Long-term outcome of the Defibrillator After Primary Angioplasty (DAPA) trial

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for the DAPA investigators

Isala, Zwolle, the Netherlands

Declaration of interest

- I have nothing to declare

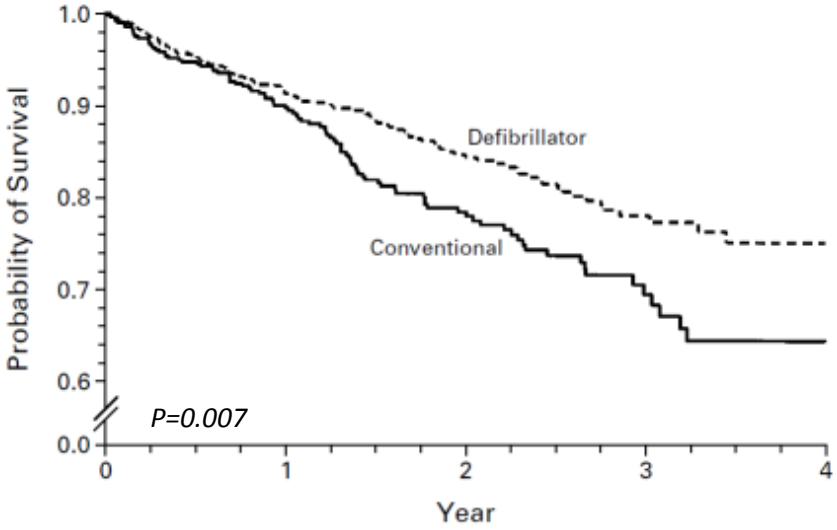
Prophylactic ICD implantation

MADIT II trial

n =1232 patiënts, LVEF ≤ 30% (ischemic CMP)

Remote myocardial infarction (mean 6.7 years)

Excluded
Revascularization <3 months
Myocardial infarction < 1 month



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

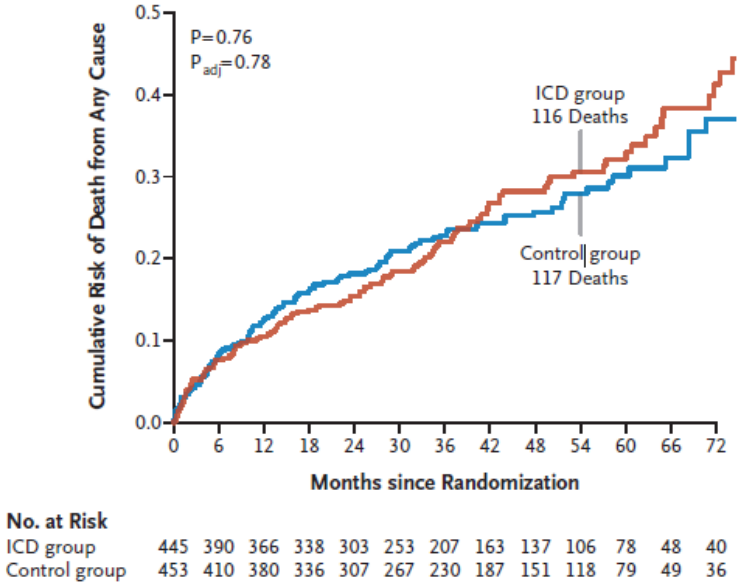
Moss et al N Engl J Med 2002; 346:877-883

Early prophylactic ICD implantation (<40 days)

IRIS trial

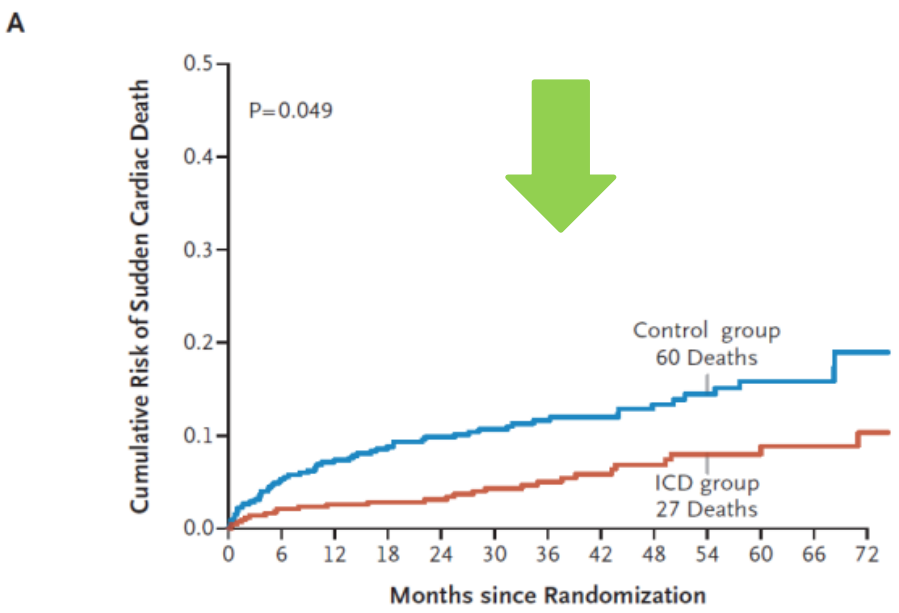
n= 898, LVEF<40%, HR >90 beats/min
with or without NSVT

ICD implantation, mean 13 days from MI

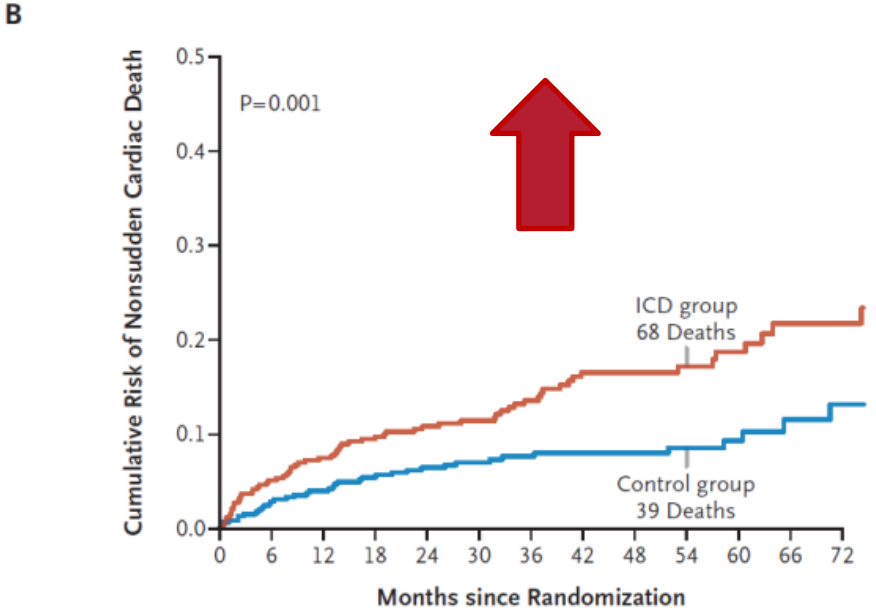


Steinbeck et al N Engl J Med 2009; 361:1427-1436

Early prophylactic ICD implantation (<40 days)



Sudden cardiac death



Non-sudden cardiac death

Steinbeck et al N Engl J Med 2009; 361:1427-1436

Guidelines

ESC 2015

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status:			
– Ischaemic aetiology (at least 6 weeks after myocardial infarction).	I	A	63,64
– Non-ischaemic aetiology.	I	B	64,316, 317

ACC 2017

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease

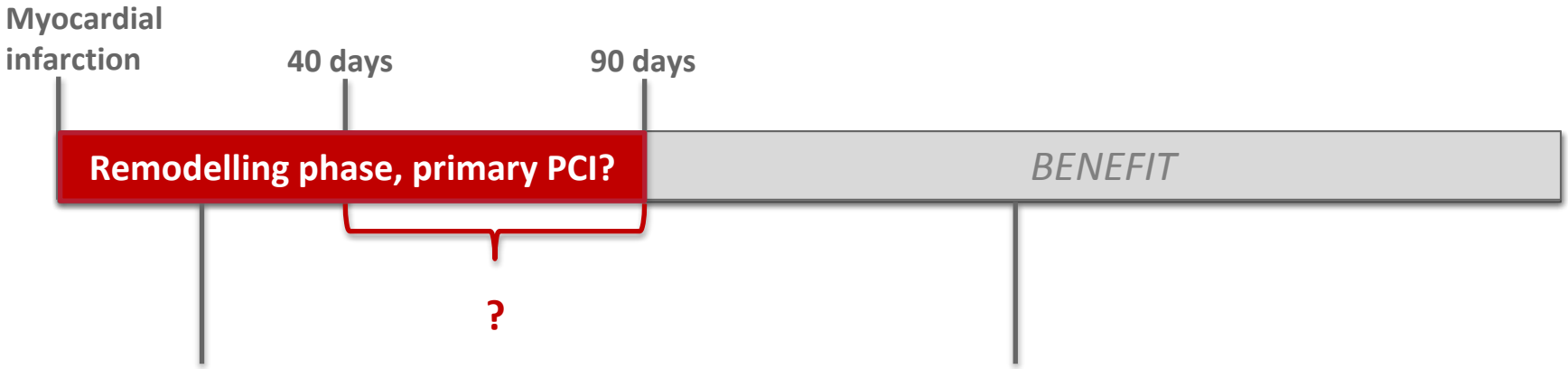
References that support the recommendations are summarized in Online Data Supplement 21.

COR	LOE	Recommendations
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.[S6.1.2-1,S6.1.2-2]

Priori et al. 2015 ESC Guidelines. 36, 2793–2867/ El-Khatib et al. 2017 AHA/ACC/HRS Guideline 2018;138:e272–e391

Timing of ICD implantation

Reduced left ventricular ejection fraction post MI



DINAMIT, IRIS

- **Timing:** < 40 days
- **Revascularization**: PCI 25-70%

MADIT II

- **Timing**: mean 6.7 years
- **Revascularization:** PCI 45%

SCD-HeFT

- **Timing**: unknown
- **Revascularization:** unknown

Gaps of knowledge

- Benefit of ICD in selected high risk STEMI patients post primary PCI

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- Definition high-risk STEMI patients for SCD in primary PCI era (based on LVEF only)

Gaps of knowledge

- ❑ Benefit of ICD in selected high risk STEMI patients post primary PCI
- ❑ Definition high-risk STEMI patients for SCD in primary PCI era (based on LVEF only)
- ❑ ICD benefit in patients with LVEF improvement post PCI

DAPA trial

To evaluate the survival benefit of early prophylactic ICD implantation in high risk STEMI patients after primary PCI

Methods

- Multicenter, prospective, controlled, randomized trial (start 2004)
- 12 hospitals in Europe (7 hospitals in the Netherlands and 5 hospitals in Poland)
- STEMI patients, treated with primary PCI & **at least 1 high risk factor**:
  1. LVEF < 30% within 4 days
  2. TIMI flow < 3 after primary PCI

  *Protocol amendment (2006): primary VF, Killip class ≥ 2
- Randomization: 30-60 days after STEMI, ICD vs control group (optimized drug-therapy only)
- ICD: shock only protocol >190 bpm

Follow-up

- ❑ Outpatient clinical visits every 6 months (including ICD interrogation)
- ❑ Cross-over, e.g. in case of class I indication for ICD
- ❑ 18 months: LVEF re-assessment with transthoracic echocardiography

  *>10% increase was considered LVEF improvement

Primary endpoint

- ❑ All-cause mortality (3 years)

→ Power analysis: 700 patients, based on estimated mortality rates of 21% (ICD group) and 32% (control group)

Premature trial ending

- 2004: First enrollment
- 2013: Premature ending study

  - Advise DSMB (Prof. Verheugt, Prof. Wellens, Prof. E. Boersma): slow inclusion rate
  - Total number of inclusions: 266 (38% of 700 patients)

Post-hoc analysis

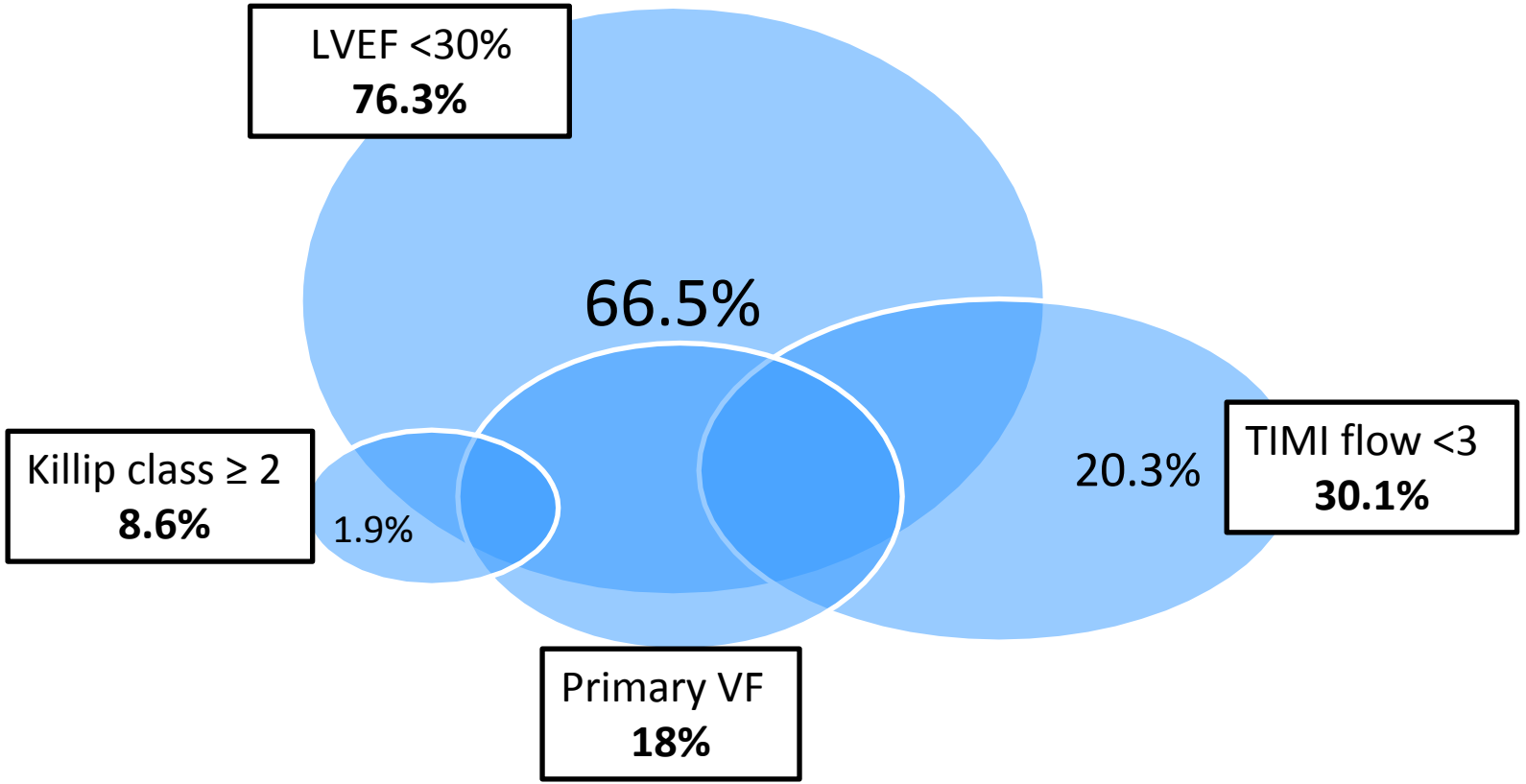
- Additional survival assessment was performed with national mortality records in February 2019 (updated <24 hours)

- Additional secondary endpoints:

  Non-cardiac death and cardiac death (heart failure, arrhythmia related death, SCD)

  *Cause of death: manual review local hospital databases, telephone contact with general practitioner

Distribution based on inclusion criteria (n=266)



Patient characteristics

	ICD (n=131)	Control group (n=135)
Age, y	60.1 ± 10.8	60.8 ± 11.8
Male gender (%)	79.4	77.0
Previous MI (%)	17.6	13.3
Multivessel (%)	40.5	46.7
STEMI		
Anterior location (%)	83	84.4
Peak creatinine kinase, U/L	5291.5 ± 3157.7	5684.0 ± 2783.4
Stent placement (%)	85.5	88.9
CABG (%)	3.1	5.9
Drug therapy		
Antiplatelet therapy (%)	97.7	99.3
Beta-blocker (%)	95.4	94.1
ACE/ATII (%)	94.6	94.8
Diuretics (%)	45.0	48.9
Spironolactone (%)	28.2	34.1

ICD implantation

- Median time from primary PCI until ICD implantation: 50 (IQR 41-60) days
- One-chamber (VVI) ICD: 82.4%
- Implantation related complications (4.6%)
  - Pocket bleeding (1.5%)
  - Local pocket infection (2.3%)
  - Pneumothorax (0.8%).
  - No deaths related to device implantation
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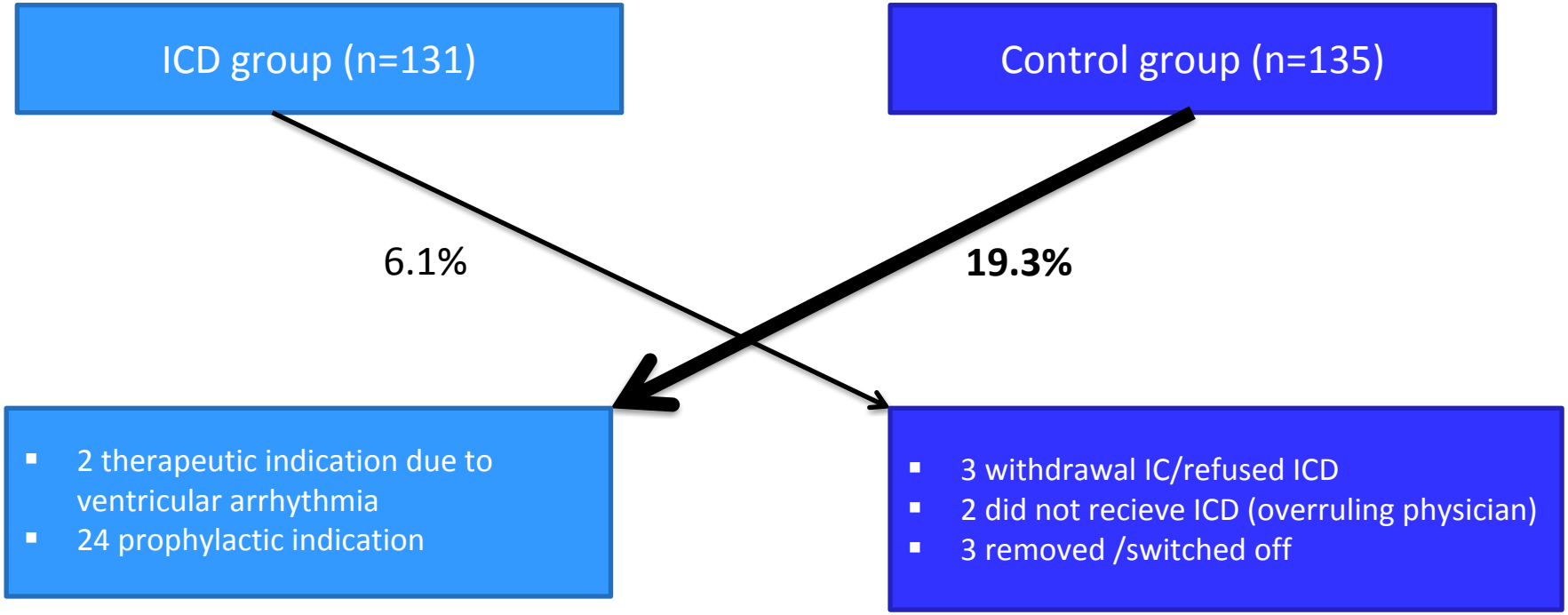
Cross-over

Until follow-up according to study protocol in 2013 (12.8%)



Follow-up

Study protocol until 2013

- 89% of patients that were still alive completed the study follow-up of 3 years (2 lost to follow-up)
- 40 patients died at 3 years follow-up (15%)

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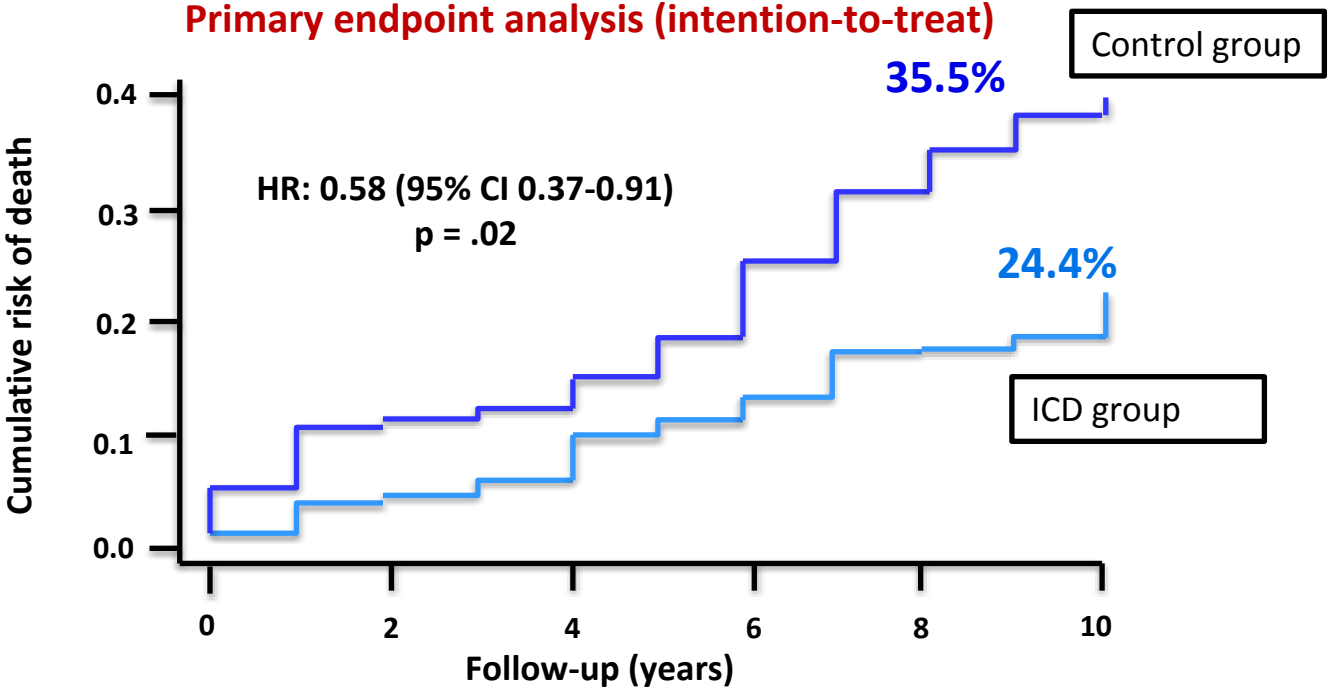
Additional survival assessment (Feb 2019)

- 80 patients (30.1%) died during median follow-up 9 [IQR 3-11] years

All-cause mortality

Primary endpoint analysis (intention-to-treat)

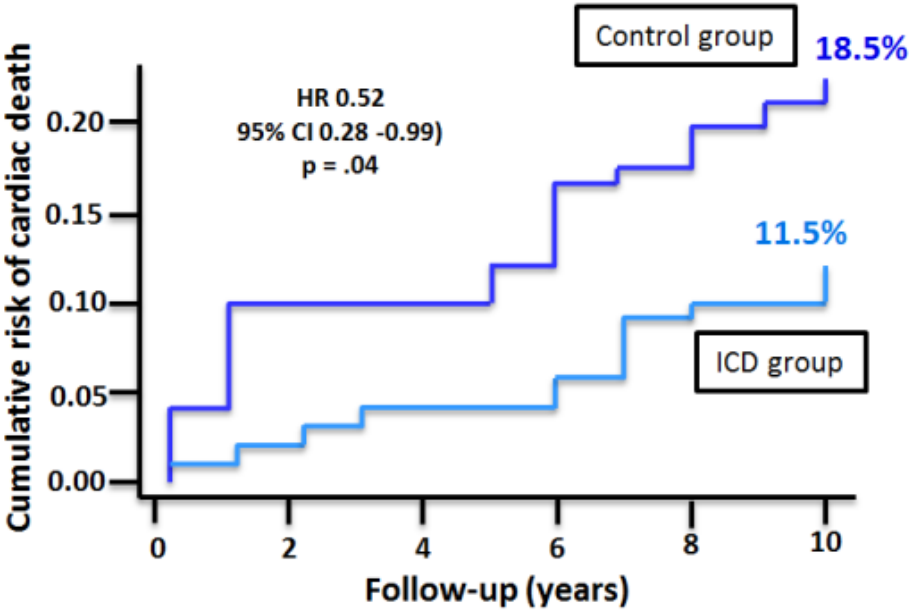


No. at risk						
ICD group	129	121	90	85	79	68
Control group	133	110	83	75	63	53

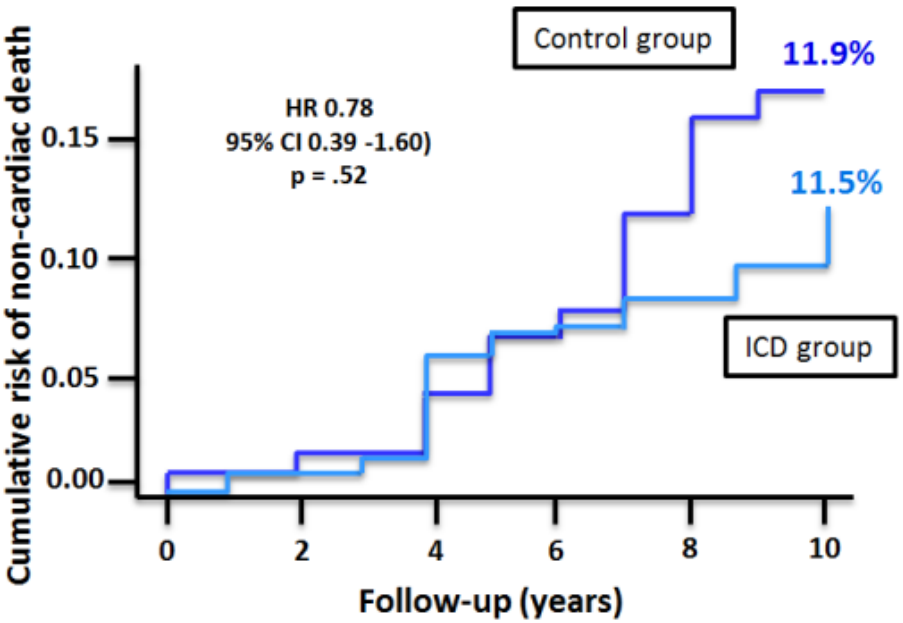
Cumulative proportion death during short, mid-term and long-term follow-up

	Total n=266 (%)	ICD group n=131 (%)	Control group n= 135 (%)	Hazard Ratio (95% CI)	P value
6 months	2.3	1	4	0.21 (0.03-1.75)	0.15
1 year	3.8	2	6	0.25 (0.05- 1.18)	0.08
3 years	8.3	5	13	0.36 (0.14-0.93)	0.04
9 years	30	19	38	0.58 (0.37-0.91)	0.02

Cardiac death

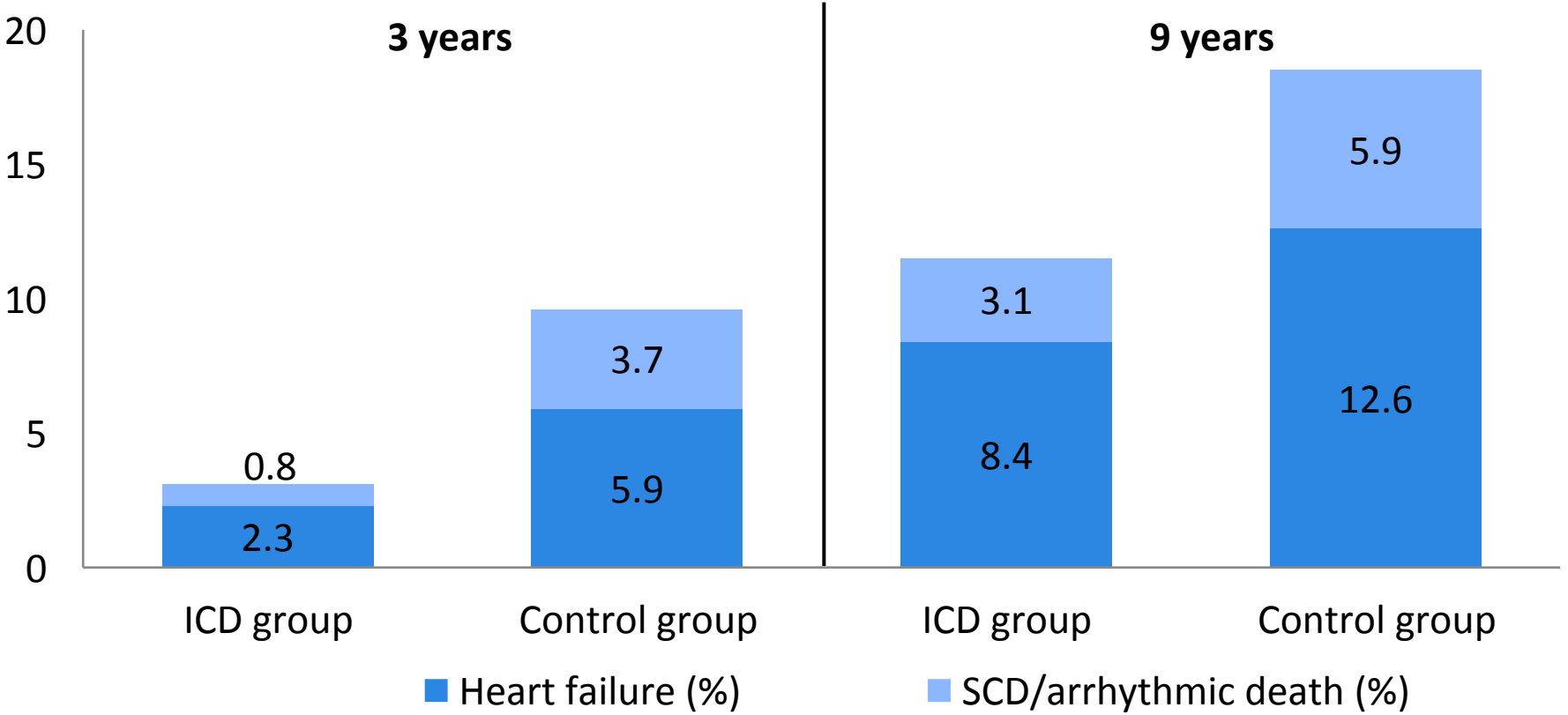


Non-cardiac death



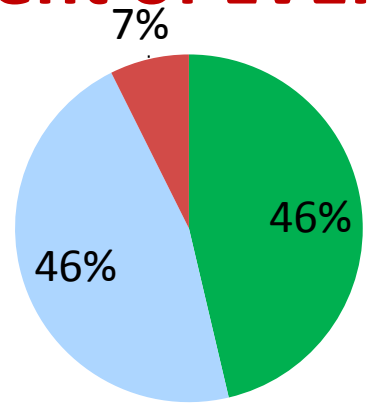
*6 patients (2.3 %) unknown cause of death (traveling abroad, home-less, loss of records)

Cardiac death

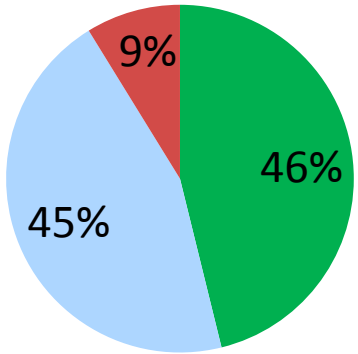


Re-assessment of LVEF at 18 months

ICD group (n=109)



Control group (n=91)

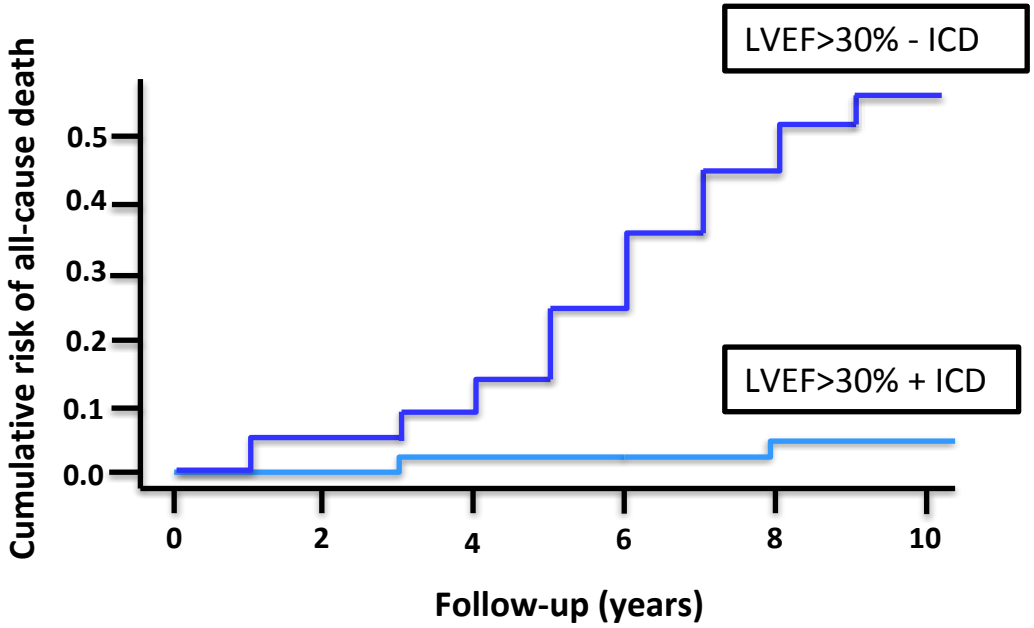


LVEF improvement
LVEF unchanged
LVEF reverse remodelling

ICD benefit in LVEF >30% at 18 months

LVEF >30% (n=110)

HR 0.47 (95% CI 0.12 – 1.90)



Discussion

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  - all STEMI patients treated with primary PCI
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- More sophisticated risk stratification tools are needed to identify patients at high risk of SCD early after STEMI

- Further research is required to evaluate ICD benefit in the era of primary PCI

Conclusion

- First randomized early prophylactic ICD implantation trial in high risk STEMI patients treated with primary PCI
- Randomization to ICD was associated with significantly lower total and cardiac mortality rates
- Despite LVEF improvement in 46% of the study population, benefit of ICD remained preserved during long-term follow-up of 9 years

Thank you for your attention

Steering committee

Dr. Ramdat Misier
Dr. Ottervanger
Prof. Schalij
Prof. Zijlstra
Dr. Wever
Prof. de Boer

On behalf of the DAPA investigators

CRO: Diagram BV, Zwolle, The Netherlands

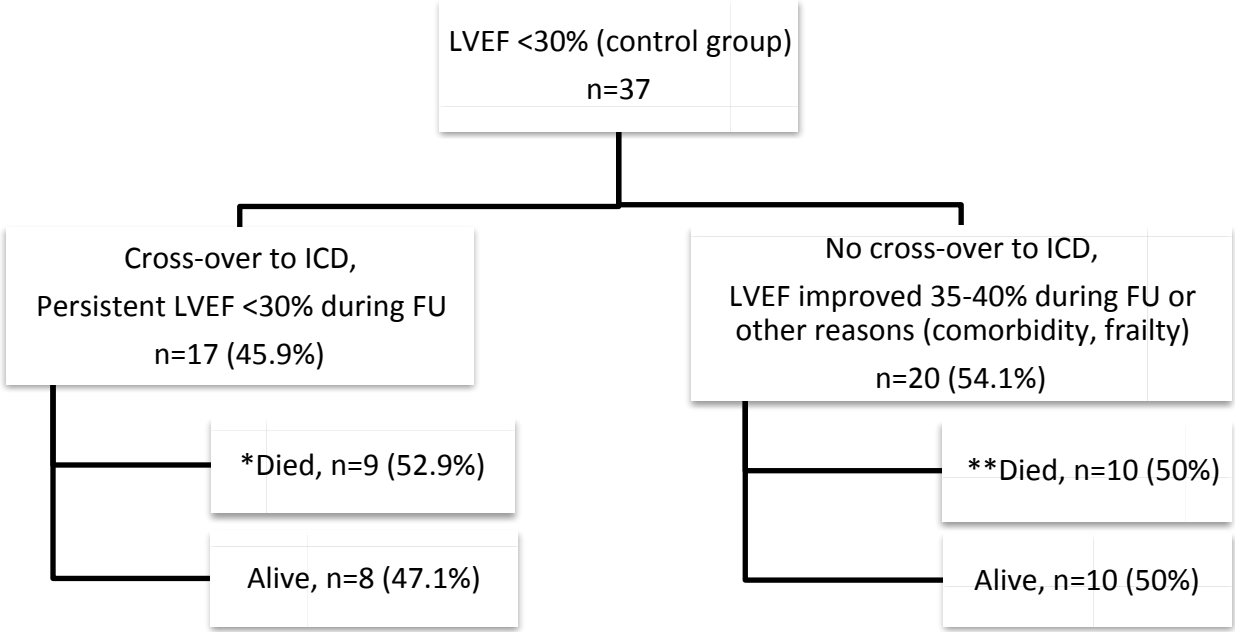
DIAGRAM

Medisch Spectrum Twente

LVEF at baseline and follow-up (18 months)

	ICD (n=128)	No ICD (n=135)	P value
Systolic LV function at Randomization, n(%)			**0.82**
<20%	7.8	5.2	
20-30%	68.8	71.9	
30-40%	17.2	17.8	
>40%	6.3	5.2	
<30%	77.3	77.0	0.95
Systolic LV function 18 months, n (%)	**N= 109**	**N = 91**	**0.52**
<20%	4.6	3.3	
20-30%	44.0	35.2	
30-40%	29.4	37.4	
>40%	22.1	24.2	
<30%	48.6	38.5	0.15

Follow-up flow-chart of patients with LVEF<30% randomized to no ICD at 18 months. LVEF, left ventricular ejection fraction.



***Cause of death**
Cancer (n=3)
Heart failure (n=3)
Infection (n=2)
Unknown (n=1)

****** Cause of death:**
Cancer (n=3)
Heart failure (n=3)
Infection (n=2)
SCD (n=1)
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