Biomarkers and Arrhythmias/Devices

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Disclosures

Honoraria, Research Grants, Medtronic
Honoraria, Research Grants, St. Jude Medical
Honoraria, Research Grants, Biotronik
Outline

• Biomarkers in Sudden Cardiac Death (SCD)
• Biomarkers in Atrial Fibrillation
• Biomarkers in Cardiac Resynchronization Therapy
• Biomarkers in Diagnosis of Device Infections
Biomarkers in SCD

- SCD is the most common cause of death in the U.S.
- Incidence 300,000 to 400,000 each year (U.S.)
- 1,000 Cardiac arrests occur daily in the U.S.
Incidence of Sudden Death in Specific Populations

GROUP

- General Population
- Patients with high coronary-risk profile
- Patients with previous coronary event
- Patients with ejection fraction <35%, Congestive heart failure
- Patients with previous out-of-hospital cardiac arrest
- Patients with previous Myocardial infarction, low ejection fraction, and ventricular tachycardia

Incidence of Sudden Death (% of group)

No. of Sudden Deaths Per Year

Huikuri, et al., NEJM, Vol. 345, No. 20 Nov. 2001
Biomarkers in SCD

- The Implantable Cardioverter Defibrillator (ICD) remains the most effective therapy in patients with structural heart disease.

- ICD implant criteria based on Ejection Fraction. It has been challenging to find other/better/additional risk predictors for ventricular arrhythmias.

- Most biomarker studies to date involve ICD patients with retrospective analysis of BNP and ICD therapy.
Biomarkers in Cardiovascular Death in the Heart Failure and Coronary Artery Disease Population

Risk Factors
Age, Hypercholesterolemia, Smoking, Diabetes Mellitus, Hypertension, Renal Dysfunction, Inflammation, Genetics, Physical Inactivity, Psycho-social factors etc.

Coronary Artery Disease
- Inflammation
  - CRP, suPAR
- Oxidative Stress
  - Aminothiols, HSP
- Neurohormonal
  - Renin-angiotensin-aldosterone
- Coagulation
- Myocardial stress
  - Troponin

Heart Failure
- Hemodynamic
  - BNP
- Myocardial stress/fibrosis
  - Troponin, sST2
- Neurohormonal
  - MR-proADM, copeptin

Vulnerable Substrate
Plaque rupture/Arrhythmia/Cardiovascular Death

Dhindsa et al., *Biomarkers to Predict Cardiovascular Death*, https://www.ncbi.nlm.nih.gov/pubmed/29173408
### 3.2.5. Biomarkers

**Recommendation for Biomarkers**

Referenced studies that support the recommendation are summarized in Online Data Supplement 7.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>1. In patients with structural heart disease, measurement of natriuretic peptides (BNP or N-terminal pro-BNP) can be useful by adding prognostic information to standard risk factors for predicting SCD or SCA (1-4).</td>
</tr>
</tbody>
</table>

Al-Khatib SM, et al., 2017 VA/SCD Guideline: Executive Summary
Biomarkers in Atrial Fibrillation

- AF is the most common clinical arrhythmia and the prevalence is projected to increase markedly in the coming decades.
- AF is independently associated with up to two-fold higher risk of death.
- AF has been estimated to contribute to 130,000 deaths each year.
- Established risk score for ischemic stroke; CHA\textsubscript{2}DS\textsubscript{2}-VASc.
- Overall, use of biomarkers has not been integrated into clinical management of AF.
### Biomarkers in Atrial Fibrillation

**Guideline Recommendations**

#### Recommendation for prediction of stroke and bleeding risk

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CHA₂DS₂-VASc score is recommended for stroke risk prediction in patients with AF.</td>
<td>I</td>
<td>A</td>
<td>368, 371, 386</td>
</tr>
<tr>
<td>Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.</td>
<td>Iia</td>
<td>B</td>
<td>384, 386, 387, 389–392</td>
</tr>
<tr>
<td>Biomarkers such as high-sensitivity troponin and natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients.</td>
<td>Iib</td>
<td>B</td>
<td>380–382, 387, 393</td>
</tr>
</tbody>
</table>

*2016 ESC Guidelines for Management of Atrial Fibrillation*
Biomarkers in Atrial Fibrillation
Troponin

- Troponin is prognostic in patients with atrial fibrillation, correlating with increased cardiovascular events such as ischemic stroke, TIA, acute coronary syndrome, acute heart failure, major bleeding and death.

- How do you implement this finding clinically?
Can troponin help detect increased risk of AF?
Not enough data

Can troponin help predict postop AF?
No clear benefit

Can troponin help in AF patients who present with chest pain, r/o MI?
Biomarkers in Atrial Fibrillation

Troponin

Biomarkers in Atrial Fibrillation

Troponin

• Can troponin help detect increased risk of AF?
  Not enough data

• Can troponin help predict postop AF?
  No clear benefit

• Can troponin help in AF patients who present with chest pain, r/o MI?
  Maybe

• Can troponin help in risk stratification in new onset AF?
Biomarkers in Atrial Fibrillation
Troponin

Biomarkers in Atrial Fibrillation
BNP and NT-proBNP

• Similar to troponin, BNP and NT-proBNP have shown to be associated with AF incidence, postoperative AF and prognosis in AF

• It has also been associated with diagnosis of heart failure in AF and predicting success of DC cardioversion for AF

• How to implement clinically?
Biomarkers in Atrial Fibrillation
B-Type Natriuretic Peptide

Biomarkers in Atrial Fibrillation

ST₂

Biomarkers in Atrial Fibrillation

ABC Death Risk Score

Cardiac resynchronization therapy (CRT) is an effective therapy for selected patients with heart failure. CRT reduces mortality and improves morbidity. CRT is has a Class I indication in patients with LVEF ≤35%, QRS duration ≥150 ms with Left Bundle Branch Block (LBBB) morphology and on optimal medical therapy (OMT). However, a non-response rate of 20%–40% exists and has remained unchanged over the last decade, despite extensive research.
Biomarkers in Cardiac Resynchronization Therapy

- Could biomarkers help predict reversal of adverse cardiac remodeling?
Biomarkers in Cardiac Resynchronization Therapy


Results:

- Consistent observation in all ECM biomarker behavior before and after CRT implantation was not observed between studies. Galectin-3 did not predict response to CRT.
Biomarkers in Cardiac Resynchronization Therapy

Biomarkers in Cardiac Resynchronization Therapy

Changes in CT-apelin and NT-proBNP levels according to response to CRT

Biomarkers in Cardiac Resynchronization Therapy

Biomarkers in Diagnosis of Device Infections

- Worldwide implantation rates of Cardiac Implantable Electronic Devices (CIED) are estimated at 1,250,000 pacemakers and 410,000 ICDs per year with an annual increase of about 5%.

- Increase implantation rates have resulted in increased complication rates and specifically a disproportionate increase in device infections.

- CIED infections are associated with significant morbidity, higher mortality and increased costs.
Biomarkers in Diagnosis of Device Infections

• In suspected device pocket infections an early diagnosis and subsequent complete device and lead removal is important to avoid progression to sepsis or endocarditis.

• Diagnosing a pocket infection can be challenging as patients may present with mild/few symptoms or lack of clear cut signs of local infection.

• Conventional inflammation related biomarkers such as WBC or ESR have low sensitivity to pocket infections. Are there better biomarkers?
Biomarkers in Diagnosis of Device Infections

Comparison of sensitivity and specificity for relevant biomarkers applying established or optimized cut-off values.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unit</th>
<th>established cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>optimized cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>mg/l</td>
<td>&gt;5.0</td>
<td>32%</td>
<td>86%</td>
<td>&gt;2.1</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td>HS-CRP</td>
<td>mg/l</td>
<td>&gt;3.35</td>
<td>44%</td>
<td>80%</td>
<td>&gt;3.0</td>
<td>56%</td>
<td>76%</td>
</tr>
<tr>
<td>PCT</td>
<td>ng/ml</td>
<td>&gt;0.5</td>
<td>0%</td>
<td>100%</td>
<td>&gt;0.05</td>
<td>60%</td>
<td>82%</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>pg/ml</td>
<td>&gt;0.12</td>
<td>28%</td>
<td>36%</td>
<td>&gt;0.24</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>TNF-α</td>
<td>pg/ml</td>
<td>&gt;6.0</td>
<td>4%</td>
<td>96%</td>
<td>&gt;0.22</td>
<td>92%</td>
<td>84%</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0172384.t004

Conclusions

- **Biomarkers in SCD** - *Class II a recommendation exists for BNP in risk stratification for SCD*
- **Biomarkers in Atrial Fibrillation** – *showing some promise, will be interesting to see if the ABC risk score gets clinical traction*
- **Biomarkers in Cardiac Resynchronization Therapy** – *we are along way from identifying any biomarkers that can help predict non response*
- **Biomarkers in Diagnosis of Device Infections** – *seems reasonable to check a PCT level in the more challenging diagnostic cases*