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Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators

The RAID Trial

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ABSTRACT

BACKGROUND Ventricular tachycardia (VT) and ventricular fibrillation (VF) remain a challenging problem in patients with implantable cardioverter-defibrillators (ICDs).

OBJECTIVES This study aimed to determine whether ranolazine administration decreases the likelihood of VT, VF, or death in patients with an ICD.

METHODS This was double-blind, placebo-controlled clinical trial in which high-risk ICD patients with ischemic or nonischemic cardiomyopathy were randomized to 1,000 mg ranolazine twice a day or placebo. The primary endpoint was VT or VF requiring appropriate ICD therapy or death, whichever occurred first. Pre-specified secondary endpoints included ICD shock for VT, VF, or death and recurrent VT or VF requiring ICD therapy.

RESULTS 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. The blinded study drug was discontinued in 199 (39.6%) patients receiving placebo and in 253 (49.6%) patients receiving ranolazine ($p = 0.001$). The hazard ratio for ranolazine versus placebo was 0.84 (95% confidence interval: 0.67 to 1.05; $p = 0.117$) for VT, VF, or death. In a pre-specified secondary analysis, patients randomized to ranolazine had a marginally significant lower risk of ICD therapies for recurrent VT or VF (hazard ratio: 0.70; 95% confidence interval: 0.51 to 0.96; $p = 0.028$). There were no other significant treatment effects in other pre-specified secondary analyses, which included individual components of the primary endpoint, inappropriate shocks, cardiac hospitalizations, and quality of life.

CONCLUSIONS In high-risk ICD patients, treatment with ranolazine did not significantly reduce the incidence of the first VT or VF, or death. However, the study was underpowered to detect a difference in the primary endpoint. In pre-specified secondary endpoint analyses, ranolazine administration was associated with a significant reduction in recurrent VT or VF requiring ICD therapy without evidence for increased mortality. (Ranolazine Implantable Cardioverter-Defibrillator Trial [RAID]; NCT01215253) (J Am Coll Cardiol 2018;72:636–45) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Patients with an implantable cardioverter-defibrillator (ICD) are at high risk of ventricular tachycardia (VT) and ventricular fibrillation (VF). In the first year after ICD implantation 10% to 17% of primary prevention patients (1,2), and 50% of patients with recent VT or VF (secondary prevention) receive appropriate ICD therapies for VT or VF (3). There are limited pharmacological treatment options for patients at high risk of VT or VF. In the majority of patients, beta-blockers alone do not provide adequate risk reduction, sotalol has been shown to be effective although it is not frequently used, and amiodarone, although effective in some patients, is frequently avoided due to its side effects (4–6).

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Both myocardial ischemia and cardiomyopathy are associated with a sodium overload of myocardial cells and augmented late sodium current plays a pivotal role in this process (7–11). Intracellular sodium overload leads to calcium overload of myocardial cells with consequent increased vulnerability of the myocardium to ventricular tachyarrhythmias (7–11). Ranolazine is an antianginal and anti-ischemic drug (12–14) with possible antiarrhythmic properties related to inhibition of the late sodium current, decrease in intracellular calcium overload, inhibition of the delayed rectifier potassium current with action potential prolongation, and improvements in diastolic relaxation of the ventricles (15–18). The anti-ischemic and antiarrhythmic properties of ranolazine might decrease the likelihood of arrhythmic events and improve the clinical course of patients with ventricular arrhythmias. In the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes) trial, ranolazine did not reduce major cardiac events and did not influence overall mortality but significantly reduced the risk of episodes of VT lasting at least 8 beats on 7-day electrocardiographic monitoring in the first week after admission for acute coronary syndrome (19,20). The RAID (Ranolazine in High-Risk ICD Patients) trial was designed to determine whether ranolazine administration would decrease the likelihood of VT, VF, or death in high-risk patients with an ICD.

ABBREVIATIONS AND ACRONYMS

ATP = antitachycardia pacing

CI = confidence interval

CRT-D = cardiac resynchronization therapy with defibrillator

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

KCCQ = Kansas City Cardiomyopathy Questionnaire

VF = ventricular fibrillation

VT = ventricular tachycardia

METHODS

STUDY DESIGN. This study was designed as a multicenter randomized, double-blind, placebo-controlled trial enrolling high-risk ICD patients on optimal medical therapy to test the hypothesis that late sodium current blockade with ranolazine would lead to a significant reduction in the risk of VT, VF, or death, whichever occurred first. The full study protocol (Online Appendix) was approved by institutional ethics committees at each study site. The University of Rochester Medical Center investigators designed and oversaw the conduct of the trial and data analysis. An independent data and safety monitoring board monitored the trial.

STUDY POPULATION. High-risk patients with ischemic or nonischemic cardiomyopathy who

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received their ICD for primary or secondary prevention of sudden cardiac death were eligible for enrollment. Patients were required to be at least 21 years of age on stable optimal pharmacologic therapy for their underlying cardiac condition. High-risk patients were initially defined as: 1) secondary prevention patients with an existing ICD or cardiac resynchronization therapy with defibrillator (CRT-D) after documented VT, VF, or cardiac arrest regardless of when the implant was received; and 2) primary prevention patients with a left ventricular ejection fraction ≤35% (initial ICD or CRT-D device implant, within 2 years of implant) who have not experienced VT or VF treated with ICD therapy but who had 1 or more of the following additional high-risk criteria: blood urea nitrogen ≥26 mg/dl, QRS duration ≥120 ms, documented evidence of paroxysmal or persistent atrial fibrillation, nonsustained VT, or >500 ventricular premature beats documented with 24-h Holter recording. In light of slower than expected recruitment, inclusion criteria were broadened to also include primary prevention patients with a left ventricular ejection fraction ≤35%, and an ICD or CRT-D device, regardless of when the device was implanted, who after device implantation had experienced at least 1 episode of VT or VF appropriately treated with antitachycardia pacing (ATP) or shock, or had untreated nonsustained VT lasting ≥10 beats with heart rate of ≥170 beats/min. Initially we were planning to enroll newly implanted patients with ICD or CRT-D devices, but subsequently we opened enrollment to patients with pre-existing devices. Detailed exclusion criteria are listed in the study protocol (Online Appendix). It is important to stress that the following Food and Drug Administration–approved prescription information for ranolazine, the following patients were excluded: those with pre-existing QTc prolongation >550 ms; patients on agents known to prolong the QT interval; patients on potent and moderately potent CYP3A inhibitors or inducers including diltiazem, ketoconazole, verapamil, macrolide antibiotics, human immunodeficiency virus protease inhibitors, and grapefruit juice; and patients with chronic renal disease with creatinine >2.5 mg/dl.

STUDY TREATMENT. Patients were randomly assigned 1:1 to ranolazine or placebo. Each patient was started on a 500-mg twice-daily dosage for 1 week with a subsequent dosage increase to 1,000 mg twice daily if the study drug was well tolerated. Drug preparation and dispensing was managed by the Clinical Material Services Unit at the University of Rochester Medical Center, Rochester, New York.

STUDY ENDPOINTS. The primary endpoint of the study was defined as a composite endpoint consisting of the time to VT or VF (requiring ATP therapy or ICD shock), or death, whichever occurred first. The protocol pre-specified the following secondary endpoints: 1) ICD shock for VT or VF or death, whichever came first; 2) recurrent VT or VF requiring ICD therapy; 3) first and recurrent inappropriate shocks; 4) hospitalization for cardiac causes or death, whichever occurred first; 5) heart failure hospitalization or death, whichever occurred first; and 6) repeated cardiovascular hospitalizations. In addition, the 6-min walk test and the Kansas City Cardiomyopathy Questionnaire (KCCQ) were evaluated as secondary endpoints. Sensitivity analyses for individual components of the primary endpoint: VT or VF requiring ATP, VT or VF requiring ICD shock, and death were pre-specified in the protocol.

Patients had follow-up clinic visits scheduled every 6 months and follow-up visits either in person or via telephone every 3 months in between. The follow-up clinic visit included dispensing study medication, acquisition of clinical information regarding cardiac events and changes in medication or device programming, and data on arrhythmias from ICD interrogations. Electronic storage media with interrogation data were forwarded to the Rochester Clinical Core Laboratory for central reading and interpretation. The ICD Interrogation Committee blindly adjudicated all arrhythmic events. The Endpoint Adjudication Committee blindly reviewed and categorized all cardiac hospitalizations and deaths cases with access to data from the ICD interrogations. Hospitalizations for cardiac causes were defined as hospitalizations related to the following conditions: heart failure, VT or VF, unstable angina, myocardial infarction, atrial fibrillation or flutter or tachycardia, hypertension, the ICD itself, pulmonary embolism, or other documented cardiac conditions.

As ICD treatments were expected to be the dominant contributor to the primary endpoint, uniform ICD programming was pursued. In primary prevention ICD patients, a monitoring zone was set at 170 to <190 beats/min without ICD therapy; a VT treatment zone was set at 190 to <220 beats/min with an initial detection duration of 5 s or equivalent in number of beats using 1 ATP therapy and followed by ICD shock if necessary; and a VF treatment zone was set at ≥220 beats/min with ATP turned off and a shock programmed after an initial detection duration of 2.5 s or equivalent in number of beats. In secondary prevention patients and primary prevention with documented VTs <190 beats/min, the VT detection zone was set at 10 to 20 beats/min below the rate of

TABLE 1 Baseline Characteristics of the Patients by Treatment Group

	Treatment Group	
	Placebo (n = 502)	Ranolazine (n = 510)
Demographics		
Age at enrollment, yrs	64.2 ± 9.9	64.3 ± 10.3
Female	86 (17)	100 (20)
Non-Caucasian	90 (18)	94 (19)
Hispanic/Latino	12 (2)	17 (3)
Clinical characteristics		
Ischemic cardiomyopathy	289 (58)	262 (51)
Nonischemic cardiomyopathy	213 (42)	248 (49)
Prior myocardial infarction	231 (48)	202 (41)
NYHA functional class		
I	115 (24)	116 (24)
II	240 (50)	228 (48)
III	120 (25)	131 (28)
IV	4 (1)	1 (0)
Hypertension	390 (78)	390 (77)
Diabetes	165 (33)	167 (33)
Atrial fibrillation	99 (20)	93 (18)
Left ventricular ejection fraction, %	31.0 ± 11.4	31.6 ± 12.0
QRS duration, ms	129 ± 32	133 ± 31
Blood urea nitrogen, mg/dl	21.5 ± 10.1	21.4 ± 10.0
Serum creatinine, mg/dl	1.1 ± 0.4	1.1 ± 0.3
GFR, ml/min/1.73 m^2	76.8 ± 25.1	75.0 ± 23.7
GFR <60 ml/min/1.73 m^2	129 (26)	143 (29)
B-type natriuretic peptide, pg/ml	1,340 ± 2,053	1,227 ± 1,630
Device-related data		
Primary prevention ICD/CRT-D without prior VT/VF	144 (29)	151 (30)
Primary prevention ICD/CRT-D with prior VT/VF	188 (37)	186 (36)
Secondary prevention ICD/CRT-D with VT/VF/cardiac arrest	170 (34)	173 (34)
ICD	292 (58)	290 (57)
CRT-D	210 (42)	220 (43)
ICD programming		
Primary prevention patients without prior VT/VF	n = 168	n = 175
VT zone rate, ms	188.3 ± 5.4	188.9 ± 5.6
VF zone rate, ms	220.9 ± 5.7	220.5 ± 8.1
VT zone delay, beats	20.8 ± 5.0	19.8 ± 5.2
VF zone delay, beats	14.9 ± 5.2	14.0 ± 5.5
Secondary or primary with prior VT/VF	n = 334	n = 335
VT zone rate, ms	177.9 ± 18.2	177.9 ± 19.2
VF zone rate, ms	219.4 ± 10.1	219.8 ± 9.0
VT zone delay, beats	15.1 ± 7.5	14.8 ± 7.4
VF zone delay, beats	14.8 ± 5.6	14.6 ± 6.0
Medications		
Beta-blocker	466 (93)	471 (93)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	437 (87)	426 (84)
Statin	384 (76)	356 (70)
Digitalis	89 (18)	81 (16)
Diuretic	362 (72)	376 (74)
Mineralocorticoid antagonist	189 (38)	180 (35)
Antiarrhythmic medication	82 (16)	86 (17)
Amiodarone	52 (10)	50 (10)

Continued in the next column

TABLE 1 Continued

Values are mean ± SD or n (%). There were no significant differences between the 2 groups except for less ischemic cardiomyopathy (p = 0.048) and less prior myocardial infarction (p = 0.021), longer QRS duration (p = 0.022), and lower use of statins (p = 0.021) in the ranolazine arm compared with the placebo arm.

CRT-D = cardiac resynchronization therapy with defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

the clinical VT, with 1 ATP followed by ICD shock if needed. Antibradycardia programming followed best practices to minimize ventricular pacing in patients without CRT devices.

SAMPLE SIZE. We estimated the 2-year cumulative endpoint rate to be 25% in the placebo arm of the trial and we hypothesized at least a 25% reduction in risk of primary endpoint. After allowing for the possibility of 10% cumulative crossover to placebo, assuming a 2-year cumulative rate of the primary endpoint of 19% in the ranolazine arm (hazard ratio [HR]: 0.75), the trial was designed to have 80% power with a 2-sided significance level of 5% to detect an HR of 0.75 with estimated 720 patients to be enrolled per arm. A sequential stopping rule with truncated triangular stopping boundaries was used to guide continuation of the clinical trial (21).

STATISTICAL ANALYSES. Analyses were conducted according to the intention to treat (statistical analysis plan in the Online Appendix). The treatment effect in the primary analysis was determined using a Cox proportional hazards regression model for time to VT or VF or death, stratified by enrolling center with 6 baseline covariates: age, ejection fraction, creatinine level (all 3 numerical), ischemic status (binary), antiarrhythmic medication at enrollment (binary), and a 3-level variable identifying the following groups: ICD and no history of VT, VF, or cardiac arrest at enrollment; CRT-D and no history of VT or VF or cardiac arrest at enrollment; and a history of VT or VF or cardiac arrest, whether before implantation of device or afterward. A p value for the primary hypothesis, an estimate of the true HR for treatment effect, and 95% confidence interval [CI] for the true HR were determined after adjusting for the sequential stopping rule (21,22) to preserve the overall type I error rate at 5%. The proportional hazards assumption was validated by computing hazard ratios by both 3- and 6-month intervals, with tests for differences among the time-

TABLE 2 Reported Reasons for Stopping Study Drug

	Placebo (n = 199)	Ranolazine (n = 253)	p Value
Unknown reason*	155 (79.1)	158 (64.2)	0.001
Dizziness	8 (4.0)	30 (11.9)	0.003
Constipation	12 (6.0)	37 (14.6)	0.004
Fatigue	7 (3.5)	11 (4.3)	0.654
Blurred vision	1 (0.5)	3 (1.2)	0.634
Elevated LFT	2 (1.0)	4 (1.6)	0.134
Other	15 (7.5)	16 (6.3)	0.699

Values are n (%). *Unknown reasons included unwillingness of patients to continue taking the study drug.
LFT = liver enzyme test.

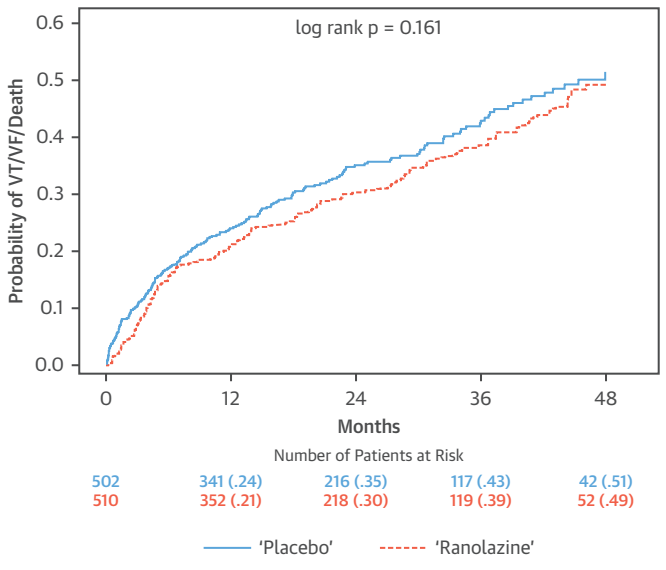
specific HRs (section 3.2 of the Statistical Analysis Plan provided in Online Appendix).

Multivariable imputation by chained equations (23,24) was used to impute missing covariate data needed for the primary analysis: creatinine was missing in 20 (2.0%) patients, ejection fraction was missing in 10 (1.0%) patients, and baseline antiarrhythmic medication use was missing in 2 (0.2%) patients. Predictive mean matching was used to impute ejection fraction and creatinine, while a logistic regression model was used to impute antiarrhythmic medication use.

The primary analysis was repeated (without adjustment for the stopping rule), adding each of a pre-specified list of covariates (if not already in the regression model), 1 at a time, and their interaction with treatment arm to the regression model, and tests for interaction carried out. This identified, to the extent feasible, different treatment effects of ranolazine across subgroups identified by the covariates.

Times to first secondary endpoint event were analyzed as described for the primary outcome, except that no adjustments were made for multiple testing. The study was not sufficiently powered to evaluate individual components of the primary endpoint. As indicated in the pre-specified statistical analysis plan, the study planned to have 80% to identify an HR of 0.72 for ranolazine versus placebo in reducing secondary endpoint of VT or VF requiring ICD shock, or death. Recurrent event analyses that were pre-specified in the statistical analysis plan conducted using Andersen-Gill models (25) when ignoring death as a competing risk and Fine and Gray models (26) when death is treated as a competing risk. The study had >80% power to detect an HR of 0.75 for recurrent VT or VF requiring ICD therapy.

FIGURE 1 Kaplan-Meier Curves for Primary Endpoint: VT or VF or Death by Treatment Arm in the Intention-to-Treat Analysis



There was no significant difference in the probability of the primary endpoint of the trial.
VF = ventricular fibrillation; VT = ventricular tachycardia.

RESULTS

STUDY CONDUCT. Enrollment started on August 2011 and was stopped in December 30, 2015. Although the actual enrollment rate was lower than projected the event rate was significantly higher (attributed to inclusion of primary prevention ICD patients who experienced VT or VF after device implantation) than had been estimated in pre-study calculations. The study was terminated by the National Institutes of Health for budgetary reasons before a pre-specified stopping boundary being reached. A total of 1,012 patients were recruited from 88 U.S. centers and 7 centers in Canada: 502 were randomized to placebo and 510 to ranolazine. The follow-up of patients continued until January 31, 2017.

BASELINE CHARACTERISTICS OF STUDY POPULATION. The mean age at enrollment was 64 years, 18% were women, 54% had ischemic cardiomyopathy, 75% had the New York Heart Association functional class I or II symptoms, 42% had implanted CRT-D devices, and 34% were implanted for secondary prevention of sudden cardiac death (Table 1). In primary prevention patients without documented VT or VF baseline ICD programming exhibited a mean VT detection zone rate at 189 beats/min and VF zone at 221 beats/min with a mean 20-beat delay in the VT zone and a 14-beat delay in the VF zone. In secondary prevention patients or in primary prevention patients who experienced VT or VF after device implantation, the mean VT detection zone was 178 beats/min and

VF detection zone was 220 beats/min with a mean 15-beat delay in both VT and VF zones.

STUDY DRUG ADMINISTRATION AND FOLLOW-UP. Mean follow-up duration was 28.3 ± 15.8 (median 27.4) months. The study drug was administered in the full dose of 1,000 mg twice a day in 872 (86%) patients. The blinded study drug was discontinued in 199 (39.6%) patients receiving placebo and in 253 (49.6%) patients receiving ranolazine (p = 0.001). Discontinuation was the highest in the first few weeks of ranolazine administration, resulting in 20.5% patients stopping active medication at 3 months versus 9.3% patients stopping placebo at 3-month follow-up. The subsequent rate of attrition of compliance was similar in both groups. Online Figure 1 shows cumulative probability of the study drug discontinuation and Online Table 1 shows rates of discontinuation at specific time points. Key known reasons for stopping drug are provided in **Table 2**.

There were 149 withdrawals from the study: 86 (9%) on ranolazine and 63 (6%) on placebo (Online Figure 2 shows cumulative probability of withdrawals by the study arm). Among 86 patients who were withdrawn in the ranolazine arm, in 57 (66%) they were due to the patient's decision and in 9 (10%) they were due to the physician's decision (76% together). Among 64 patients who were withdrawn in the placebo arm, 35 (56%) were due to the patient's decision and 12 (19%) were due to the physician's decision (75% together). There were 4 subjects in the placebo arm and 6 in the ranolazine arm who were lost to follow-up.

STUDY ENDPOINTS IN PRE-SPECIFIED ANALYSES. **Figure 1** shows the Kaplan-Meier plots for the primary study endpoint of VT or VF or death by treatment assignment. In the pre-specified intention-to-treat analysis, the primary endpoint of VT or VF requiring ICD therapy (ATP or shock), or death, occurred in 174 patients (34.1%) in the ranolazine arm and in 198 (39.4%) in the placebo arm (HR: 0.84; 95% CI: 0.67 to 1.05; p = 0.117).

As shown in **Table 3**, the pre-specified secondary ventricular tachyarrhythmia endpoint of VT or VF requiring ICD shock or death was not different between treatment arms, whereas recurrent VT or VF requiring ATP or ICD shock were significantly less frequent in the ranolazine arm than in the placebo arm, with an HR of 0.70 (95% CI: 0.51 to 0.96; p = 0.028).

Among other pre-specified secondary analyses, inappropriate ICD therapies were infrequent (5.9%), and the risk of first and of recurrent inappropriate therapy was not significantly different between treatment arms. There was no significant difference between treatment arms in cardiovascular or heart failure hospitalization endpoints (**Table 3**).

TABLE 3 Primary, Secondary, and Sensitivity Analyses of Pre-Specified Endpoints by Treatment Group in the Intention-to-Treat Analyses

	Placebo (n = 502)	Ranolazine (n = 510)	HR for Ranolazine vs. Placebo (95% CI)	p Value
Primary endpoint				
VT/VF requiring ICD therapy or death*	198 (39.4)	174 (34.1)	0.84 (0.67–1.05)	0.117
Pre-specified secondary endpoints				
Arrhythmic endpoints				
VT/VF requiring ICD shock or death	145 (28.9)	131 (25.7)	0.98 (0.76–1.26)	0.891
Recurrent VT/VF requiring ATP or ICD shock†	650 (986)	433 (741)	0.70 (0.51–0.96)	0.028
Inappropriate ICD shock	20 (4.0)	16 (3.1)	0.75 (0.38–1.47)	0.398
Recurrent inappropriate shocks†	26 (29)	19 (20)	0.74 (0.36–1.52)	0.414
Hospitalization endpoints				
Cardiovascular hospitalization or death	222 (44.2)	237 (46.5)	1.10 (0.91–1.34)	0.316
Heart failure hospitalization or death	140 (27.9)	144 (28.2)	1.07 (0.84–1.37)	0.577
Recurrent cardiovascular hospitalizations†	436	412	1.05 (0.86–1.28)	0.621
Pre-specified sensitivity analysis endpoints				
Death	78 (15.5)	70 (13.7)	0.97 (0.69–1.38)	0.871
VT/VF requiring ICD shock	84 (16.7)	79 (15.5)	1.01 (0.73–1.41)	0.947
VT/VF requiring ICD therapy	144 (28.7)	126 (24.7)	0.81 (0.62–1.04)	0.100
VT requiring ATP	117 (23.3)	92 (18.0)	0.73 (0.55–0.98)	0.038

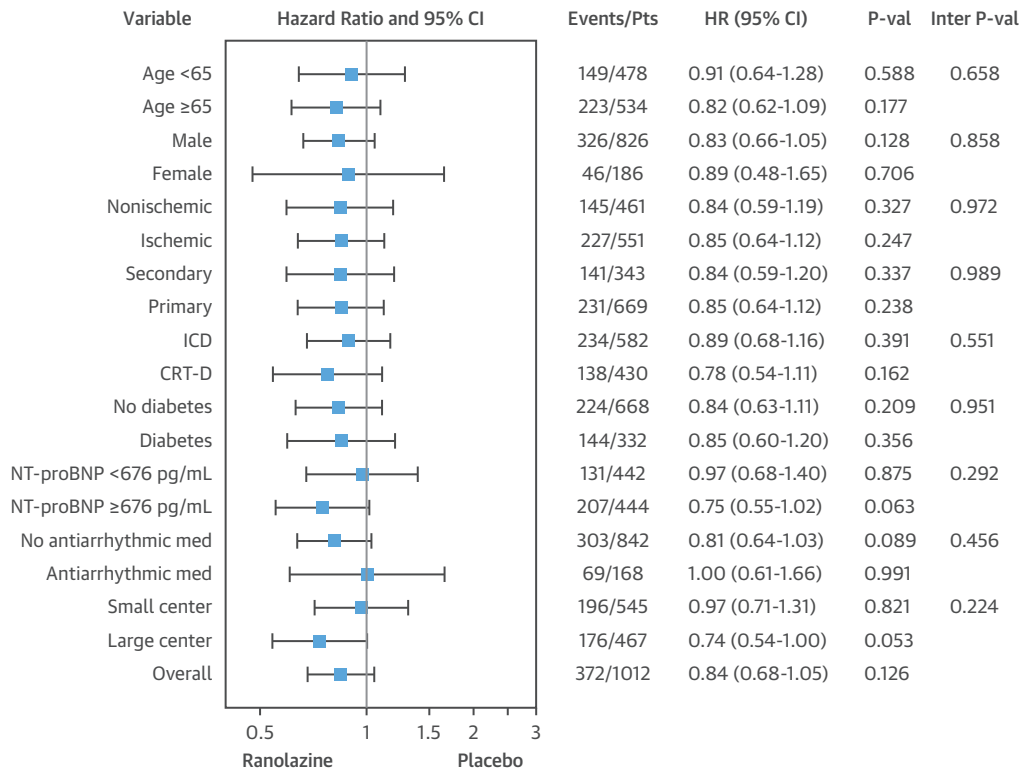
Values are n (%) or n unless otherwise indicated. For first events, values are absolute numbers with percentage in parentheses. For recurrent events, the first number reflects the number of events with censoring events to a maximum 1 per day and the number in parentheses provides all events including multiple per day. Hazard ratios are computed based on events censored to 1 per day. All analyses adjusted for age, ischemic cardiomyopathy, ejection fraction, ICD type, VT/VF history, creatinine levels, and antiarrhythmic medications (multiple imputation by chained equations used to impute missing data), and stratified by enrolling center. *Adjusted for sequential stopping rule. †Andersen-Gill analyses are based on recurrent events censored to 1 per day.

ATP = antitachycardia pacing; other abbreviations as in **Table 1**.

There were significant differences in clinical characteristics between patients who stopped versus those who did not stop study medication (Online Table 2). Patients who stopped the study drug were older and sicker as indicated by higher New York Heart Association functional class, more frequent atrial fibrillation, lower ejection fraction, and higher blood urea nitrogen, creatinine, and brain natriuretic peptide levels. However, when analyzing the impact of these variables on the primary endpoint and an interaction with the tested treatment (ranolazine vs. placebo) (Online Table 3), none of these variables significantly affected HRs of ranolazine versus placebo.

We also evaluated the effects of ranolazine on exercise capacity measured by the 6-min walk test and in the quality of life measured by the KCCQ. None of the comparisons between ranolazine and placebo arm in the 6-MWT and KCCQ measures were significantly different at the 12-month follow-up versus baseline or the 24-month follow-up versus baseline (Online Table 4).

FIGURE 2 Primary Endpoint of VT or VF or Death by Treatment Arm in Prespecified Subgroups Analyses Subgroups in the Intention-to-Treat Analysis



Hazard ratios (HRs) adjusted for age, ejection fraction, creatinine level, ischemic cardiomyopathy, prior VT/VF, device type, and antiarrhythmic therapy, and stratified by enrolling center. The HR and 95% confidence interval (CI) represent the risk of primary endpoint in the ranolazine versus placebo arms of the study, with corresponding p values (P-val) for each pre-specified subgroup, not adjusted for sequential stopping rule. Interaction p values (Inter P-val) were not significant for any of the comparisons. CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

SENSITIVITY ANALYSES. Pre-specified sensitivity analyses investigated components of the primary endpoint: death was observed in 70 (13.7%) patients in the ranolazine arm versus 78 (15.5%) patients in the placebo arm (HR: 0.97; 95% CI: 0.69 to 1.38; p = 0.871). VT or VF requiring ICD shock was similar in both arms (HR: 1.01; 95% CI: 0.73 to 1.41; p = 0.947). VT or VF requiring ICD therapy (ATP or shock) had an HR of 0.81 (95% CI: 0.62 to 1.04; p = 0.100) and VT requiring ATP only was observed in 92 (18.0%) patients in the ranolazine arm and in 117 (23.3%) patients in the placebo arm (HR: 0.73; 95% CI: 0.55 to 0.98; p = 0.038).

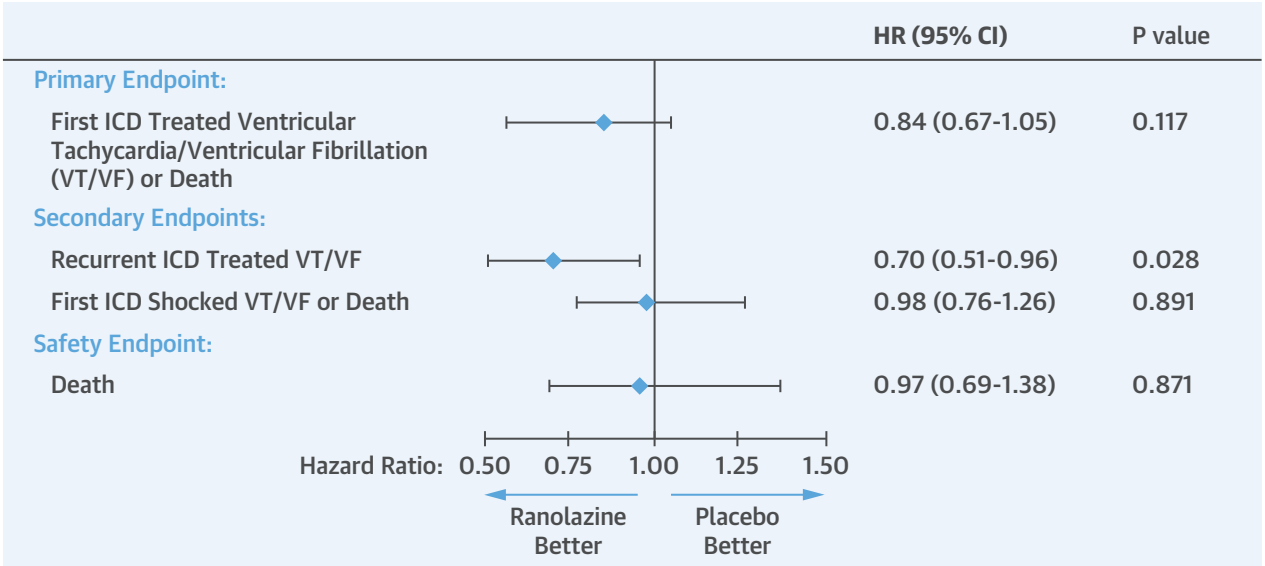
Figure 2 shows HRs for the primary endpoint in the pre-specified subgroups of interest: age, sex, ischemic versus nonischemic cardiomyopathy, primary or secondary ICD indications, device type (ICD vs. CRT-D), diabetes, antiarrhythmic medication at baseline, and large centers versus small centers

TABLE 4 Side Effects of Study Drugs

	Placebo (n = 502)	Ranolazine (n = 510)	p Value
Dizziness	11 (2)	39 (8)	<0.001
Nausea	6 (1)	30 (6)	<0.001
Constipation	3 (1)	18 (4)	0.001
Vomiting	2 (0)	9 (2)	0.036
Palpitations	2 (0)	0 (0)	0.246
Abdominal pain	2 (0)	0 (0)	0.246
Dry mouth	0 (0)	3 (1)	0.249
Headaches	8 (2)	12 (2)	0.386
Cough	2 (0)	1 (0)	0.622
Fatigue	8 (2)	11 (2)	0.509
Indigestion	1 (0)	3 (1)	0.624
Chest pain	1 (0)	1 (0)	1.000
Shortness of breath	3 (1)	4 (1)	1.000
Swelling of ankles	0 (0)	1 (0)	1.000

Values are n (%).

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.

(enrolling at least 20 patients). None of the interaction terms was significant.

SAFETY AND SIDE EFFECTS OF RANOLAZINE. An important secondary aim was to evaluate the safety of ranolazine in high-risk patients, the majority of whom were also heart failure patients. As indicated previously, there was no evidence for an increased mortality or increased risk of VT or VF requiring ICD shocks. There were only 48 patients who had at least 1 ICD-treated polymorphic VT episode. The Cox regression analysis resulted in the HR of 0.81 (95% CI: 0.46 to 1.43; p = 0.471) for polymorphic VT when comparing patients assigned to the ranolazine arm versus the placebo arm. Therefore, there was no evidence for a proarrhythmic response to ranolazine in comparison with placebo.

The heart rates of first VT treated by ATP were similar in ranolazine versus placebo arms (189 ± 31 beats/min vs. 187 ± 31 beats/min; p = NS), as were the heart rates of first VT or VF requiring shocks (240 ± 58 beats/min vs. 236 ± 58 beats/min; p = NS).

Patients in the ranolazine arm had significantly (p < 0.05) more frequent side effects than did patients in the placebo arm: dizziness, nausea, constipation, and vomiting (2.0% vs. 0.4%). Table 4 shows detailed listing of side effects in both arms of the study.

DISCUSSION

In high-risk ICD patients, treatment with ranolazine did not significantly reduce the incidence of the primary composite outcome of VT or VF or death. There was no significant difference in the risk of VT or VF requiring ICD shocks or death between treatment arms. However, ranolazine administration was associated with a marginally significant 30% reduction in pre-specified secondary endpoint of recurrent VT or VF requiring an ICD therapy (Central Illustration). It is worth emphasizing that a significant reduction in the occurrence of recurrent VT or VF requiring ICD therapy on ranolazine versus placebo was observed without significant difference in mortality between arms (HR for ranolazine vs. placebo: 0.97), and without evidence for proarrhythmia (the HR for VT or VF requiring ICD shocks was 0.97 and for polymorphic VT the HR was 0.81 when comparing patients assigned to the ranolazine arm vs. the placebo arm). There were no other significant reductions in any of the other pre-specified secondary endpoint.

The absence of any difference in mortality between high-risk ICD patients treated with ranolazine versus placebo is consistent with the results of the MERLIN and RIVER-PCI (Ranolazine in Patients with Incomplete Revascularization after Percutaneous Coronary Intervention) trials (19,27). We showed that there was no significant difference in the risk of first VT or VF requiring ICD shocks (HR: 1.01) or in the risk of recurrent VT or VF requiring ICD shocks (HR: 0.97). These observations indicate that the risk of fast ventricular tachyarrhythmias appears not to be influenced by ranolazine, and is in contrast to some preclinical studies suggesting that late sodium current inhibition with ranolazine reduces the susceptibility to VF (28–30).

The significant reduction in the risk of pre-specified secondary endpoint of recurrent VT or VF requiring ICD therapy attributed to reduction of recurrent VT requiring ATP therapy and reduction in the first VT requiring ATP therapy in pre-specified sensitivity analyses in the ranolazine arm is consistent with preclinical observations showing that ranolazine inhibits early and delayed afterdepolarizations; reduces transmural dispersion of repolarization; inhibits spatially discordant repolarization alternans; prevents pacing-induced re-entry; and reduces the incidence, frequency, and duration of VT (6–11,16–18). The late sodium current seems to be less prominent at high heart rates, and therefore VT or VF at high heart rates may not be driven by late sodium current (31).

STUDY LIMITATIONS. Nonadherence to the study drug (both ranolazine and placebo) is a significant limitation of the trial. In the 10-year old MERLIN trial (19), which investigated ranolazine in less sick post-infarction patients, the discontinuation of treatment occurred in 28% of patients in the ranolazine group and 22% in the placebo group during a median 1-year follow-up; these rates are similar to those observed in our study at the 1-year time point. In the more recent RIVER-PCI trial (27), 2,604 coronary artery disease patients were observed over a median 21-month follow-up, 40% of patients on ranolazine and 36% on placebo discontinued the study drug, with 12-month rates of 28% and 23%, respectively. Our trial did not have sufficient funds to pursue typical on-site monitoring and our efforts to maintain adherence were not as successful. Poor adherence to the study drug provides an important and concerning lesson from the RAID trial that requires further research (32–34).

Limitations of this prospective randomized trial include slower than expected enrollment that led to lower than the planned number of enrolled patients, making this study statistically underpowered despite the fact that event rate was significantly higher than initially proposed. Furthermore, high drug discontinuation rate (almost 40% in placebo arm and almost 50% in ranolazine arm over a mean 28 months of follow-up) further lowered statistical power of the study. Despite this limited statistical power, compensated to some degree by higher than expected event rates, we observed significant reduction in the incidence of VT or VF requiring ICD therapy, namely VT episodes. However, these findings need to be interpreted with caution and full realization that the study missed the primary endpoint of VT or VF or death (HR: 0.84).

CONCLUSIONS

Treatment with ranolazine in high-risk ICD patients did not significantly reduce the incidence of the primary composite outcome of VT, VF, or death. However, the study was underpowered to detect a difference in the primary endpoint. In pre-specified secondary endpoint analyses, ranolazine administration was associated with a significant reduction in recurrent VT or VF requiring ICD therapy without evidence for increased mortality.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In high-risk patients with heart failure and implanted defibrillators, ranolazine failed to reduce the primary endpoint of VT, VF, or death. In secondary analyses, however, ranolazine reduced recurrent VT or VF requiring ICD therapy, mainly through reduction in episodes of VT without increasing proarrhythmia or associated mortality.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare the efficacy and safety of chronic ranolazine versus amiodarone therapy in high-risk patients with heart failure.

REFERENCES

1. Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004;110:3760–5.

2. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.

3. Kowey PR, Crijns HJ, Aliot EM, et al. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: the ALPHEE study. Circulation 2011;124:2649–60.

4. Bollmann A, Husser D, Cannom DS. Antiarrhythmic drugs in patients with implantable cardioverter-defibrillators. Am J Cardiovasc Drugs 2005;5:371–8.

5. Thireau J, Pasquié JL, Martel E, Le Guennec JY, Richard S. New drugs vs. old concepts: a fresh look at antiarrhythmics. Pharmacol Ther 2011;132:125–45.

6. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. N Engl J Med 1999;340:1855–62.

7. Makielski JC, Farley AL. Na+ current in human ventricle: implications for sodium loading and homeostasis. J Cardiovasc Electrophysiol 2006;17 Suppl 1:S15–20.

8. Noble D, Noble PJ. Late sodium current in the pathophysiology of cardiovascular disease: consequences of sodium-calcium overload. Heart 2006;92 Suppl 4:iv1–5.

9. Makielski JC. Late sodium current: A mechanism for angina, heart failure, and arrhythmia. Trends Cardiovasc Med 2016;26:115–22.

10. Zaza A, Belardinelli L, Shryock JC. Pathophysiology and pharmacology of the cardiac "late sodium current". Pharmacol Ther 2008;119:326–39.

11. Wagner S, Maier LS, Bers DM. Role of sodium and calcium dysregulation in tachyarrhythmias in sudden cardiac death. Circ Res 2015;116:1956–70.

12. Stone PH, Chaitman BR, Stocke K, Sano J, DeVault A, Koch GG. The anti-ischemic mechanism of action of ranolazine in stable ischemic heart disease. J Am Coll Cardiol 2010;56:934–42.

13. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375–82.

14. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation 2006;113:2462–72.

15. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.

16. Song Y, Shryock JC, Wu L, Belardinelli L. Antagonism by ranolazine of the pro-arrhythmic effects of increasing late INa in guinea pig ventricular myocytes. J Cardiovasc Pharmacol 2004;44:192–9.

17. Antzelevitch C, Burashnikov A, Sicouri S, Belardinelli L. Electrophysiologic basis for the antiarrhythmic actions of ranolazine. Heart Rhythm 2011;8:1281–90.

18. Dhalla AK, Wang WQ, Dow J, et al. Ranolazine, an antianginal agent, markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion. Am J Physiol Heart Circ Physiol 2009;297:H1923–9.

19. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775–83.

20. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. Circulation 2007;116:1647–52.

21. Whitehead J. The Design and Analysis of Sequential Clinical Trials. Revised 2nd edition. New York, NY: Wiley, 1997.

22. Hall WJ. The distribution of Brownian motion on linear stopping boundaries. Seq Anal 1997;16:345–52; addendum 1998;17:123–4.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–99.

24. van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. J Stat Soft 2011;45:1–67.

25. Andersen PK, Gill RD. Cox's regression model counting process: a large sample study. Ann Stat 1982;10:1100–20.

26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

27. Weisz G, Généreux P, Iñiguez A, et al. Ranolazine in patients with incomplete revascularization after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:136–45.

28. Frommeyer G, Rajamani S, Grundmann F, et al. New insights into the beneficial electrophysiologic profile of ranolazine in heart failure: prevention of ventricular fibrillation with increased post-repolarization refractoriness and without drug-induced proarrhythmia. J Card Fail 2012;18:939–49.

29. Verrier RL, Kumar K, Nieminen T, Belardinelli L. Mechanisms of ranolazine's dual protection against atrial and ventricular fibrillation. Europace 2013;15:317–24.

30. Azam MA, Zamiri N, Massé S, et al. Effects of late sodium current blockade on ventricular refibrillation in a rabbit model. Circ Arrhythm Electrophysiol 2017;10:e004331.

31. Li W, Yu Y, Hou JW, et al. Larger rate dependence of late sodium current in cardiac Purkinje cells: a potential link to arrhythmogenesis. Heart Rhythm 2017;14:422–31.

32. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc 2011;86:304–14.

33. Glader EL, Sjölander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years afterstroke. Stroke 2010;41:397–401.

34. Breckenridge PA, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov 2017;16:149–50.

KEY WORDS implantable cardioverter-defibrillator, ranolazine, ventricular fibrillation, ventricular tachycardia

APPENDIX For expanded Methods sections, supplemental figures and tables, and a list of RAID Trial Investigators, please see the online version of this paper.