Amiodarone Interaction With β-Blockers

Analysis of the Merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) Databases

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Background—Investigations with in vitro and animal models suggest an interaction between amiodarone and β-blockers. The objective of this work was to explore if an interaction with β-blocker treatment plays a role in the decrease of cardiac arrhythmic deaths with amiodarone in patients recovered from an acute myocardial infarction.

Methods and Results—A pooled database from 2 similar randomized clinical trials, the European Amiodarone Myocardial Infarction Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT), was used. Four groups of post–myocardial infarction patients were defined: β-blockers and amiodarone used, β-blockers used alone, amiodarone used alone, and neither used. All analyses were done on an intention-to-treat basis. Unadjusted and adjusted relative risks for all-cause mortality, cardiac death, arrhythmic cardiac death, nonarrhythmic cardiac death, arrhythmic death, or resuscitated cardiac arrest were lower for patients receiving β-blockers and amiodarone than for those without β-blockers, with or without amiodarone. The interaction was statistically significant for cardiac death and arrhythmic death or resuscitated cardiac arrest ($P=0.05$ and 0.03, respectively). Findings were consistent across subgroups.

Conclusions—These findings are based on a post hoc analysis. However, they confirm prior results from in vitro and animal experiments suggesting an interaction between β-blockers and amiodarone. In practice, not only is the adjunct of amiodarone to β-blockers not hazardous, but β-blocker therapy should be continued if possible in patients in whom amiodarone is indicated. **(*Circulation*. 1999;99:2268-2275.)**

Key Words: antiarrhythmia agents ■ myocardial infarction ■ trials

Amiodarone is an antiarrhythmic agent with unique properties. In a meta-analysis of clinical trials it decreased total mortality rates by 13%.[1] It has complex, multifaceted effects at the cellular and tissue levels as well as in whole-animal or human experiments.[2] This includes an antiadrenergic effect.[3] An interaction between amiodarone and pharmacological β-blockade has been postulated on the basis of this effect, although it has not been not proven. Evidence from nonrandomized studies has suggested a synergistic effect on ventricular arrhythmias in patients.[4] However, neither the reality nor the exact mechanism of this interaction has been firmly established. EMIAT (European Amiodarone Myocardial Infarction Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) were randomized, double-blind, placebo-controlled trials of amiodarone used in patients recovering from a myocardial infarction.[5,6] In both trials independently, an interaction between β-blockers and amiodarone was suggested. If confirmed, such an interaction would have important consequences, both practical in terms of patient care and fundamental in terms of understanding of the mechanism of action of amiodarone. The purpose of this study was to explore the amiodarone–β-blocker interaction by means of an individual record pooling of the data from EMIAT and CAMIAT. This project, called ECMA (EMIAT-CAMIAT Meta-Analysis), was the result of a decision of both the EMIAT and CAMIAT Steering Committees to pool the 2 trial databases because they were the largest trials with amiodarone in patients after myocardial infarction with sim-

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TABLE 1. Results From Pooled Trials and ECMA Database

	CAMIAT	EMIAT	ECMA	P*	P†
No.	1201	1486	2687		
Total death					
Events	125	205	330	0.51	0.36
Relative risk	0.82	1.00	0.93		
95% CI	0.57–1.16	0.76–1.32	0.75–1.15		
Cardiac death					
Events	99	174	273	0.31	0.49
Relative risk	0.78	0.95	0.88		
95% CI	0.52–1.16	0.71–1.28	0.70–1.12		
Arrhythmic cardiac death					
Events	57	83	140	0.02	0.84
Relative risk	0.71	0.66	0.68		
95% CI	0.42–1.20	0.42–1.02	0.48–0.95		
Nonarrhythmic cardiac death					
Events	42	91	133	0.37	0.28
Relative risk	0.89	1.33	1.17		
95% CI	0.49–1.63	0.88–2.01	0.83–1.64		
Arrhythmic death or resuscitated cardiac arrest					
Events	65	103	168	0.01	0.84
Relative risk	0.64	0.68	0.67		
95% CI	0.39–1.06	0.46–1.01	0.49–0.91		
Noncardiac death					
Events	26	31	57	0.55	0.52
Relative risk	0.97	1.37	1.17		
95% CI	0.45–2.10	0.67–2.80	0.70–1.98		

*P value for pooled effect (ECMA).
†P value for heterogeneity between trials.

ilar protocols. The combined database totals 2687 patients corresponding to 4654 patient-years.

Methods

Pooling and Variables

Data from all patients randomized in the CAMIAT and the EMIAT trials were pooled in a common file. Selected variables common to the 2 data sets were study treatment, baseline patient characteristics, concomitant treatments at entry, date of final follow-up, and the occurrence (and date) of the following 5 outcomes that were the primary or secondary efficacy criteria in either one or both trials: all-cause mortality, cardiac death, arrhythmic cardiac death, nonarrhythmic cardiac death, arrhythmic death, or resuscitated cardiac arrest. We also looked at noncardiac death to check the consistency between the 2 pooled trials. Definition of arrhythmic death was slightly different in CAMIAT and EMIAT. The definition of cardiac deaths was similar in both trials except for arrhythmic deaths. Sudden and unobserved death, when no other cause was identified, was coded as arrhythmic death in both trials. However, presumed arrhythmic death, the third component of arrhythmic death, has a broader acceptation in EMIAT. Resuscitated cardiac arrest was defined similarly in EMIAT and CAMIAT.

Heart rates were measured at rest during the clinical bedside examination (pulse), on ECG, and on a 24-hour Holter monitor. However, only pulse heart rates were available for all patients. Holter recording was not mandatory in CAMIAT. In the ECMA database, 81% of the cases have Holter data. Hence, heart rate based on pulse findings was considered as the first-line parameter in the analysis. However, because pulse records were thought to be less reliable than Holter records, all the analyses have been performed again with the heart rate based on Holter data. For this analysis, the average heart rate over the entire record of beats was used.

The heart rate variable was analyzed on a continuous scale in the multivariate models but was stratified into 3 categories (<65, 65 to 80, and >80) for further statistical explorations. The choice of thresholds was arbitrary and aimed to reflect low, medium, and high heart rates at baseline.

Compliance to amiodarone, placebo for amiodarone, and β-blockers was assessed at each follow-up visit through a standardized questionnaire.

Statistical Analysis

Multivariate proportional hazard models were used to estimate the interaction of amiodarone with β-blockers, taking into account the possible confounding effects of other covariates. Such confounding effects may occur when baseline covariates are related to the risk of the event and are not evenly distributed in patients with and those without β-blockers. The following covariates were considered as candidates for the models: age, sex, smoking habits, diabetes, history

TABLE 2. Comparison of Baseline Findings Between 4 Pooled Groups

	Placebo		Amiodarone		
β-Blocker	No (n=657)	Yes (n=682)	No (n=657)	Yes (n=691)	*P*
Age, mean (SD), y	63.2 (9.6)	61.6 (10.7)	62.8 (9.9)	60.7 (10.7)	0.0001
Male, %	81.9	85.3	82.2	84.4	0.05
Current smoker, %	47.3	42.7	49.3	40.8	0.003
Diastolic blood pressure, mean (SD), mm Hg	74.5 (10.5)	74.7 (10.0)	73.9 (10.6)	74.2 (10.4)	0.48
Systolic blood pressure, mean (SD), mm Hg	122.5 (20.0)	121.7 (17.9)	121.2 (18.1)	121.4 (18.0)	0.65
Heart rate, mean (SD), bpm	76.8 (12.9)	67.0 (11.5)	76.7 (13.5)	66.6 (11.2)	0.0001
Medical history, %					
Previous myocardial infarction	32.7	27.6	38.1	27.0	0.001
Hypertension	34.4	37.3	36.1	39.3	0.10
High cholesterol	28.2	28.3	28.7	34.3	0.11
Diabetes	22.1	12.2	20.7	11.6	0.001
Liver disorder	1.2	1.5	2.7	1.0	0.13
Concomitant therapy at inclusion, %					
Thrombolytic	49.1	61.1	47.5	56.1	0.001
Digoxin	19.5	7.3	23.0	6.4	0.001
Calcium antagonist	24.3	15.2	25.9	14.2	0.001
Vitamin K antagonist	25.0	23.9	25.3	23.1	0.34
ACE inhibitor	54.8	37.1	55.9	37.5	0.001
Myocardial dysfunction at inclusion, %					
Pulmonary edema since acute myocardial infarction	27.5	14.4	29.2	11.5	0.001
NYHA class					0.001
I	56.4	75.3	50.8	76.2	
II	35.7	22.1	40.0	20.1	
III	8.0	2.6	9.2	3.6	
Qualifying myocardial infarction, %					
New Q waves	71.7	68.3	68.7	71.7	0.929
Anterior/lateral	70.9	68.0	72.8	66.2	0.02
Posterior	4.6	4.7	6.0	5.2	0.72
Inferior	34.4	35.6	33.0	35.7	0.35
Indeterminate	2.2	1.7	3.0	2.0	0.25

of myocardial infarction, heart rate, pulmonary edema at entry, heart failure (New York Heart Association classification), systolic blood pressure, hypercholesterolemia, thrombolytic treatment at entry, delay between admission to hospital and inclusion in the study, and use of ACE inhibitors, vitamin K antagonists, calcium channel blockers, and digoxin. Models were stratified on the trials to allow the differential baseline hazards from CAMIAT and EMIAT. The amiodarone effect in patients with and those without β-blockers was directly estimated from the models as a risk ratio. In tables, rates of events are summarized as the number of events per 100 patients followed for 1 year.

All analyses maintained all randomized patients in the treatment group to which they were allocated. The intention-to-treat principle applied also to β-blocker treatments: Patients were said to be receiving a β-blocker if this treatment was coded as present at baseline. Comparisons leading to $P<0.05$ were considered statistically significant; 95% confidence limits were computed.

Results

The total numbers of patients with and those without β-blockers at entry was well balanced: 1314 and 1373, respectively. The results from the pooling of the 2 trials were consistent with the results on amiodarone efficacy already published[3,4] (Table 1).

The baseline characteristics of the 4 groups, amiodarone plus β-blockers, amiodarone alone, β-blockers alone, and neither, are shown in Table 2. Patients with β-blockers had a better predicted prognosis than those without β-blockers. They presented less often with a history of myocardial infarction or a pulmonary edema at entry. They were less likely to receive digoxin or ACE inhibitors and were treated more often with thrombolytics. Their heart rate was lower; however, this could be the results of their treatment. All the baseline characteristics that were not balanced between the 4 groups were entered into the multivariate adjustment model (see Methods).

The combination group had a better survival. The relative risks, unadjusted and adjusted, for the various outcomes for amiodarone versus placebo patients, in β-blocker–treated and untreated patients, are shown in Figure 1 and detailed in Table 3 and Figure 2A. The survival curves for arrhythmic

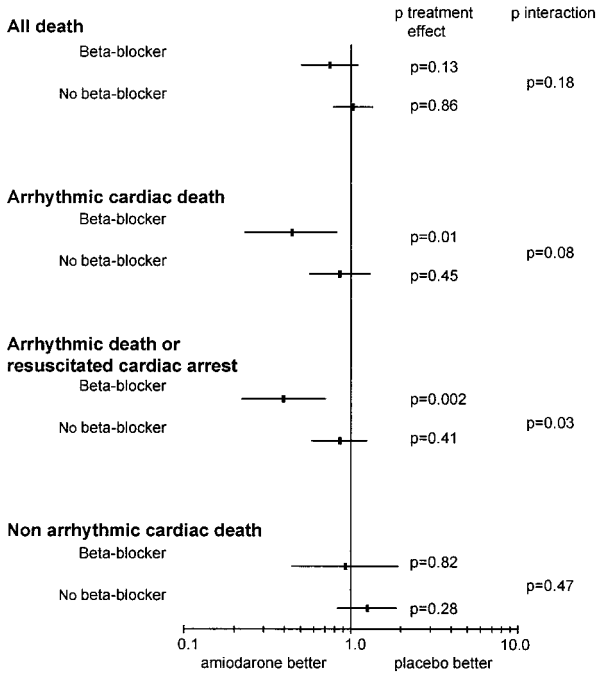

Figure 1. Relative risks for selected outcomes.

death or resuscitated cardiac arrest for the 4 groups are shown in Figure 3. Both adjusted and unadjusted relative risks for the 5 outcomes were lower in patients receiving β-blockers at entry and randomized to amiodarone than for those receiving amiodarone alone, indicating a tendency for a more favorable effect of amiodarone in the patients treated with β-blockers. The interaction was statistically significant for cardiac death and arrhythmic death or resuscitated cardiac arrest ($P=0.05$ and 0.03, respectively). The 95% CIs for relative risk that do not include 1.0 are all observed for β-blocker–treated patients, for cardiac death, arrhythmic death, and arrhythmic death, or resuscitated cardiac arrest. Adjustment for baseline covariates had very little effect on the values of the relative risk and the confidence limits, indicating that these variables do not explain the statistical interaction between amiodarone and β-blockers for the considered outcomes. Neither heart rate at entry nor signs of overt heart failure or secondary risk factors[7] when introduced into the model made the correlation disappear. More specifically, the results showed a reinforced positive antiarrhythmic effect of amiodarone in patients receiving β-blockers compared with patients in any of the other 3 treatment groups, leaving the slight excess of noncardiac deaths in the subgroups of patients without β-blockers.

To explore more precisely the role of heart rate at entry, we computed the adjusted relative risks for 3 classes of heart rate (Figure 2B and Table 4). Figure 2B does not show any trend for an interaction between the effect of amiodarone and heart rate on any of the death categories. In particular, the antiarrhythmic effect of amiodarone appears to be similar whatever the level of patient's heart rate. In all but 3 cross-tabulated cells of Table 4, the relative risk was lower in the group of patients treated with β-blockers than in those not treated, suggesting that the same trend for an interaction between amiodarone and β-blockers is observed whatever the level of the patient's heart rate. In one of the 3 cells, that is, the heart rate ranging from 65 to 80 bpm and the nonarrhythmic cardiac death, the 2 values are quite close, and both 95% CIs include 1.0. The 2 others concern patients with heart rate at entry <65 bpm and arrhythmic death or arrhythmic death or resuscitated cardiac arrest. Although the difference between

TABLE 3. Amiodarone Effect in Patients With and Those Without β-Blocker at Entry (Nonadjusted and Adjusted Hazard Ratio and 95% CI)

	No β-Blocker		β-Blocker		Relative Risk (95% CI)			Adjusted Relative Risk (95% CI)		
	Placebo	Amiodarone	Placebo	Amiodarone	No β-Blocker	β-Blocker	*P*	No β-Blocker	β-Blocker	*P*
Patients, n	657	657	682	691						
Patient-years	1111	1104	1199	1241						
All death										
Events, No.	109	115	61	45	1.06	0.72	0.10	1.04	0.74	0.15
Rate/y, %	9.81	10.42	5.09	3.63	(0.81–1.37)	(0.49–1.06)		(0.79–1.36)	(0.50–1.09)	
Cardiac death										
Events, No.	96	101	48	28	1.06	0.57	0.03	1.04	0.59	0.04
Rate/y, %	8.64	9.15	4.00	2.26	(0.80–1.40)	(0.38–0.91)		(0.78–1.39)	(0.37–0.94)	
Arrhythmic cardiac death										
Events, No.	51	43	32	14	0.85	0.43	0.07	0.86	0.44	0.08
Rate/y, %	4.59	3.90	2.67	1.13	(0.56–1.27)	(0.23–0.80)		(0.57–1.30)	(0.23–0.82)	
Nonarrhythmic cardiac death										
Events, No.	45	58	16	14	1.29	0.86	0.33	1.28	0.92	0.43
Rate/y, %	4.05	5.26	1.33	1.13	(0.87–1.90)	(0.42–1.75)		(0.86–1.92)	(0.44–1.91)	
Arrhythmic death or resuscitated cardiac arrest										
Patient-years	1105	1097	1182	1239						
Events, No.	60	52	40	16	0.87	0.38	0.02	0.85	0.39	0.03
Rate/y, %	5.43	4.74	3.38	1.29	(0.60–1.26)	(0.23–0.69)		(0.58–1.24)	(0.22–0.70)	

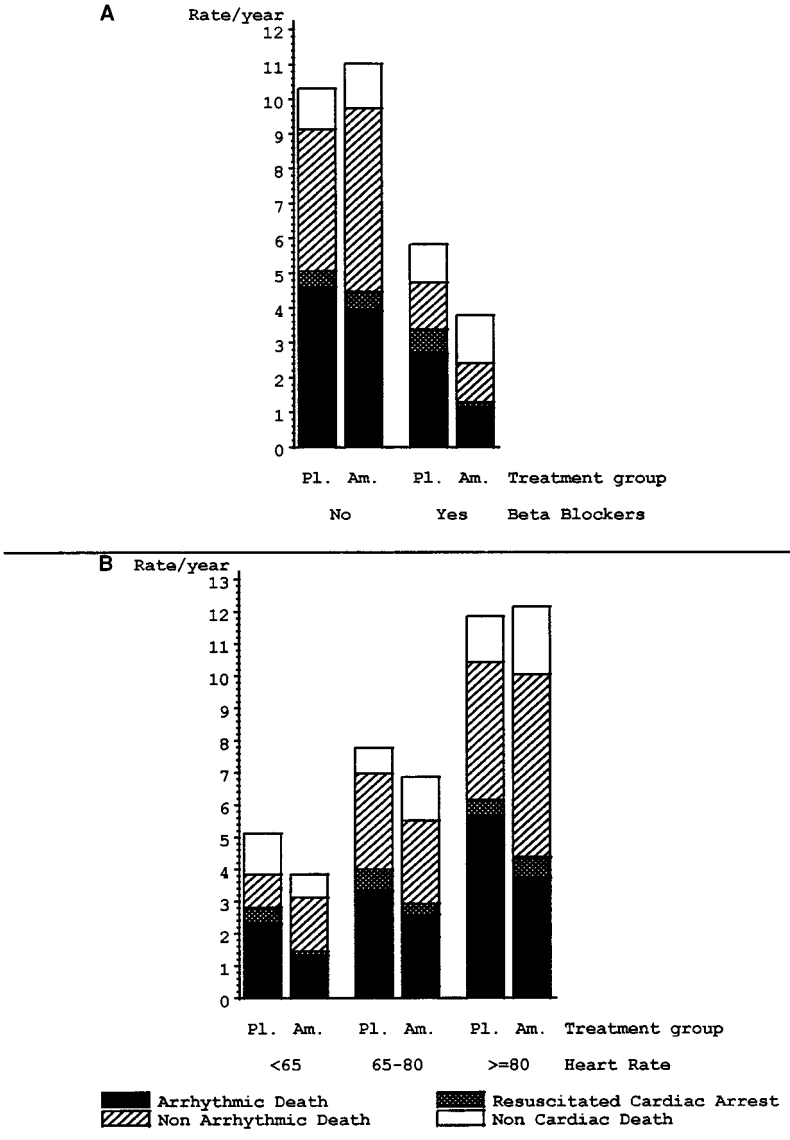

Figure 2. A, Death rates according to amiodarone and β-blocker at entry; B, death rates according to amiodarone and heart rate. Pl indicates placebo; Am, amiodarone.

the relative risks in β-blocker–treated and untreated subgroups are marked, only 1 CI does not contain 1.0. The 95% CIs are wide because of the small number of events in each of the cells. In addition, a number of CIs were computed. Hence the differences in the relative risk between patients with and those without β-blockers according to heart rate values are likely to be chance findings. Visual inspection of Figure 4 confirms the data presented in Table 4 and shows no major contrast in the interaction between amiodarone and β-blockers across the 3 categories of heart rate. The same analyses were performed on the average heart rate from the entry 24-hour-Holter recordings available for 81% of the patients. Similar results were found. They are shown only for arrhythmic death or resuscitated cardiac arrest in Table 4.

Finally, the observed interaction could be due to difference in withdrawal rates for patients receiving β-blockers and amiodarone. The discontinuation survival curves shown in Figure 5 do not support this hypothesis. Combination with β-blocker does not seem to alter the withdrawal rate from amiodarone. Discontinuation of amiodarone because of excessive bradycardia was no more frequent in the amiodarone plus β-blockers group than in the amiodarone alone group: 1.2% and 1.0%, respectively. Regarding discontinuation of β-blockers, there were more patients withdrawn who were receiving the combination group than receiving β-blockers alone (Table 5).

Discussion

From this analysis it is clear that the effect of amiodarone is greater in patients recovering from a recent myocardial infarction already receiving β-blockers. This interaction between amiodarone and β-blocker treatment at entry is not likely to be a chance finding. It does not appear to be explained by the differences in baseline characteristics between patients receiving and those not receiving β-blockers. Correcting for these differences did not affect the observed interaction. This finding is provisional because it is based on a post hoc analysis, and a prospective trial is needed to confirm it. If such a trial is not performed, new evidence can only come from investigations on animal models and in vitro

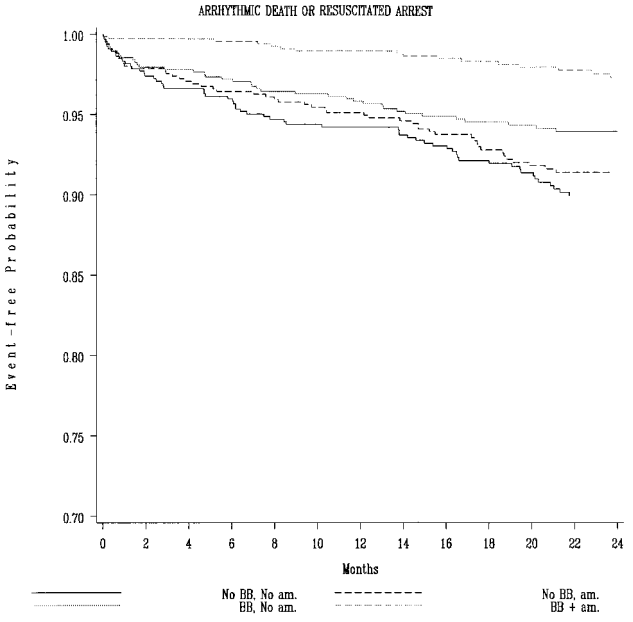

Figure 3. Survival curves for arrhythmic death or resuscitated cardiac arrest in the 4 groups. BB indicates β-blocker; am, amiodarone.

experiments. Their results can increase the biological plausibility of the interaction. However, they will not confirm it.

The definition of arrhythmic deaths was not exactly the same in the 2 trials pooled in ECMA. However, this is likely to have only a marginal impact on our findings. First, adjudication of causes of death was blinded in both trials. Second, the relative risks for presumed arrhythmic death were quite similar: 0.66 in EMIAT (95% confidence limits 0.43 to 1.01) and 0.71 in CAMIAT (95% confidence limits 0.42 to 1.19).

We searched for a third-level interaction between heart rate at entry, β-blocker treatment at entry, and amiodarone. First, the unadjusted rates of the outcomes of interest in the 4 subgroups were compared according to 3 classes of heart rate at entry (Figures 2B and 4). The adjusted relative risks then were computed according to the same 3 classes (Table 4). Finally, the relative risks were adjusted on all the covariates, including heart rate (Table 3). To check the internal validity of this finding, we repeated the analyses with heart rate derived from the Holter data in the 81% of the cases with Holter data in the database. We did not find any marked interaction with heart rate. There were only marginal differences in the values of the relative risks. Apparent discrepancy

TABLE 4. Adjusted Relative Risks With 95% CI According to Heart Rate and β-Blocker at Entry

	HR <65 bpm		HR 65–79 bpm		HR ≥80 bpm	
	No β-Blocker	β-Blocker	No β-Blocker	β-Blocker	No β-Blocker	β-Blocker
Pulse HR, n	234	667	528	488	552	218
All death						
n	27	40	78	42	119	24
RR	1.09	0.66	1.05	0.88	1.06	0.62
95% CI	(0.50–2.37)	(0.35–1.24)	(0.67–1.64)	(0.48–1.61)	(0.73–1.52)	(0.27–1.41)
Cardiac death						
n	24	27	68	33	105	16
RR	0.98	0.84	1.10	0.53	1.03	0.35
95% CI	(0.43–2.24)	(0.39–1.78)	(0.68–1.79)	(0.26–1.09)	(0.70–1.52)	(0.11–1.08)
Arrhythmic death						
n	13	16	31	21	50	9
RR	0.25	0.86	1.37	0.33	0.84	0.13
95% CI	(0.07–0.92)	(0.32–2.31)	(0.67–2.81)	(0.12–0.90)	(0.48–1.48)	(0.02–1.01)
Nonarrhythmic cardiac death						
n	11	11	37	12	55	7
RR	4.22	0.71	0.92	1.06	1.25	0.83
95% CI	(0.90–19.6)	(0.21–2.35)	(0.48–1.78)	(0.34–3.28)	(0.73–2.16)	(0.18–3.69)
Arrhythmic death+resuscitation						
n	14	20	40	25	58	11
RR	0.34	0.56	1.17	0.33	0.88	0.23
95% CI	(0.10–1.12)	(0.23–1.38)	(0.63–2.19)	(0.13–0.81)	(0.52–1.49)	(0.05–1.04)
Holter HR, n	140	463	479	518	436	143
Arrhythmic death+resuscitation						
n	11	13	26	21	54	5
RR	0.34	0.49	0.92	0.48	1.03	0.21
95% CI	(0.09–1.33)	(0.16–1.49)	(0.42–1.99)	(0.18–1.24)	(0.60–1.79)	(0.02–1.91)

HR indicates heart rate; RR, relative risk.

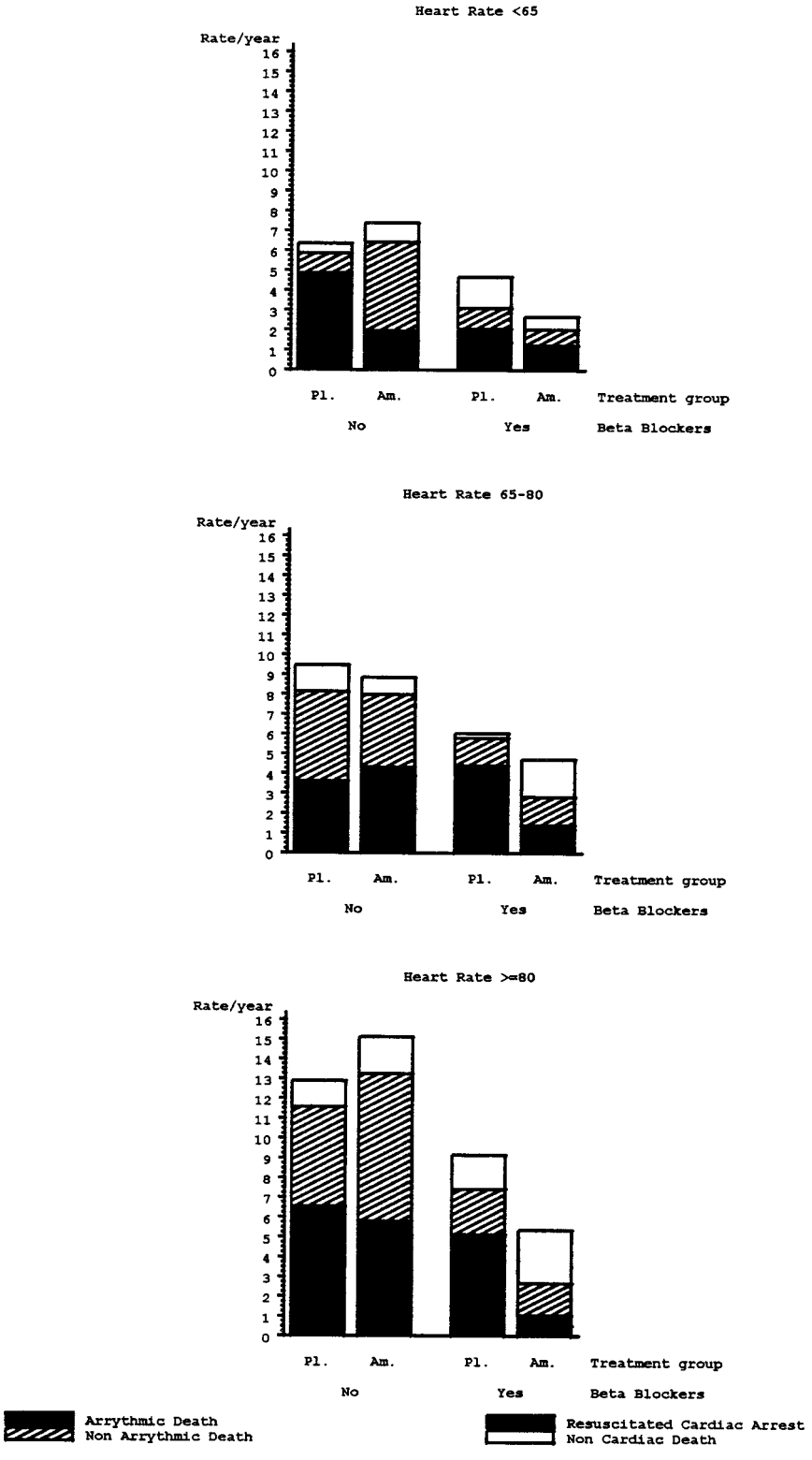

Figure 4. Death rates according to amiodarone (Am) and β-blocker in 3 categories of heart rate at baseline. Pl indicates placebo.

between our findings and earlier results from a subgroup analysis performed on the EMIAT file can be explained by the integration of the CAMIAT data and the fact that data were considered all together, contrasting with the subgroup approach in the previous report.[8] Formal statistical analysis of this type is limited by the number of subgroups, the small number of events in each subgroup, and the large number of comparisons or CIs that lead to spuriously marked contrasts because of random fluctuation.

There is no obvious explanation for the β-blocker–amiodarone interaction observed. One can speculate whether it might be due to a pharmacological synergistic effect. Indeed, the antiadrenergic effect of amiodarone suggested a different interaction with β-blockers. One might have expected little or

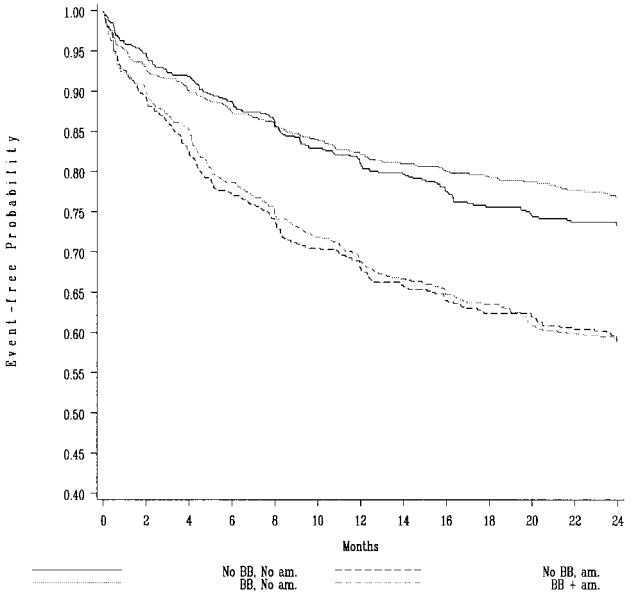

Figure 5. Discontinuation rate of amiodarone (am) and placebo according to β-blocker (BB) at entry.

no effect of amiodarone in patients already receiving a full β-blockade state because of the similarity in the effects of the 2 pharmacological interventions. In dogs, amiodarone partially inhibits the effects of adrenaline administration mediated by the α, β_1, and β_2 adrenoreceptors.[9] It decreases the number of cardiac β-receptors.[10] In vitro it decreases the binding capacity to β-receptors and increases the dissociation rate from these receptors.[11] It inhibits the adenylate cyclase activity in a noncompetitive way.[11] In patients, amiodarone blunts the effects of isoproterenol administration.[12] However, all these effects of amiodarone could increase the effects of a partial β-receptor blockade, especially the decrease in the number of receptors, by making a suboptimal dose of β-blocker more active. Sympathetic activation might be of shorter duration because of the increase in the dissociation rate. Also, since amiodarone can reduce the atrial pace,[2] a purely additive effect in patients should also be considered. However, this would not explain the interaction that has been identified in this analysis of the ECMA database because what was observed is not just an addition of β-blocker and amiodarone efficacy but rather a synergistic effect.

TABLE 5. Compliance of β-Blockers in Patients Receiving β-Blockers at Entry

	No. of Patients		Patients Still Receiving β-Blockers, %	
	Amiodarone	Placebo	Amiodarone	Placebo
Inclusion	691	682	100.0	100.0
2 wk	687	674	91.0	94.6
4 mo	679	659	71.3	83.1
8 mo	661	645	60.5	75.2
12 mo	648	623	54.5	71.7
16 mo	595	561	52.4	71.1
20 mo	522	488	48.8	71.5

For the clinician treating a patient after myocardial infarction or any patient with significant arrhythmia in whom treatment with amiodarone is planned, the results of this analysis is clear. Amiodarone does not replace a β-blocker. β-blocker therapy should be continued if possible.

Acknowledgments

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