Atrial fibrillation and stroke

Isabelle C Van Gelder
University Medical Center Groningen
The Netherlands
Stroke – what is the problem for patients with AF?

Does abolishing AF prevents stroke?

Is AF a mechanism or just a marker for stroke?

AF is progressive disease and AF progression is associated with stroke, heart failure and mortality
Content

- Stroke – what is the problem for patients with AF?
AF and HRs for stroke and other vascular events

Primary care research database, UK population (87% white)
Linked with secondary care data and cause-specific mortality data
4.3 million adults, included at standard GP with 1 RR 1990-2013 FU 7 yrs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
<th>Test for interaction</th>
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<tbody>
<tr>
<td>Haemorrhagic stroke</td>
<td></td>
<td>2.22</td>
<td>[1.60; 3.08]</td>
<td>p=0.0674</td>
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<tr>
<td>No antithrombotic therapy</td>
<td></td>
<td>2.22</td>
<td>[1.60; 3.08]</td>
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<tr>
<td>Antithrombotic therapy</td>
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<td>1.54</td>
<td>[1.24; 1.92]</td>
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<tr>
<td>Ischemic stroke</td>
<td></td>
<td>2.72</td>
<td>[2.19; 3.38]</td>
<td>p&lt;0.0001</td>
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<tr>
<td>No antithrombotic therapy</td>
<td></td>
<td>2.72</td>
<td>[2.19; 3.38]</td>
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<tr>
<td>Antithrombotic therapy</td>
<td></td>
<td>1.15</td>
<td>[1.02; 1.29]</td>
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<tr>
<td>Unspecified stroke</td>
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<td>2.59</td>
<td>[2.25; 2.99]</td>
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<td>2.59</td>
<td>[2.25; 2.99]</td>
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<td>1.15</td>
<td>[1.06; 1.24]</td>
<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td></td>
<td>2.52</td>
<td>[2.23; 2.84]</td>
<td>p&lt;0.0001</td>
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<tr>
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<td>2.52</td>
<td>[2.23; 2.84]</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td></td>
<td>0.76</td>
<td>[0.70; 0.82]</td>
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<tr>
<td>Heart failure</td>
<td></td>
<td>3.80</td>
<td>[3.50; 4.12]</td>
<td>p&lt;0.0001</td>
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<td>3.80</td>
<td>[3.50; 4.12]</td>
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<tr>
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<td>1.60</td>
<td>[1.53; 1.68]</td>
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<tr>
<td>Peripheral artery disease</td>
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<td>2.09</td>
<td>[1.73; 2.53]</td>
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<td>2.09</td>
<td>[1.73; 2.53]</td>
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<tr>
<td>Antithrombotic therapy</td>
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<td>0.87</td>
<td>[0.78; 0.96]</td>
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<td>Aortic aneurysm</td>
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<td>1.02</td>
<td>[0.67; 1.54]</td>
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<td></td>
<td>1.02</td>
<td>[0.67; 1.54]</td>
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<td></td>
<td>0.92</td>
<td>[0.74; 1.13]</td>
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<tr>
<td>Chronic kidney disease</td>
<td></td>
<td>1.42</td>
<td>[1.31; 1.54]</td>
<td></td>
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<td>1.42</td>
<td>[1.31; 1.54]</td>
<td></td>
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<tr>
<td>Antithrombotic therapy</td>
<td></td>
<td>1.10</td>
<td>[1.05; 1.15]</td>
<td></td>
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<tr>
<td>Vascular dementia</td>
<td></td>
<td>1.57</td>
<td>[1.14; 2.17]</td>
<td></td>
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<td>No antithrombotic therapy</td>
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<td>1.57</td>
<td>[1.14; 2.17]</td>
<td></td>
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<tr>
<td>Antithrombotic therapy</td>
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<td>1.29</td>
<td>[1.08; 1.54]</td>
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<tr>
<td>Any vascular event</td>
<td></td>
<td>2.15</td>
<td>[2.05; 2.24]</td>
<td>p&lt;0.0001</td>
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<td>[1.12; 1.18]</td>
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</table>
Individuals with stroke

47 countries – 15,400 AF pts admitted to emergency dept 1 year follow-up
11% died: 6% with primary AF; 16% with secondary AF
4% had stroke: 3% vs 5%

Healey RE-LY registry Lancet 2016
Content

- Stroke – what is the problem for patients with AF?
- Does abolishing AF prevents stroke?
**New drug targets for AF**

**Outline**
- 32% rhythm control
- 3% rate control
- 4% rate control

**Stroke**

**A Death from Any Cause**

32% rhythm control
3% rate control

Hazard ratio, 0.97 (95% CI, 0.80–1.17)
P = 0.73

**B Stroke**

3% rhythm control
4% rate control

Hazard ratio, 0.74 (95% CI, 0.40–1.35)
P = 0.32

**C Worsening Heart Failure**

28% rhythm control
31% rate control

Hazard ratio, 0.87 (95% CI, 0.72–1.06)
P = 0.17

**D Composite Outcome**

43% rhythm control
46% rate control

Hazard ratio, 0.90 (95% CI, 0.77–1.06)
P = 0.20

**No. at Risk**

**A Death from Any Cause**

<table>
<thead>
<tr>
<th></th>
<th>Rhythm control</th>
<th>Rate control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>593</td>
<td>604</td>
</tr>
<tr>
<td>12</td>
<td>514</td>
<td>521</td>
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<td>24</td>
<td>378</td>
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<td>228</td>
<td>219</td>
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<tr>
<td>48</td>
<td>82</td>
<td>69</td>
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</table>

**B Stroke**

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<tbody>
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<td></td>
</tr>
<tr>
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<td>589</td>
<td>596</td>
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<tr>
<td>12</td>
<td>507</td>
<td>512</td>
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<tr>
<td>24</td>
<td>367</td>
<td>373</td>
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<td>36</td>
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<td>216</td>
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<td>48</td>
<td>79</td>
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**C Worsening Heart Failure**

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<tr>
<th></th>
<th>Rhythm control</th>
<th>Rate control</th>
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</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>523</td>
<td>509</td>
</tr>
<tr>
<td>12</td>
<td>436</td>
<td>419</td>
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<tr>
<td>24</td>
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<td>165</td>
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<td>48</td>
<td>63</td>
<td>54</td>
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**D Composite Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Rhythm control</th>
<th>Rate control</th>
</tr>
</thead>
<tbody>
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<td>Months</td>
<td></td>
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<tr>
<td>0</td>
<td>518</td>
<td>502</td>
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<tr>
<td>12</td>
<td>432</td>
<td>412</td>
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<td>303</td>
<td>281</td>
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<td>36</td>
<td>169</td>
<td>162</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
<td>53</td>
</tr>
</tbody>
</table>
**Early treatment of AF for Stroke prevention Trial EAST**

**Pre-Study Screening**

- Patients at risk for cardiovascular events ($\equiv$ CHA$_2$DS$_2$VASc score $\geq 2^*$)
  - and having
  - recent onset atrial fibrillation ($\leq$ 1 year duration or first documented by ECG)

*Detailed inclusion criteria:
One of the following: age $>$ 75 years or prior stroke / TIA
OR
Two of the following: age $>$ 65 years; female sex; arterial hypertension; diabetes mellitus;
previous myocardial infarction; CABG or PCI; stable heart failure (NYHA II or LVEF$<$50%);
left ventricular hypertrophy ($>$15 mm wall thickness); chronic kidney disease (MDRD stage III - IV); peripheral artery disease.

**Study Procedures**

- Early Rhythm Control
  - anticoagulation, rate control and either antiarrhythmic drug therapy or pulmonary vein isolation (PVI)
  - in case of recurrent AF: Re-PVI, adaptation of antiarrhythmic drug therapy
  - ECG monitoring of therapy

- Usual Care
  - anticoagulation, rate control, supplemented by rhythm control only in symptomatic patients on optimal rate control therapy

- outpatient FU at 12, 24, 36 moths (both study groups)
- therapy of underlying heart disease (both study groups)
- blind assessment of primary outcomes (both study groups)
Content

- Stroke – what is the problem for patients with AF?
- Does abolishing AF prevents stroke?
- Is AF a mechanism or just a marker for stroke?
Temporal disconnect

monitoring

VKA therapy

stroke

Brambatti for the ASSERT Investigators Circulation 2014

Parekh et al. Circ 2006
AF: mechanism or marker for stroke?

SCAF episodes are associated with AF but only a minority had SCAF in the month before their stroke.
AF and stroke – mechanism more complicated

Hyper-coagulability and other mechanisms

AF: mechanism or marker for stroke?

Risk factors → Atrial myopathy

Atrial fibrillation → and AF progression

Atrial myopathy → Atrial fibrillation
Content

- Stroke – what is the problem for patients with AF?
- Does abolishing AF prevents stroke?
- Is AF a mechanism or just a marker for stroke?
- AF is progressive disease and AF progression is associated with stroke, heart failure and mortality
AF progression is associated with vascular risks

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>FU, years</th>
<th>AF progression</th>
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<tr>
<td>Euro Heart Survey AF, 2010</td>
<td>1219</td>
<td>1</td>
<td>15%</td>
</tr>
<tr>
<td>Record-AF, 2012</td>
<td>2137</td>
<td>1</td>
<td>15%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>AF progression</th>
<th>No AF progression</th>
<th>p value</th>
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<tbody>
<tr>
<td>De Vos, Crijns, Euro Heart Survey JACC 2010</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CV admissions (%)</td>
<td>71 %</td>
<td>50 %</td>
<td>&lt;0.001</td>
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<tr>
<td>Stroke</td>
<td>6 %</td>
<td>2 %</td>
<td>0.003</td>
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<tr>
<td>CV mortality</td>
<td>7 %</td>
<td>3 %</td>
<td>0.005</td>
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Risk of ischemic stroke or embolism in SCAF

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months</th>
<th>Hazard Ratio with Subclinical Atrial Tachyarrhythmias (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Present (N=261)</td>
<td>Absent (N=2319)</td>
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<tr>
<td>--------------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>no. of events</td>
<td>%/yr</td>
<td>no. of events</td>
</tr>
<tr>
<td>Ischemic stroke or systemic embolism*</td>
<td>11</td>
<td>1.69</td>
<td>40</td>
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<tr>
<td>Ischemic stroke</td>
<td>10</td>
<td>1.54</td>
<td>36</td>
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<tr>
<td>Systemic embolism</td>
<td>1</td>
<td>0.15</td>
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Longer subclinical AF: higher risk of stroke

Van Gelder, Healey for the ASSERT Investigators Eur Heart J 2017
Conclusions

- Stroke is still a significant problem in AF, next to heart failure
- Mechanism of stroke in AF still not completely known
- AF mechanism or bystander of stroke, anyway AF often increases risk of stroke
CHA$_2$DS$_2$-VASc score is not static!

- Not static
- Most pts with ischemic stroke developed $\geq$1 new stroke risk factor
Stroke – what is the problem for patients with AF?

Does abolishing AF prevents stroke?

Is AF a mechanism or just a marker for stroke?

AF is progressive disease and AF progression is associated with stroke, heart failure and mortality

Hypercoagulability not only mechanism of stroke but also of AF progression?
Hypercoagulability and remodeling

Associated disease

Thrombin activation

Structural Remodeling
- Enlarged atria
- Hypertrophy
- Fibrosis
- Dedifferentiation
- Apoptosis
- Myolysis

Focal triggers of AF

Atrial Fibrillation

Electrical Remodeling

Cellular Ca\(^{2+}\) overload

Endothelin-1

Natriuretic peptides

Heat shock proteins

Inflammation oxidative stress

De Jong, Cardiovasc Res, 2011
Hypercoagulability and remodeling

- Hypercoagulability represents a so far unrecognized key mechanism in atrial remodeling and AF progression
Hypercoagulability associated with atrial remodeling

**Hypercoagulability**

- Thrombin

Cardiac fibroblast

- IL-6
- MCP-1
- TGF-β

Pro-fibrotic and inflammatory cytokines

Dedifferentiation (Myofibroblasts)

Collagen synthesis

<table>
<thead>
<tr>
<th>MCP-1</th>
<th>α-SMA</th>
<th>(^{3}\text{H}-\text{proline incorporation} )</th>
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<tbody>
<tr>
<td>Thrombin (0.01U/ml) +72%</td>
<td>+200%</td>
<td>+120%</td>
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<tr>
<td>Thrombin + Dabigatran ns</td>
<td>ns</td>
<td>ns</td>
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</table>

**Fibroblasts incubated with thrombin**

Spronk et al. Eur Heart J 2016
Thrombin promotes AF

Wildtype mice

TM pro/pro transgenic mice with enhanced thrombin activity (hypercoagulable phenotype)

AF inducible (%)

AF Duration (s)
Hypercoagulability and remodeling

AF

Hypertension, heart failure

Thrombin activation

PAR stimulation

Atrial remodeling *

AF progression

Stroke and other MACCE

* Capillary rarefaction, Inflammation, Myocyte death, Fibroblast proliferation, Fibrosis, Dispersion of conduction & repolarisation

IL-6

MCP-1

TGF-β
Hypercoagulability is one of the key mechanisms in AF progression (permanent AF and CV morbidity and mortality)

Hypercoagulability varies depending on duration of AF and severity of the underlying vascular diseases

Thrombin inhibitors, Factor Xa inhibitors and vitamin K antagonists differ with respect to prevention of AF progression
Study design RACE V

- Multicenter, prospective, observational study
- 750 patients with self-terminating AF
  - Extensive phenotyping and characterization
  - Continuous rhythm monitoring
- Total inclusion duration 2 years
- Total follow-up 2.5 years
- Main study endpoint AF progression
- Expected AF progression rate 10%/ year → 187 AF progression events
Continuous rhythm monitoring RACE V

Medtronic Advisa Pacemaker

CareLink system

Medtronic Reveal LINQ

FOCUSON™
- 65 year old female
- Symptomatic atrial fibrillation
- Risk factor for AF hypertension
- Near collaps ~19.15 h
Content

- Stroke – what is the problem for patients with AF?
- Does abolishing AF prevents stroke?
- Is AF a mechanism or just a marker for stroke?
- AF is progressive disease and AF progression is associated with stroke, heart failure and mortality
- Hypercoagulability not only mechanism of stroke but also of AF progression?
ILR diagnostics

Red ILR alert
- Asystole/ pause > 4.5 sec
- Sustained bradycardia < 30/min
- Sustained tachycardia > 182/min
- Sustained VT > 182 bpm
- Any torsade des pointes (TdP)

Diagnoses / treatments

- Pacemaker adjustments as needed
- Adjust AAD: control AF(L)
- Adjust AAD, electrolytes: prevent TdP
- Adjust rate control / heart failure drugs
- Consider acute catheter ablation / ECV
- ACS therapy / PCI as needed

Yellow ILR alert
- Successive AF(L) or AT > 20 beats
- AF progression
- Sinus arrests, sympt. bradycardia
- Progressive sinus tachycardia *

- Cardioversion if persistent AF
- Consider catheter ablation
- Pacemaker as needed
- Adjust AAD: control AF(L)/ prevent TdP
- Adjust rate control / heart failure drugs
- Antithrombotics / PLAAO as needed
- ACS therapy / PCI as needed
- Blood pressure management

Red alert
- should be dealt with within one working day, subject to care by in-house 24/7 care service

Yellow alert or symptomatic patient
- Should be dealt with within 1 week

COMPASS guided diagnosis
- Decreased HRV and/or activity support heart failure, uncontrolled hypertension, or points to impact of AF w/o tachycardia if any episodes
- Increased HRV supports SSS

*) COMPASS current heart rate being > 1 week more than 25% or > 20 bpm higher than initial or set point heart rate; may indicate heart failure
1 month – 53 patients

**Transmissions Classification**

- 85% Green
- 14% Amber
- 1% Red

**Event Types**

- 2 Tachyarrhythmia
- 151 AT/AF
- 20 False positives
- 5 Low Battery
- 5 Other

**Transmissions reviewed**

- 338

**Transmissions with events (in charts)**

- 181

**Transmissions with red or amber events in 17 patients**

- 155
All,

<table>
<thead>
<tr>
<th>Episode ID#</th>
<th>Episode Date and Time</th>
<th>Report type</th>
<th>Comment</th>
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<tbody>
<tr>
<td>7 - 16</td>
<td>maart 2017</td>
<td>Full 8 maart 2017 15:43</td>
<td>CareAlert AF, alle episoden tonen AF/PAF met snelle kamerrespons. Tevens zijn er een aantal breed complex tachycardieen zichtbaar max. duur 20 seconden (#8) mogelijk VT, SVT/AT aberrante geleiding niet uitgesloten.</td>
</tr>
</tbody>
</table>
- 35 year old male
- Symptomatic atrial fibrillation
- Obesity, BMI 31, no other risk factors
Remote monitoring of patients with implantable cardiac devices has benefits both for patients and physicians

- Earlier detection of clinically relevant events not limited to SCAF
- Probable a reduction of health care costs and consumption

However, an issue is how to handle all those data efficiently

The FOCUSON™ monitoring and triaging center may help to manage an adequate handling of all transmitted ECG data

And it may potentially help to improve cardiovascular outcome
Thank you for your attention
AF is progressive disease

- AF is the most frequent arrhythmia: > 1 million will have AF by 2040
- AF is not benign being associated with MACCE
- AF is a growing health care problem

Atrial Fibrillation is a progressive disease

- … often progresses from self-terminating to non-selfterminating AF

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