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

for the DAPA investigators

Isala, Zwolle, the Netherlands
Declaration of interest

- I have nothing to declare
Prophylactic ICD implantation

MADIT II trial

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

- Remote myocardial infarction (mean 6.7 years)
- \textbf{Excluded}
  - Revascularization < 3 months
  - Myocardial infarction < 1 month

\( P = 0.007 \)

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

Early prophylactic ICD implantation (<40 days)

Sudden cardiac death

Non-sudden cardiac death

### ESC 2015

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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:</td>
<td>I</td>
<td>A</td>
<td>63,64</td>
</tr>
<tr>
<td>– Ischaemic aetiology (at least 6 weeks after myocardial infarction).</td>
<td>I</td>
<td>B</td>
<td>64,316, 317</td>
</tr>
<tr>
<td>– Non-ischaemic aetiology.</td>
<td></td>
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</tbody>
</table>

### 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.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>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. 56.1.2.1,56.1.2.2</td>
</tr>
</tbody>
</table>

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
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)
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)

- LVEF <30% 76.3%
- Killip class ≥ 2 8.6%
- Primary VF 18%
- TIMI flow <3 30.1%
### Patient characteristics

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

- No deaths related to device implantation
Cross-over

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

ICD group (n=131):
- 2 therapeutic indication due to ventricular arrhythmia
- 24 prophylactic indication

Control group (n=135):
- 3 withdrawal IC/refused ICD
- 2 did not receive ICD (overruling physician)
- 3 removed/switched off
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%)
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%)

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)

HR: 0.58 (95% CI 0.37-0.91)

p = .02

Cumulative risk of death

Follow-up (years)

Control group

ICD group

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

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

Non-cardiac death

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

ICD group vs Control group

Heart failure (%)
3 years:
- ICD group: 2.3%
- Control group: 5.9%

9 years:
- ICD group: 8.4%
- Control group: 12.6%

SCD/arrhythmic death (%)
3 years:
- ICD group: 0.8%
- Control group: 3.7%

9 years:
- ICD group: 3.1%
- Control group: 5.9%
Re-assessment of LVEF at 18 months

ICD group (n=109)
- LVEF improvement: 46%
- LVEF unchanged: 46%
- LVEF reverse remodelling: 7%

Control group (n=91)
- LVEF improvement: 46%
- LVEF unchanged: 45%
- LVEF reverse remodelling: 9%
ICD benefit in LVEF >30% at 18 months

LVEF >30% (n=110)

HR 0.47 (95% CI 0.12 – 1.90)
Discussion

- Additional value of the current study
  - all STEMI patients treated with primary PCI
  - early ICD implantation
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- Premature termination of the trial and lack of ICD therapy data, limits interpretation of the results
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- More sophisticated risk stratification tools are needed to identify patients at high risk of SCD early after STEMI
Discussion

- Additional value of the current study
  - all STEMI patients treated with primary PCI
  - early ICD implantation

- Premature termination of the trial and lack of ICD therapy data, limits interpretation of the results

- 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       Prof. Zijlstra
Dr. Ottervanger        Dr. Wever
Prof. Schalij           Prof. de Boer

On behalf of the DAPA investigators

CRO: Diagram BV, Zwolle, The Netherlands
### LVEF at baseline and follow-up (18 months)

<table>
<thead>
<tr>
<th></th>
<th>ICD (n=128)</th>
<th>No ICD (n=135)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic LV function at Randomization, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>7.8</td>
<td>5.2</td>
<td>0.82</td>
</tr>
<tr>
<td>20-30%</td>
<td>68.8</td>
<td>71.9</td>
<td></td>
</tr>
<tr>
<td>30-40%</td>
<td>17.2</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>&gt;40%</td>
<td>6.3</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>77.3</td>
<td>77.0</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Systolic LV function 18 months, n (%)</strong></td>
<td>N= 109</td>
<td>N = 91</td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>4.6</td>
<td>3.3</td>
<td>0.52</td>
</tr>
<tr>
<td>20-30%</td>
<td>44.0</td>
<td>35.2</td>
<td></td>
</tr>
<tr>
<td>30-40%</td>
<td>29.4</td>
<td>37.4</td>
<td></td>
</tr>
<tr>
<td>&gt;40%</td>
<td>22.1</td>
<td>24.2</td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>48.6</td>
<td>38.5</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Follow-up flow-chart of patients with LVEF<30% randomized to no ICD at 18 months. LVEF, left ventricular ejection fraction.

LVEF <30% (control group)  
n=37

Cross-over to ICD,  
Persistent LVEF <30% during FU  
n=17 (45.9%)
  * Died, n=9 (52.9%)  
  Alive, n=8 (47.1%)

No cross-over to ICD,  
LVEF improved 35-40% during FU or other reasons (comorbidity, frailty)  
n=20 (54.1%)
  ** Died, n=10 (50%)  
  Alive, n=10 (50%)

*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)  
Unknown (n=1)