

Efficacy of ICD Therapy in Higher Risk Post-MI Patients with Better-preserved LV Function

Derek Exner on behalf of the *REFINE ICD Investigators*

Risk Estimation Following Infarction Noninvasive Evaluation - ICD efficacy

NCT00673842

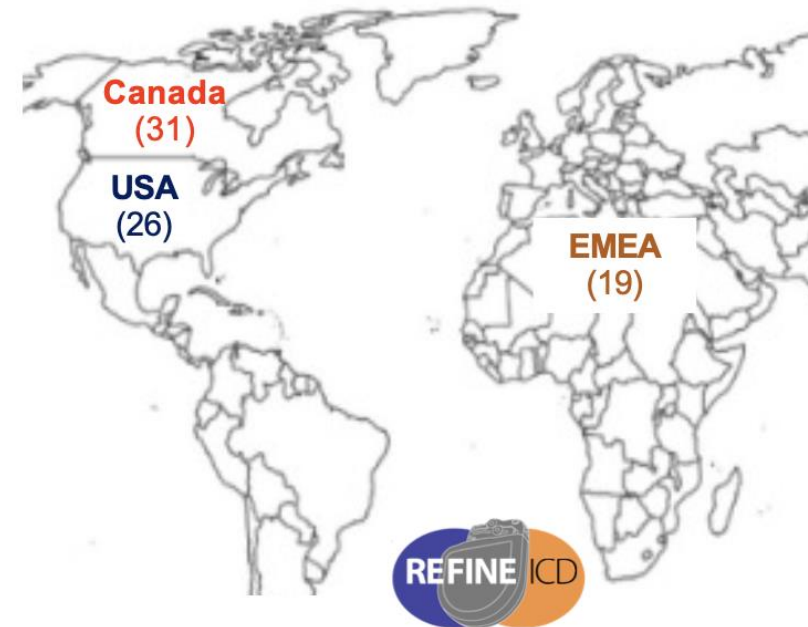
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Funding / Acknowledgments

Investigator-initiated / run trial
Unrestricted support from

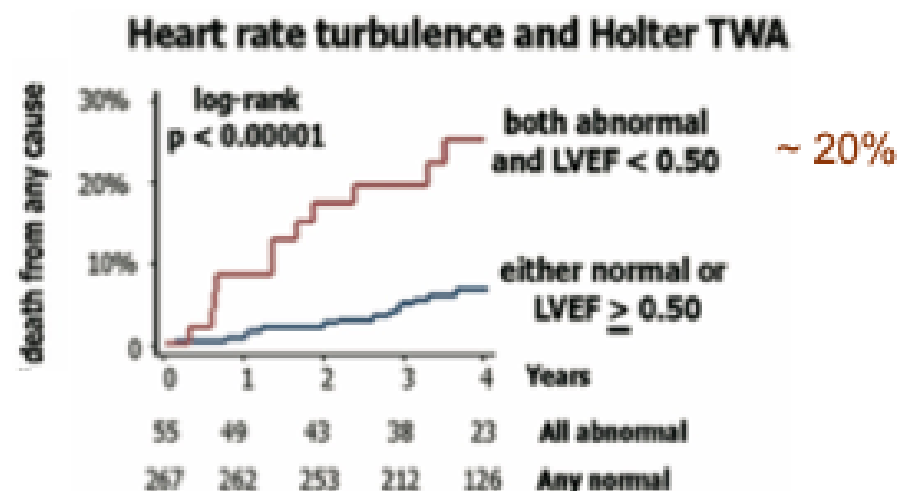
Gratitude to the patients, 76 sites, and
investigators who made this possible



REFINE - Scalable Multi-parameter Approach

Risk Estimation Following Infarction Noninvasive Evaluation (n = 322)

Parameter assessment ~ 2 months post-MI
yielded reliable estimate of longer-term risk



JACC 2007; 50:2275- 84

Incomplete LV Remodeling
(Residual Scar; LVEF < 50%)

+

**Impaired Dynamic Autonomic
Tone (Heart Rate Turbulence)**

JACC 2008;52:1353-65

+

**Abnormal Beat to Beat T Wave
Dynamics (T Wave Alternans)**

JACC 2011;58:1309-24



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Hypothesis

An ICD compared to usual care will increase the probability of survival in subjects with LVEF values 36% to 50%, impaired heart rate turbulence (HRT), and abnormal modified moving average T-wave alternans (TWA) measured ≥ 2 months after an index MI

Outcomes

1°: All-cause mortality (intention to treat)

2 °: Mortality, by adjudicated modes of death (intention to treat)



Methods

Design: Randomized, prospective, open-label, investigator-initiated, multi-centre trial

Patients: Confirmed MI & LVEF 36% to 50% measured at least 2 months after the index MI

Main Exclusion Criteria: > 80 years, renal failure on dialysis, persistent or permanent AF, chronic amiodarone, indication for or existing PM / ICD, or a contraindication to an ICD

Holter: Ambulatory ECG at site / central laboratory assessment of heart rate turbulence (HRT) and modified moving average T wave alternans (TWA) using consensus criteria

Sample Size: 80% power (alpha 0.05) to detect a 30% relative reduction in mortality (44.7% vs 31.3%; 151 deaths)

Interim analysis: > 106 deaths (70%)

Enrolment :

1st subject enrolled: 18-Apr-2011

- Pilot: 15 sites, Canada & USA
- Full-scale: 76 sites, Canada, USA & Europe, Middle East & Africa
- Final: 31 sites (+ sub), Canada

Last visit: 23-May-2025 (14 years)

JACC 2008;52:1353-65 & JACC 2011;58:1309-24



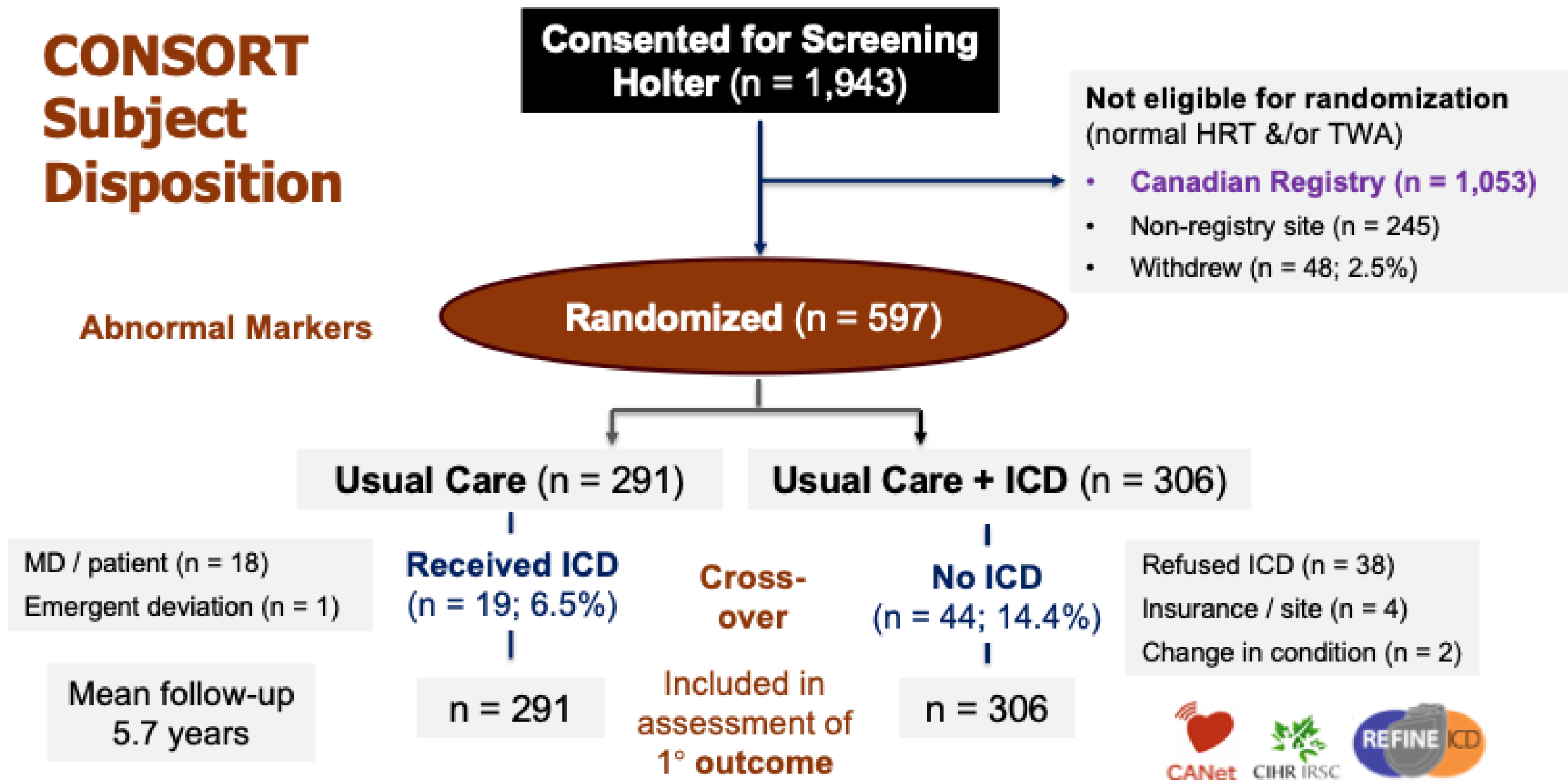
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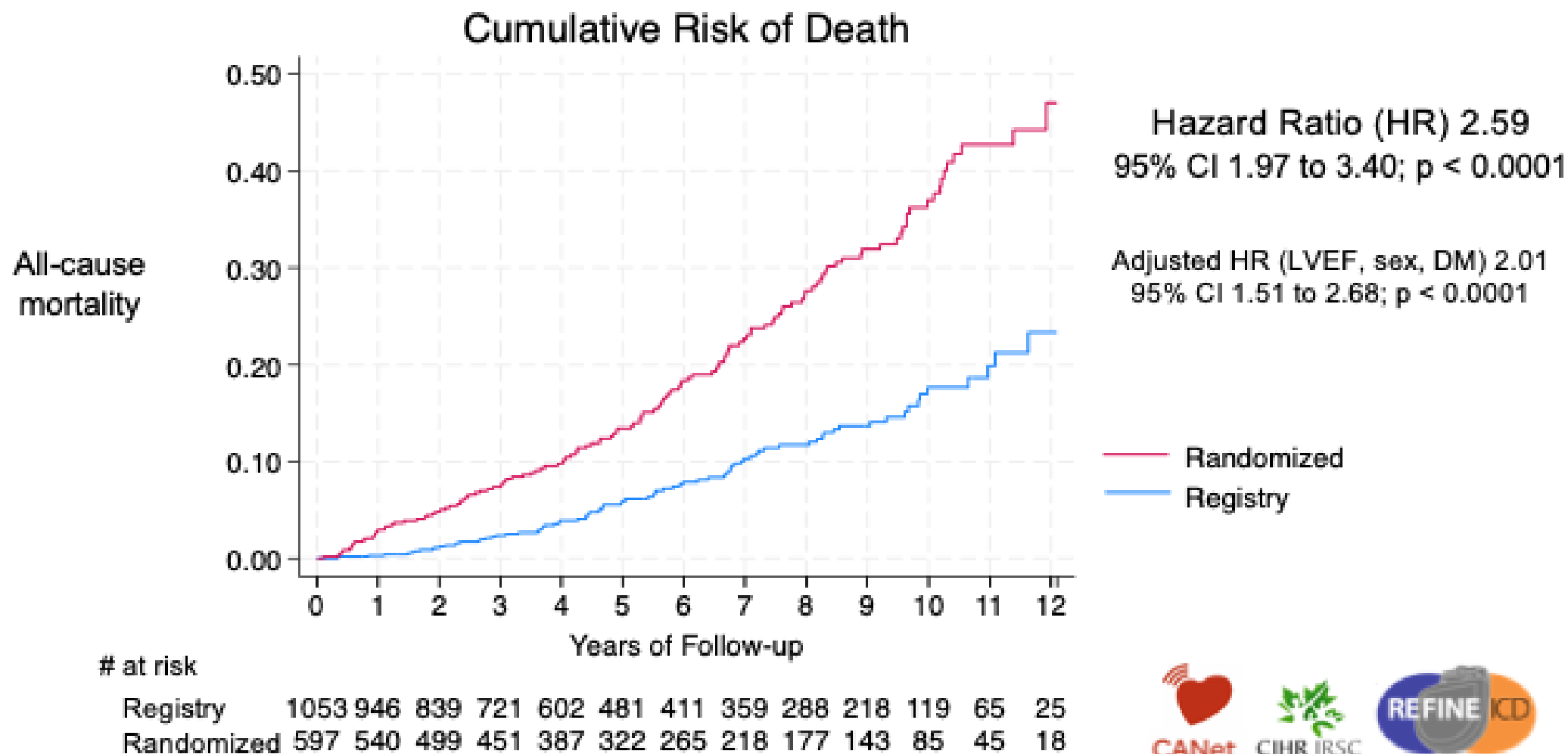
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CONSORT Subject Disposition



Risk of Death: Randomized versus Registry



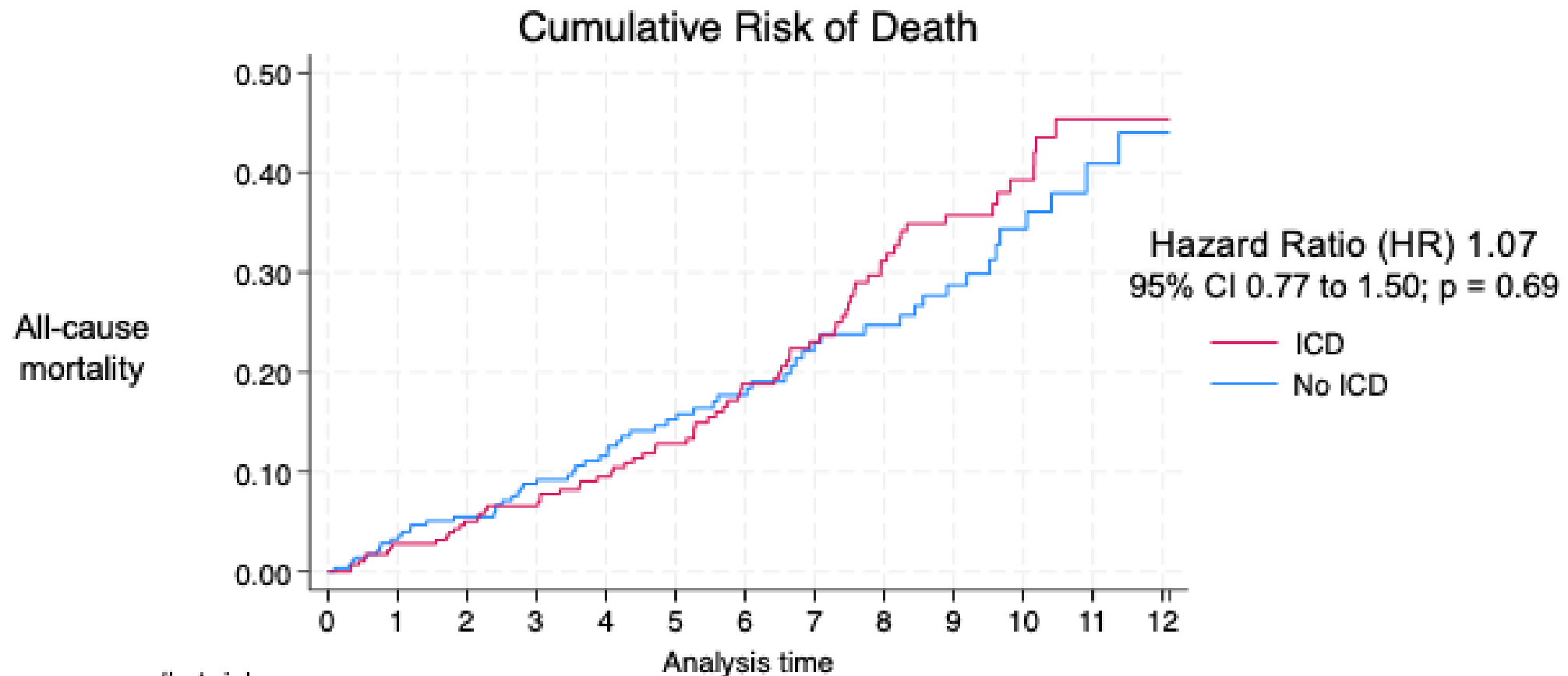
Baseline Characteristics: Randomized

	ICD arm (n = 306)	No ICD arm (n = 291)
Age, years (mean $\pm$ sd)	65.0 $\pm$ 8.7	64.5 $\pm$ 8.3
Female Sex	19.9%	21.6%
BMI (mean $\pm$ sd)	29.9 $\pm$ 6.4	29.3 $\pm$ 5.7
NYHA I / II / III or IV (%)	63.7 / 30.1 / 6.2	67.4 / 28.2 / 4.5
LVEF stratum 36 to 40% (37.4%)	38.4 $\pm$ 1.4	38.6 $\pm$ 1.4
41 to 50% (62.6%)	44.9 $\pm$ 2.6	45.4 $\pm$ 2.8
Prior coronary revascularization	81.1%	87.6%
Comorbidities		
Hypertension	72.9%	76.9%
Diabetes mellitus	50.0%	46.1%
TIA / Stroke	9.5%	11.0%
History of AF	12.9%	9.3%
Chronic obstructive lung disease	15.6%	8.2%
Sleep Apnea	18.0%	16.9%

Labs, Functional Capacity & Medications: Randomized

	ICD arm (n = 306)	No ICD arm (n = 291)
QRS duration (msec; mean $\pm$ sd)	105.7 $\pm$ 23.3	107.0 $\pm$ 39.9
6-minute hall walk distance (m; mean $\pm$ sd)	594.7 $\pm$ 417.3	592.5 $\pm$ 442.4
Creatinine (μ mol/L; mean $\pm$ sd)	88.4 $\pm$ 55.6	87.2 $\pm$ 62.4
β -Blocker	88.2%	92.8%
Statin	95.2%	96.1%
RAAS inhibitor	84.3%	87.6%
Mineralocorticoid receptor antagonist	27.1%	30.9%
Aspirin / antiplatelet agent	92.1%	93.7%
Oral anticoagulant	16.6%	19.3%
Diuretic	9.0%	10.2%
Calcium channel blocker	12.4%	12.6%

1° Outcome: All-cause Mortality (intention to treat)



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Outcomes: Adjudicated Deaths (intention to treat)

	ICD (n = 306)	No ICD (n = 291)	HR (95% CI)
All-cause mortality	75 (24.5%)	62 (21.3%)	1.07 (0.77,1.50)
Cardiac Death	27 (8.8%)	22 (7.6%)	1.11 (0.63, 1.945)
Sudden	8 (2.6%)	11 (3.8%)	0.66 (0.27, 1.62)
Non-Sudden (Ischemic / HF)	16 (5.2%)	9 (3.1%)	1.62 (0.71, 3.66)
Other Non-sudden	3 (1.0%)	2 (0.7%)	1.41 (0.23, 8.46)
Non-Cardiac	39 (12.8%)	26 (8.9%)	1.34 (0.82, 2.19)
Unknown Death	9 (2.9%)	14 (4.8%)	0.56 (0.25, 1.27)



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Conclusions

Prophylactic ICD therapy did not reduce total mortality, cardiac death, or sudden death in patients with a prior MI, persistent LVEF values of 36% to 50% plus evidence of both impaired autonomic tone and abnormal cardiac repolarization on a Holter

Yet, these patients had twice the risk of death as compared to subjects with similar characteristics, but without both Holter risk markers

