Medikamentöse Therapien bei Kammerarrhythmien

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Helios

Einführung: medikamentöse Therapien

Idiopathische Kammertachykardien

Kanalopathien

VA bei ES

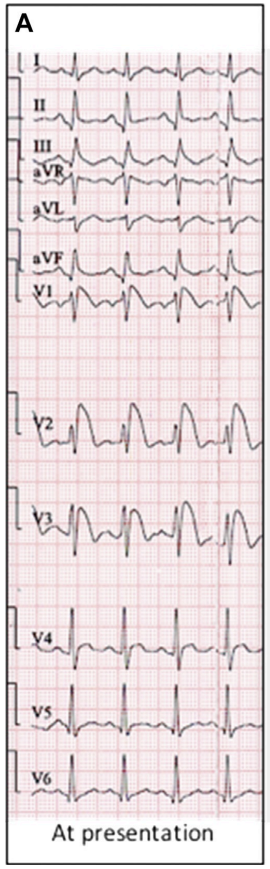
VA bei Patienten mit ICD

Brugada-Syndrom

A 54-year-old man presented to the emergency room with 10 ICD shocks over a 1-hour period.

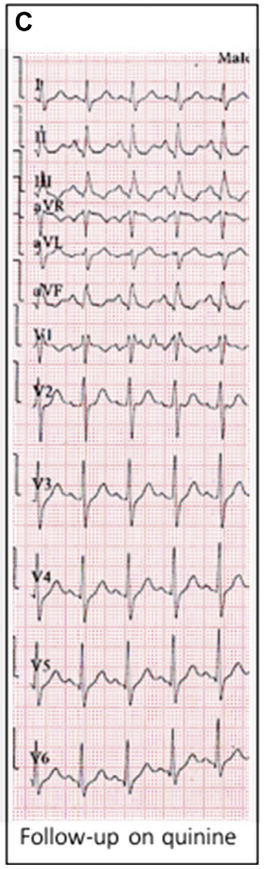
cilostazol 100 mg twice daily

(It increases cellular cAMP levels and L-type calcium currents, and, like isoproterenol, counteracts Ito, resulting in attenuation or abolishment of the electrical inhomogeneity of action potentials.)



KEY TEACHING POINTS

- Electrical storms in Brugada syndrome (BrS) can be recurrent and life threatening.
- Quinidine, the drug of choice for treatment and prevention of recurrent ventricular fibrillation (VF) in BrS, is not available in many countries around the world.
- Oral quinine sulfate is effective in management of electrical storms and recurrent VF in BrS patients.
- The common neurocognitive side effects of quinine is easily managed by a diet containing high levels of tryptophan.
- In the present case, cilostazole was not effective in the prevention of recurrent ventricular arrhythmias.
- Oral quinine sulfate is an effective alternative to quinidine for the treatment of lethal ventricular arrhythmias in BrS patients in countries where quinidine is not available.



Heart Rhythm Case Reports 2017;3:470–474

Brugada-Syndrom

Table 1: List of Medications for the Therapy of Brugada Syndrome and their Utility, Based on Level of Evidence

	Dosing	Storm	VF prophylaxis	Asymptomatic BrS
Quinidine	HQ 600–900 mg/day; BSQ 1,000–2,250 mg/day	*** ***	*** ***	**
Disopyramide	300–600 mg/day		*	
Isoproterenol	0.003 ± 0.003 µg/kg/min	***		
Denopamine	30 mg/day		*	
Orciprenaline	IV bolus 0.5 mg, followed by IV drip 3.3 µg/min	*		
Cilostazol	200 mg/day		*	
Bepridil	100–200 mg/day		*	

** = evidence from case reports,; ** = evidence from small cohort studies; *** = evidence from several large cohort studies, BSQ = bisulfate quinidine; HQ = hydroquinidine chlorhydrate; IV = intravenous; VF = ventricular fibrillation.*

Arrhythmia & Electrophysiology Review 2018;7(2):135–42

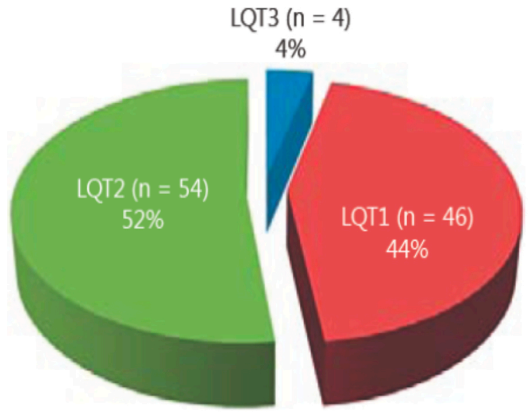
Long-QT-Syndrom

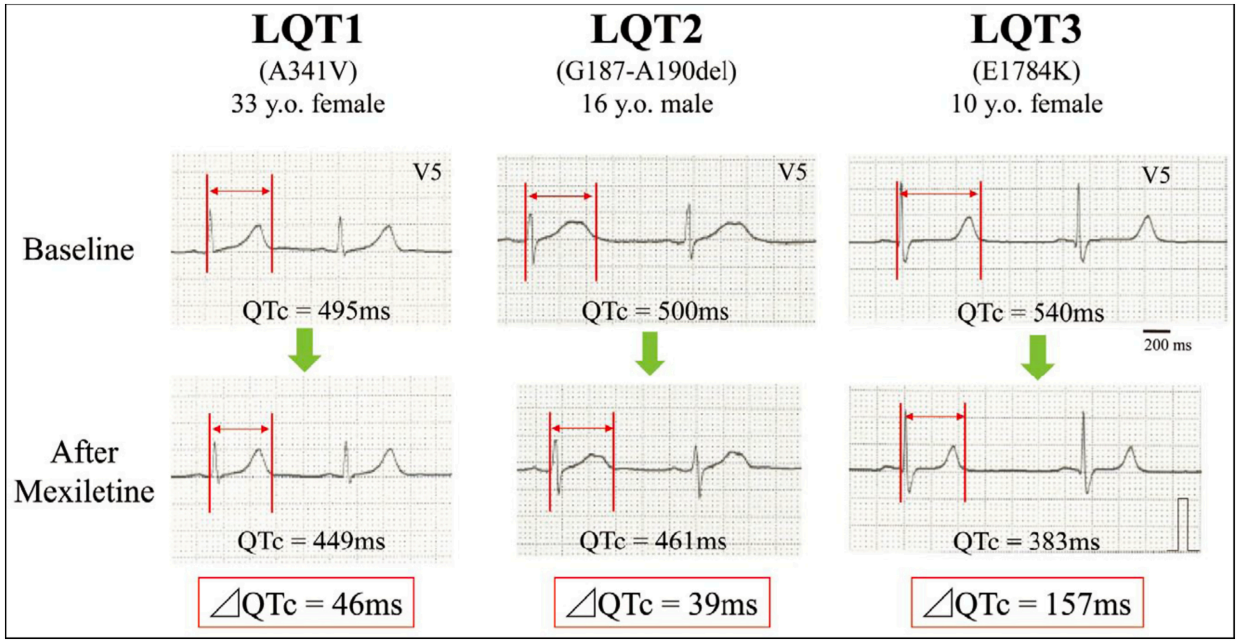
Over 1300 LQTS-causing mutations in at least 17 genes encoding or regulating cardiac potassium, sodium and calcium ion channels have been identified.

Beta-blocker medication has remained as the first-line therapy for congenital.

In most of LQT3 patients, as well as in a subset of LQT1 and LQT2 patients showing markedly prolonged QT interval at a slow heart rate, beta-blockers may do harm in patients with bradycardia-dependent QT prolongation.

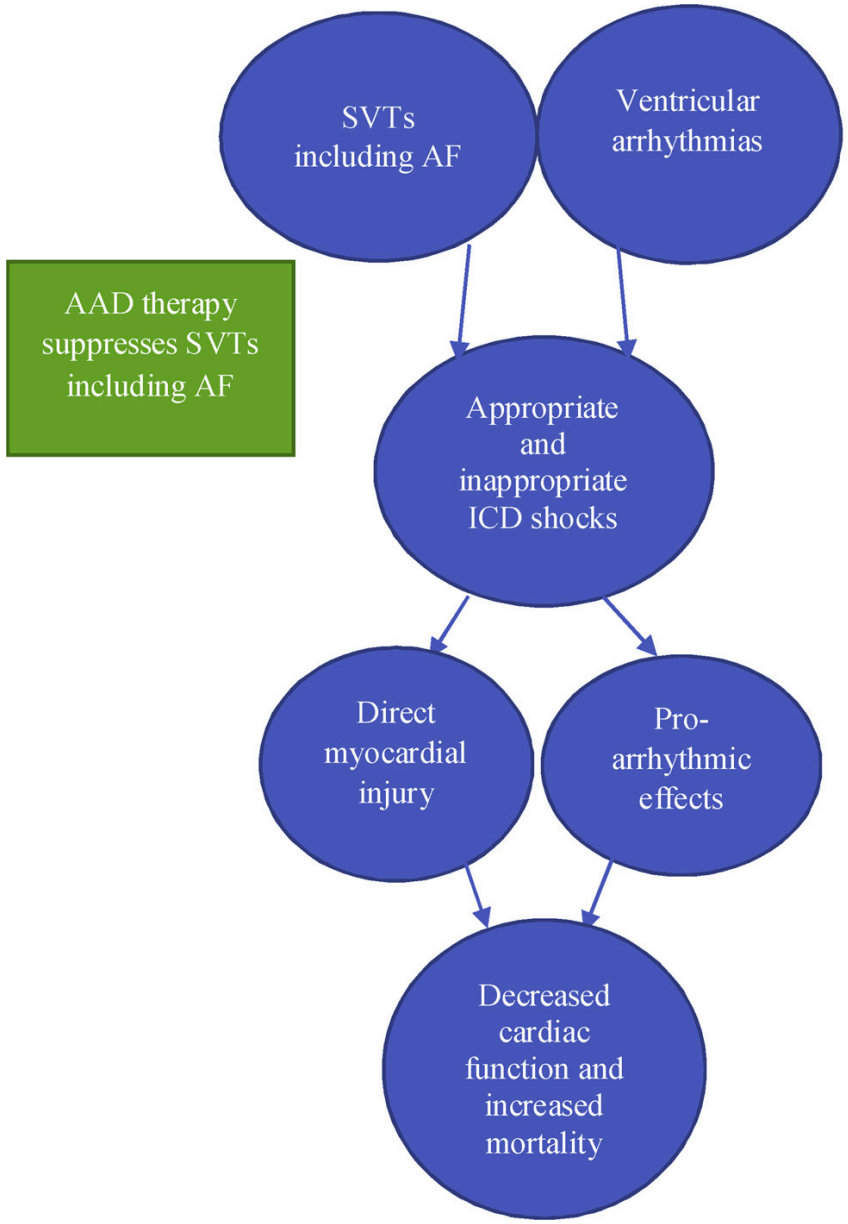
Mexiletine, a Vaughan-Williams class Ib antiarrhythmic agent, can shorten the action potential duration by selectively suppressing INa-L without affecting the speed of AP upstroke (evidence for absence of significant peak INa block), thus shortening of prolonged QT interval without widening of the QRS duration.





VA bei ES/ICD

In patients who receive an ICD for primary prophylaxis, around 21% will have appropriate ICD shocks necessitating further therapy, usually with AADs. The proportion of patients who require therapy is even higher in patients who have an ICD implanted for secondary prevention, ranging from 45% to 68% at one to two year follow-up.



Pharmacol Res. 2019 May;143:133-142.

Table 1
Possible benefits and adverse effects of anti-arrhythmic drug therapy in patients with an ICD.

Potential Benefits	Potential Adverse Effects
Prolongs VT cycle length which increases ATP success	Pro-arrhythmic effects including ventricular arrhythmias
Ventricular arrhythmia suppression which decreases appropriate ICD shocks and symptomatic VT episodes	Increase in defibrillator or pacing threshold
Rhythm and rate control of supraventricular arrhythmias which decreases inappropriate ICD shocks	Bradycardia and conduction delays with increased pacing frequency
Prevents VT storm	Decreasing the ventricular tachycardia rate below the detection threshold of ICD therapy with potential untreated sustained VT
Decrease in appropriate and inappropriate shock improves psychological well-being of ICD recipients	

Beta-Blockers:

Currently there is no strong evidence to support the use of a particular beta blocker with regards to superiority in reducing ventricular arrhythmias. However, propranolol has been shown to be superior in the setting of the electrical storm.

in an analysis of the MADIT II trial, beta-blockers significantly reduced the risk for VT or VF and decreased mortality in patients with ischemic cardiomyopathy who received an ICD.

In a sub-analysis of the MADIT-CRT trial, carvedilol was associated with a 36% lower rate of inappropriate ATP and shock therapy compared with metoprolol.

Caution should be taken when administering beta-blockers to patients with a **recent myocardial infarction** and **two or more risk factors** for **cardiogenic shock** such as age>70 years, tachycardia>110 beats per minute and a blood pressure below 120 mmHg systolic. In a large registry, such patients had an **increased risk of shock or mortality** if given beta-blockers.

Sotalol:

Adjunctive therapy in patients with ICDs to decrease the risk of appropriate and inappropriate shock:

Study A: Pacifico et al. randomized 302 patients with ICDs, the majority of whom had ischemic cardiomyopathy, to d-l-sotalol or placebo in a double-blind trial. Sotalol reduced the risk of appropriate shocks by 44% and inappropriate shocks by 64%.

Study B: Kuhlkamp et al. randomized patients with inducible ventricular arrhythmias on electrophysiologic testing who were then implanted with ICDs, to receive either sotalol or placebo. Sotalol reduced the absolute risk of recurrence of ventricular tachycardia or fibrillation by 21% (30% versus 51%).

Women are more likely to develop torsades de pointes particularly when receiving sotalol

OPTIC [46]	Sotalol/ amiodarone	Population: VT, VF, or cardiac arrest or inducible VT/VF and LVEF ≤ 40%. Intervention: Amiodarone + beta blocker or beta blocker or sotalol Follow-up: 12 months	No difference in mortality between amiodarone + beta blocker (6, 4.3%), beta blocker (2, 1.4%) or sotalol (4, 3.0%). Amiodarone plus β-blocker significantly reduced the risk of shock compared with β-blocker alone (HR, 0.27; 95% CI, 0.14-0.52; log-rank P < .001) and sotalol (HR, 0.43; 95% CI, 0.22-0.85; log-rank P = .02).

Amiodaron:

Amiodarone, as second line therapy in patients treated with betablockers, is the mainstay of secondary prevention of VA in patients with ICDs.

In the 412 patients enrolled in the OPTIC trial, amiodarone plus beta-blocker significantly reduced the risk of shock compared with beta-blocker alone (HR, 0.27; 95% CI, 0.14-0.52; log-rank P < .001) and sotalol (HR, 0.43; 95% CI, 0.22-0.85; log-rank P=0.02).

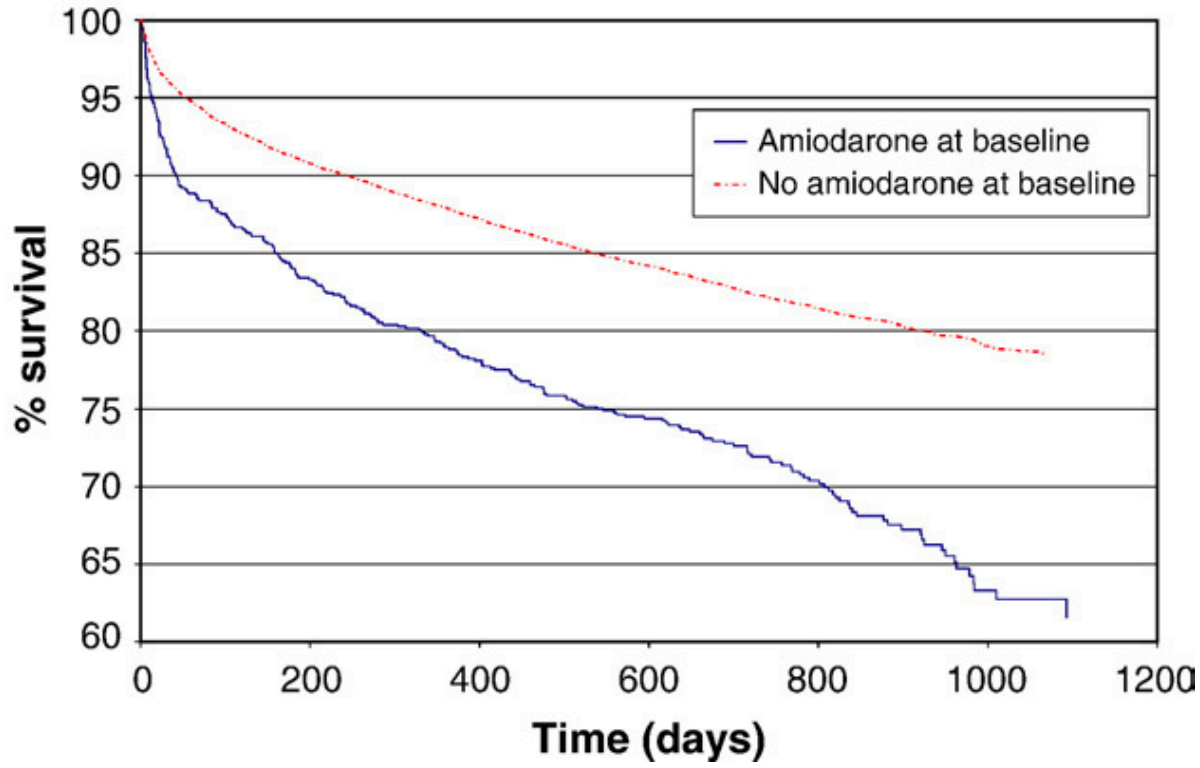
CAMIAT+EMIAT: patients who received a combination of beta-blockers and amiodarone had a decreased relative risk of all-cause mortality, cardiac death and arrhythmic cardiac death compared with those not receiving beta-blockers regardless of whether they were receiving amiodarone. **These findings suggest that beta-blockers should be considered for all patients with ventricular arrhythmias who are receiving amiodarone therapy.**

Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality

Kevin L. Thomas, MD,[a] Sana M. Al-Khatib, MHS, MD,[a] Yuliya Lokhnygina, PhD,[a] Scott D. Solomon, MD,[b] Lars Kober, MD,[c] John J.V. McMurray, MD,[d] Robert M. Califf, MD,[a] and Eric J. Velazquez, MD[a] *Durham, NC; Boston, MA; Copenhagen, Denmark; and Glasgow, Scotland*

This study used data from VALIANT, a randomized comparison of valsartan, captopril, or both in patients with acute myocardial infarction with HF and/or left ventricular systolic dysfunction.

The authors compared baseline characteristics of 825 patients treated with amiodarone at randomization with 13875 patients not treated with amiodarone.

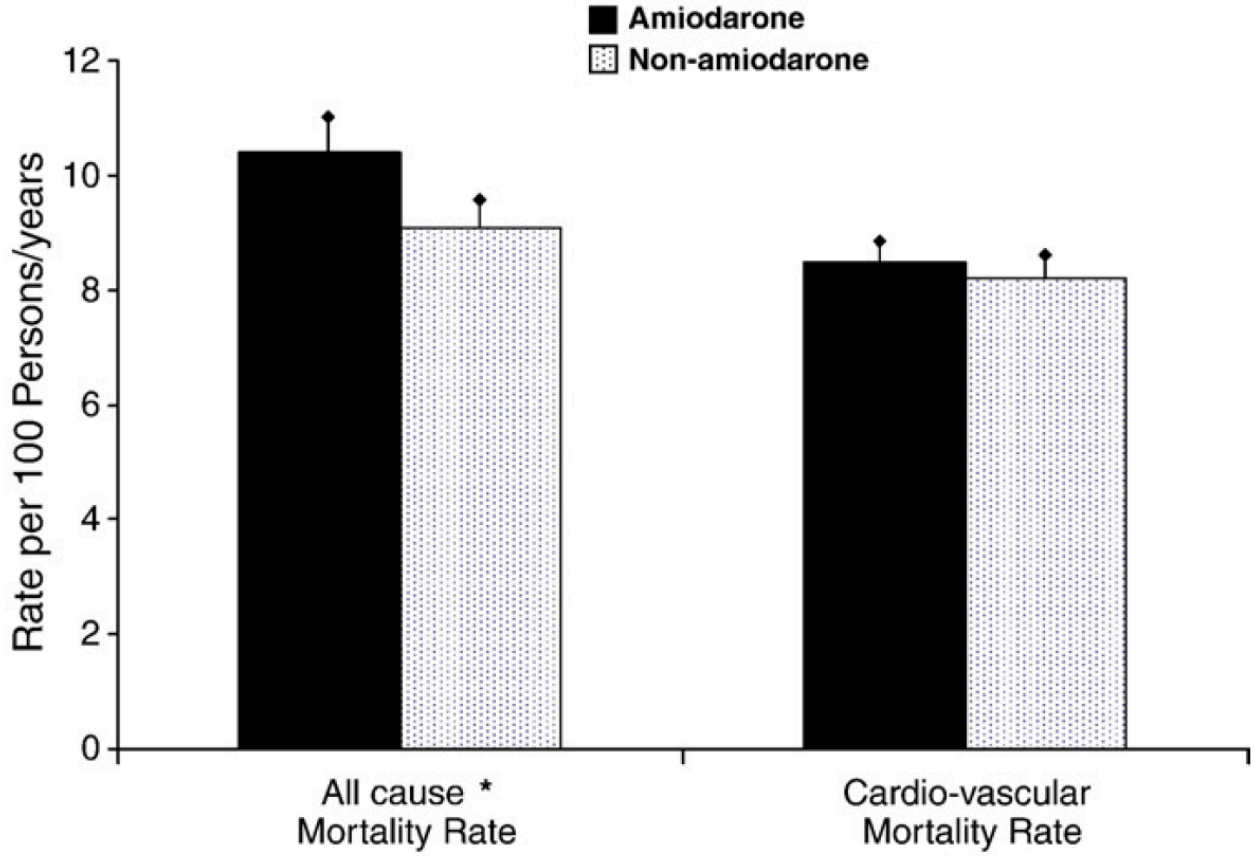


Am Heart J 2008;155:87-93

Mortality of newly diagnosed heart failure treated with amiodarone
A propensity-matched study

Jose L. Andrey, Francisco M. Gomez-Soto, Sotero P. Romero, Miguel A. Escobar, A. Antonio García-Egido, Rocio Garcia-Arjona, Francisco Gomez *
and for the GAMIC (Grupo para la Atencion Medica Integrada de Cadiz)

Prospective cohort study over 7 years on 3734 patients with HF. Main outcomes were all-cause and cardiovascular mortality,



Rates are during follow-up among propensity-matched patients with heart failure treated with Amiodarone

* $P < 0.001$ for all cause mortality of Amiodarone therapy vs Non-amiodarone therapy.

$P = 0.371$ for cardiovascular mortality of Amiodarone therapy vs Non-amiodarone therapy.

J.L. Andrey et al. / International Journal of Cardiology 151 (2011) 175–181

Mexiletine:

Mexiletine for Control of Drug-Resistant Ventricular Tachycardia: Clinical and Electrophysiologic Results in 44 Patients

AJC Volume 51, Issue 7, April 1983, Pages 1175-1181

Waspe et al. (1983) showed that while mexiletine has limited efficacy in preventing recurrent ventricular arrhythmias when used alone, the addition of mexiletine to other AADs **may be effective in 30% of patients with drug-resistant arrhythmias**.

Adverse effects occurred in 27 of 44 patients **(61%)** and were gastrointestinal in 17 and/or neurologic in 22.

Ranolazine:

Ranolazine is an approved anti-anginal medication with calcium channel blocking properties. It has a structure that is similar to lidocaine, and its **major anti-arrhythmic action occurs via late sodium channel blockade (also Blocks delayed IK)**.

12(age 65 ± 9.7 years) were treated with ranolazine. Eleven (92%) were male, and 10 (83%) had IHD with an mean LVEF of 0.34 ± 0.13.

All patients were on a **class III AAD** (11 amiodarone, one sotalol), with **six (50%) receiving mexilitene or lidocaine**.

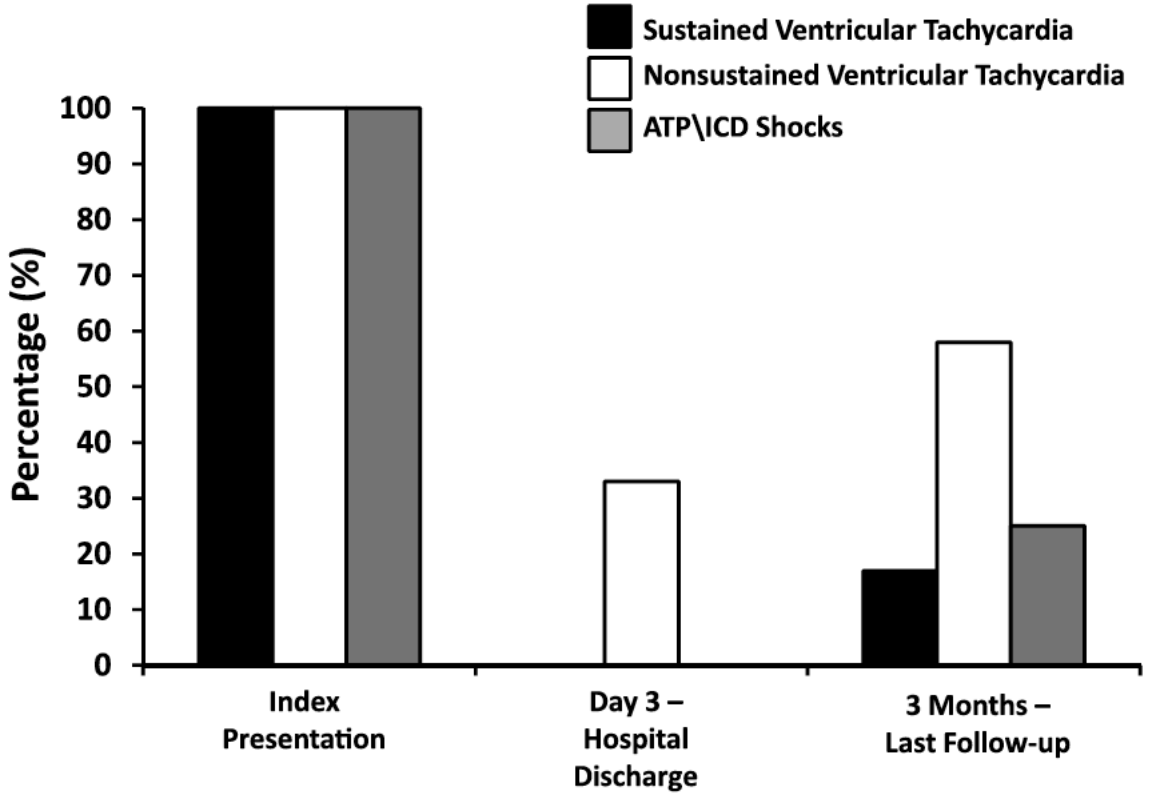


Figure 2. *The time-based outcomes of patients treated with ranolazine. Three time periods are shown: the index hospitalization, the steady state (day 3) to hospital discharge, and 3 months to last follow-up. All patients presented with ICD therapies and both sustained and nonsustained VT. Sustained VT, nonsustained VT, and ICD therapies were all reduced during the study observation period.*

PACE 2011; 34:1600–1606

Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators

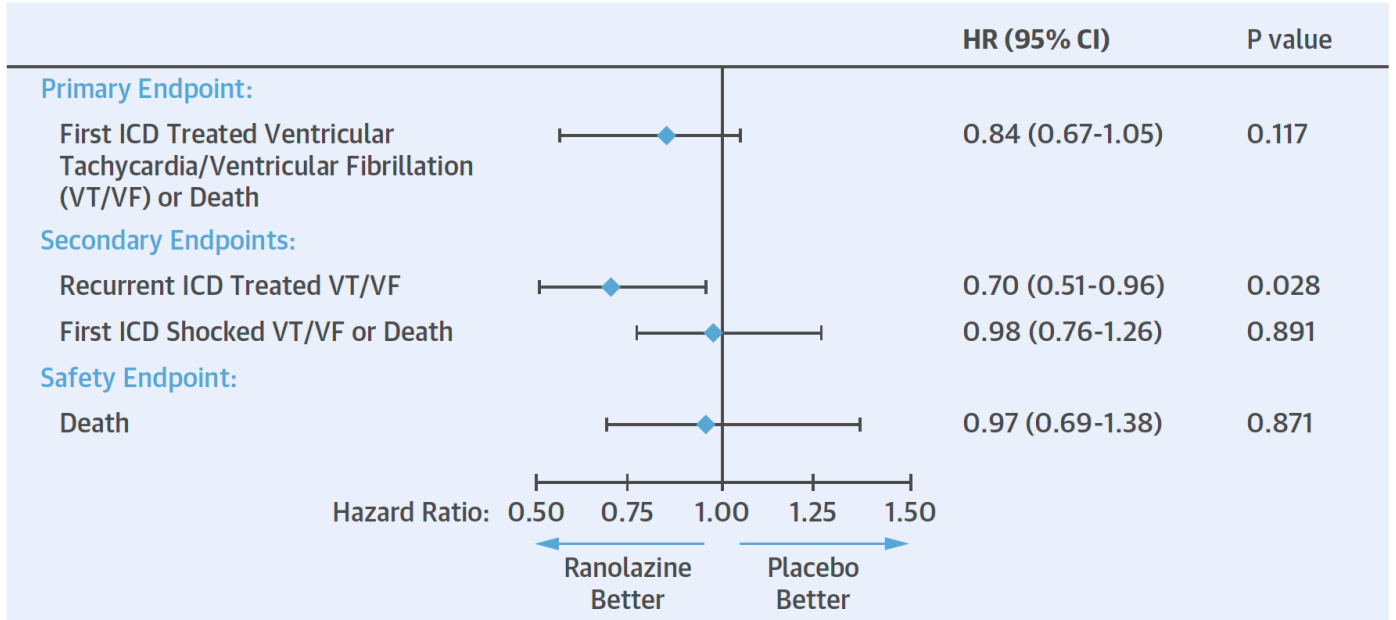
The RAID Trial

J Am Coll Cardiol 2018;72:636–45

Among 1,012 ICD patients (510 randomized to ranolazine and 502 to placebo) the mean age was 64±10 years and 18% were women. During 28±16 months of follow-up there were 372 (37%) patients with primary endpoint, 270 (27%) patients with VT or VF, and 148 (15%) deaths.

Ranolazine administration was associated with a **significant reduction in recurrent VT or VF requiring ICD therapy without evidence for increased mortality**.

CENTRAL ILLUSTRATION **Effect of Ranolazine Versus Placebo on Ventricular Tachyarrhythmias and Death in Implantable Cardioverter-Defibrillator (ICD) Patients**



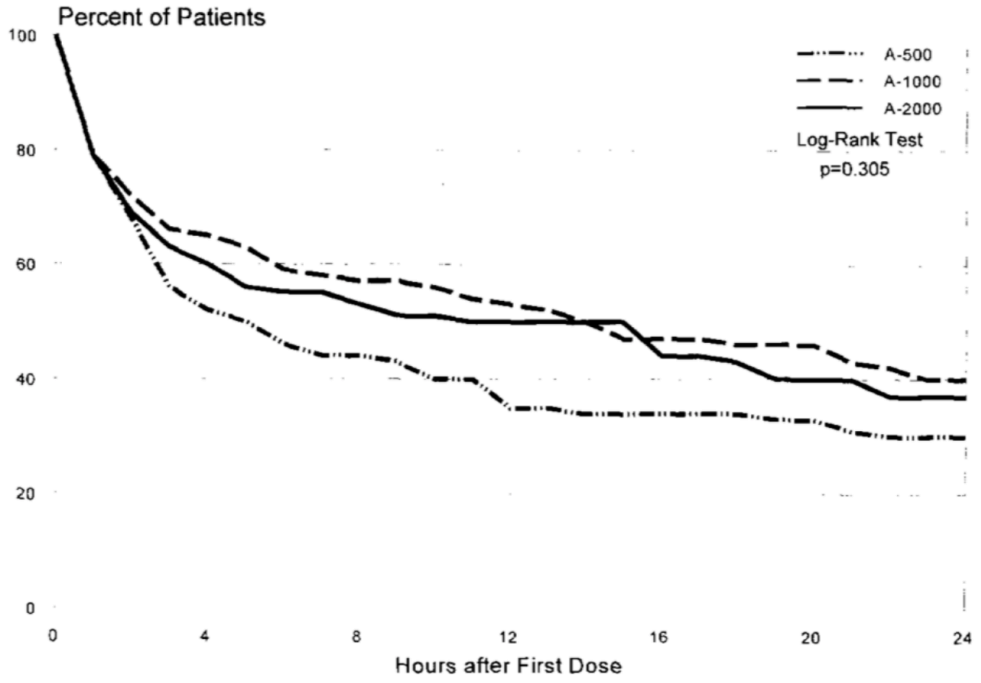
Zareba, W. et al. J Am Coll Cardiol. 2018;72(6):636-45.

Ranolazine did not reduce significantly the primary endpoint of ventricular tachycardia (VT), ventricular fibrillation (VF), or death, whereas the secondary endpoint of recurrent implantable cardioverter-defibrillator (ICD)-treated VT or VF was reduced by 30% (hazard ratio [HR]: 0.70; p = 0.028). No effect of ranolazine was observed on the first ICD-shocked VT or VF, or death, and on death alone. CI = confidence interval.

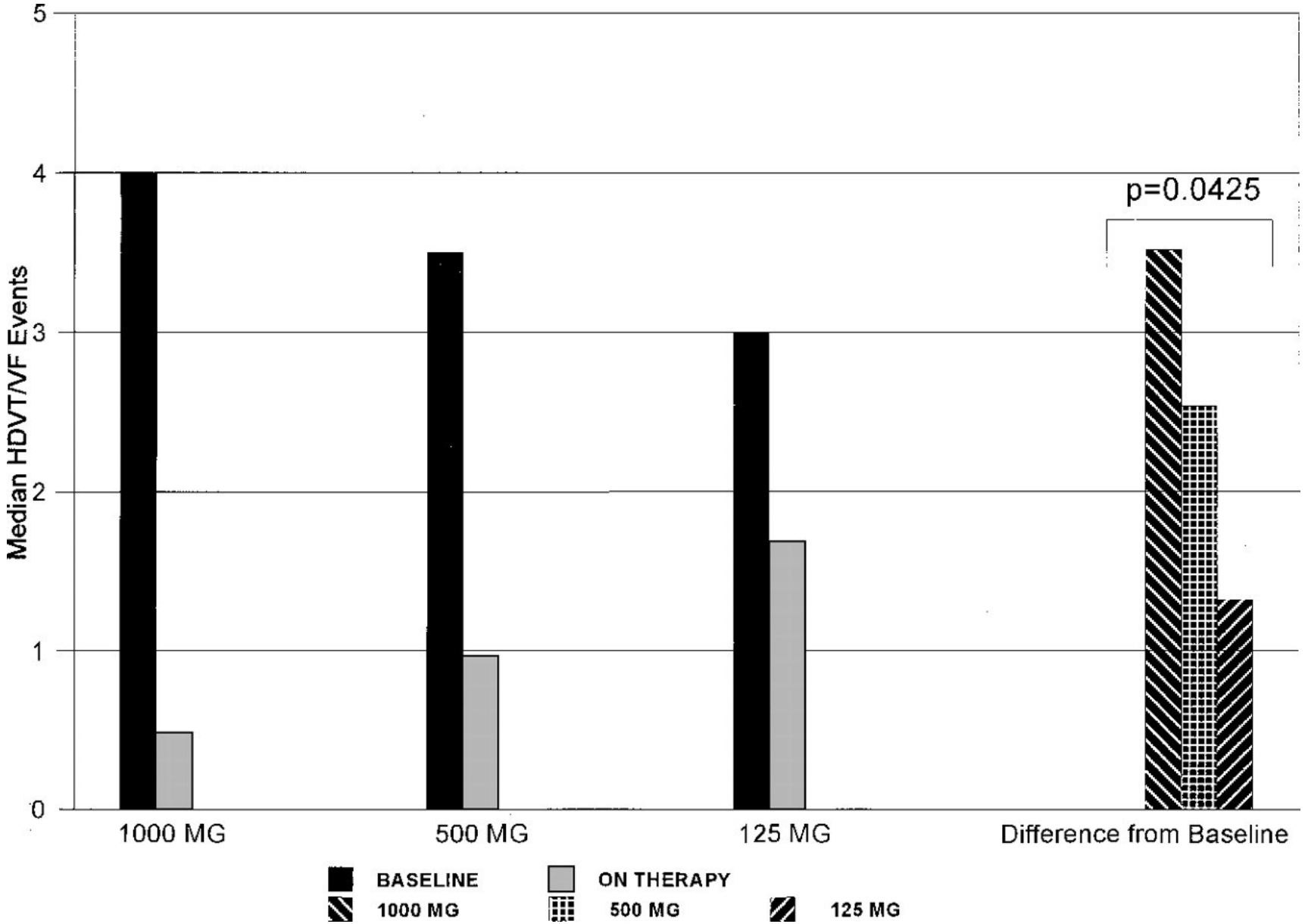
Anti-arrhythmic therapy during electrical storm:

Amiodarone is the first line AAD therapy in patients with electrical storm. Amiodarone significantly reduces ventricular tachyarrhythmias and can be safely administered during electrical storm.

Of the 273 patients, 110 **(40.3% response rate)** survived 24 h without another VT while being treated with intravenous amiodarone as a single agent (primary end point).



J Am Coll Cardiol. 1996 Jan;27(1):67-75.

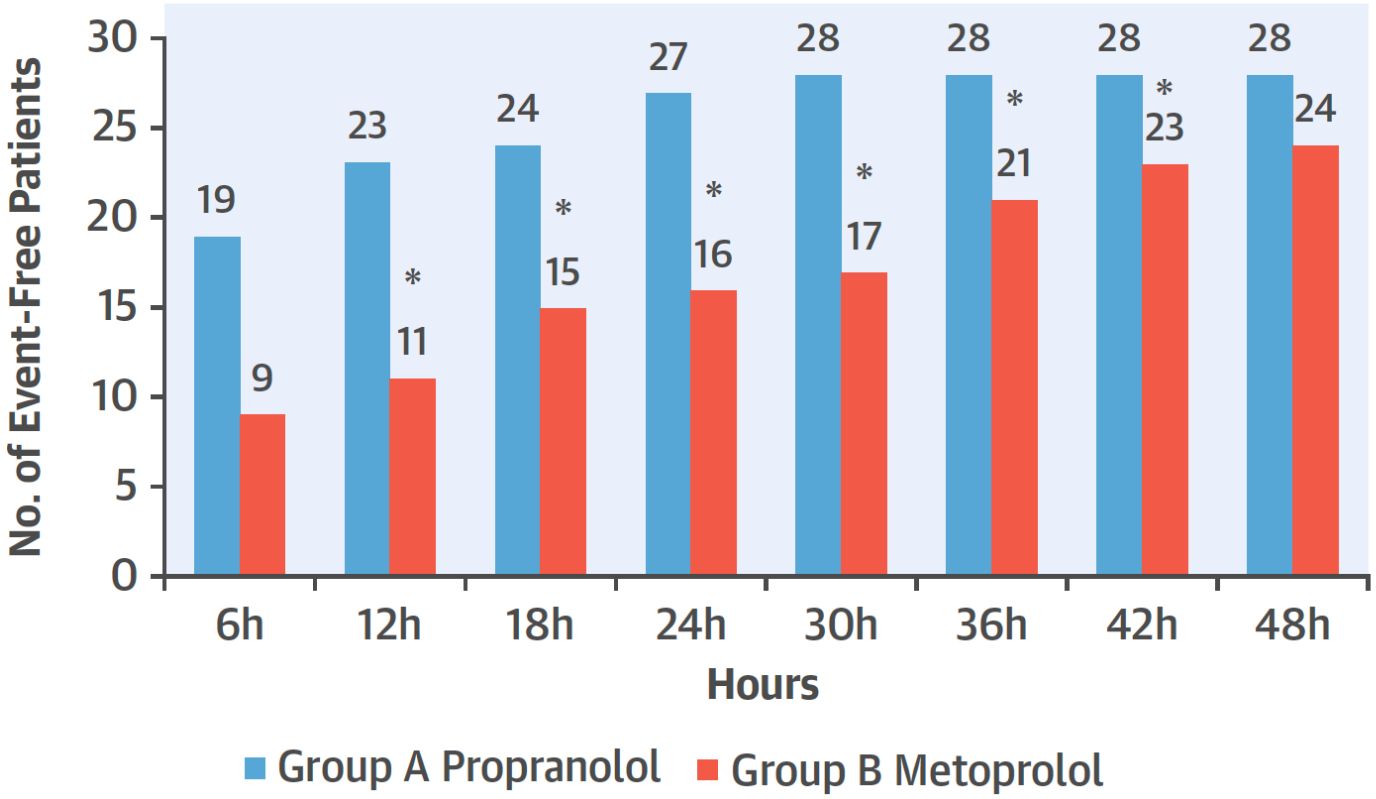


Circulation. 1995;92:3264–3272

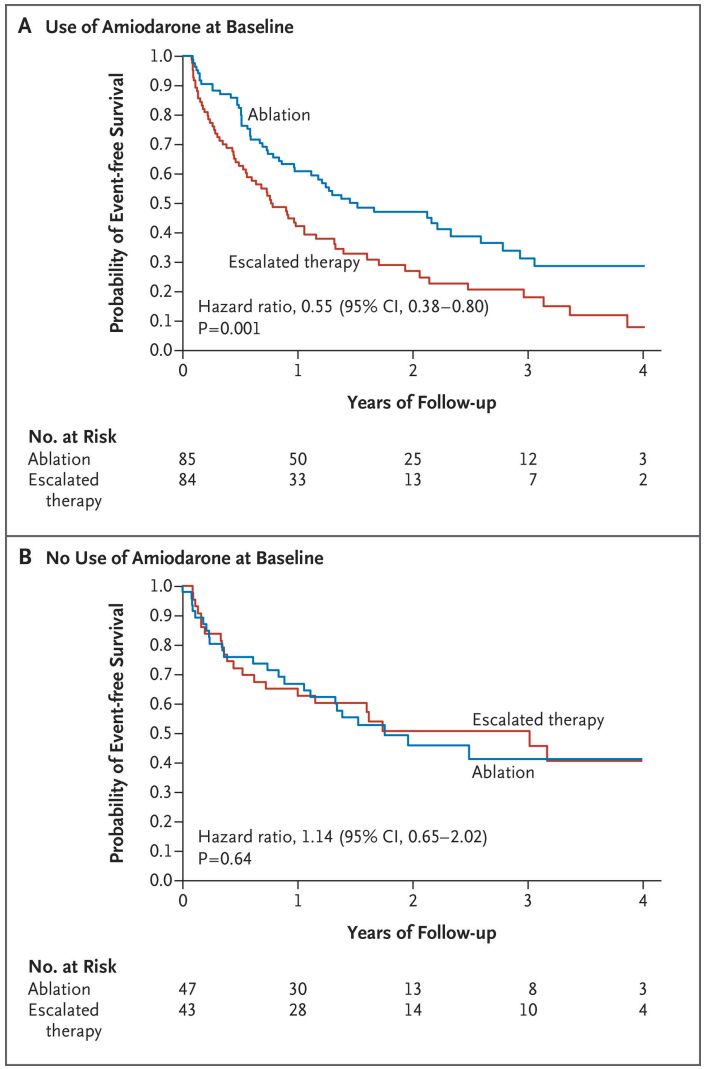
Propranolol Versus Metoprolol for Treatment of Electrical Storm in Patients With Implantable Cardioverter-Defibrillator

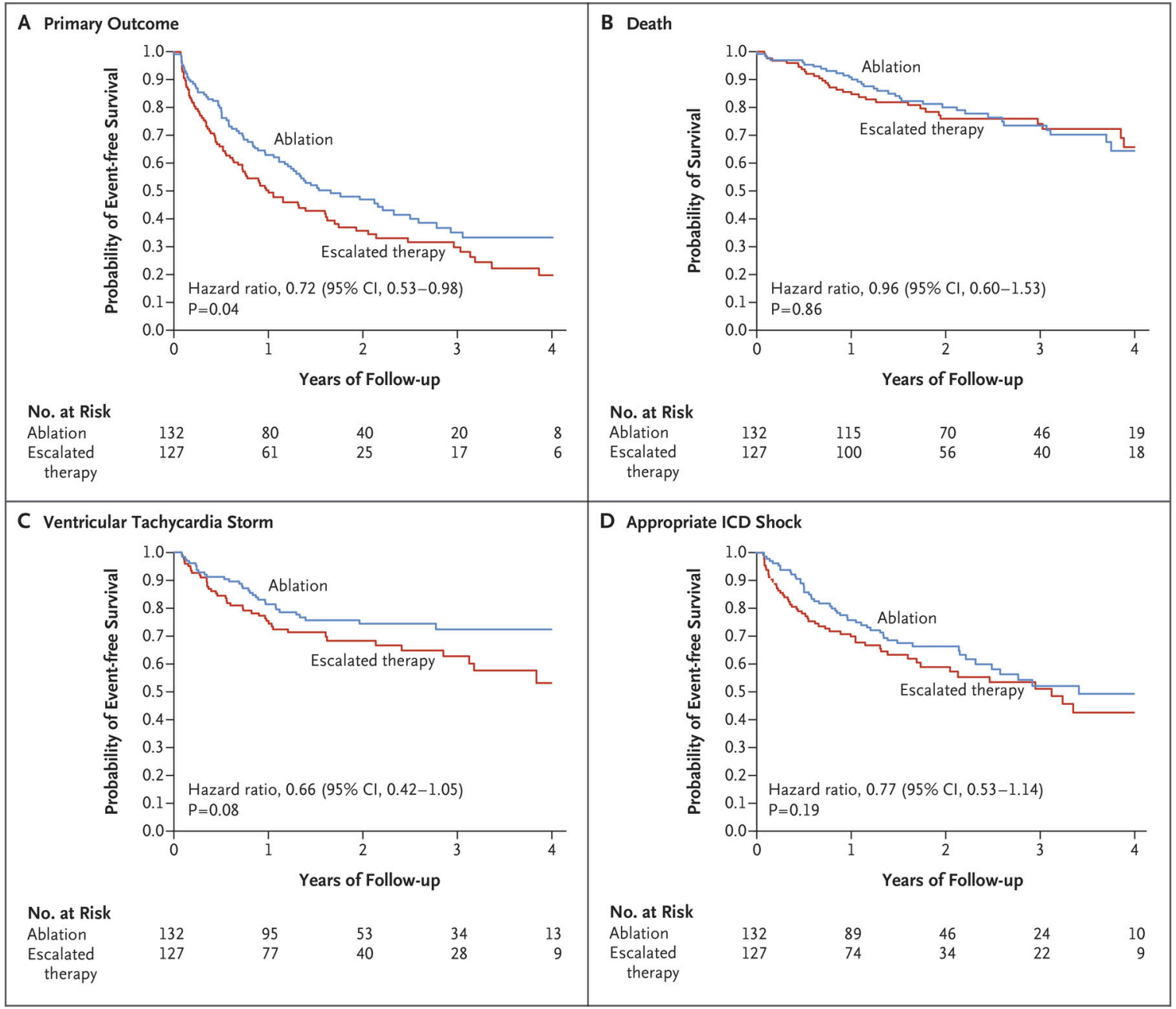
J Am Coll Cardiol 2018;71:1897–906

Between 2011 and 2016, 60 ICD patients (45 men, mean age 65.0±8.5 years) with ES developed within 24 h from admission were randomly assigned to therapy with either propranolol (160 mg/24 h, Group A) or metoprolol (200 mg/24 h, Group B), combined with IV amiodarone for 48 h.



Of the 259 patients who were enrolled, 132 were assigned to the ablation group and 127 to the escalated-therapy group.





N Engl J Med 2016; 375:111-121

Recommendations for catheter ablation of VAs in patients with IHD

COR	LOE	Recommendations	References
I	B-R	1. In patients with IHD who experience recurrent monomorphic VT despite chronic amiodarone therapy, catheter ablation is recommended in preference to escalating AAD therapy.	S4.4.1
I	B-NR	2. In patients with IHD and recurrent symptomatic monomorphic VT despite AAD therapy, or when AAD therapy is contraindicated or not tolerated, catheter ablation is recommended to reduce recurrent VT.	S4.4.2–S4.4.4
I	B-NR	3. In patients with IHD and VT storm refractory to AAD therapy, catheter ablation is recommended.	S4.4.5–S4.4.9
IIa	C-EO	4. In patients with IHD and recurrent monomorphic VT, in whom AADs are not desired, catheter ablation can be useful.	

Recommendations for catheter ablation of VT in NICM

COR	LOE	Recommendations	References
I	B-NR	1. In patients with NICM and recurrent sustained monomorphic VT for whom antiarrhythmic medications are ineffective, contraindicated, or not tolerated, catheter ablation is useful for reducing recurrent VT and ICD shocks.	S4.5.1–S4.5.6
I	B-NR	2. In patients with NICM and electrical storm refractory to AAD therapy, catheter ablation is useful for reducing recurrent VT and ICD shocks.	S4.5.7–S4.5.9
IIa	B-NR	3. In patients with NICM, epicardial catheter ablation of VT can be useful after failure of endocardial ablation or as the initial ablation approach when there is a suspicion of an epicardial substrate or circuit.	S4.5.4, S4.5.10–S4.5.13
IIa	B-NR	4. In patients with cardiac sarcoidosis and recurrent VT despite medical therapy, catheter ablation can be useful to reduce the risk of VT recurrence and ICD shocks.	S4.5.14–S4.5.18
IIa	C-EO	5. In patients with NICM and recurrent sustained monomorphic VT for whom antiarrhythmic medications are not desired, catheter ablation can be useful for reducing recurrent VT and ICD shocks.	

Europace (2019) 00, 1–147

Question:

What is the effect of catheter ablation of scar-related VT on **cardiac mortality**?

Methods:

Data from 1,064 patients who underwent VT ablation for scar-related VT at **seven international centers** were analyzed.

Successful catheter ablation of VT in patients with scar-related VT is independently associated with **lower mortality** during long-term follow-up.

Results:

TABLE 2 Adjusted HR Mortality Estimates

	HR	95% CI	p Value
Age	1.03	1.01–1.06	0.001
Noninducible post-ablation*	0.65	0.53–0.79	<0.001
NYHA functional class†			
II	0.89	0.39–2.03	0.78
III	1.68	0.79–3.56	0.18
IV	1.77	0.69–4.54	0.24
History of AF	1.83	1.14–2.93	0.01
Diabetes	1.58	1.17–2.13	<0.01
Noninducible at onset	0.54	0.29–1.01	0.06
Incessant VT	1.31	1.09–1.57	<0.01

Cox regression model (n = 671; included patients in whom all data were available for analysis). *Compared with inducible or no stimulation performed post-ablation. †Reference = I.

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; other abbreviations as in Table 1.

J Am Coll Cardiol. 2015;65(18):1954-9

Question:

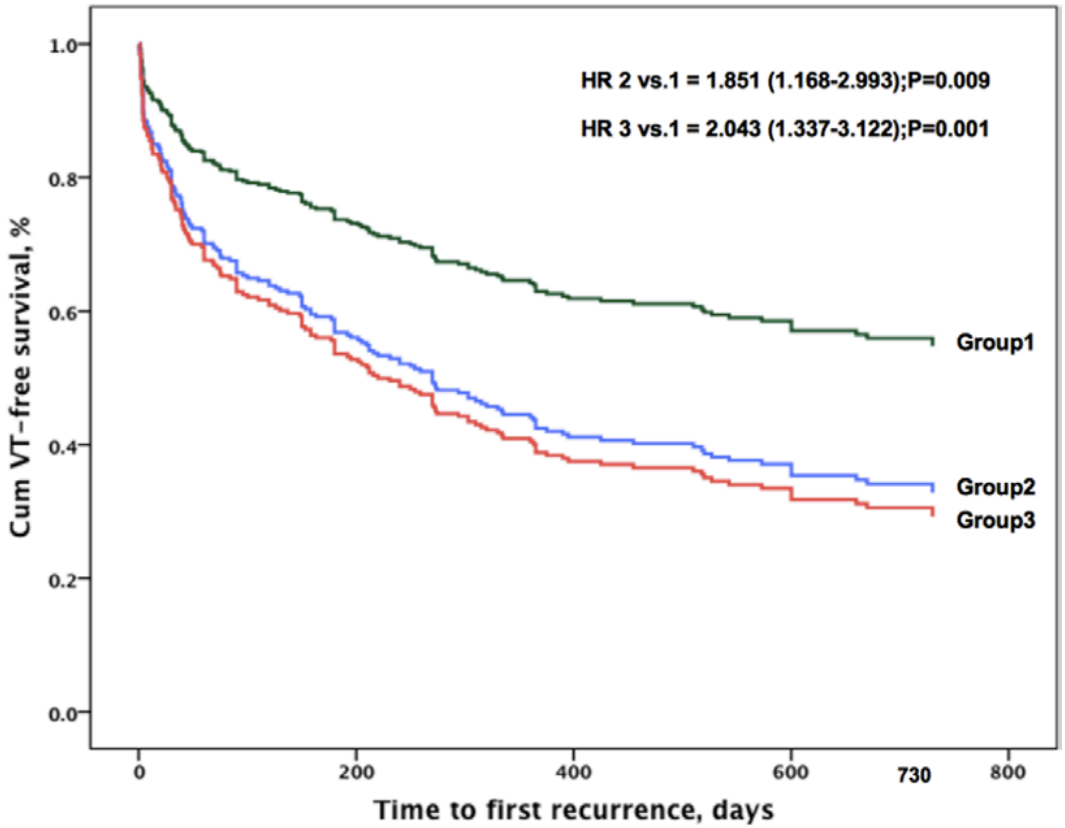
What is the effect of time to catheter ablation of scar-related VT on acute success, VT recurrence, and cardiac mortality?

Methods:

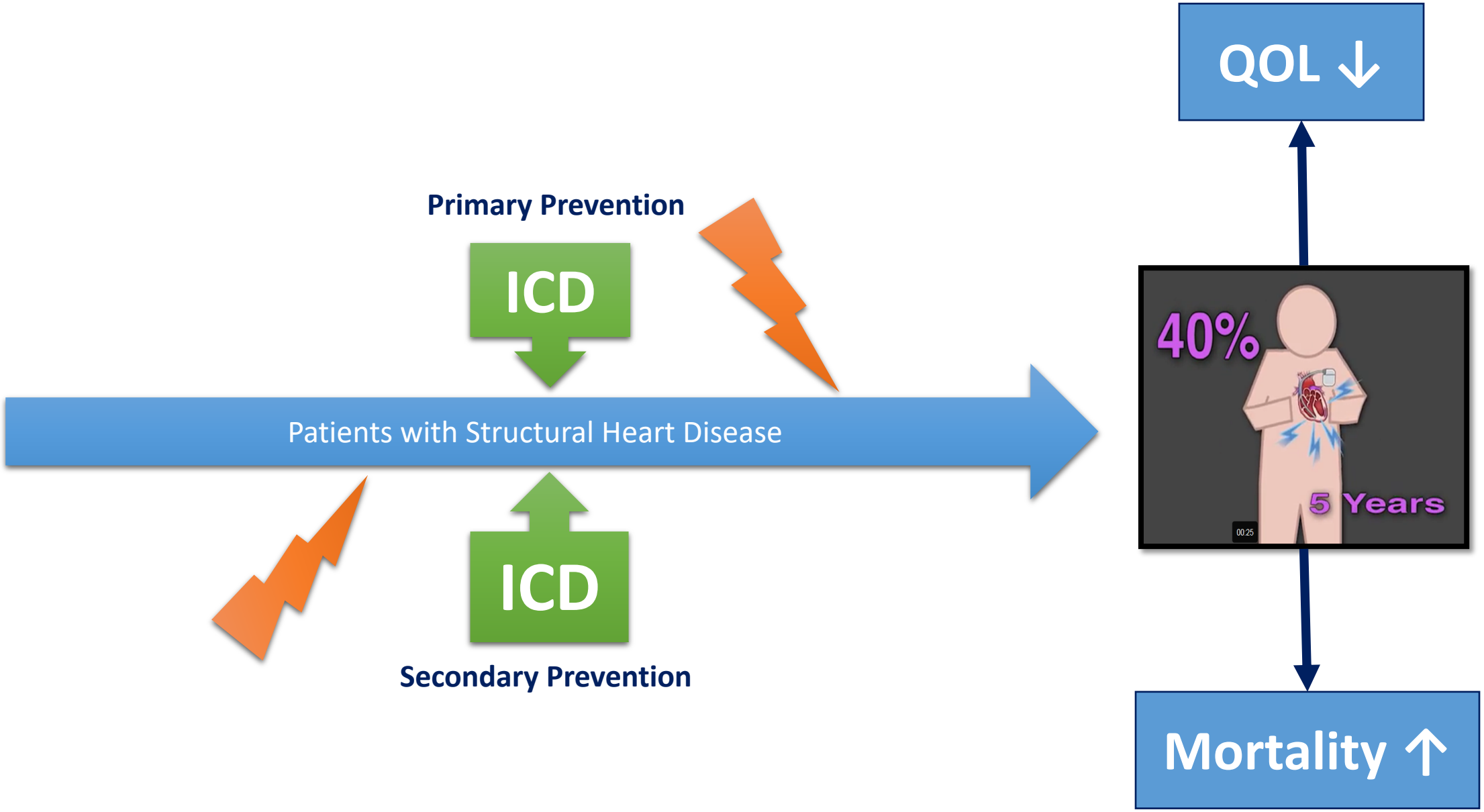
We studied 300 patients after catheter ablation of sustained scar-related VT to assess the effect of timing of the ablation on the outcome of these patients.

Circulation Arrhythm Electrophysiol. 2014 Dec;7(6):1144-51.

Results:



Catheter ablation of scar-related VT performed **within 30 days** after the first documented VT was associated with **improved acute and long-term success and outcome**.


QOL ↓
Primary Prevention
ICD
Patients with Structural Heart Disease
ICD
Secondary Prevention
40%
5 Years
00:25
Mortality ↑