TOLERABILITY OF TARGET DOSES OF METOPROLOL VS CARVEDILOL IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

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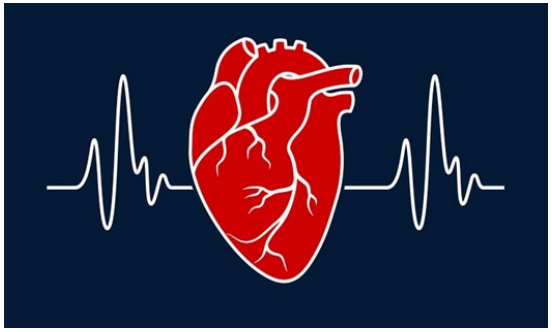
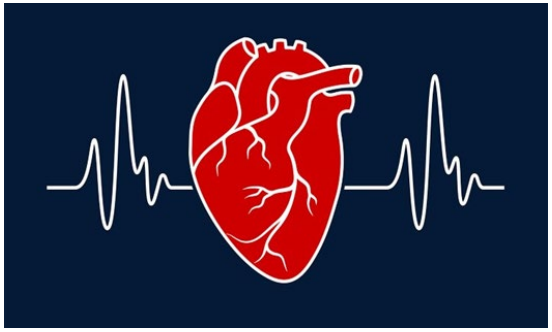
BACKGROUND



- Heart failure (HF) is an increasingly common condition
  - 5.1 million affected individuals in 2006
  - 5.7 million affected individuals currently
- Therapy focuses on preserving function and reducing cardiovascular mortality
- Guidelines recommend beta blockers as one of the mainstays of therapy
- Metoprolol succinate and carvedilol have demonstrated mortality benefit in prior clinical trials
  - US Carvedilol Heart Failure Study
  - MERIT-HF

Go, *Circulation* 2013.
2017 ACC/AHA/HFSA Guideline for the Management of Heart Failure. *Journal of Cardiac Failure* 2017.
US Carvedilol Heart Failure Study, *NEJM*, 1996.
Packer, *ACC Current Journal Review* 1997.
MERIT-HF, *The Lancet*, 1999.

COMPARATIVE STUDIES



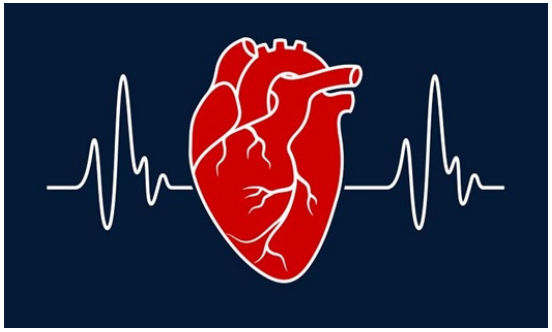
- Prior studies sought to differentiate benefits between carvedilol and metoprolol
  - COMET trial
  - Frolich and colleagues
  - Ajam and colleagues

	B1 antagonism	B2 antagonism	Alpha-1 antagonism	NO production
Carvedilol	+	+	+	+
Metoprolol	+	--	--	--

COMET, *ACC Current Journal Review* 2003.
Frolhlich, *Circulation* 2015.
Ajam, *American Heart Journal* 2018.

	Comparative Studies		
	COMET	**Frolich et al.**	**Ajam et al.**
Study Population	3029 patients with chronic heart failure (NYHA II-IV), EF $\leq$ 35%, on ACE-I and loop diuretic	4016 patients with objective evidence of HF and EF < 45% identified via the Norwegian Heart Failure Registry and University of Heidelberg Heart Failure Registry	114,745 patients diagnosed with HFrEF prescribed carvedilol or metoprolol succinate identified on the VA patient database
Methods	Carvedilol 25 mg twice daily or metoprolol tartrate 50 mg twice daily	Patients were matched based on dose equivalence of carvedilol or metoprolol succinate	Propensity score matching comparing carvedilol vs metoprolol
Primary Endpoint	All-cause mortality	Mortality	Mortality
Results	Superior survival with carvedilol HR: 0.83 95% CI: 0.74-0.93 p = 0.0017	No difference in mortality HR: 0.93 95% CI: 0.57-1.50 p = 0.36	Superior survival with carvedilol HR: 1.069 95% CI: 1.046-1.092 p < 0.001

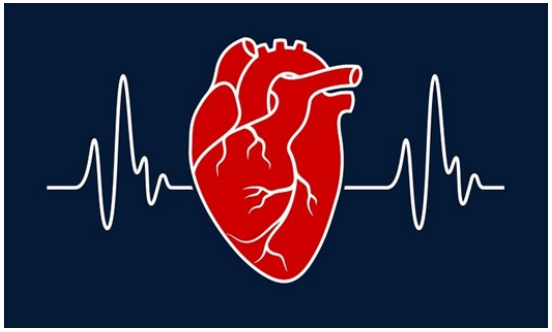
THERAPEUTIC LIMITATIONS



- One common limitation of therapy is dosage titration
  - CIBIS-ELD
    - Compared bisoprolol vs. carvedilol in 883 elderly patients with HFrEF
    - The primary endpoint was tolerability, defined as reaching and maintaining guideline-recommended target doses after 12 weeks
    - No difference in tolerability – 32% at target dose of carvedilol vs. 31% of bisoprolol
    - *Principle reason for restricted titration was a HR < 60 bpm*
  - CHAMP-HF
    - 3,518 patients from 150 cardiology practices
    - Only 28% of patients were at target dose of beta blocker

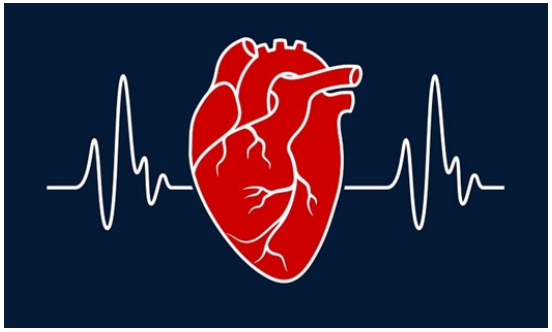
Tandon P, McAlister FA, Tsuyuki RT, et al. *Arch Intern Med* 2004.
CIBIS-ELD. *Eur J Heart Fail*. 2011
CHAMP-HF, *ACC* 2018.

OBJECTIVE



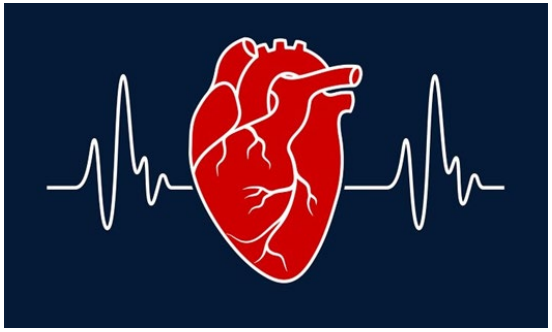
To evaluate the ability of patients with heart failure with reduced ejection fraction to achieve guideline recommended target doses of metoprolol succinate versus carvedilol

METHODS



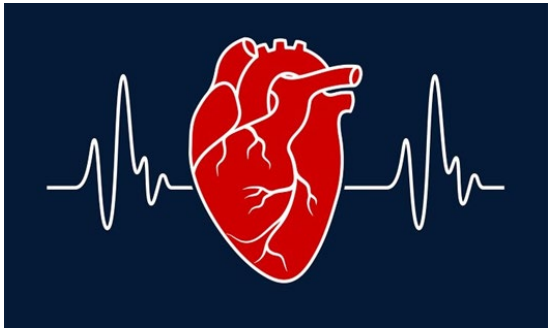
- Single-center, retrospective cohort study at Missouri Baptist Medical Center
- Data collected from electronic medical records of patients treated by BJC Medical Group Cardiology providers
- Primary outcome
  - The ability to achieve guideline recommended target doses of metoprolol succinate or carvedilol
    - Metoprolol succinate 200 mg daily
    - Carvedilol 25 mg twice daily
- Secondary outcomes
  - Reason for discontinuation or down-titration of beta blocker therapy
  - Adverse effects related to beta blocker therapy

METHODS



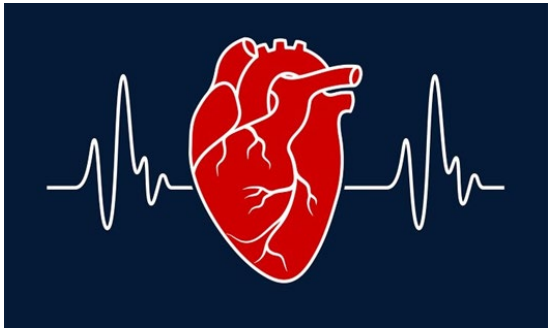
Inclusion Criteria	Exclusion Criteria
• Recent (within 6 months) diagnosis of heart failure with reduced ejection fraction indicated by ICD10 codes • Prescribed carvedilol or metoprolol succinate and at least one other guideline directed medical therapy between December 1st, 2016 – December 1st, 2018 • Known start date of beta blocker therapy	• Patients without at least 12 months of follow-up data • Patients requiring mechanical circulatory support (Left ventricular assist device or Extracorporeal membrane oxygenation) • Patients on medical therapy with a non-dihydropyridine calcium channel blocker (NDHPCCB) or sotalol

STATISTICAL ANALYSIS



Data	Statistical Analysis
Baseline Demographics	Chi-Square or Fisher's Exact, Student's T-test
Primary Outcome	Chi-Square or Fisher's Exact
<u>Secondary outcomes:</u> Reason for discontinuation Adverse effects	Chi-Square or Fisher's Exact

PATIENT SELECTION



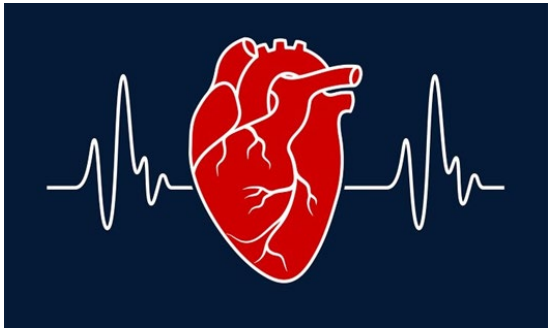
1508 Patients screened for inclusion

1424 Excluded

687 not recently diagnosed
333 lacked adequate follow-up
165 unknown date of beta blocker initiation
115 LVEF > 40%
62 without a diagnosis of HFrEF
45 not on beta blocker therapy
11 on a NDHPCCB
5 on sotalol
1 receiving mechanical circulatory support

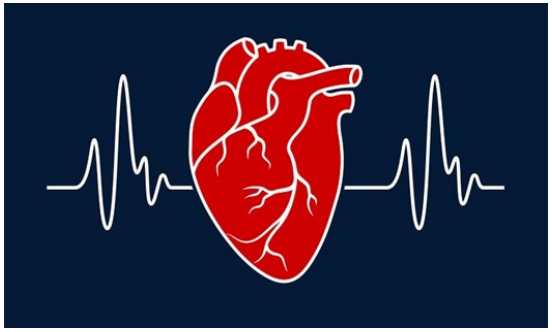
84 included for analysis

BASELINE CHARACTERISTICS



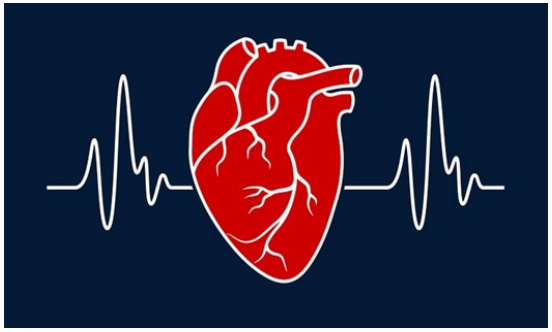
- A total of 84 patients were included for analysis, 28 treated with metoprolol succinate and 56 treated with carvedilol
  - Patient cohorts were based on highest dose of beta blocker achieved during study period
- Baseline demographics were well-balanced between the two patient cohorts
- Predominantly Caucasian population, with a mean LVEF of 27%, mainly non-ischemic cardiomyopathy, and with high use of guideline-directed medical therapy

BASELINE CHARACTERISTICS



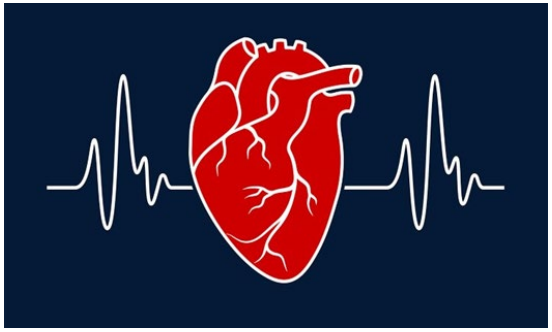
Characteristic, n (%)	Metoprolol (n = 28)	Carvedilol (n = 56)	Total (n = 84)
Age (mean)	69	68	68
Male Gender	15 (53.6)	29 (69.6)	54 (64.3)
LVEF (%, mean)	29	26	27
Heart Failure Type	--	--	--
Ischemic	8 (28.6)	14 (25)	22 (26.2)
Non-ischemic	17 (60.7)	29 (51.8)	46 (54.8)
Unknown	3 (10.7)	13 (23.2)	16 (19)

BASELINE CHARACTERISTICS



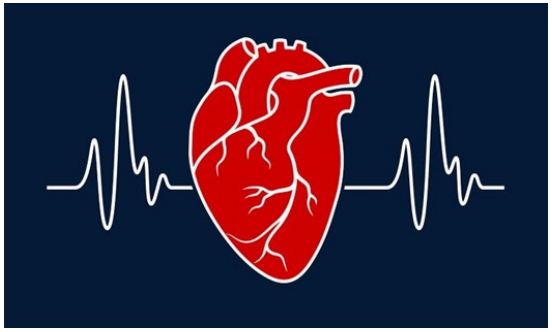
Characteristic, n (%)	Metoprolol (n = 28)	Carvedilol (n = 56)	Total (n = 84)
Comorbid Condition	--	--	--
Hypertension	14 (50)	41 (73.2)	55 (65.5)
Type II diabetes	7 (25)	22 (39.3)	29 (34.5)
Atrial fibrillation	9 (32.1)	8 (14.3)	17 (20.2)
Coronary artery disease	9 (32.1)	22 (39.3)	31 (36.9)

BASELINE CHARACTERISTICS



Characteristic, n (%)	Metoprolol (n = 28)	Carvedilol (n = 56)	Total (n = 84)
Concomitant Medications	--	--	--
RAAS inhibitor	26 (92.9)	46 (82.1)	72 (85.7)
ACE inhibitor	5 (17.9)	19 (33.9)	24 (28.6)
ARB	9 (32.1)	7 (12.5)	16 (19)
ARNI	12 (42.9)	20 (35.7)	32 (38.1)
Aldosterone antagonist	11 (39.3)	31 (55.4)	42 (50)
Digoxin	0 (0)	2 (3.6)	2 (2.4)
Calcium channel blocker	1 (3.6)	0 (0)	1 (1.2)
Hydralazine	0 (0)	7 (12.5)	7 (8.3)
Nitrates	1 (3.6)	5 (8.9)	6 (7.1)
Loop diuretics	11 (39.3)	25 (44.6)	36 (42.9)

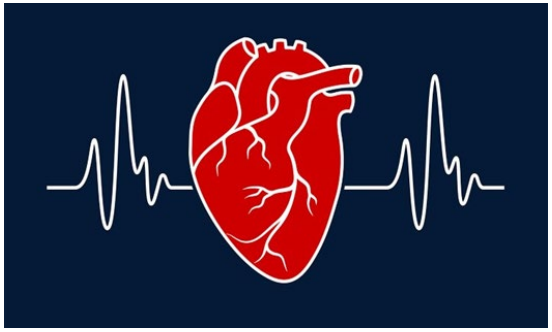
STUDY OUTCOMES



- **Primary Outcome**:
  - 14.3% (n = 4) on metoprolol achieved target dose vs. 39.3% (n = 22) on carvedilol **(P = 0.019)**

	Metoprolol (n = 28)	Carvedilol (n = 56)	P-value
Achieved target dose, n (%)	4 (14.3)	22 (39.3)	0.019
Mean total daily dose (mg)	93.8	33	--

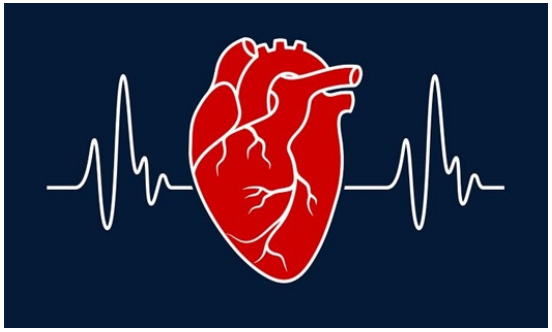
STUDY OUTCOMES



- **Secondary Outcomes:**
  - Hypotension occurred in 25% (n = 7) of patients on metoprolol succinate and 21.4% (n = 12) of carvedilol patients **(P = 0.712)**

	Metoprolol (n = 28)	Carvedilol (n = 56)	P-value
Reason for discontinuation or down-titration, n (%)	--	--	--
Hypotension	7 (25)	3 (5.3)	0.014
Hypotensive-like symptoms	1 (3.6)	1 (1.8)	1.00
Fatigue	1 (3.6)	3 (5.3)	1.00
Left bundle-branch block	0 (0)	1 (1.8)	1.00
Other	2 (7.2)	0 (0)	0.108
Hospitalized for HF, n (%)	4 (14.3)	7 (12.5)	1.00
Total hospitalizations for HF	6	7	--
Mortality due to HF	0	1	1.00

DISCUSSION

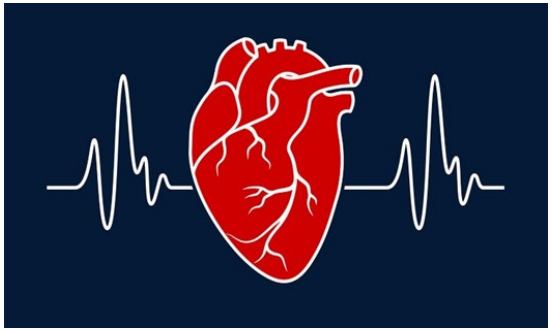


- In this retrospective review of patients with HFrEF treated with metoprolol succinate or carvedilol, there was a difference in the ability to achieve target dose favoring carvedilol

- 25 mg twice daily selected given unclear rationale for why weight-based dosing was developed and the inconsistent weight based target dose in clinical trials

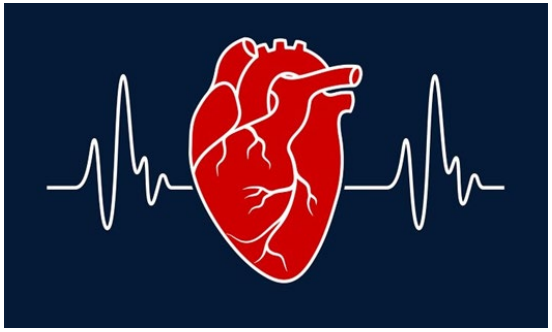
- Incidence of hypotension was no different between groups
  - Significantly more patients treated with metoprolol succinate were cited as discontinuing or down-titrating therapy due to hypotension

DISCUSSION



- Low incidence of mortality and hospitalizations between both groups
- No difference in baseline characteristics after correction for ability to achieve target dose or between patients in either cohort that were able to achieve target doses
- Study data is consistent with landmark trials demonstrating percentage of patients able to achieve target dose
  - MERIT-HF: 64%
  - US Carvedilol Heart Failure Study: 80%

CONCLUSION



Patients treated with carvedilol for HFrEF may be more likely to achieve guideline-recommended target doses than those treated with metoprolol succinate. Additional research in a larger patient cohort is warranted to further quantify this difference

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