Thrombozytenaggregation und DOAKs
aus der Sicht der Kardiologie

Kurt Huber, MD, FESC, FACC, FAHA
3rd Medical Department
Cardiology & Emergency Medicine
Wilhelminenhospital
Vienna, Austria

Murau, 5.6.2014

Disclosures

DISCLOSURE STATEMENT OF FINANCIAL INTEREST
Kurt Huber, MD, FESC, FACC

Research Grants from Bristol-Myers Squibb, Eli Lilly, Medtronic, Sanofi-Aventis

Consulting Fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Fibrex, Eli Lilly, Portola, Sanofi-Aventis, Schering-Plough, The Medicines Company

Lecture Fees from AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cordis / Johnson&Johnson, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Pfizer, and Sanofi-Aventis.
“triple”-Therapy in pts. with Atrial Fibrillation after ACS (or Elective Stent Implantation)

8-10% of Afib patients of cardiology departments develop ACS (or need elective stent implantation)

AND

15-20% of post ACS / electively stented patients develop Afib and are automatically prone for anticoagulation

Lip, Andreotti, Huber et al. EJ 2010

(The problem: You can not simultaneously prevent all three!)

Stent thrombosis

DAPT

Stroke

OAC

Major Bleeding
• Over 82,000 Danish Patients with AF
• National Registry
• 1997-2006
• Mean Follow-up: 3.3 Years
• 11.4% developed a non fatal or fatal bleeding

Arch Intern Med. 2010;170(16):1433-41

HR for Risk of Bleeding

10-13% major bleeding per year

Arch Intern Med. 2010;170(16):1433-41
76 year old woman with high-risk NSTEMI

- Elective angiography 2 years after PCI+stenting (LAD) and 12 months after CABG (venous grafts to ACx and RCA)
- Cardiac cath day after admission, patent grafts to RCA and LCX; 75% stenosis in stented segment of LAD, received XienceTM DES
- Creatinine increased to 2.2 mg/dL (195 µmol/L)
- Day 3, developed atrial fibrillation with worsened dyspnea

ACS, DES, who develops Afib with CHADS score of 4, CHADS-VASc of 7.
Which treatment?

A. Aspirin, clopidogrel, warfarin for one year
B. Aspirin, clopidogrel, warfarin; stop clopidogrel after 3 months
C. Aspirin, ticagrelor, warfarin; stop ticagrelor after 3-6 months
D. Clopidogrel and warfarin (stop aspirin after 0-30 days)
E. Aspirin and clopidogrel alone, due to high risk of bleeding
ESC Guidelines in AF patients at moderate to high thromboembolic risk in whom OAC is required

**Low bleeding risk**
- Elective BMS*
- Elective DES (alimimus)
- Elective DES (paclitaxel)
- ACS + BMS/DES

**High bleeding risk**
- Elective BMS
- ACS + BMS

---

A North-American consensus document on antithrombotic therapy in AF patients and a coronary stent with moderate/high stroke risk (CHADS₂ ≥2)

**Low stent thrombosis risk and low bleeding risk**
- BMS
- DES

**High stent thrombosis risk and low bleeding risk**
- BMS
- DES

**Any stent thrombosis risk and high bleeding risk**
- BMS
- DES

Dabigatran 2x110 mg was discussed for the first time as possible replacement of VKAs

---

Adapted from Camm J et al. Eur Heart J 2010;31:2369-2429

Adapted from Faxon DP. Circ Cardiovasc Interv 2011;4:522-534
Bleeding According to Antiplatelet Rx

Series of no, single, and dual antiplatelet therapy

HRs adjusted for age, gender, warfarin experience, SBP, CAD, HF, hypertension, diabetes, TIA, CrCl and statin use.

Circulation. published online December 27, 2012

Novel oral anticoagulants in patients with AF and ACS and/or coronary stents

- Rivaroxaban PIONEER
- Dabigatran RE-DUAL
- Apixaban AAA
- Edoxaban being considered
72 year old male

- Class II Angina Pectoris
- Mild HTN, hyperlipidemia
- Beta-blockade (sotalol), long acting oral nitrate, aspirin
- Paroxysmal atrial fibrillation 1-2 episodes per year. CHADS2 = 1, CHADS2-Vasc-Score = 2
- Normal rest ECG, normal LVEF on echo
- Referred for exercise testing
  - 8.5 minutes Bruce protocol; mild angina at peak
  - 1 mm ST depression at 7.5 minutes; resolves 5 min
What to Do?

- Medical therapy
- Medical therapy plus PCI
- Medical therapy plus PCI plus catheter based pulmonary vein isolation
- Medical therapy plus CABG
- Medical therapy plus CABG plus surgical MAZE plus surgical LAA ligation

Decision was …

- Medical therapy
- Medical therapy plus PCI
- Medical therapy plus PCI plus catheter based pulmonary vein isolation
- Medical therapy plus CABG
- Medical therapy plus CABG plus surgical MAZE plus surgical LAA ligation
Which post-PCI pharmacologic strategy should be chosen?

- Aspirin, clopidogrel and VKA (INR-goal 2.0-2.5) for 3 (-6) months followed by aspirin or clopidogrel plus VKA up to 12 months
- Aspirin, clopidogrel and VKA (INR-goal 2.0-2.5) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin, clopidogrel and a DOAC (reduced dosage) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin and clopidogrel for 12 months
- Aspirin and clopidogrel for 3 (-6) months, followed by dual therapy (aspirin or clopidogrel plus an anticoagulant)
- Clopidogrel and VKA (INR-goal 2.0-2.5) for 12 months
We decided …

• Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus VKA up to 12 months
• Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
• Aspirin, clopidogrel and a DOAC (reduced dosage) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
• Aspirin and clopidogrel for 12 months
• Aspirin and clopidogrel for 3 (-6) months, followed by dual therapy (aspirin or clopidogrel plus an anticoagulant)
• Clopidogrel and VKA (INR-goal 2,0-2,5) for 12 months

Should we skip aspirin?
Primary endpoint (any bleeding) and secondary endpoint (death, myocardial infarction, stroke, target vessel revascularisation and stent thrombosis)

**Primary outcome:** major/clinically relevant bleeding (through 6-12 months)

**Secondary objective:** exclude substantial increased risk of stent and substantial increased risk of stroke

**Inclusion**
- AF (prior, persistent, and/or >6 hours duration)
- CHADS ≥ 1
- Physician decision that oral anticoag is indicated
- Coronary stent (with (≥ 1/3) or without ACS)

**Randomize**
- **n ≥ 5,000 after successful stenting**

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, moderate/severe MS)

Trial of NOAC in stented patients with AF

- NOAC
- Warfarin

- ASA
- placebo
- ASA
- placebo

- Triple therapy for all for 2-4 weeks, then randomize. Duration of DAPT depends on ACS and on stent type

**Primary outcome:** major/clinically relevant bleeding (through 6-12 months)

**Secondary objective:** exclude substantial increased in risk of stent and substantial increased risk of stroke
**RE-DUAL PCI**

*Randomize*  
*Event driven*

- **Dabigatran 110 bid + single APT**  
- **Dabigatran 150 bid + single APT**  
- **Warfarin + dual APT**

**Outcomes:**  
Bleeding, death, MI, and stroke


**Duke Clinical Research Institute**

---

**PIONEER AF-PCI**

Study Diagram: Clinical Protocol RIVAROXAF3003

- N = 2,100 total  
  700 subjects per treatment strategy
- PCI (with stent placement)
- Percutaneous,  
  Persistent,  
  or Permanent non-valvular APTs
- RANDOMIZATION  
  (up to 72 hours after catheterization)  
  INR must be 2.3 or below at the time of randomization

**End-of-treatment**  
12 months

- Rivaroxaban 15 mg once daily = Clopidogrel
- Rivaroxaban 2.5 mg twice daily = DAPT
- Rivaroxaban 15 mg once daily  
  + Low-dose ASA

**Intended DAPT duration**  
1, 6, or 12 months

- Vitamin K antagonist  
  + DAPT
- Vitamin K antagonist  
  + Low-dose ASA

(Target INR: 2.0 to 3.0^)
Figure 1
Benefit and Safety With Triple Therapy Versus Dual Therapies in AF Patients After Myocardial Infarction and Coronary Intervention

Triple therapy (oral anticoagulant [OAC] plus aspirin plus clopidogrel [dotted line]) is used as reference (hazard ratio 1.00).
Conclusions

• Multiple antithrombotics clearly increase bleeding
  – Benefits on ischemic events less clear
• “Triple Therapy” has to be redefined
  – New P2Y12 inhibitors: prasugrel, ticagrelor
  – DOACs
• Results of ongoing trials are essential for future recommendations
  – Does aspirin add benefit or just risk?
• Right patient, right drugs, right dosage, right duration

Future Recommendations for combination therapy

• All oral anticoagulants will be allowed (VKA, DOACs)
  – If VKA: INR 2,0-2,5
  – If DOAC: lower dose (2x110 mg dabigatran, 1x15 mg rivaroxaban, 2x2,5 mg apixaban)

• DAPT (ASA+Clopi) or dual therapy (DOAC or VKA+Clopi) may be used in patients with low ischemic risk (CHADs-VASc =1)
  – Do not switch from DOACs to a VKA if patients are already on treatment
  – Start with a VKA **OR** a DOAC if patients are not pre-treated
Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data

- Over 40,000 patients
- Registries from Denmark
- 2000-2005
- Mean Follow-up 476 days
- 4.6% of patients were admitted to hospital with bleeding

The Lancet. 2009;374(9706):1967-74

Figure 2
WOEST trial: Primary endpoint (any bleeding) and secondary endpoint (death, myocardial infarction, stroke, target vessel revascularisation and stent thrombosis)


**Primary Endpoint: Total number of bleeding events (TIMI criteria)**

- **Triple therapy group**: 44.9%
- **Double therapy group**: 19.5%

Cumulative incidence of bleeding over time:

- **Triple therapy group**: HR = 0.36, 95% CI [0.26-0.50], p < 0.001
- **Double therapy group**: 

*Note: Time from PCI/ACS, n at risk, and Cumulative incidence of bleeding values are provided in the table below.*

---

**Table: Cumulative Incidence of Bleeding**

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Triple therapy group</th>
<th>Double therapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>60</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>90</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>120</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>180</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>270</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>365</td>
<td>75%</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Legend:**
- **Red**: Triple therapy group
- **Black**: Double therapy group
- **Orange**: Oral Anticoagulation
- **Blue**: Aspirin 75-160 mg daily
- **Green**: Clopidogrel 75 mg daily
Secondary Endpoint (Death, MI, TVR, Stroke, ST)

- **Triple therapy group**
- **Double therapy group**

Cumulative incidence

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>270</th>
<th>365</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>28</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

- **p=0.025**
- **HR=0.60  95%CI[0.38-0.94]**

\[ n = \text{at risk:} 279, 276, 273, 270, 266, 261, 252, 242, 234 \]

**Hazard Ratios for Bleeding**

- **A Non-fatal and fatal bleeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard ratio (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin alone</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Clopidogrel alone</td>
<td>1.33</td>
<td>1.11</td>
<td>1.59</td>
</tr>
<tr>
<td>Vitamin K antagonist alone</td>
<td>1.23</td>
<td>0.94</td>
<td>1.61</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1.47</td>
<td>1.28</td>
<td>1.69</td>
</tr>
<tr>
<td>Aspirin plus vitamin K antagonist</td>
<td>1.84</td>
<td>1.51</td>
<td>2.23</td>
</tr>
<tr>
<td>Clopidogrel plus vitamin K antagonist</td>
<td>3.52</td>
<td>2.42</td>
<td>5.11</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>4.05</td>
<td>3.08</td>
<td>5.33</td>
</tr>
</tbody>
</table>

- **10-13% per year**

The Lancet. 2009;374(9706):1967-74
### CHA₂DS₂-VASc

**Assessment of Thromboembolic Risk**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
<th>Annual Stroke Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF/LV dysfunction</td>
<td>1</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Age (≥75)</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td>9.8</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>Total Score 0 – 9</strong></td>
<td></td>
<td><strong>Validated in 1084 NVAF patients not on OAC with known TE status at 1 year in Euro Heart Survey</strong></td>
</tr>
</tbody>
</table>

10-20% annual risk of stroke

---

### Yearly Incidence of Bleeding

- **Aspirin**: 2.6%
- **Clopidogrel**: 4.6%
- **Warfarin**: 4.3%
- **Aspirin plus clopidogrel**: 3.7%
- **Aspirin plus Warfarin**: 5.1%
- **Warfarin plus clopidogrel**: 12.3%
- **Triple Therapy**: 12.0%
Major Bleeding* per Year
Odds Ratios

* non-fatal and fatal

Hansen et al. Arch Intern Med 2010;170:1433-1441
ARISTOTLE
Effects of apixaban vs. warfarin with and without aspirin

What we know
Atrial fibrillation and coronary artery disease frequently occur in the same patients

Patients with AF have worse outcomes

What we don’t know

- How should we use aspirin, clopidogrel, and warfarin, given the high risk of both thrombotic and bleeding outcomes?
  - Even less known about new P2Y12 inhibitors
  - Even less known about NOACs
What to Do?

- Medical therapy
- Medical therapy plus warfarin or other antithrombin/Factor Xa inhibitor
- Medical therapy plus stress test with imaging
- Medical therapy and proceed with coronary angiography
- Something else

Decision was …

- Medical therapy
- Medical therapy plus warfarin or other antithrombin/Factor Xa inhibitor
- Medical therapy plus stress test with imaging
- Medical therapy and proceed with coronary angiography
- Something else
WOEST Trial - Study Design

1:1 Randomisation:
Double therapy group: OAC + 75mg Clopidogrel qd
1 month minimum after BMS
1 year after DES

Triple therapy group: OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS
1 year after DES

Follow up: 1 year

Primary Endpoint: The occurrence of all bleeding events (TIMI criteria)

Secondary Endpoints:
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

COMPASS
(n = 19,500)

CAD without indication for DAPT*, or PAD

Riva 5 mg bid
PPI no PPI

Riva 2.5 mg bid + ASA 100 mg qd
PPI no PPI

ASA 100 mg qd
PPI no PPI

*previous MI, or
*CAG > 1vd, or
*PCI > 1 vessel, or
*CABG > 1 vessel > 4yr

• primary efficacy endpoint: CV death/MI/ischemic stroke
• safety endpoint: ISTH major bleeding