Prevention of Sudden Cardiac Death

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Presenter Disclosure Information

Gerhard Hindricks has received honoraria for lectures from Biosense, St. Jude Medical, Biotronik, Medtronic, Boehringer Ingelheim

Gerhard Hindricks has received research grants from St. Jude Medical, Biotronik, Biosense

Gerhard Hindricks is a member of the Advisory Board / consultant for Biosense, St. Jude Medical, Biotronik, Stereotaxis
More people die from SCD than AIDS, breast cancer and lung cancer combined.

- SCD (300,000)
- AIDS (16,000)
- BREAST CANCER (40,600)
- LUNG CANCER (157,400)

Sources:
More people die from SCD than AIDS, breast cancer and lung cancer combined.

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Sources:
Prevention of SCD: Agenda

• brief overview: epidemiology of SCD

• risk stratification for SCD
  - noninvasive markers
  - invasive markers
  - genetic markers

• preventive strategies
  - role of CAD / HF prevention
  - role of the ICD
  - ….beyond the ICD?
Epidemiology of SCD: USA 2012

- annual rate 184,000 – 462,000 (1)
- about 50% - 70% arrhythmic deaths (2)
- vast majority of victims have organic heart disease (1,2)
  - clinically diagnosed
  - unknown / subclinical diseases
    [195,000 silent MI / yr in US]
- significant impact of age, race, and gender (1)

(1) AHA Heart disease and stroke statistics - 2012 update; Circulation 2012
(2) Goldberger JJ et al.; Circulation 2011
Sudden Cardiac Death

First rhythm documented at time of arrhythmic SCD

adopted from Bayes de Luna et al; Am Heart J 1989
Sudden Cardiac Death

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Structural heart disease in SCD survivors

Deo R, Albert CM; Circulation 2012
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Sudden Cardiac Death

Incidence of SCD according to age, race, and gender

Deo R, Albert CM; Circulation 2012
Sudden Cardiac Death

Absolute number of events and event rates of SCD

adopted from: Meyerburg RJ; Circulation 1992
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Sudden Cardiac Death

Absolute number of events and event rates of SCD

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SCD risk stratification: an ongoing dilemma

- LVEF (< 35%)
- QRS-duration
- micro T wave alternans
- ventricular ectopy
- ventricular late potentials
- heart rate turbulence
- heart rate variability
- baroreflex sensitivity
- programmed ventricular stimulation
SCD risk stratification: an ongoing dilemma

- LVEF (< 35%)
- QRS-duration
- micro T wave alternans
- ventricular ectopy
- ventricular late potentials
- heart rate turbulence
- heart rate variability
- baroreflex sensitivity
- programmed ventricular stimulation

No strategy proved effective predicting SCD to achieve guideline relevance
Sudden Cardiac Death

**SCD risk stratification: an ongoing dilemma**

- LVEF (< 35%)
- QRS-duration
- micro T wave alternans
- ventricular ectopy
- ventricular late potentials
- heart rate turbulence
- heart rate variability
- baroreflex sensitivity
- programmed ventricular stimulation

*Importance of Risk Stratification*

*Given the relatively poor performance of current risk stratification approaches for SCD and the aforementioned various challenges and limitations, it is reasonable to query whether further efforts should be devoted to this area. From a therapeutic perspective, there is great need for risk stratification for SCD. Although lifestyle modifications and medical*  

*Goldberger et al.; Circulation 2011*
SCD risk stratification: an ongoing dilemma

- risk factors are not static but dynamic
- quantitative and qualitative durability of risk markers not defined
- temporal variation of risk factors occur as a function of
  - time of the day
  - day of the week
  - season of the year
- role of rest/exertion for risk marker assessment unclear
- frequency of risk marker assessment
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Critical pathways leading to electrical instability and SCD

Deo R, Albert CM; Circulation 2012
Sudden Cardiac Death

Critical pathways leading to electrical instability and SCD

Shared Risk Factors:
- Age
- HTN
- Diabetes
- Smoking
- Obesity
- Kidney disease
- Inflammation
- Genetics

CHD
- Fibrous/Scar
- Ischemia
- LV Dilation/Myocardial Stretch

CHF
- Hypertrophy
- Fibrous/Scar
- Myocardial Inflammation
- Altered Repolarization

Altered Calcium Regulation
- Fibrous/Scar
- LV Dilation/Myocardial Stretch
- Hypertrophy

Vulnerable Substrate

Triggers
- Sympathetic activation
- Ischemia
- Environmental stress
- Electrolyte flux
- Acute hemodynamic stress

Membrane Stabilizers
- N-3 PUFAs
- Magnesium
- NEFAs

Genetic Predisposition
- Automaticity
- Conduction
- Repolarization

SCD

Deo R, Albert CM; Circulation 2012
SCD risk stratification: role of genetic risk assessment

- Genetic testing has proved effective for risk stratification in some patients with suspected channelopathies such as LQT-syndrome, Brugada syndrome, or CPVT.

- However, these patients represent only a small minority of SCD victims.

- Identification of genes affecting cardiac electrophysiology and modulating SCD risk has raised the possibility that common genetic variants or polymorphisms in the same region may account for SCD risk in non-channelopathy patients as well.
### SCD risk stratification: role of genetic risk assessment

**Table 3. Candidate Genes for SCD in the General Population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Gene</th>
<th>Frequency of Variant Allele</th>
<th>Population</th>
<th>N (SCD Cases/Controls)</th>
<th>Findings/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Westaway et al 2011</td>
<td>CASQ2 GPD1L</td>
<td>10–45%</td>
<td>Americans of European ancestry, general population</td>
<td>670/299</td>
<td>Polymorphisms in these genes are associated with SCD</td>
</tr>
<tr>
<td>Albert et al 2010</td>
<td>KCNQ1 KCNH2</td>
<td>60–70%</td>
<td>Americans of European ancestry, general population</td>
<td>516/1522</td>
<td>2 intronic variants (1 in KCNQ1 and 1 in SCN5A) were associated with SCD</td>
</tr>
<tr>
<td>Stecker et al 2005</td>
<td>SCN5A</td>
<td>1–4%</td>
<td>Americans of European ancestry with coronary disease</td>
<td>67/91</td>
<td>No association was observed between SCN5A polymorphisms or mutations with SCD</td>
</tr>
<tr>
<td>Burke et al 2005</td>
<td>SCN5A (Y1102A)</td>
<td>9%</td>
<td>Blacks, general population</td>
<td>162/107</td>
<td>Y1102A was associated with unexplained arrhythmic death and SCA</td>
</tr>
<tr>
<td>Splotkowski et al 2002</td>
<td>SCN5A (Y1102A)</td>
<td>13%</td>
<td>Blacks, general population</td>
<td>23/100</td>
<td>Variant is associated with an increased risk of SCD or medication induced QTc prolongation</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gavin et al 2011</td>
<td>β2AR (Gln27Glu)</td>
<td>45%</td>
<td>Americans of European ancestry, general population</td>
<td>492/1388</td>
<td>When combined with the 2 analyses below, the β2AR polymorphism is associated with SCD</td>
</tr>
<tr>
<td>Tseng et al 2008</td>
<td>β2AR and β1AR</td>
<td>30–40% (β2AR) 10–30% (β1AR)</td>
<td>Aborted SCD and history of MI/CAD, 75% Americans of European ancestry</td>
<td>107/388</td>
<td>No association was observed between any of the βAR polymorphisms and SCD</td>
</tr>
<tr>
<td>Sooodehnia et al 2006</td>
<td>β2AR (Gln27Glu)</td>
<td>43% whites, 19% blacks</td>
<td>American cohort (4441 European ancestry, 808 Blacks)</td>
<td>195/5249</td>
<td>The β2AR variant is associated with SCD in whites but not blacks</td>
</tr>
<tr>
<td>Snapir et al 2003</td>
<td>Alpha23-AR</td>
<td>48%</td>
<td>Finnish, population based</td>
<td>278/405</td>
<td>The deletion/deletion genotype of the α23 adrenoceptor gene increased the risk for SCD in middle-aged men</td>
</tr>
</tbody>
</table>
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**SCD risk stratification: role of genetic risk assessment**

- Genetic testing has proved effective for risk stratification in patients with suspected channelopathies such as LQT-syndrome, Brugada syndrome, or CPVT.

- However, these patients represent only a small minority of SCD victims.

- Identification of genes affecting cardiac electrophysiology and modulating SCD risk has raised the possibility that common genetic variants or polymorphisms in the same region may account for SCD risk in non-channelopathy patients as well.

- Although a rapidly increasing set of knowledge in this field has been reported, no genetic strategies for SCD risk assessment in non-channelopathy patients are currently available.
Prevention of SCD: Agenda

- brief overview: epidemiology of SCD

- risk stratification for SCD
  - noninvasive markers
  - invasive markers
  - genetic markers

- preventive strategies
  - role of CAD / HF prevention
  - role of the ICD
  - ....beyond the ICD?
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Structural heart disease in SCD survivors

Deo R, Albert CM; Circulation 2012
Sudden Cardiac Death

Absolute number of events and event rates of SCD

adopted from: Meyerburg RJ; Circulation 1992
Sudden Cardiac Death

Epstein et al. JACC 2008, 52: 1122-1127
## Sudden Cardiac Death

### ICD therapy to prevent SCD

<table>
<thead>
<tr>
<th>Study</th>
<th>Amiodarone</th>
<th>BB</th>
<th>ACEI/AT1</th>
<th>Statin</th>
<th>Total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amiodarone</td>
<td>BB</td>
<td>ACEI/AT1</td>
<td>Statin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>Control</td>
<td>ICD</td>
<td>Control</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>6</td>
<td>3</td>
<td>16</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>MADIT</td>
<td>7</td>
<td>45</td>
<td>27</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>MUSTT</td>
<td>?</td>
<td>?</td>
<td>33</td>
<td>23</td>
<td>76</td>
</tr>
<tr>
<td>MADIT II</td>
<td>13</td>
<td>10</td>
<td>70</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>8</td>
<td>14</td>
<td>87</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>AVID</td>
<td>9</td>
<td>82</td>
<td>39</td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>CIDS</td>
<td>0</td>
<td>85</td>
<td>30</td>
<td>22</td>
<td>?</td>
</tr>
<tr>
<td>CASH</td>
<td>0</td>
<td>48</td>
<td>0</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>AMIOVIRT</td>
<td>0</td>
<td>66</td>
<td>53</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>4</td>
<td>7</td>
<td>86</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>0</td>
<td>100/0</td>
<td>69</td>
<td>69/69</td>
<td>94</td>
</tr>
</tbody>
</table>
ICD therapy to prevent SCD in non-ischemic CM

Bänsch D. Circulation. 2002; 105; 1453-1458

Strickberger SA. J Am Coll Cardiol. 2003; 41: 1707-12

ICD therapy to prevent SCD in non-ischemic CM

<table>
<thead>
<tr>
<th></th>
<th>HR (97.5% CI)</th>
<th>P-Wert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodaron vs. Plazebo</td>
<td>1.07 (0.76-1.51)</td>
<td>0.65</td>
</tr>
<tr>
<td>ICD Therapie vs. Plazebo</td>
<td>0.73 (0.50-1.07)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

NIDCM = n.s.
Sudden Cardiac Death

ICD therapy to prevent SCD post MI

Sudden Cardiac Death

ICD therapy to prevent SCD: role of competing RF

Prevention of SCD beyond the ICD: options

- Primary prevention of CAD / heart failure
  - life style modifications
  - prevention / treatment of metabolic syndrome

- Genetic risk stratification

- Appropriate / intense treatment of CAD / HF

- Electrical treatment of HF (CRT-P)

- EP interventions:
  - catheter ablation / substrate modification
  - modulation of autonomic tone
# Sudden Cardiac Death

## Absolute number of events and event rates of SCD

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td></td>
</tr>
<tr>
<td>High-risk subgroups</td>
<td></td>
</tr>
<tr>
<td>Any prior coronary event</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effort less than 30% or HF</th>
<th>MADIT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest survivor</td>
<td>SCD-HeFT</td>
</tr>
<tr>
<td>Arrhythmia risk markers, post MI</td>
<td>AVID, CIDS, CASH</td>
</tr>
<tr>
<td></td>
<td>MADIT I, MUSTT</td>
</tr>
</tbody>
</table>

Percent | Absolute Number
---|---
0 | 0
10 | 0
20 | 0
30 | 0

---

adopted from: Meyerburg RJ; Circulation 1992
Prevention of SCD beyond the ICD: “green group”

- Primary prevention of CAD / heart failure
  - lifestyle modifications
  - prevention / treatment of metabolic syndrome

- Genetic risk stratification (?)

- Appropriate treatment of CAD / HF incl. CRT-P

- EP interventions:
  - catheter ablation / substrate modification
  - modulation of autonomic tone (?)
Prevention of SCD: role of renal denervation?
Sudden Cardiac Death

Prevention of SCD: role of renal denervation?

Repeated measures ANOVA: P<0.001 for SBP & DBP
P<0.0001 vs. baseline for each SBP & DBP

Prevention of SCD beyond the ICD: “red group”

- Genetic risk stratification (?)
- Appropriate treatment of CAD / HF incl. CRT-P / D
- Evidence based ICD / CRT therapy
  - updated set of prospective studies
- EP interventions:
  - catheter ablation / substrate modification (?)
  - modulation of autonomic tone (?)