

All-Cause Mortality Endpoint Comparison in Large Beta-Blocker Heart Failure Trials: United States (US) vs. Rest of World (ROW)

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Background

- Large randomized, controlled trials have shown that b-blockers reduce mortality by 34-35% in moderate to severe systolic dysfunction heart failure patients (COPERNICUS, MERIT-HF, and CIBIS-II)^{1,2,3}.
- However, the majority of patients enrolled in these trials were from outside the US (i.e. Rest of World, ROW). BEST, the only intention-to-treat mortality trial which enrolled almost exclusively US patients, showed only a 13% reduction in mortality⁴.
- Geographically distinct populations can have different genetic profiles that can affect the safety and efficacy of drugs and devices⁵.
- We investigated whether or not improvement in survival was different due to enrollment of ROW populations.

Methods:

- We compared the primary endpoint of all cause mortality and annual placebo mortality rate for the 4 trials.
- BEST contained a DNA substudy which has been previously described. Results from the Very Favorable (β 1-adrenergic receptor 389 Arginine homozygous) genotype subgroup were compared to the overall study cohorts.⁶

Endpoints:

- All-Cause Mortality
- CV Mortality
- Mortality + Cardiac Transplant
- Mortality + HF Hospitalizations
- Heart Failure Progression
- Heart Failure Hospitalization (time to event)
- Heart Failure Hospitalization Days
- Total MI in HF Patients

- Trial data other than BEST was obtained from the literature¹⁻¹⁰.
- All cause mortality hazard ratios were generated using the Cox Proportional Hazards Model.
- Relative risk in the US vs. ROW table was calculated using the rate of event among active / rate of event among control. For the All Studies row, we calculated relative risk on the overall rates.
- HF Hosp Days % = % reduction from active mean to placebo mean.

Results:

Table 1. Baseline Demographic and Clinical Characteristics for Patients

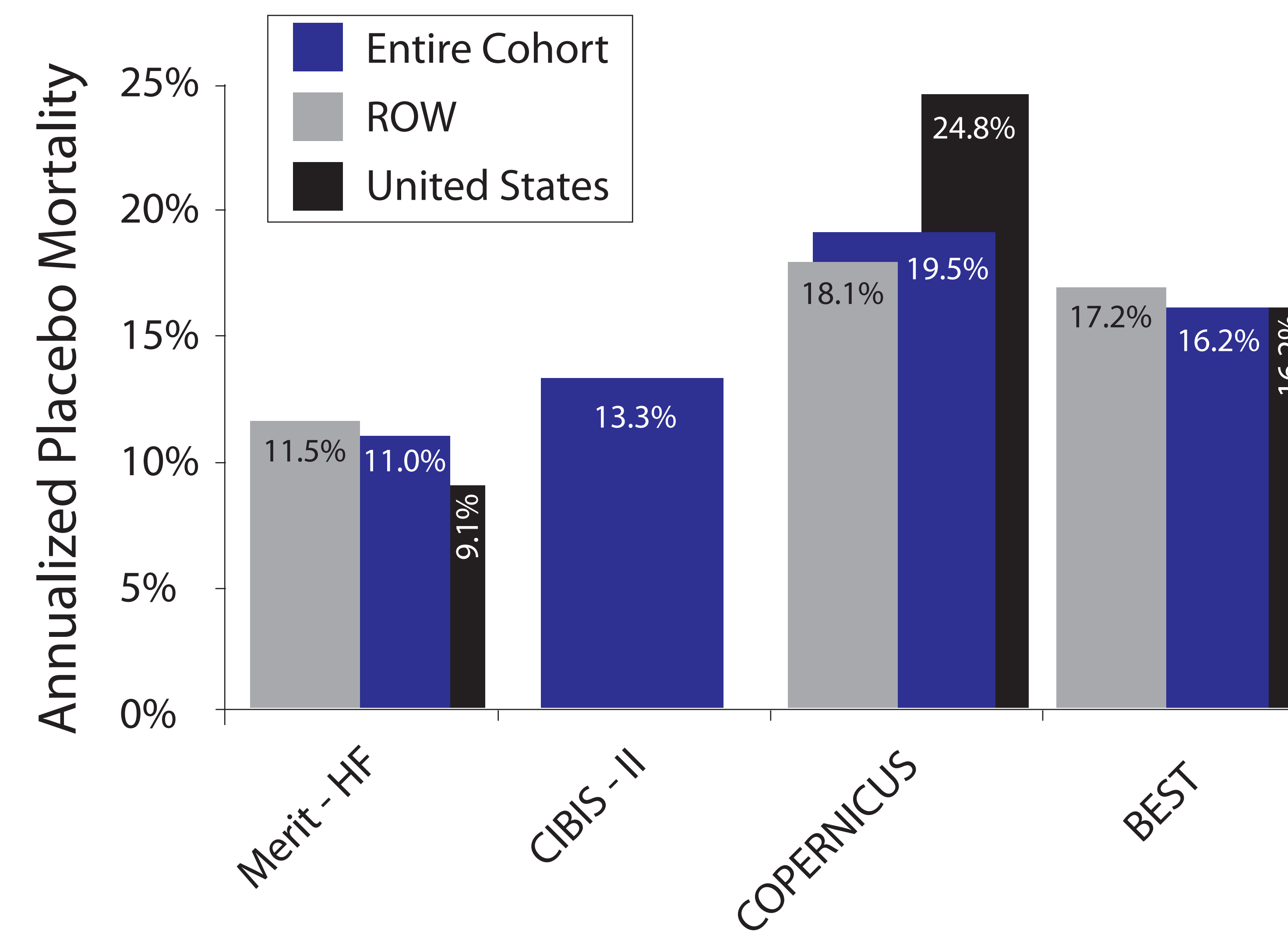
| | MERIT-HF | CIBIS-II | COPERNICUS | BEST |
|-------------------------|----------|----------|------------|------|
| Number of Patients | 3991 | 2647 | 2289 | 2708 |
| Age (years) | 64 | 61 | 63 | 60 |
| Sex (%) | | | | |
| Male | 81 | 80 | 80 | 78 |
| Female | 19 | 20 | 20 | 22 |
| Race (%) | | | | |
| Non-black | 95 | - | 95 | 77 |
| Black | 5 | - | 5 | 23 |
| NYHA Class | | | | |
| II | 41 | 0 | (NR*) | 0 |
| III | 55 | 83 | | 92 |
| IV | 4 | 17 | | 8 |
| LVEF(%) | 28 | 27 | 20 | 23 |
| SBP | 129 | 130 | 123 | 117 |
| Heart rate | 83 | 80 | 83 | 82 |
| Diabetes (%) | 25 | 12 | - | 35 |
| Atrial fibrillation (%) | 13 | 20 | - | 12 |

Table 2. All-cause Mortality (ACM) Comparison

| Clinical Trial/ (β -blocker studied) | # Patients | ACM HR [CI] Log rank p value | Actual # US Deaths/total (Rel. Risk) [CI] | Actual # ROW Deaths/total (Rel. Risk) [CI] |
|---|----------------|---|---|---|
| COPERNICUS (carvedilol) | 2289 (US=482) | 191/1133 P 132/1156 C 0.65 [0.52 -0.81] (p=0.0014) | 50/233 P 44/249 C (0.82) [0.57-1.18] | 141/900 P 88/907 C (0.62) [0.48-0.80] |
| MERIT-HF (metoprolol CR/XL) | 3991 (US=1071) | 217/2001 P 145/1990 M 0.66 [0.53 -0.81] (p=0.00009) | 49/539 P 51/532 M (1.05) [0.73-1.53] | 168/1462 P 94/1458 M (0.56) [0.44-0.71] |
| CIBIS-II (bisoprolol) | 2647 (US=0) | 228/1320 P 156/1327 B 0.66 [0.54 -0.81] (p<0.0001) | No U.S. pts | 228/1320 156/1327 (0.68) [0.56-0.82] |
| BEST (bucindolol) | 2708 (US=2645) | 439/1354 P 402/1354 B 0.87 [0.76 -1.0] (p=0.053) | 428/1322 P 391/1323 B (0.91) [0.81-1.02] | 11/32 P 11/31 B (1.03) [0.53-2.03] |
| All Studies (Relative Risk) | 11,635 | 1075/5808 (19%) P 835/5827 486/2104 (14%) β -bTx (23.1%) β -bTx (0.774) [0.71-0.84] | 527/2094 (25.2%) P 486/2104 (9.3%) β -bTx (0.918) [0.82-1.02] | 548/3714 (14.8%) P 349/3723 (9.3%) β -bTx (0.635) [0.56-0.72] |

Results, continued:

Figure 1. Annualized Placebo Mortality



Comparison of Beta-blocker Studies*: US & WW:

Table 3. Comparison of Beta-Blocker Studies: US & WW

| | Bucindolol n = 2645 | Metoprolol n = 1071 | Carvedilol n = 482 | Bucindolol (V. Fav. Genotype) n = 482 | Bucindolol n = 2708 | Metoprolol n = 3991 | Carvedilol n = 2289 |
|----------------------------------|---------------------|---------------------|--------------------|---------------------------------------|---------------------|---------------------|---------------------|
| Trial Name | BEST | MERIT | COPERNICUS | BEST | BEST | MERIT | COPERNICUS |
| Trial Location | US | US | US | US | WW | WW | WW |
| All-cause Mortality* | -13%† | +5% | -20% ^a | -44%† | -13%* | -34%‡ | -35%‡ |
| CV Mortality* | -17%† | -3% ^a | - | -51%† | -16%† | -38%‡ | No Data |
| Mortality + Cardiac Transplant* | -15%† | - | - | -49%‡ | -14%† | -32%‡ | No Data |
| Mortality & HF Hospitalizations* | -21%‡ | - | - | -38%‡ | -21%‡ | -31%‡ | -33%‡ |
| Heart Failure Progression* | -21%‡ | - | - | -37%‡ | -20%‡ | - | - |
| HF Hospitalizations, TTE* | -24%‡ | No Data | - | -40%‡ | -23%‡ | NA | No Data |
| HF hospitalization days | -27%‡ | No Data | - | -52%‡ | -26%‡ | -36%‡ | -41%‡ |
| Total MI in HF Patients* | -47%† | No Data | - | -65% | -41%-46%† | No Data | No Data |

* Not head-to-head studies

† p ≤ 0.050; ‡ p ≤ 0.007; *, p = 0.053

based on hazard ratios & based on relative risk

Conclusions:

- The magnitude of beta-blocker (BB) survival effect was either reduced (HR 0.80) or neutral (HR 1.05) in large US populations included in COPERNICUS and MERIT-HF, respectively.
- These effects are more comparative to BEST trial results with bucindolol in US patients.
- The Very Favorable genotype subgroup in BEST showed significantly improved mortality reduction compared to other beta-blockers.
- Such findings suggest that differences in BB survival benefit observed in clinical trials may be significantly influenced by inclusion of varying geographic populations (US vs. ROW).
- Genetic diversity should be considered in the relevance of cardiovascular trials and interpretation of results⁵.

Limitations:

- Comparisons were not prospectively defined at the time of the randomized trials.
- There is no adjustment for differences in baseline characteristics of the trial populations.

References:

- Packer M, Coats AJ, Fowler MB et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344:1651-8.
- MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353:2001-7.
- CIBIS II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353:9-13.
- The Beta Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344:1659-67.
- Glickman, McHutchison, Peterson et al. Ethical and Scientific Implications of the Globalization of Clinical Research. N Engl J Med. Feb 2009; 360(8): 816-823.
- O'Connor C et al. J Card Failure 2008;14(6): [Supp 1]:S69.
- CDER. Division of Cardio-renal drug products. Clinical review. 2008. Available at: http://www.fda.gov/cder/foi/nda/2001/20-2975007_Coreg_medr.pdf.
- Domanski MJ, Krause-Steinrauf H, Massie BM, et al. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS II, MERIT-HF, and COPERNICUS. J Card Fail. 2003;9:354-363.
- Ghali JK, Pina IL, Gottlieb SL, Deedwania PC, Wikstrand JC; MERIT-HF Study Group. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in MERIT-HF. Circulation. 2002;105:1585-1591.
- Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation. 2001;103:375-380.

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