertaken by our reviewers.

An analysis by site (that is, by center) is a routine practice even when it is obvious that sample sizes are too small to have any reasonable power and when it is well known that the usual statistical test used can only detect phenomenal differences (very insensitive tests). It is almost routine to see country-by-country interaction analyzed (for example, the eptifibatide analysis); in fact I think most supervisors would complain if they did not see such analyses done. When Dr. Cui decided to do a USA-vs.-Europe analysis, I thought that to be a perfectly reasonable thing to do, as reasonable as by-gender, as reasonable as by-age, etc. In your memo of June 12, 2000, you suggest insight will come from closer examination of 7 non-cardiovascular and 5 non-sudden deaths (a total of 12 deaths) in order to make sense of something that the analysis of the 362 deaths observed in the trial could not explain. So, doing subgroup analyses is a common occurrence, too common, in my judgement.

I certainly agree with the notion that the best estimate of benefit of a treatment comes from an analysis of all patients randomized and such an analysis is pursuasive only when done on the prospectively declared end point or end points. I also agree that those are the results that should be the overwhelmingly prominent factor used in decision making. Subgroup analyses should be at best hypothesis generators (even when prospectively declared) and frequently they should be simply disregarded even when it might make biological sense to some clever and imaginative investigator.

As put by Peto in a Chapter written in 1966:

> "Treatment that is appropriate for one patient may be inappropriate for another. Ideally, therefore, what is wanted is not only an answer to the question 'Is this treatment helpful on average for a wide range of patients?', but also an answer to the question 'For which recognizable categories of patient is this treatment helpful?'. However, this ideal is difficult to attain directly because the direct use of clinical trial results in particular subgroups of patients is surprisingly unreliable. Even if the real sizes of the effects of treatment in specific subgroups are importantly different, standard subgroup analyses are so statistically insensitive that they may well fail to demonstrate these differences. Conversely, even if there is a highly significant 'interaction' (i. e., an apparent difference between the sizes of the therapeutic effects in different subgroups and the results seem to suggest that the treatment works in some subgroups but not in others (thereby giving the appearance of a 'qualitative interaction'), this may still not be good evidence for subgroup-specific treatment preferences."

Despite such generally recognized "truths", we have certainly seen totally retrospective analyses, utilizing totally retrospectively defined end-points result in decision-making even when primary endpoints (trial by trial) did not distinguish drug from placebo (carvedilol). At other times, suspicion that adverse effects might be present (no proof, no statistics, no predefined rules) led to major decisions (tasosartan). Judgement is always involved; general and sensible rules are frequently materially altered by specifics. The question then is when should one pay attention to subgroup analyses? The answer is not never, and the answer is not always. I don't think I know the answer to the question, which is why it is interesting.

In the specific case of metoprolol, MERIT and the US-vs.-Europe analysis, the number of events for all-cause death in the US was 100 events out of the 362 deaths observed in the entire study (that is a respectable number of events) and the relative risk was 1.05 (a little on the adverse side). Any way you cut the cake, this numerical result is not comforting (whether it is rejected, whether it is accepted, whether it is debated, etc.), since we are being asked to make a judgement with respect to approving metoprolol for use in the United States. In the past few years we have seen other instances of US-vs.-other country differences but never needed to come to grips with determining whether we believed it or not, since the US population fared well (say, eptifibatide) or where the data were inadequate although the US population fared poorly (ramipril; HOPE), or where there was no US experience at all (thrombolytics). That is not the case for MERIT. Although the subgroup was retrospective, the analysis does not violate the randomization, and classical interaction calculations give a $p = 0.003$ (with a very insensitive test that usually finds nothing).

Dr. Fenichel's graphically based search for covariates that could be important found no plausible covariate that might explain the results. After grappling with the data, he thought (as does Dr. Cui and others) that the US-vs.-Europe findings should be considered real (i.e., not "just a play of chance"). From my point of view, I am convinced that the magnitude of effect on total mortality in the US population is less than that observed in Europe, but I am certainly not convinced (nor even remotely suspect) that the US population was harmed with respect to total mortality. In other words, I do not think the effect of metoprolol on total mortality is in the opposite direction, but I do think the effect is probably smaller (although I cannot quantitate the probability).

Summary

So what to do? The overall trial result (either end point) is as strong as I have seen. There is no doubt that metoprolol is useful in the treatment of patients with chronic systolic heart failure when added to any and/or all conventional therapies (except carvedilol), so it is approvable.

For a single trial, the all-cause-mortality end point does not quite make the 0.00125 standard and there is a some cloud hanging over the inference that the US population shared in the all-cause-mortality benefit. Fortunately, there was a second primary end point, the combination of all-cause mortality plus all-cause hospitalization. That end point, even when corrected (p = 00002) is an order of magnitude better than 0.00125. Without any assumptions, without any compromise, without any denial of any analysis, without any second-guessing or assumptions about what is "true", metoprolol can be approved on the basis of the combined end point, and the indications should read like the other combined end point indications currently approved.

The only question is what to say in labeling regarding the US-vs.-Europe analysis. My suggestion is that nothing be said at all. Labeling is not where I think we should reflect on an inability to make a rational ultimate decision. I think there is a low probability that this finding was "chance", but the probability is finite, so it could have been. I am confident that the US population will enjoy treatment benefits of metoprolol (if

not for total mortality, then at least for hospitalizations). I am not sure of what the inference should be, but the finding is pretty strong.

We have better evidence that controlled release metoprolol is useful it the treatment of congestive heart failure than we had for carvedilol, so the package insert should not penalize metoprolol because we have uncertainty with respect to how to handle the US-vs.-Europe analysis!

Indications should read essentiaily like carvedilol's, the only other beta-blocker approved for heart failure. My suggestion is:

INDICATIONS

Trade Name is indicated for the

DRAFT LABELING

Trade Name i DRAFT LABELING

Again, in the description of the clinical trial, I would avoid much attention to the US-vs.-Europe comparison. In the approval, we are basically saying that this result should not be believed. If that is what we think, I think it inhumane to pass guilt to the reader by suggesting that maybe an effect will not happen, but go ahead and use it anyway.

CLINICAL TRIALS

DRAFT LABELING

For reasons enumerated in the sponsor's submission of 23 June 2000, I support granting a waiver from the requirements for pediatric studies.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL