

# **Effectiveness of Controlled-Release Metoprolol versus Carvedilol as Prescribed for Veterans with Heart Failure**

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## Research Objectives

- Describe the prescribing of carvedilol and CR metoprolol for veterans with heart failure
- Test the null hypothesis that the time to hospitalization or death after the first prescription of CR metoprolol versus carvedilol would not be different

## Methods: Cohort Identification

- National PBM data searched for first VA prescription for either beta-blocker in the period from Oct 1999 to Sept 2003
  - Excluded if had prescription for any beta-blocker in prior year
  - Excluded if did not have any VA prescriptions in prior year
  - Date first prescription dispensed = index date

## Methods: Cohort Identification

- National VA inpatient and outpatient administrative records searched to confirm a diagnosis of heart failure within 2 years before the index date
- Required enrollment in fee-for-service Medicare during year prior to index date for more complete ascertainment of health care utilization and co-morbidity

# Methods: Baseline Variables

- Demographics including VA station
- Outpatient VA prescriptions
  - Grouped by 37 VA formulary classes
  - Prescribed dose of beta-blocker extracted from prescription records
- Diagnoses listed on inpatient and outpatient records from VA and Medicare
  - Published algorithm used to define co-morbidity variables for chronic conditions

## Methods: Follow-up

- Censored as at end of Dec 2004 based on available Medicare data
  - Censored before if disenrolled from FFS
- Searched VA and Medicare records for first hospital admission after index date
  - Extracted primary diagnosis
- Searched VA Vital Status file for dates of death

## Methods: Data Analysis

- Intent-to-treat & on-treatment censored after last or different beta-blocker prescription
- Logistic regression on baseline variables to estimate propensity to prescribe carvedilol
- Cox proportional hazard regression for time to outcome event within 7 propensity score strata where beta-blocker groups were balanced with respect to baseline variables
- Sensitivity to unmeasured confounders

## Results: Cohort Identification

Criterion	Carvedilol	CR Metoprolol
First VA $\beta$ -B Rx Oct 99-Sept 03	37,662	44,380
VA HF Dx	29,229 (78%)	13,746 (40%)
FFS Medicare	17,759 (47%)	8,910 (20%)
Alive outpatient	17,429 (46%)	8,683 (20%)

## Results: Initiation of $\beta$ -Blockers

	Carvedilol n=17,429	CR Metoprolol n=8,683
1999	2%	<1%
2000	19	6
2001	28	16
2002	28	37
2003	23	40
Initial Dose	0.125 (0.125-0.25) <sup>a</sup>	0.125 (0.125-0.25)

<sup>a</sup>Median (IQR) expressed as fraction of target doses of 50 mg/day of carvedilol and 200 mg/day of CR metoprolol

## Results: Continuation of Initial $\beta$ -Blocker

	Carvedilol n=17,429	CR Metoprolol n=8,683
Multiple Rx	15,799 (91%)	7,379 (85%)
Months	24 (7-38)	14 (3-28)
Last Dose	0.25 (0.125-0.50)	0.25 (0.125-0.25)
Up-titration	7,076 (41%)	2,281 (25%)
Target Dose	3,476 (22%)	307 (4%)

## Results: Continuation of Initial $\beta$ -Blocker

	Carvedilol n=17,429	CR Metoprolol n=8,683
Switched $\beta$ -Blockers	2409 (14%)	3004 (35%)
Months to switch	15 (6-26)	12 (4-22)
Switched to		
carvedilol	-	691 (8%)
CR metoprolol	819 (5%)	-
metoprolol tartrate	1108 (6%)	2012 (23%)
other (atenolol, etc)	482 (3%)	301 (4%)

## Results: Baseline Characteristics

	Carvedilol n=17,429	CR Metoprolol n=8,683
Age (yrs)	74 (69-79)	75 (69-80)
Male (%)	99	98
Race, Ethnicity (%)		
white, not hispanic	88	86
black, not hispanic	10	12
other	2	2

# Results: Baseline Characteristics

Selected Co-morbidity (%)	Carvedilol n=17,429	CR Metoprolol n=8,683
Hypertension	84	86
Ischemic heart disease	86	79
Cardiac valve disease	40	32
Cardiac arrhythmia	64	58
Chronic pulmonary disease	46	45
Diabetes mellitus	46	45
Renal disease	18	16
Depression	16	18

# Results: Baseline Characteristics

Heart Failure Medications (%)	Carvedilol n=17,429	CR Metoprolol n=8,683
Loop diuretic	66	53
ACE inhibitor	67	62
Angiotensin receptor blocker	10	9
Spiranolactone	16	10
Digoxin	49	33

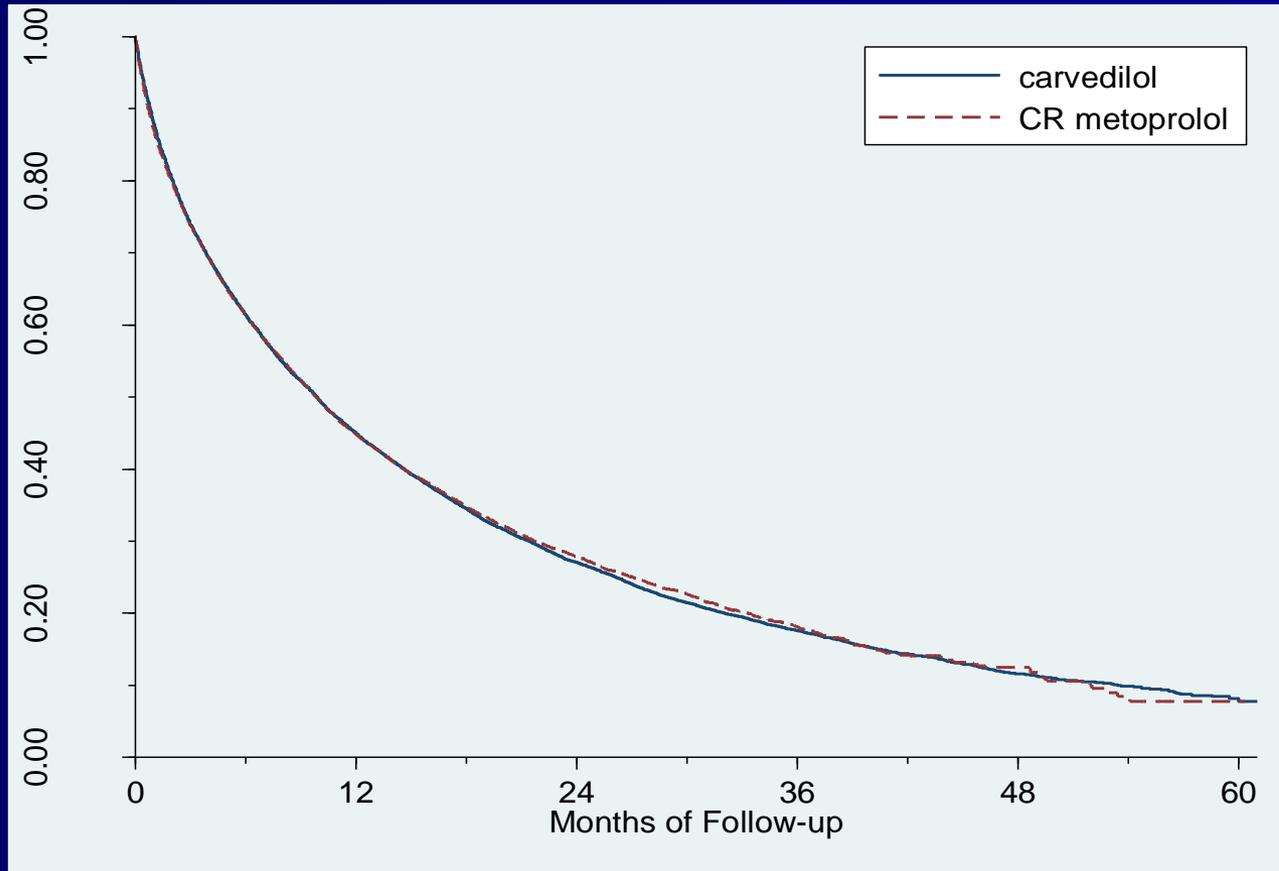
## Results: Baseline Characteristics

Selected Other Medications (%)	Carvedilol n=17,429	CR Metoprolol n=8,683
Nitrate	39	34
Calcium channel blocker	25	33
Antiarrhythmic	11	8
Warfarin	26	22
Diabetes therapy	34	33
Respiratory therapy	25	27
Antidepressant	22	24
Lipid lowering	51	52

# Results: Baseline Hospital Admissions

	Carvedilol n=17,429	CR Metoprolol n=8,683
Any diagnosis (%)		
none	46	47
1	30	31
2	13	13
> 2	11	9
Heart failure diagnosis (%)		
none	77	85
1	18	12
> 1	5	3

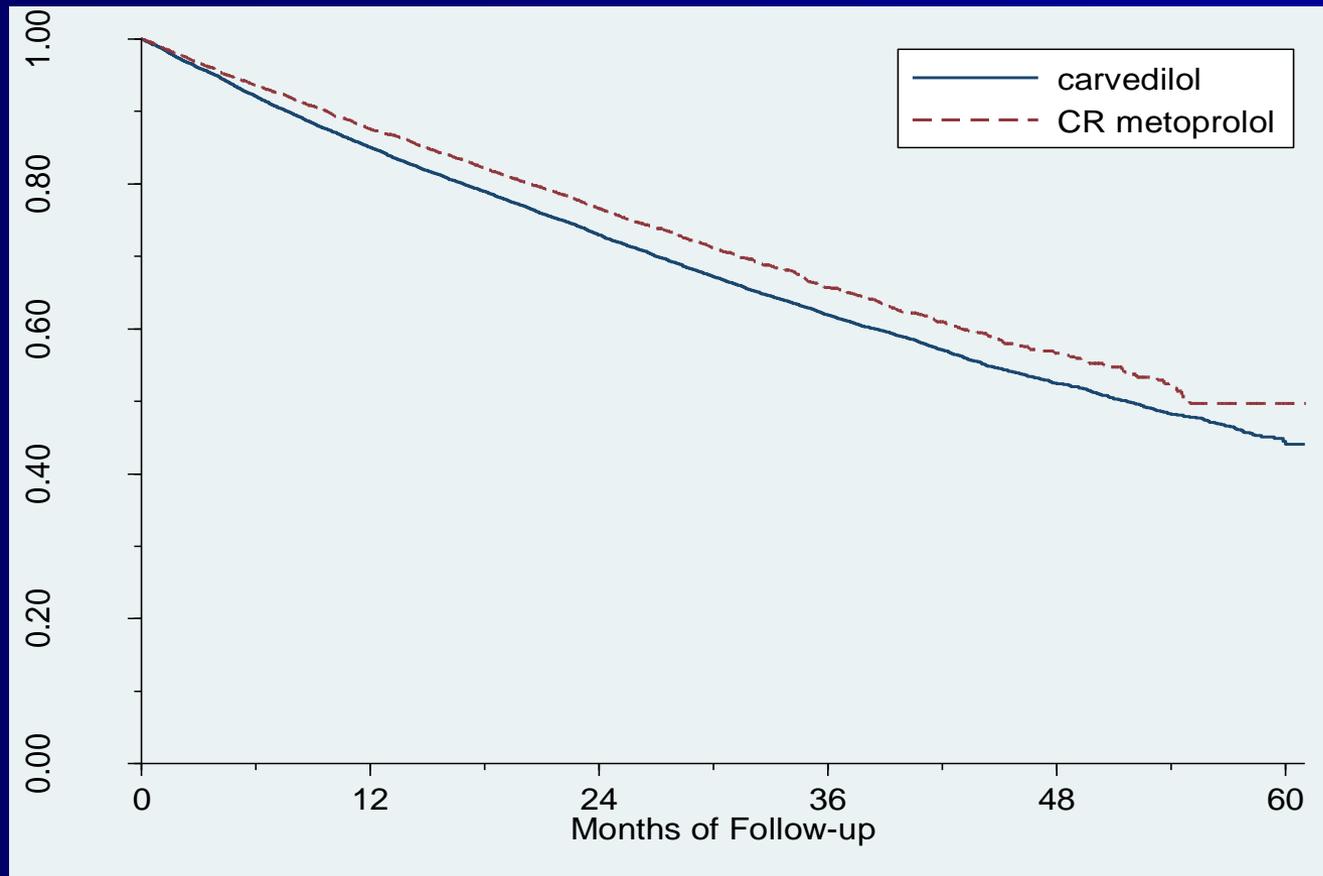
# Results: Unadjusted Intent-to-Treat Analysis of Survival without Hospital Admission



# Results: Main Diagnoses for Hospital Admission Endpoints

	Carvedilol n=13,083 (75%)	CR Metoprolol n=6,130 (71%)
Heart failure	25%	19%
Dyspnea, pulm. edema, fatigue	5	4
Ischemic heart disease	17	19
Cardiac arrhythmia/conduction	10	9
Pneumonia/Respiratory	11	12
Hypotension	7	5
Renal dysfunction	2	2
Other	23	30

# Results: Unadjusted Intent-to-Treat Analysis of Survival



# Results: Hazards of CR Metoprolol Relative to Carvedilol

	Survival without Hospitalization	Survival
Unadjusted		
intent-to-treat	0.99 (0.95 to 1.04)	0.86 (0.79 to 0.92)
on-treatment	0.98 (0.94 to 1.04)	0.88 (0.80 to 0.96)
Adjusted		
intent-to-treat	0.99 (0.96 to 1.03)	0.91 (0.85 to 0.96)
on-treatment	0.97 (0.93 to 1.01)	0.90 (0.83 to 0.98)

Hazard ratio (95% confidence interval)

# Results: Sensitivity of Survival Hazard Ratio to Unmeasured Confounder(s)

HR for Confounder	↑ Presence with Carvedilol	HR (95% CI)
-	-	0.91 (0.85 to 0.96)
1.25	5	0.92 (0.86 to 0.97)
1.50	5	0.93 (0.87 to 0.98)
2.00	5	0.95 (0.89 to 1.00)
1.25	10	0.93 (0.87 to 0.98)
1.50	10	0.96 (0.90 to 1.01)

## Summary of Key Observations

- Doses of  $\beta$ -blockers prescribed for thousands of veterans with heart failure remained well below target doses after several prescriptions
- Use of CR metoprolol was associated with significantly better survival than carvedilol. However, the observed difference could be explained by plausible differences in unmeasured confounders.

## Conclusions

- The results do not provide strong evidence for preferential use of CR metoprolol rather than carvedilol for patients with heart failure
- Whether or not the effectiveness of  $\beta$ -blockers being prescribed for veterans with heart failure can be improved by efforts to increase doses warrants further study

# Baseline Differences Between Carvedilol & CR Metoprolol in Propensity Score Strata

	All Subjects	0 to 0.099 Stratum	0.5 to 0.599 Stratum
Number	17429/8683	12/256	1832/1609
Mean Propensity	0.74/0.53	0.07/0.05	0.55/0.55
Start Year 2001	11.6 %	9.0 %	-1.5 %
2003	-17.4 %	1.8 %	1.5 %
HF admission	8.2 %	4.2 %	1.3 %
Digoxin	16.7 %	<1 %	<1 %
Ischemic heart disease	7.2 %	14.8 %	1.5 %