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Rates of Sudden Death After Myocardial Infarction—Insights From the VALIANT and PARADISE-MI Trials

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IMPORTANCE Sudden death is a leading cause of death after acute myocardial infarction (AMI). The Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) and Valsartan in Acute Myocardial Infarction (VALIANT) trials enrolled patients with pulmonary congestion and/or left ventricular dysfunction after AMI. Whether the prognosis in such patients has changed over time has not been examined.

OBJECTIVE To compare the rate of sudden death/resuscitated cardiac arrest (RCA) after AMI in the PARADISE-MI and VALIANT trials.

DESIGN, SETTING, AND PARTICIPANTS This was a secondary analysis of multicenter randomized clinical trials enrolling patients after AMI. In the primary analysis, the VALIANT cohort was restricted to patients with "PARADISE-MI–like" characteristics (eg, at least 1 augmenting risk factor and no history of heart failure). The baseline characteristics of people in both trials were compared. The VALIANT trial enrolled from December 1998 to June 2001, and the PARADISE-MI trial enrolled between December 2016, and March 2020. The median follow-up in the VALIANT and PARADISE-MI trials was 24.7 and 22 months, respectively. People with AMI, complicated by pulmonary congestion and/or left ventricular dysfunction, were included in the analysis.

EXPOSURE Sudden death after AMI.

RESULTS A total of 5661 patients were included in the PARADISE-MI cohort (mean [SD] age, 63.7 [11.5] years; 4298 male [75.9%]), 9617 were included in the VALIANT (PARADISE-MI–like) cohort (mean [SD] age, 66.1 [11.5] years; 6504 male [67.6%]), and 14 703 patients were included in the VALIANT (total) cohort (mean [SD] age, 64.8 [11.8] years; 10 133 male [68.9%]). In the PARADISE-MI–like cohort of the VALIANT trial, 707 of 9617 participants (7.4%) experienced sudden death/RCA. A total of 148 of 5661 people (2.6%) in the PARADISE-MI trial experienced sudden death/RCA. Sudden death rates were highest in the first month after infarction in both trials: 19.3 (95% CI, 16.4-22.6) per 100 person-years in the VALIANT trial and 9.5 (95% CI, 7.0-12.7) per 100 person-years in the PARADISE-MI trial, and these rates declined steadily thereafter. Compared with the VALIANT cohort, people in the PARADISE-MI trial were more often treated with percutaneous coronary intervention for their qualifying AMI and received a β-blocker, statin, and mineralocorticoid receptor antagonist more frequently.

CONCLUSIONS AND RELEVANCE After AMI, the risk of sudden death/RCA was highest in the first month, declining rapidly thereafter. Results revealed that compared with counterparts from 20 years ago, the rate of sudden death/RCA in patients with a reduced left ventricular ejection fraction and/or pulmonary congestion was 2- to 3-fold lower in people receiving contemporary management. Interventions to further protect people in the highest risk first month after infarction are needed.

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Editor's Note

Supplemental content

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Historically, the first month after an acute myocardial infarction (AMI) was a period of particular risk for sudden death. Effective networks of care now rapidly diagnose AMI and early revascularization has improved survival,[1,2] although whether sudden death rates after infarction have decreased in number has not, to our knowledge, been described. The primary objective of this study was to examine whether sudden death rates after AMI complicated by pulmonary congestion and/or left ventricular dysfunction have changed over time. We compared sudden death/resuscitated cardiac arrest (RCA) rates in the Valsartan in Acute Myocardial Infarction (VALIANT) trial and the Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) trial.[3,4] We also compared the characteristics of people in both trials.

Key Points

Question Has the sudden death rate after myocardial infarction and the characteristics of people dying suddenly changed over time?

Findings In this secondary analysis of the VALIANT (Valsartan in Acute Myocardial Infarction) and PARADISE-MI (Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) trials including 30 364 participants, PARADISE-MI results revealed that contemporarily managed patients had higher rates of revascularization, β-blockers, and mineralocorticoid receptor antagonists than people in the VALIANT trial. In the PARADISE-MI study, the rate of sudden death was highest up to 1 month after myocardial infarction but was 2- to 3-fold lower than in the VALIANT trial.

Meaning Results suggest that contemporary treatments have substantially reduced the rate of sudden death, yet the first month after infarction remains a particularly high-risk period.

Methods

The PARADISE-MI trial was a controlled, double-blind, randomized clinical trial comparing treatment with sacubitril/valsartan against ramipril after AMI. The trial enrolled participants between December 2016, and March 2020. Participants were 18 years and older; had an LVEF of 40% or less; clinical or radiographic evidence of pulmonary congestion, or both; and 1 or more of the following risk-augmenting factors: age of 70 years or older, estimated glomerular filtration rate (eGFR) less than 60, diabetes, a prior MI, atrial fibrillation (AF), or LVEF less than 30% after the index AMI, Killip class III/IV, or ST-segment-elevation MI without reperfusion within 24 hours.

The VALIANT trial was a controlled, double-blind, randomized clinical trial examining valsartan, captopril, or both after AMI. Patients had a left ventricular ejection fraction of 40% or less, clinical or radiologic evidence of pulmonary congestion, or both, ie, similar to the PARADISE-MI cohort without the additional risk-augmenting factors. The VALIANT trial enrolled participants from December 1998 to June 2001.

In both the VALIANT and PARADISE-MI trials, participants self-identified with the following races and ethnicities: Asian, Black, Native American, Pacific Islander, White, and unknown. Both trials were approved by local ethics committees, and participants provided written informed consent. The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Definition of Sudden Death and RCA

Deaths and RCA events were adjudicated in both trials by a blinded end point committee. In the VALIANT trial, sudden death was defined as an unexpected death in a stable patient. RCA was defined as a cardiac arrest where the patient regained consciousness and cognitive function. In the PARADISE-MI trial, sudden death was defined as a death in an otherwise stable patient. RCA was defined as sudden, unexpected cardiovascular collapse or arrest followed by resuscitation and a meaningful recovery.

Statistical Analysis

Baseline characteristics in both trials were compared using *t* tests and χ^2 tests as appropriate. Event rates per 100 person-years were calculated. The risk of sudden death/RCA accounting for the competing risk of other causes of mortality was analyzed using the cumulative incidence function. The primary analysis was restricted to a PARADISE-MI–like cohort in VALIANT (eg, had similar augmenting risk factors and no prior heart failure [HF]). Analyses were performed using Stata, version 16 (StataCorp). Two-sided *P* values <.05 were considered statistically significant. No adjustments were made for multiple comparisons.

Results

Baseline Characteristics

A total of 5661 patients were included in the PARADISE-MI cohort (mean [SD] age, 63.7 [11.5] years; 1363 female [24.1%]; 4298 male [75.9%]), 9617 were included in the VALIANT (PARADISE-MI–like) cohort (mean [SD] age, 66.1 [11.5] years; 3113 female [32.4%]; 6504 male [67.6%]), and 14 703 patients were included in the VALIANT (total) cohort (mean [SD] age, 64.8 [11.8] years; 4570 female [31.1%]; 10 133 male [68.9%]). Participants self-identified with the following races and ethnicities in each study cohort: PARADISE-MI, 953 Asian (16.8%), 75 Black (1.3%), 4263 White (75.3%), and 370 other (6.5%); VALIANT (PARADISE-MI–like), 83 Asian (0.9%), 255 Black (2.7%), and 9022 White (93.8%), and 257 other (2.7%); and VALIANT (total), 141 Asian (1.0%), 407 Black (2.8%), and 13 748 White (93.5%), and 407 other (2.8%).

Compared with PARADISE-MI–like counterparts in the VALIANT trial, people in the PARADISE-MI cohort had lower systolic blood pressure (mean [SD] systolic, 120.9 [13.3] mm Hg vs 122.6 [16.9] mm Hg), higher body mass index (mean [SD], 28.1 [5.0] vs 27.8 [5.4]; calculated as weight in kilograms divided by height in meters squared), higher eGFR level (mean [SD], 71.8 [22.4] vs 68.8 [20.9]), and higher proportions in Killip class I/III (I, 2281 [41.6%] vs 2207 [23.0%]; III, 1141 [20.8%]

Table 1. Baseline Characteristics Comparing Patients in the PARADISE-MI Trial, VALIANT Trial With PARADISE-MI–like Characteristics,[a] and the Total VALIANT Cohort

Characteristic	PARADISE-MI (n = 5661)	VALIANT (PARADISE-MI–like) (n = 9617)	*P* value	VALIANT (total cohort) (n = 14 703)	*P* value
Age, mean (SD), y	63.7 (11.5)	66.1 (11.5)	<.001	64.8 (11.8)	<.001
Sex, No. (%)					
Female	1363 (24.1)	3113 (32.4)	<.001	4570 (31.1)	<.001
Male	4298 (75.9)	6504 (67.6)		10 133 (68.9)	
Race, No. (%)					
Asian	953 (16.8)	83 (0.9)	<.001	141 (1.0)	<.001
Black	75 (1.3)	255 (2.7)		407 (2.8)	
White	4263 (75.3)	9022 (96.4)		13 748 (96.2)	
Other	370 (6.5)	0		0	
Heart rate, mean (SD) bpm	75.7 (11.8)	76.7 (13.0)	<.001	76.2 (12.8)	.006
Systolic blood pressure, mean (SD), mm Hg	120.9 (13.3)	122.6 (16.9)	<.001	122.7 (17.0)	<.001
BMI, mean (SD)[b]	28.1 (5.0)	27.8 (5.4)	<.001	27.9 (5.3)	.005
eGFR, mean (SD)	71.8 (22.4)	68.8 (20.9)	<.001	70.2 (21.3)	<.001
Killip class (%)					
Class I	2281 (41.6)	2207 (23.0)	<.001	4099 (28.0)	<.001
Class II	1764 (32.2)	4716 (49.1)		7076 (48.3)	
Class III	1141 (20.8)	1924 (20.0)		2529 (17.3)	
Class IV	296 (5.4)	757 (7.9)		931 (6.4)	
LVEF, mean (SD), %	36.5 (9.4)	34.6 (10.1)	<.001	35.3 (10.4)	<.001
History of MI, No. (%)	920 (16.3)	2571 (26.7)	<.001	4104 (27.9)	<.001
History of stroke, No. (%)	263 (4.6)	588 (6.1)	<.001	895 (6.1)	<.001
Hypertension, No. (%)	3676 (64.9)	5409 (56.2)	<.001	8100 (55.1)	<.001
Diabetes, No. (%)	2401 (42.4)	2513 (26.1)	<.001	3400 (23.1)	<.001
Current smoking, No. (%)	1196 (21.1)	2838 (29.5)	<.001	4664 (31.7)	<.001
Atrial fibrillation, No. (%)	726 (12.8)	504 (5.2)	<.001	960 (6.6)	<.001
Prior PCI, No. (%)	827 (14.6)	680 (7.1)	<.001	1067 (7.3)	<.001
Prior CABG, No. (%)	205 (3.6)	592 (6.2)	<.001	1026 (7.0)	<.001
No. of days from index MI to randomization, mean (SD)	4.3 (1.8)	5.2 (2.6)	<.001	5.1 (2.6)	<.001
Location of qualifying AMI, No. (%)[c]					
Anterior	3853 (68.1)	5572 (57.9)	<.001	8392 (57.1)	<.001
Inferior	1053 (18.6)	3203 (33.3)	<.001	4805 (32.7)	<.001
Other/unknown	755 (13.3)	842 (8.8)	<.001	1506 (10.2)	<.001
Thrombolytic therapy, No. (%)	253 (4.5)	3106 (32.3)	<.001	5170 (35.2)	<.001
PCI to treat qualifying AMI, No. (%)[d]	4980 (88.0)	2249 (23.4)	<.001	3683 (25.0)	<.001
β-blocker, No. (%)	4827 (85.3)	6648 (69.1)	<.001	10 350 (70.4)	<.001
ACE/ARB use before randomization, No. (%)[e]	4436 (78.4)	3804 (39.6)	<.001	5954 (40.5)	<.001
Statin, No. (%)	5370 (94.9)	3099 (32.2)	<.001	5014 (34.1)	<.001
Aspirin, No. (%)	5574 (98.5)	8777 (91.3)	<.001	13 418 (91.3)	<.001
MRA/potassium-sparing diuretic, No. (%)[f]	2338 (41.3)	863 (9.0)	<.001	1330 (9.0)	<.001

Abbreviations: ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; ECG, electrocardiogram; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PARADISE-MI, Enrolled in the Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI; PCI, percutaneous coronary intervention; VALIANT, Valsartan in Acute Myocardial Infarction.

[a] For example, similar augmenting risk factors and no prior history of heart failure.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] In the VALIANT trial, location of AMI was defined by changes on ECG. Other or unknown includes, eg, patients with left bundle branch block or a missing baseline ECG.

[d] People who had primary PCI, nonprimary PCI, or both performed for the qualifying AMI and before randomization.

[e] Within 24 hours in VALIANT and within 7 days in PARADISE-MI.

[f] MRA use was reported in PARADISE-MI but not specifically collected in the VALIANT trial, which reported on potassium-sparing diuretic use.

vs 1924 [20.0%]), despite a higher LVEF (mean [SD], 36.5% [9.4%] vs 34.6% [10.1%]). Fewer people in PARADISE-MI had a prior stroke (263 [4.6%] vs 588 [6.1%]), MI (920 [16.3%] vs 2571 [26.7%]), or coronary artery bypass graft (205 [3.6%] vs 592 [6.2%]), whereas higher proportions of people had diabetes (2401 [42.4%] vs 2513 [26.1%]), hypertension (3676 [64.9%] vs 5409 [56.2%]), AF (726 [12.8%] vs 504 [5.2%]), and prior percutaneous coronary intervention (PCI; 827 [14.6%] vs 680 [7.1%]). Compared with PARADISE-MI–like counterparts in the VALIANT trial, people in the PARADISE-MI trial were more likely to have an anterior AMI (3853 [68.1%] vs 5572 [57.9%]), and substantially more were treated with PCI for their qualifying AMI (4980 [88.0%] vs 2249 [23.4%]) and received a β-blocker (4827 [85.3%] vs 6648 [69.1%]), statin (5370 [94.9%]

Table 2. All-Cause Death, Sudden Death/Resuscitated Cardiac Arrest (RCA) and Non-Sudden Rates in the VALIANT Trial, Restricted to Patients Who Had PARADISE-MI–Like Characteristics[a,b]

	Overall		1-2 wk, Days 1-15		3-4 wk, Days 16-30		1 mo		1 mo-3 mo		3 mo-1 y		>1 y	
Outcomes	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years
All-cause death	1892	9.9 (9.5-10.4)	277	70.2 (62.4-79.0)	126	32.6 (27.4-38.9)	403	51.6 (46.8-56.9)	288	19.1 (17.0-21.4)	545	8.4 (7.8-9.2)	656	6.3 (5.9-6.8)
Sudden death/RCA	707	3.7 (3.5-4.0)	102	25.9 (21.3-31.4)	48	12.5 (9.4-16.6)	150	19.3 (16.4-22.6)	123	8.2 (6.9-9.8)	231	3.6 (3.2-4.1)	203	2.0 (1.7-2.3)
Non-sudden death	1281	6.7 (6.4-7.1)	215	54.5 (47.7-62.3)	89	23.1 (18.7-28.4)	304	38.9 (34.8-43.6)	174	11.5 (10.0-13.4)	334	5.2 (4.6-5.8)	469	4.5 (4.1-5.0)

Abbreviations: PARADISE-MI, Enrolled in the Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI; RCA, VALIANT, Valsartan in Acute Myocardial Infarction.

[a] PARADISE-MI–like characteristics include similar augmenting risk factors and no prior history of heart failure.

[b] Number of patients in cohort: 9617.

Table 3. All-Cause Death, Sudden Death/Resuscitated Cardiac Arrest (RCA), and Non-Sudden Death Rates in the PARADISE-MI Trial

	Overall		1-2 wk, Days 1-15		3-4 wk, Days 16-30		0-1 mo		1 mo-3 mo		3 mo-1 y		>1 y	
Outcomes	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years	No.	Per 100 person-years
All-cause death	455	4.2 (3.9-4.7)	77	32.9 (26.3-41.1)	29	12.5 (8.7-18.0)	106	22.7 (18.8-27.5)	62	6.7 (5.3-8.7)	126	3.1 (2.6-3.7)	161	3.0 (2.6-3.5)
Sudden death/RCA	148	1.4 (1.2-1.6)	33	14.1 (10.0-19.9)	11	4.8 (2.6-8.6)	44	9.5 (7.0-12.7)	24	2.6 (1.8-3.9)	37	0.9 (0.7-1.3)	43	0.8 (0.6-1.1)
Non-sudden death	341	3.2 (2.9-3.5)	63	26.9 (21.0-34.4)	19	8.2 (5.2-12.8)	82	17.6 (14.2-21.8)	39	4.2 (3.1-5.8)	94	2.3 (1.9-2.9)	126	2.4 (2.0-2.8)

Abbreviation: PARADISE-MI, Enrolled in the Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI.

vs 3099 [32.2%]), and mineralocorticoid receptor antagonist (MRA; 2338 [41.3%] vs 863 [9.0%]) (**Table 1**).

Event Rates in VALIANT vs PARADISE-MI Trials

Among 9617 patients in the PARADISE-MI–like cohort of the VALIANT trial, 1892 (19.7%) died over a median (IQR) follow-up of 24.7 (19.6-31.1) months. A total of 403 of 1892 people (21.3%) died of all causes within the first month after AMI, at a rate of 51.6 per 100 person-years, which declined thereafter (**Table 2**). A total of 707 people (7.4%) experienced sudden death/RCA, of whom 150 (21.2%) did so in the first month, at a rate of 19.3 (95% CI, 16.4-22.6) per 100 person-years. Sudden death/RCA rates declined thereafter (Table 2).

Of the 5661 patients randomized in the PARADISE-MI trial, 455 (8.0%) died over a median (IQR) follow-up of 22.2 (15.1-28.6) months. A total of 106 of these 455 people (23.3%) died within 1 month, giving an all-cause death rate of 22.7 per 100 person-years (95% CI, 18.8-27.5). The death rate declined thereafter (**Table 3**). A total of 148 people (2.6%) in the PARADISE-MI trial experienced sudden death/RCA, of whom 114 died suddenly, and 34 people had an adjudicated RCA. Forty-four of 148 people (29.7%) experienced sudden death/RCA within the first month after AMI giving a rate of 9.5 per 100 person-years (95% CI, 7.0-12.7). The rate of sudden death/RCA reduced steadily after the first month (Table 3).

The cumulative incidence of sudden death/RCA was lower in the PARADISE-MI trial compared with the VALIANT trial in the competing risks analysis (**Figure**). The event rates in the total VALIANT cohort (eTable 1 in Supplement 1) were consistent with those observed in the primary analysis.

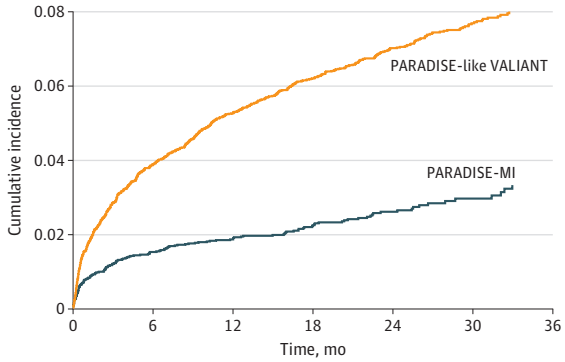
Discussion

We found that the highest incidence of death, including sudden death, in contemporary patients was within the first 30 days after infarction. In the PARADISE-MI trial, the rate of sudden death/RCA at 1 month was 3 times higher than at 3 months, and 10 times higher than at 1 year. Across follow-up, people in the PARADISE-MI trial had a 2- to 3-fold lower sudden death/RCA rate after AMI than people in the VALIANT cohort. This was also observed when the competing risk of other causes of death was taken into account.

Important differences in treatments might explain the decline in sudden death/RCA rate. Principally, in the PARADISE-MI trial, a greater proportion of patients had PCI to treat the index AMI compared with those in the VALIANT cohort,[4] likely reducing the substrate for sudden death by limiting cardiomyocyte necrosis and scar formation.[5-7] Notably, in the PARADISE-MI cohort, patients who died, including sudden death/RCA, were less often treated with PCI (eTables 2 and 3 in Supplement 1). There was higher use of β-blockers and MRAs, both of which reduce sudden death after AMI,[8-10] in the PARADISE-MI cohort compared with the VALIANT cohort.

The declining death rate after AMI questions the absolute benefit of primary prevention defibrillators in contemporary

Figure. Cumulative Incidence of Sudden Death/Resuscitated Cardiac Arrest in the Valsartan in Acute Myocardial Infarction (VALIANT) and Prospective ARNi vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) Trials



The VALIANT trial has a PARADISE-MI–like cohort of patients, that is, similar augmenting risk factors and no prior history of heart failure.

practice. The all-cause death rate per year in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), VALIANT, and PARADISE-MI trials was 7.2%, 9.8%, and 4.2% respectively.[3,4,11] With an arrhythmic death rate of 3.5% per year in the DINAMIT control group and a sudden death/RCA rate of 3.7% and 1.4% per year in the VALIANT and PARADISE-MI cohorts, respectively, the proportion of overall deaths that may be arrhythmic and the absolute number of deaths that could be averted by a defibrillator appear to be decreasing. Future studies of interventions to prevent sudden death after AMI are likely to require large cohorts, enriched with people who have high-risk characteristics. Strategies to identify these patients, the most likely to benefit from such interventions, are potentially valuable, although this is not easy, at least with conventional routinely collected clinical variables. The comparison between trials of patients after AMI suggests that the best way to reduce sudden death is to ensure that early revascularization is complemented by optimal medical therapy, including β-blockers, renin-angiotensin system blockers, MRAs, statins, and antithrombotic medications, along with other guideline-directed therapies in individuals developing HF after AMI.

Limitations

This study has some limitations. We did not have data on factors such as scar on cardiac magnetic resonance imaging or specific electrocardiographic characteristics that are associated with sudden death. The study participants were selected for clinical trials and may not represent the broader population of patients with AMI.

Conclusions

In this secondary analysis of the VALIANT and PARADISE-MI trials, results showed that the first month after an AMI remains the highest risk period for sudden death/RCA. Results revealed that compared with 20 years ago, the rate of sudden death/RCA was 2- to 3-fold lower in people receiving contemporary management. Interventions to further protect people in the highest risk first month after infarction are needed.

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