Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 15, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.03.087

Impact of Carvedilol and Metoprolol on Inappropriate Implantable Cardioverter-Defibrillator Therapy

The MADIT-CRT Trial (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy)

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Objectives The goal of this study was to evaluate the effects of carvedilol and metoprolol on the endpoint of inappropriate implantable cardioverter-defibrillator therapy in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) study.

Background The impact of carvedilol and metoprolol on inappropriate therapy in heart failure patients with devices has not yet been investigated.

Methods All patients in the MADIT-CRT study who received a device (N = 1,790) were identified. Using time-dependent Cox regression analysis, we compared patients treated with different types of beta-blockers or no beta-blockers on the primary endpoint of inappropriate therapy, delivered as antitachycardia pacing (ATP) or shock therapy. Secondary endpoints were inappropriate therapy due to atrial fibrillation and atrial tachyarrhythmias, also evaluated as ATP or shock therapy.

Results Inappropriate therapy occurred in 253 (14%) of 1,790 patients during a follow-up period of 3.4 ± 1.1 years. Treatment with carvedilol was associated with a significantly decreased risk of inappropriate therapy compared with metoprolol (hazard ratio [HR]: 0.64 [95% confidence interval (CI): 0.48 to 0.85]; p = 0.002). The reduction in risk was consistent for inappropriate ATP (HR: 0.66 [95% CI: 0.48 to 0.90]; p = 0.009) and inappropriate shock therapy (HR: 0.54 [95% CI: 0.36 to 0.80]; p = 0.002). The risk of inappropriate therapy caused by atrial fibrillation was also reduced in patients receiving carvedilol compared with metoprolol (HR: 0.50 [95% CI: 0.32 to 0.81]; p = 0.004). General use of beta-blockers (93%) and adherence in this study was high.

Conclusions In heart failure patients undergoing either cardiac resynchronization therapy with a defibrillator or with an implantable cardioverter-defibrillator device, carvedilol was associated with a 36% lower rate of inappropriate ATP and shock therapy compared with metoprolol. Inappropriate therapy due to atrial fibrillation was associated with a 50% lower rate in patients receiving carvedilol compared with those receiving metoprolol. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; NCT00180271) (J Am Coll Cardiol 2013;62:1343–50) © 2013 by the American College of Cardiology Foundation

Inappropriate implantable cardio-verter-defibrillator (ICD) therapy remains a devastating problem for patients treated with ICDs and cardiac resynchronization therapy with defibrillators (CRT-Ds), leading to pain and impaired quality of life (1–5). Multiple inappropriate shocks may lead to progression of heart failure (HF) (3,6). Strategies to

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Manuscript received January 22, 2013; revised manuscript received March 6, 2013, accepted March 26, 2013.

Abbreviations and Acronyms

ATP = antitachycardia pacing

CI = confidence interval

CRT-D = cardiac resynchronization therapy with defibrillator

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

prevent or reduce inappropriate therapy are warranted, and clinical trials have been undertaken in attempts to reduce this burden (7). Carvedilol and metoprolol are the beta-blockers most commonly used in patients with HF. Carvedilol improves cardiac performance to a greater extent than metoprolol, and the differences may be related to carvedilol's greater antiadrenergic activity (8). It has previously been shown that carvedilol, compared with metoprolol, led to an overall significant reduction in hospitalizations for HF, ventricular arrhythmias (9), and cardiovascular deaths (10,11). Current guidelines, however, do not specifically comment on issues related to inappropriate therapy. To our knowledge, the general and individual impact of beta-blockers on the risk of inappropriate ICD therapy has not yet been investigated.

See page 1351

The goal of the current study was to evaluate the effects of carvedilol and metoprolol on the endpoint of inappropriate ICD therapy in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) study.

We hypothesized that carvedilol would be associated with a decreased risk of inappropriate therapy due to its greater antiadrenergic effect.

Methods

MADIT-CRT. The protocol and primary report of the MADIT-CRT study have previously been published (12,13). The study included 1,820 patients with ischemic cardiomyopathy New York Heart Association class I or II, nonischemic cardiomyopathy New York Heart Association class II, a left ventricular ejection fraction ≤30%, and a QRS duration ≥130 ms. Patients were enrolled from 110 centers in the United States, Europe, and Canada and randomized (3:2) to receive CRT-D and ICD devices.

Patients were excluded if they had atrial fibrillation at enrollment; a history of atrial fibrillation was not an exclusion criterion. Of the 1,820 patients included in the MADIT-CRT study, 30 patients (2%) never received a device, leaving a study population of 1,790 patients.

BETA-BLOCKER THERAPY. Patients had to be on optimal pharmacotherapy in accordance with HF guidelines (14). However, the choice of beta-blockers and other HF therapy was left to the discretion of the physician performing the implantation. All medication, including type of beta-blocker, and the doses were recorded at baseline and during clinical follow-up at 1 month and then at 3-month intervals until termination of the trial.

DEVICE PROGRAMMING AND INTERROGATION. All devices were programmed according to the prespecified protocol (13). The ventricular tachycardia zone was programmed from 180 beats/min up to 250 beats/min, and ventricular fibrillation was defined as a ventricular rate faster than 250 beats/min with disorganized ventricular electrograms.

All devices were interrogated 1 month after enrollment and thereafter every 3 months and adjudicated by an independent core laboratory for predefined categories of appropriate or inappropriate therapy.

ENDPOINTS. The primary endpoint of the current study was defined as occurrence of inappropriate therapy, delivered as antitachycardia pacing (ATP) or shock therapy, without the presence of ventricular tachycardia or ventricular fibrillation. The secondary endpoints were inappropriate therapy for atrial tachyarrhythmia and inappropriate therapy for atrial fibrillation and/or atrial flutter. All endpoints of inappropriate therapy were secondarily subdivided into inappropriate ATP or shock therapy. Last, inappropriate therapy caused by nonarrhythmic events and other inappropriate arrhythmic events were investigated (the Online Appendix provides specific definitions).

Statistics. Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. As shown in Table 1, patients were divided into 4 groups based on their beta-blocker use: metoprolol, carvedilol, other beta-blockers (bisoprolol, atenolol, and others), or no beta-blockers. Baseline characteristics were compared between patients by using the chi-square test for binary variables and the Kruskal-Wallis test for continuous variables.

Beta-blocker therapy was assessed in the multivariate model in a time-dependent manner (i.e., by incorporating into the Cox model, data for each patient that identifies the effect of each follow-up time "on" and "off" beta-blocker therapy during the trial). The effects of time-dependent beta-blocker therapy on the endpoints were assessed with interaction-term analysis.

Univariate and multivariate time-dependent Cox proportional hazards regression analysis were performed on the primary and secondary endpoints of inappropriate therapy and also divided into ATP or shock therapy. In the multivariate model, we adjusted for relevant variables for the outcome of inappropriate therapy found by stepwise selection, setting the limits for entry into the model at 0.05. Five variables were found to have a significant impact on the results ($p < 0.05$) in the main model on inappropriate therapy: previous ventricular arrhythmias, female sex, QRS duration, use of statins, and diastolic blood pressure. Results are reported as hazard ratios (HRs) with their 95% confidence intervals (CIs) and 2-sided p values. The cumulative probability of inappropriate therapy, ATP, and shocks were displayed by the Kaplan-Meier method using

Table 1 Baseline Characteristics of the Study Population

Clinical Characteristic	No Beta-Blockers	Carvedilol	Metoprolol	Other Beta-Blockers	p Value
n	120 (6.7)	1,077 (60.5)	438 (24.6)	146 (8.2)	
Female	17 (14)	309 (29)	91 (21)	25 (17)	<0.001
CRT-D assigned treatment	71 (59)	637 (59)	275 (63)	89 (61)	NS
Dual-chamber ICD	38 (78)	268 (61)	79 (48)	32 (56)	<0.001
Age at enrollment (yrs)	69.0 ± 9.4	63.5 ± 11.0	65.0 ± 10.3	65.8 ± 9.8	<0.001
Cardiac history					
Ischemic NYHA class I	27 (23)	119 (11)	80 (18)	31 (21)	<0.001
Ischemic NYHA class II	50 (42)	393 (36)	208 (47)	67 (46)	<0.001
Nonischemic NYHA class II	43 (36)	565 (52)	150 (34)	48 (33)	<0.001
Hospitalization in prior year	50 (42)	464 (43)	224 (53)	84 (58)	<0.05
Previous hospitalization for heart failure	36 (31)	413 (39)	168 (39)	50 (35)	NS
Previous coronary bypass surgery	52 (43)	264 (25)	147 (34)	53 (36)	<0.001
Cerebrovascular accident	10 (8)	69 (6)	26 (6)	9 (6)	NS
Diabetes	40 (33)	314 (29)	131 (30)	52 (36)	NS
Hypertension	67 (56)	659 (61)	303 (69)	100 (68)	<0.05
Previous non-CABG revascularization	28 (23)	262 (24)	140 (32)	52 (36)	<0.05
Previous MI	57 (49)	393 (37)	226 (53)	83 (59)	<0.001
Non-U.S. implanting center	35 (29)	275 (26)	137 (31)	99 (68)	NS
Previously smoked	69 (59)	550 (52)	226 (52)	98 (69)	NS
Previous atrial arrhythmias	26 (22)	109 (10)	52 (12)	21 (15)	<0.001
Previous ventricular arrhythmias	15 (13)	60 (6)	37 (9)	12 (8)	<0.05
Medications					
Antiarrhythmic use, including amiodarone and sotalol	25 (21)	71 (7)	35 (8)	15 (10)	<0.001
ACE Inhibitor or ARB	109 (91)	1,034 (96)	419 (96)	140 (96)	<0.05
Aldosterone antagonist	4 (3)	12 (1)	10 (2)	3 (2)	NS
Calcium channel blocker	12 (10)	62 (6)	46 (11)	13 (9)	NS
Digitalis	23 (19)	303 (28)	111 (25)	21 (14)	NS
Diuretic	75 (63)	734 (68)	293 (67)	103 (71)	NS
Statins	81 (68)	706 (66)	306 (70)	110 (75)	NS
Thrombolytic agent, excluding aspirin	30 (25)	192 (18)	90 (21)	27 (18)	NS
Clinical characteristics at enrollment					
QRS duration (ms)	159.0 ± 19.0	158.4 ± 19.9	156.5 ± 18.7	160.5 ± 21.9	NS
LBBB	77 (64)	780 (72)	302 (69)	101 (69)	NS
RBBB	25 (21)	113 (11)	64 (15)	20 (14)	<0.001
Heart rate (beats/min)	68.5 ± 13.2	67.7 ± 10.2	67.8 ± 11.5	67.4 ± 11.5	NS
BMI (kg/m^2)	28.3 ± 5.1	28.7 ± 5.3	29.2 ± 5.6	27.4 ± 3.8	NS
BUN (mg/dl)	23.6 ± 9.7	21.2 ± 8.8	21.6 ± 9.1	21.6 ± 8.5	<0.05
Creatinine (mg/dl)	1.31 ± 0.64	1.14 ± 0.32	1.18 ± 0.33	1.14 ± 0.27	<0.001
BNP level	127.5 ± 132.3	125.1 ± 170.4	117.0 ± 131.5	173.6 ± 233.0	NS
Systolic blood pressure (mm Hg)	123.3 ± 17.9	121.7 ± 17.0	123.8 ± 17.5	124.6 ± 18.8	NS
Diastolic blood pressure (mm Hg)	71.9 ± 10.5	71.4 ± 10.3	71.8 ± 10.3	72.6 ± 10.2	NS
Echocardiographic characteristics at enrollment					
EF (%)	24.0 ± 4.8	23.6 ± 5.3	23.9 ± 5.2	24.4 ± 4.9	NS
LVEDV (ml)	240.3 ± 51.1	248.4 ± 62.0	249.0 ± 64.7	250.4 ± 57.8	NS
LVEDD (mm)	63.3 ± 4.5	64.0 ± 5.4	63.8 ± 5.4	64.1 ± 4.8	NS
LVESV (ml)	172.7 ± 42.2	177.3 ± 50.1	177.3 ± 52.0	179.1 ± 45.4	NS
LVESD (mm)	53.6 ± 4.8	53.9 ± 5.5	53.7 ± 5.5	54.0 ± 4.7	NS
LAV (ml)	96.0 ± 22.4	93.6 ± 22.1	92.8 ± 21.3	94.8 ± 19.2	NS

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization device with defibrillator; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; MI = myocardial infarction; LAV = left atrium volume; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricle end-systolic diameter; LVESV = left ventricle end-systolic volume; RBBB = right bundle branch block.

the log-rank test to compare cumulative events. A 2-tailed p value ≤0.05 was considered statistically significant.

Analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

A total of 1,790 patients received either ICD or CRT-D; of these, 1,077 (61%), 438 (24%), 94 (5%), and 40 (2%)

received carvedilol, metoprolol, bisoprolol, and atenolol, respectively. Only 12 patients received other beta-blockers, and a combination of beta-blockers was used in 9 patients. A total of 120 (7%) patients were not receiving beta-blockers due to intolerance, asthma, and other causes.

Compared with patients taking carvedilol, metoprolol was more frequently used in patients of older age, patients with ischemic cardiomyopathy and hypertension, and in those who had previously undergone revascularization (Table 1). Notably, the highest proportion of patients taking carvedilol were from U.S. centers; the highest users of bisoprolol (94%) were from non-U.S. centers (data not shown).

Primary endpoint. Inappropriate therapy occurred in 253 (14%) of 1,790 patients during the follow-up period of 3.4 ± 1.1 years. There was no difference between patients receiving an ICD and those who received a CRT-D ($p = 0.944$).

A univariate comparison of the 4 groups is presented in Figure 1 showing an overall significant difference. Carvedilol and "other beta-blockers" (composed of bisoprolol and atenolol) are markedly separated from patients taking metoprolol. Figures 2 and 3 present the head-to-head comparison of carvedilol and metoprolol on overall cumulative probability of inappropriate ATP and inappropriate shock therapy, with significant differences between them. The multivariate time-dependent Cox regression analysis in Table 2 displays a significant relative risk reduction in all inappropriate therapies associated with the use of carvedilol compared with metoprolol (HR: 0.64 [95% CI: 0.48 to 0.85]; $p = 0.002$). This finding was consistent and also evident for inappropriate ATP (HR: 0.66 [95% CI: 0.48 to 0.90]; $p = 0.009$) and for inappropriate shocks (HR: 0.54 [95% CI: 0.36 to 0.80]; $p = 0.002$).

Secondary endpoints. Inappropriate therapy caused by atrial fibrillation occurred in 86 (5%) of 1,790 patients; 16 (19%) of these patients had a history of atrial arrhythmias requiring treatment.

Table 3 displays the multivariate analysis comparing beta-blockers. There was a reduction in risk of inappropriate therapy due to atrial fibrillation in patients treated with carvedilol compared with metoprolol (HR: 0.50 [95% CI: 0.32 to 0.81]; $p = 0.004$). This reduction in risk, however, was driven primarily by the use of ATP (HR: 0.44 [95% CI: 0.25 to 0.78]; $p = 0.005$), whereas there was no significant reduction in risk of inappropriate shock therapy for atrial fibrillation associated with the use of carvedilol. For inappropriate therapy for all atrial tachyarrhythmias, a significant risk reduction was associated with the use of carvedilol regarding both inappropriate ATP and inappropriate shock therapy compared with metoprolol (Table 4).

Finally, no differences were found in inappropriate therapy for nonatrial tachyarrhythmias in a comparison of the beta-blockers, and no differences were found for nonarrhythmic causes of inappropriate therapy (total of 29 and 22 events, respectively [data not shown]).

Doses. The mean doses of beta-blockers at baseline and after first change are shown in Table 5; only minor changes in dose occurred after the first change. Few patients switched

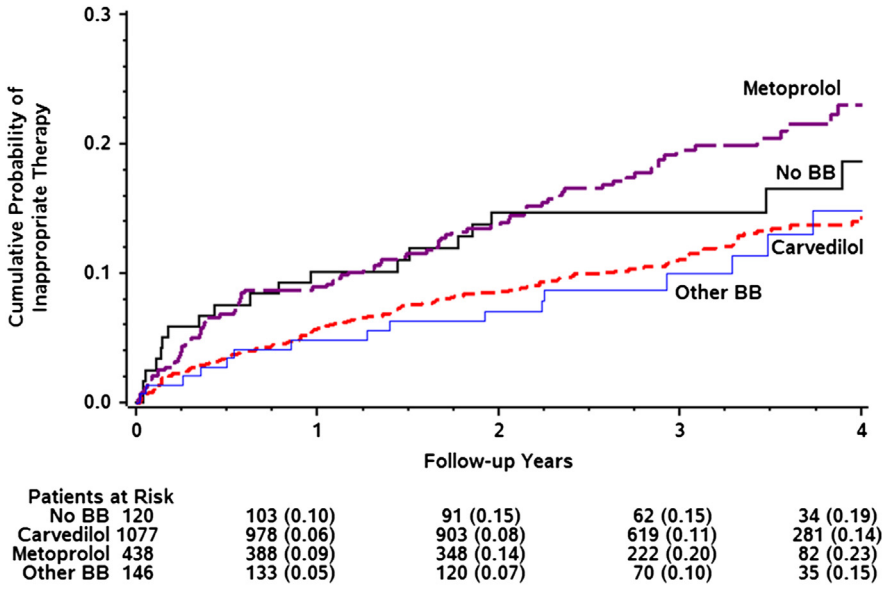

Figure 1 Cumulative Probability of All Inappropriate ICD Therapy Among the 4 Study Groups

The cumulative probability of inappropriate implantable cardioverter-defibrillator (ICD) therapy differed significantly among the 4 groups (metoprolol, carvedilol, other beta-blockers [BB], and no BB). The 4-year cumulative probability of inappropriate therapy among patients receiving carvedilol was 14% compared with a 4-year cumulative probability of inappropriate ICD therapy among patients receiving metoprolol of 23%. Unadjusted overall comparison of the 4 groups, $p = 0.002$.

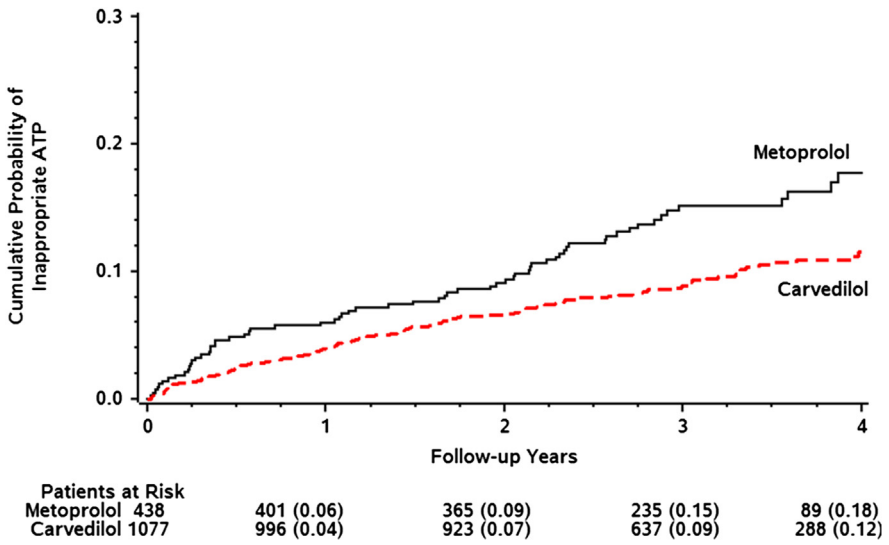

Figure 2 **Cumulative Probability of All Inappropriate ATP Comparing Metoprolol and Carvedilol**

The cumulative probability of inappropriate antitachycardia pacing (ATP) differed significantly between patients who were treated with carvedilol compared with patients treated with metoprolol. Unadjusted p = 0.005.

from 1 type of beta-blocker to the other, and these changes were taken into account in the time-dependent analyses. The mean dose increase for carvedilol was higher than for metoprolol throughout the course of the study, but when exploring baseline dose-dependent relationships on the endpoints, we found no clear association. In addition, when adjusting for baseline and first change doses of carvedilol dose-equivalents in the Cox regression models, the results were not altered.

Discussion

The major and novel finding of the current study was the significant difference in all measured outcomes between

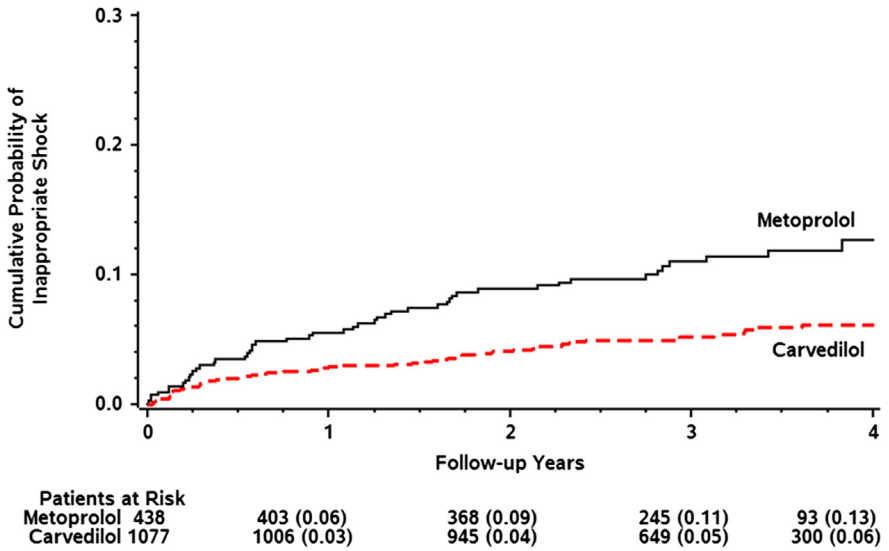

Figure 3 **Cumulative Probability of Inappropriate Shock Therapy Comparing Metoprolol and Carvedilol**

The cumulative probability of inappropriate shock therapy differed significantly between patients treated with carvedilol compared with patients treated with metoprolol. Unadjusted p <0.001.

Table 2 Multivariate Cox Regression Analysis for Inappropriate Therapy for Primary Endpoints

Therapy	No. of Events	Hazard Ratio Metoprolol (Ref.)	95% Confidence Intervals	p Value
Inappropriate therapy	253			
Carvedilol		0.64	0.48–0.85	0.002
Bisoprolol		0.68	0.38–1.22	0.193
Atenolol		0.75	0.28–2.07	0.583
No beta-blocker		1.07	0.66–1.74	0.788
ATP	200			
Carvedilol		0.66	0.48–0.90	0.009
Bisoprolol		0.67	0.34–1.30	0.234
Atenolol		0.74	0.23–2.35	0.606
No beta-blocker		1.09	0.64–1.87	0.754
Shock therapy	123			
Carvedilol		0.54	0.36–0.80	0.002
Bisoprolol		0.70	0.31–1.56	0.383
Atenolol		0.35	0.05–2.56	0.302
No beta-blocker		1.04	0.53–2.02	0.920

Adjusted for previous ventricular arrhythmias, female sex, QRS duration, statin use, and diastolic blood pressure.
ATP = antitachycardia pacing.

carvedilol and metoprolol. Carvedilol was associated with a significant reduction in risk of inappropriate therapy and remained independently significant throughout the study regarding inappropriate ATP and shock therapy, enforcing these results. The analysis also found that carvedilol was significantly associated with a reduced risk of inappropriate therapy for atrial tachyarrhythmias, which was also consistent when subdivided into ATP and shock therapy. The subdivision of inappropriate therapy is important to establish that the reduction in risk is not driven by ATP alone but rather by inappropriate shock therapy and thus is clinically very important. Furthermore, the subdivision into atrial tachyarrhythmias and atrial fibrillation is clinically important and implies that the reduction in risk associated with the use of carvedilol is not driven by other nonarrhythmic inappropriate causes.

Although there were significant differences at baseline between the allocated beta-blocker groups, factors clinically relevant for development of inappropriate therapy were taken

Table 3 Multivariate Cox Regression Analysis for Inappropriate Therapy for Atrial Fibrillation

Therapy	No. of Events	Hazard Ratio Metoprolol (Ref.)	95% Confidence Interval	p Value
Inappropriate therapy for atrial fibrillation or atrial flutter				
Carvedilol	86	0.50	0.32–0.81	0.004
Bisoprolol		0.97	0.42–2.21	0.936
Atenolol		NA	NA	NA
No beta-blocker		0.89	0.39–2.03	0.779
ATP for atrial fibrillation or atrial flutter	56			
Carvedilol		0.44	0.25–0.78	0.005
Bisoprolol		1.18	0.48–2.94	0.720
Atenolol		NA	NA	NA
No beta-blocker		0.54	0.16–1.81	0.316
Shock therapy for atrial fibrillation or atrial flutter	51			
Carvedilol		0.70	0.37–1.34	0.284
Bisoprolol		1.20	0.39–3.66	0.750
Atenolol		NA	NA	NA
No beta-blocker		1.65	0.63–4.32	0.304

Adjusted for previous ventricular arrhythmias, female sex, QRS duration, statin use, and diastolic blood pressure.
ATP = antitachycardia pacing; NA = not available.

Table 4 Multivariate Cox Regression Analysis for Inappropriate Therapy for Atrial Tachyarrhythmias

Therapy	No. of Events	Hazard Ratio Metoprolol (Ref.)	95% Confidence Interval	p Value
Inappropriate therapy for AT	201			
Carvedilol		0.64	0.47–0.88	0.006
Bisoprolol		0.68	0.35–1.33	0.262
Atenolol		0.49	0.12–1.99	0.314
No beta-blocker		1.17	0.69–1.98	0.561
ATP for AT	163			
Carvedilol		0.62	0.44–0.88	0.007
Bisoprolol		0.65	0.31–1.37	0.257
Atenolol		0.59	0.14–2.44	0.469
No beta-blocker		1.07	0.59–1.94	0.816
Shock therapy for AT	95			
Carvedilol		0.58	0.37–0.92	0.020
Bisoprolol		0.85	0.35–2.05	0.720
Atenolol		NA	NA	NA
No beta-blocker		1.33	0.65–2.73	0.437

Adjusted for past ventricular arrhythmias, female sex, QRS duration, statin use, and diastolic blood pressure.
AT = atrial tachyarrhythmia; other abbreviations as in Table 3.

into account when adjusting for factors in the multivariate analysis. This point is very important, and factors associated with increased risk of death or hospitalizations as a whole are not necessarily the same as the factors associated with inappropriate therapy. Previous studies have shown similar clinically relevant covariates as our model selected, in which primarily the nonuse of statins, previous ventricular or atrial arrhythmias, younger age, and male sex are considered risk factors for development of inappropriate therapy (3,6,15–17).

In the current study, carvedilol, in doses comparable to metoprolol as well as in real-life doses, was associated with a significant reduction in inappropriate therapy. One previous study was underpowered to show a significant effect of beta-blockers on inappropriate therapy (18), and other studies have generally only compared beta-blockers versus other antiarrhythmic agents. Thus, no previous comparison of different beta-blockers has been undertaken on this clinically important endpoint. Amiodarone and sotalol are drugs associated with wide adverse effects, and preferably any beta-blocker with an optimal impact on appropriate and inappropriate therapy should be the first choice for treatment, particularly because beta-blockers are standard therapy for HF. This, along with previous results (9), suggests that carvedilol may be the drug of choice in HF patients with implanted devices.

Table 5 Doses of Beta-Blockers Used at Baseline and at First Change of Dose

Beta-Blocker	Dose at Baseline	Dose at First Change	p Value
Carvedilol	18 ± 13	30 ± 20	<0.001
Metoprolol	66 ± 48	78 ± 54	<0.001
Metoprolol as carvedilol equivalents	16 ± 12	20 ± 14	<0.001
Bisoprolol	5.4 ± 3.8	5.3 ± 5.3	0.041
Atenolol	34 ± 18	39 ± 25	0.13

Values are mean ± SD (in mg).

We found that the relative doses of beta-blockers used in the MADIT-CRT study were comparable to those used in real-life scenarios of HF patients, supported by numerous previous nonrandomized or observational studies reporting the mean doses of beta-blockers (19–21). Hypothesized factors associated with reduced risk of inappropriate therapy in patients treated with carvedilol may be differences in the adrenergic receptor selectivity and ancillary properties. Metoprolol acts selectively on $beta_1$-receptors, and carvedilol blocks all 3 adrenergic receptors ($alpha_1$, $beta_1$, and $beta_2$) implicated in facilitating harmful effects of catecholamines on the heart. Carvedilol decreases levels of cardiac norepinephrine and suppresses beta-receptors, whereas metoprolol increases catecholamines and enhances the sensitivity of the heart to beta-receptor stimulation. These actions may help explain, in part, the electrophysiological differences between carvedilol and metoprolol in the current study and may be due to different effects at the cellular level (8,22,23). Furthermore, a meta-analysis has indicated a greater increase in left ventricular ejection fraction in patients with HF treated with carvedilol (24).

Study limitations. This was a retrospective, nonrandomized post hoc study. Although multivariate analysis showed that carvedilol was superior to metoprolol when taking many confounders into consideration, it was not a prospective randomized trial comparing these drugs, and other confounders not included in the analyses may have biased our results. An adjusted multivariate analysis was performed, taking into account many confounders associated with inappropriate therapy and those that played a significant role on this outcome in our population. Our study patients were, on average, not receiving recommended doses of beta-blocker therapy and thus

were not ideal for generalizing. However, we find our results reflect real-life scenarios of patients with HF.

Conclusions

In patients with mildly symptomatic HF with either a CRT-D or ICD device, carvedilol was associated with a 36% reduction in inappropriate ATP and shock therapy compared with patients taking metoprolol. Inappropriate therapy due to atrial fibrillation was reduced by 50% in patients taking carvedilol compared with metoprolol. Further prospective studies are needed to confirm these results.

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Key Words: beta-blockers ▪ defibrillator ▪ heart failure ▪ inappropriate therapy.

APPENDIX

For supplementary study definitions, please see the online version of this article.