«Αντιθρομβωτική αγωγή στο στεφανιαίο ασθενή με αγγειοπλαστική και κολπική μαρμαρυγή»

ΚΑΛΑΝΤΖΗ ΚΑΛΛΙΡΡΟΗ
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Atrial fibrillation and PCI

• 5-8% of patients who undergo PCI have AF

• 20-30% of AF patients have co-existing CAD and therefore may require PCI (1-2 million anticoagulated patients in Europe)

• Despite overlap in the occurrence of these syndromes, the pharmacotherapies used to manage AF and PCI differ

Lip et al. Thromb Ahemost 2010
The Optimal Management of Atrial Fibrillation and ACS Differ

**Atrial Fibrillation (ACTIVE W)**\(^1\): The combination of aspirin and clopidogrel is not as effective as *warfarin* in patients with AF\(^1\)

*However*

**Stenting (STARS)**\(^2\): The combination of *aspirin and a thienopyridine* is more effective than warfarin in patients with coronary stents\(^2\)

Atrial fibrillation and PCI

Coronary stent implantation + Atrial fibrillation

- Cumulative Incidence (%)
  - Days after Stenting
  - Oral Anticoagulation
  - Dual Antiplatelet

- ISAR, NEJM 1996

- Dual Antiplatelet + Oral Anticoagulation

- Cumulative Incidence
  - Years
  - ACTIVE-W Lancet 2006
The management of AF patients who undergo stent placement is challenging.
Combined antiplatelets and (N)OACs after acute coronary syndrome: three is a crowd!

Bleeding is bad...

Bleeding associated with warfarin, aspirin and clopidogrel in patients with AF, $n = 82854$

Combination therapy increases risk of fatal and non-fatal bleeding

Hansen et al. Arch Int Med 2010; 170: 1433-1441
What combination of therapy is optimal for patients with AF undergoing PCI?

AF
- Anticoagulant therapy
  - For prevention of stroke in patients with additional risk factors

PCI
- Antiplatelet therapy
  - For prevention of stent thrombosis following PCI
  - Dual antiplatelet therapy superior to ASA alone

AF and PCI
- DUAL THERAPY: anticoagulant and single antiplatelet?
- OR
- TRIPLE THERAPY: anticoagulant and dual antiplatelet therapy?

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Combination Therapy

- **Atrial Fibrillation Plus Coronary Artery Stent**
  - **High Risk of Stroke? (CHADS$_2$>1)**
    - **Yes**
      - **High Risk of Bleeding?**
        - **Yes**
          - **Dual Antiplatelet Therapy**
        - **No**
          - **No**
          - **Triple Therapy**
    - **No**
      - **No**
      - **Yes**
        - **Dual Antiplatelet Therapy**

- **AF patient in need of OAC after an ACS**
  - **Bleeding risk low compared to risk for ACS or stent thrombosis**
    - **1 month**
      - **Triple therapy (RxB)**
    - **3 months**
      - **Double therapy (RxC)**
    - **5 months**
      - **OAC monotherapy (RxA)**
    - **12 months**
      - **OAC monotherapy (RxA)**
  - **Bleeding risk high compared to risk for ACS or stent thrombosis**
    - **1 month**
      - **Triple therapy (RxB)**
    - **3 months**
      - **Double therapy (RxC)**
    - **5 months**
      - **OAC monotherapy (RxA)**
    - **12 months**
      - **OAC monotherapy (RxA)**

- **Patients with an indication for oral anticoagulation undergoing PCI**
  - **Concerns about ischaemic risk prevailing**
    - **Time from treatment initiation**
      - **1 month**
        - **Triple Therapy**
      - **3 months**
        - **Double Therapy**
    - **Beyond 12 months**
      - **OAC alone**

- **ESC 2016-2017 AF Guidelines**

- **Circulation 2010**
TRIPLE THERAPY: clinical evidences

WOEST Trial

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L. De Smet, Jean-Paul Herman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijssen, Arnoud W van ’t Hof, Jurriën M ten Berg, for the WOEST study investigators

Lancet 2013;381:1107-15
Primary outcome: any bleeding episode within 1 year of PCI
Secondary Endpoint

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Double therapy group</th>
<th>p-value</th>
<th>Triple therapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.6</td>
<td>0.027</td>
<td>3.3</td>
</tr>
<tr>
<td>MI</td>
<td>3.3</td>
<td>0.382</td>
<td>4.7</td>
</tr>
<tr>
<td>TVR</td>
<td>7.3</td>
<td>0.876</td>
<td>6.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1</td>
<td>0.128</td>
<td>2.9</td>
</tr>
<tr>
<td>ST</td>
<td>1.5</td>
<td>0.165</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Lancet 2013:381:1107-1115
ISAR-TRIPLE

- 600 pts
- Indication to VKA+DES (ACS or elective)
- 9-month follow-up
- Composite endpoint: death, MI, stroke, ST, TIMI-bleeding
TripleTherapy in AF and PCI for 6 wks vs 6 months: ISAR-TRIPLE

J Am Coll Cardiol 2015;65:1619–1629
Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.
Patients With Atrial Fibrillation Undergoing
Coronary Stent Placement: PIONEER AF-PCI

- Primary endpoint: TIMI major + minor + bleeding requiring medical attention (clinically significant bleeding)
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d).
∆Open label VKA

Gibson et al. AHA 2016
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.

Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016
Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

Cardiovascular Death, Myocardial Infarction, or Stroke (%)

<table>
<thead>
<tr>
<th>Days</th>
<th>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Riva + DAPT</th>
<th>VKA + DAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>694</td>
<td>648</td>
<td>633</td>
<td>628</td>
</tr>
<tr>
<td>704</td>
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<td>579</td>
<td>607</td>
<td>607</td>
<td>579</td>
</tr>
</tbody>
</table>

Riva + P2Y<sub>12</sub> v. VKA + DAPT

HR=1.08 (95% CI: 0.69-1.68)
p=0.750

Riva + DAPT v. VKA + DAPT

HR=0.93 (95% CI: 0.59-1.48)
p=0.765

6.5%
6.0%
5.6%

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg OD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg OD comparing VKA) two-sided log rank test.

6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines.

Gibson et al. AHA 2016
All Cause Hospitalization for an Adverse Event

Rivo + P2Y₁₂ v. VKA + DAPT
HR=0.77 (95% CI: 0.65-0.92)
p=0.005
ARR=7.4
NNT=14

Rivo + DAPT v. VKA + DAPT
HR=0.74 (95% CI: 0.61-0.88)
p=0.001
ARR=10.3
NNT=10

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016
Summary

A strategy of either rivaroxaban 15 mg daily plus a P2Y$_{12}$ or rivaroxaban 2.5 mg BID + DAPT was associated with a reduction in clinically significant bleeding compared with conventional triple therapy of VKA + DAPT (HR = 0.59 (0.47-0.76), p < 0.001, NNT 11, and HR = 0.63 (0.50-0.80), p <0.001, NNT 12 respectively ).

CV death / MI / stroke were comparable among the groups (Riva 15 mg+ P2Y$_{12}$ = 6.5%, Riva 2.5 mg+ DAPT = 5.6%, VKA + DAPT = 6.0%) with broad confidence intervals

Rates of all cause death or hospitalization were reduced in the Rivaroxaban arms (Riva 15 mg + P2Y$_{12}$ = NNT 15, Riva 2.5 + DAPT, NNT =10)
Among stented AF participants, administration of either rivaroxaban 15 mg daily plus P2Y$_{12}$ monotherapy for one year or rivaroxaban 2.5 mg BID plus 1, 6, or 12 months of DAPT reduced the risk of clinically significant bleeding as compared with standard of care VKA plus 1, 6, or 12 months of DAPT and yielded comparable efficacy with broad confidence intervals.
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*
Study Design: Multicenter, randomized, open-label trial following a PROBE design

Randomization ≤120 hours post-PCI

- Patients with AF undergoing PCI with stenting
- N=2725

Dabigatran 150 mg BID + P2Y12 inhibitor

Dabigatran 110 mg BID + P2Y12 inhibitor

Warfarin (INR 2.0–3.0) + P2Y12 inhibitor + ASA

6-month minimum treatment duration with visits every 3 months for the first year, then visits and telephone contact alternating every 3 months and a 1-month post-treatment visit

Mean duration of follow-up: ~14 months

Dabigatran (110 or 150 mg) + P2Y12 inhibitor

Warfarin + P2Y12 inhibitor

1 month of ASA (BMS) + 3 months of ASA (DES)

*Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (~72 hrs is preferable). PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016
# Inclusion and exclusion criteria

## Key inclusion criteria

- Patients aged ≥18 years with paroxysmal, persistent or permanent NVAF
- ACS successfully treated by PCI and stenting (BMS or DES)
- Stable CAD with ≥1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (BMS or DES)

## Key exclusion criteria

- Cardiogenic shock during current hospitalization
- Use of fibrinolytics within 24 hrs of randomization that, in the investigator’s opinion, will put patient at high risk of bleeding
- Stroke or major bleeding event within 1 month prior to screening visit
- Severe renal impairment (CrCl <30mL/min)
The primary endpoint was time to first ISTH major or clinically relevant non-major bleeding.

Formally tested and powered endpoints included:
- Non-inferiority of 110 mg and 150 mg dual therapy groups on time to first ISTH major or clinically relevant non-major bleeding event.
- Non-inferiority of both dual therapy groups combined on time to first event of death, thromboembolic event (MI, stroke, systemic embolism) or unplanned revascularization.
- Superiority testing of the bleeding endpoints.

100% of outcome events were independently adjudicated by blinded external committee.

ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction; Non-inferiority testing (margin 1.38)
Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)
Rates of TIMI major bleeding

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb ≥5 g/dL.

Dabigatran 110 mg dual therapy (n=981)

- 1.4% (ARR: 2.4%)
- HR: 0.37 (95% CI: 0.20–0.68)
- P=0.0015

Warfarin triple therapy (n=981)

- 3.8%
- HR: 0.51 (95% CI: 0.28–0.93)
- P=0.028

Dabigatran 150 mg dual therapy (n=763)

- 2.1% (ARR: 1.8%)

Warfarin triple therapy (n=764)

- 3.9%
Rate of intracranial haemorrhage

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

HR: 0.30 (95% CI: 0.08–1.07)  
P=0.064

ARR: 0.7%  
0.3%  
Dabigatran 110 mg dual therapy (n=981)  
Warfarin triple therapy (n=981)

HR: 0.12 (95% CI: 0.02–0.98)  
P=0.047

ARR: 0.9%  
0.1%  
Dabigatran 150 mg dual therapy (n=763)  
Warfarin triple therapy (n=764)
Time to death or thromboembolic event, or unplanned revascularization

HR: 1.04 (95% CI: 0.84–1.29)  
Non-inferiority P=0.0047  

Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization.
Conclusions

In patients with AF who have undergone PCI:

- Dual therapy with dabigatran and a P2Y12 antagonist significantly reduced the risk of bleeding versus warfarin triple therapy, with non-inferiority for overall thromboembolic events.

- Absolute risk reductions with dabigatran dual therapy were 11.5% and 5.5% in ISTH major or clinically relevant non-major bleeding at the 110 mg and 150 mg doses, respectively, compared with warfarin triple therapy.

- These dabigatran dual therapy regimens, using doses approved worldwide for stroke prevention, offer clinicians two additional options for managing Afib patients post-PCI.
Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

Inclusion
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for 6 months

Randomize
n = 4,600 Patients

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

Apixaban
- P2Y12 inhibitor for all patients x 6 months
- Aspirin for all on the day of ACS or PCI
- Aspirin versus placebo after randomization

Warfarin
- ASA
- placebo

Primary outcome: major/clinically relevant bleeding (through 6 months)
Secondary objective: Death, MI, Stroke, Stent thrombosis

ClinicalTrials.gov Identifier: NCT02415400
ENTRUST-AF-PCI Study Design

PROBE design: prospective, randomized, open label, blinded evaluation edoxaban based regimen vs VKA based regimen in N = 1500 AF patients

12 months: end of treatment

Inclusion Criteria:
- OAC indication for AF for at least 12 months
- Successful PCI with stent placement (goal of at least 25% ACS)

Randomize

Edoxaban 60 mg/day*

P2Y₁₂ antagonist** (without ASA)

Vitamin K Antagonist***

P2Y₁₂ antagonist (ASA 1 - 12 months)****

Primary outcome: ISTH major and clinically relevant non-major bleeding

*Edoxaban dose reduction to 30 mg OD
- if CrCL ≤ 50 ml/min
- BWS ≤ 80 kg
- certain P-gp inhibitors

**Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily, predefined at randomization

*** VKA, target INR 2-3

**** ASA 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), CHA₂DS-VA₆c, and HAS_BLED

ClinicalTrials.gov Identifier: NCT02866175
In practice... what to do?

Personalize antithrombotic therapy according to:
- Thromboembolic risk (CHA$_2$DS$_2$VASC)
- Bleeding risk (HAS-BLED)
- Clinical situation (elective PCI or in the setting of an acute coronary syndrome)
- Stent type (DES vs BMS)
- Time from PCI/ACS
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)
**Prediction of stroke and bleeding risk**

### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CHA\textsubscript{2}DS\textsubscript{2}-VASc score is recommended for stroke risk prediction in patients with AF.</td>
<td>I</td>
<td>A</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>
</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>
</tr>
</tbody>
</table>

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**Note:**
- Maximum score is 9 since age may contribute 0, 1, or 2 points.

### Table 2—Clinical Characteristics Composing the HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristics</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drug or alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**HAS-BLED** = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years). Drugs/alcohol concurrently. INR = international normalized ratio.

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[www.escardio.org/guidelines](http://www.escardio.org/guidelines)

European Heart Journal - doi:10.1093/eurheartj/ehw210
The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

ESC Chairperson: Marco Valgimigli (Switzerland).

Authors/Task Force Members: Héctor Bueno (Spain), Robert Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain).

Additional Contributor: Glenn Levine (USA).
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)
### Dual antiplatelet therapy duration in patients with indication for oral anticoagulation (continued)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range &gt;65–70%.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Strategies to avoid bleeding complications in patients treated with oral anticoagulant

- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA\textsubscript{2}\text{DS}\textsubscript{2}-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.

- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.

- Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.

- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.

- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.

- Clopidogrel is the P2Y\textsubscript{12} inhibitor of choice.

- Use low-dose (≤100 mg daily) aspirin.

- Routine use of PPIs.
Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

- Short life expectancy.
- Ongoing malignancy.
- Poor expected adherence.
- Poor mental status.
- End stage renal failure.
- Advanced age.
- Prior major bleeding/prior haemorrhagic stroke.
- Chronic alcohol abuse.
- Anaemia.
- Clinically significant bleeding on dual antithrombotic therapy.
Risk scores validated for dual antiplatelet therapy duration decision-making

<table>
<thead>
<tr>
<th>Time of use</th>
<th>PRECISE-DAPT score</th>
<th>DAPT score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT duration strategies assessed</td>
<td>Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)</td>
<td>Standard DAPT (12 months) vs. Long DAPT (30 months)</td>
</tr>
<tr>
<td>Score calculation</td>
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<tr>
<td>HB</td>
<td>22 11 5 11 10.5 ±10</td>
<td>Age</td>
</tr>
<tr>
<td>WBC</td>
<td>≤ 8 10 12 14 16 18 ≥20</td>
<td>≥75</td>
</tr>
<tr>
<td>Age</td>
<td>55 60 70 80 90 ≥90</td>
<td>65 to &lt;75</td>
</tr>
<tr>
<td>GFR</td>
<td>120 90 60 40 20 0</td>
<td>&lt;65</td>
</tr>
<tr>
<td>Prior Bleeding</td>
<td>No</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Score Points</td>
<td>2 4 8 10 12 14 16 18 20 22 24 26 28 30</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MI at presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior PCI or prior MI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel-eluting stent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stent diameter &lt; 3 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHF or LVEF &lt; 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vein graft stent</td>
</tr>
<tr>
<td>Score range</td>
<td>0 to 100 points</td>
<td>-2 to 10 points</td>
</tr>
<tr>
<td>Decision making cut-off suggested</td>
<td>Score ≥25  Short DAPT</td>
<td>Score ≥2  Long DAPT</td>
</tr>
<tr>
<td></td>
<td>Score &lt;25  Standard/long DAPT</td>
<td>Score &lt;2  Standard DAPT</td>
</tr>
<tr>
<td>Calculator</td>
<td><a href="http://www.precisedaptscore.com">www.precisedaptscore.com</a></td>
<td><a href="http://www.daptstudy.org">www.daptstudy.org</a></td>
</tr>
</tbody>
</table>

ESC European Society of Cardiology

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with FACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)
**Bleeding risk assessment tools**

<table>
<thead>
<tr>
<th>HAS-BLED³³</th>
<th>ATRIA³⁴</th>
<th>ORBIT³⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension – uncontrolled (&gt;160 mmHg systolic)</td>
<td>1</td>
<td>Anemia³⁶</td>
</tr>
<tr>
<td>Abnormal renal function (SCr ≥200 μmol/L or dialysis or transplantation) or abnormal hepatic function⁵</td>
<td>1 or 2</td>
<td>Severe renal disease (eGFR &lt;30 mL/min or dialysis)</td>
</tr>
<tr>
<td>Stroke history</td>
<td>1</td>
<td>≥75 years old</td>
</tr>
<tr>
<td>Bleeding history or predisposition to bleeding (eg. anemia and bleeding diathesis)</td>
<td>1</td>
<td>Any prior hemorrhage</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
<td>Diagnosed hypertension</td>
</tr>
<tr>
<td>Elderly (&gt;65 years old)</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week)</td>
<td>1 or 2</td>
<td>–</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>Maximum score</td>
</tr>
</tbody>
</table>
Assessment of Risk of Bleeding
HAS-BLED

- Hypertension (current) 1
- Abnormal renal/liver function 1/2
- Stroke 1
- Bleeding 1
- Labile INR 1
- Elderly (age > 65 years) 1
- Drugs or alcohol 1/2

Score 0 – 9

Bleeds per 100 patient-years

0 1.13
1 1.02
2 1.88
3 3.74
4 8.70

C statistic 0.72

Validated in 3978 NVAF patients with known TE status at 1 year in Euro Heart Survey
C statistic 0.72 (similar to HEMORRHAGES)
0.91 vs 0.85 for patients on ASA or no therapy

Pisters et al. 2010 Chest 138:1053-100
# Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

<table>
<thead>
<tr>
<th>Modifiable bleeding risk factors:</th>
<th>Non-modifiable bleeding risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (especially when systolic blood pressure is $&gt;160$ mmHg)</td>
<td>Age ($&gt;65$ years) ($\geq75$ years)</td>
</tr>
<tr>
<td>Labile INR or time in therapeutic range $&lt;60%$ in patients on vitamin K antagonists</td>
<td>History of major bleeding</td>
</tr>
<tr>
<td>Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs</td>
<td>Previous stroke</td>
</tr>
<tr>
<td>Excess alcohol ($\geq8$ drinks/week)</td>
<td>Dialysis-dependent kidney disease or renal transplant</td>
</tr>
<tr>
<td><strong>Potentially modifiable bleeding risk factors:</strong></td>
<td>Cirrhotic liver disease</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>Genetic factors</td>
</tr>
<tr>
<td>Impaired liver function</td>
<td><strong>Biomarker-based bleeding risk factors:</strong></td>
</tr>
<tr>
<td>Reduced platelet count or function</td>
<td>High-sensitivity troponin</td>
</tr>
<tr>
<td></td>
<td>Growth differentiation factor-15</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine/estimated CrCl</td>
</tr>
</tbody>
</table>
**Modifiable risk factors for bleeding in anticoagulated patients with atrial fibrillation**

**Modifiable bleeding risk factors:**

- Hypertension (especially when systolic blood pressure is >160 mmHg)
- Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
- Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
- Excess alcohol (≥8 drinks/week)

➢ Διασφαλίστε την κατάλληλη Αναγνώριση, Αξιολόγηση και Θεραπεία Υποκείμενων Παραγόντων Κινδύνου
➢ Ο υψηλός αιμορραγικός κίνδυνος δεν πρέπει γενικά να οδηγεί στη στέρηση της αντιπηκτικής αγωγής. Οι παράγοντες αιμορραγικού κινδύνου θα πρέπει να αναγνωρίζονται και οι τροποποιήσιμοι να αντιμετωπίζονται

www.escardio.org/guidelines
## Management of bleeding

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When dabigatran is used, a reduced dose (110 mg twice daily) may be considered in patients &gt;75 years to reduce the risk of bleeding.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Genetic testing before the initiation of VKA therapy is not recommended.</td>
<td>III (no benefit)</td>
<td>B</td>
</tr>
<tr>
<td>Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the cause of bleeding is resolved.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Why did WOEST decide to drop aspirin instead of dropping clopidogrel?

... «sensation» among the interventionalists that clopidogrel is more effective than aspirin in preventing stent thrombosis...

The truth is: NO DATA!
Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators

**Figure 3:** Cumulative risk of stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at Risk</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel + aspirin</td>
<td>3335</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3268</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3219</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2419</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>941</td>
<td>3.5</td>
</tr>
<tr>
<td>Oral anticoagulation therapy</td>
<td>3371</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3232</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2456</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>930</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Lancet 2006; 367: 1903–12*
Bleeding is not an innocuous consequence of excessive antithrombotic therapy

- In several previous trials – e.g., OASIS-V, HORIZON-AMI, less initial bleeding translated into increased mortality
- Therefore there was hope that reducing antithrombotic therapy in such conditions could not only reduce bleeding (expected), but possibly also reduce mortality
20–30% of patients with AF and an indication for continuous OAC have coexisting CAD and therefore may require PCI.

An estimated 1–2 million anticoagulated patients in Europe are candidates for PCI procedures.

Stenting requires follow-up treatment with antiplatelets, which puts anticoagulated patients at higher risk of bleeding.

CAD, coronary artery disease; PCI, percutaneous coronary intervention; Lip et al. Thromb Haemost 2010
Ischaemic stroke associated with warfarin, aspirin and clopidogrel in patients with AF n = 82854

Hansen et al. Arch Int Med 2010; 170: 1433-1441
NOACS in association with DAPT (aspirin+clopidogrel)?

• In all NOACS trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) patients were excluded from enrollment if receiving new P2Y12.

• And conversely, AF patients requiring OAC were systematically excluded from recent ACS trials.

• Some data are available in non AF patients.
Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D., Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D., Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D., Danny Liaw, M.D., Ph.D., Steen E. Husted, M.D., Jose Lopez-Sendon, M.D., Raffaele De Caterina, M.D., Petr Jansky, M.D., Harald Darius, M.D., Dragos Vinereanu, M.D., Jan H. Cornel, M.D., Frank Cools, M.D., Dan Atar, M.D., Jose Luis Leiva-Pons, M.D., Matyas Keltai, M.D., Hisao Ogawa, M.D., Ph.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Witold Ruzyllo, M.D., Rafael Diaz, M.D., Harvey White, M.D., Mikhail Ruda, M.D., Margarida Geraldes, Ph.D., Jack Lawrence, M.D., Robert A. Harrington, M.D., and Lars Wallentin, M.D., Ph.D., for the APPRAISE-2 Investigators*


97% patients were taking aspirin
81% patients were taking aspirin plus a P2Y12-receptor inhibitor (predominantly clopidogrel)
Primary Outcome
CV Death, MI, Ischemic Stroke

Apixaban  279 (7.5%)
Placebo   293 (7.9%)
HR 0.95; 95% CI 0.80-1.11; p=0.509
TIMI Major Bleeding

- Apixaban: 48 (1.3%)
- Placebo: 18 (0.5%)

HR 2.59; 95% CI 1.50–4.46; p=0.001
Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

N = 15,526*

ATLAS ACS 2 TIMI 51

Stratum 1: ASA alone (7%)
- Placebo n = 355
- Rivaroxaban 2.5 mg bid n = 349
- Rivaroxaban 5 mg bid n = 349

Stratum 2: ASA + thienopyridine (93%)
- Placebo n = 4821
- Rivaroxaban 2.5 mg bid n = 4825
- Rivaroxaban 5 mg bid n = 4827

Event-driven study – 1002 events

Mega et al, 2011
Primary efficacy endpoint (CV death/MI/stroke)
Both rivaroxaban doses, both strata

2-year Kaplan–Meier estimate
- Placebo: 10.7%
- Rivaroxaban: 8.9%

HR = 0.84
(0.74–0.96)
ARR = 1.7%

mITT p = 0.008
ITT p = 0.002

NNT = 56

Number at risk
- Placebo: 5,113 4,307 3,470 2,664 1,831 1,079 421
- Rivaroxaban: 10,229 8,502 6,753 5,137 3,554 2,084 831

Mega et al, 2011

ATLAS ACS 2 TIMI 51
<table>
<thead>
<tr>
<th>Safety endpoint</th>
<th>Rivaroxaban 2.5 mg bid (n=5115)</th>
<th>Rivaroxaban 5 mg bid (n=5110)</th>
<th>Placebo (n=5125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-CABG TIMI major bleed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>1.8%</td>
<td>2.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td><em>p</em> value versus placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td><em>p</em> value versus placebo</td>
<td>0.04</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td><em>p</em> value versus placebo</td>
<td>0.45</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal ICH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K–M estimate at 2 years</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td><em>p</em> value versus placebo</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Mega et al, 2011
Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the RELY Trial

Major Bleed
- HR=1.87 (95% CI: 1.54, 2.27)
- HR=2.14 (95% CI: 1.75, 2.61)
- HR=2.05 (95% CI: 1.66, 2.54)

Minor Bleed
- HR=1.47 (95% CI: 1.34, 1.62)
- HR=1.33 (95% CI: 1.20, 1.47)
- HR=1.44 (95% CI: 1.29, 1.59)

Extracranial Bleed
- HR=1.84 (95% CI: 1.48, 2.29)
- HR=2.14 (95% CI: 1.74, 2.64)
- HR=2.07 (95% CI: 1.66, 2.59)

Intracranial Bleed
- HR=1.85 (95% CI: 1.22, 2.82)
- HR=1.98 (95% CI: 1.04, 3.77)
- HR=1.53 (95% CI: 0.70, 3.34)

Event Rate (% per year)

RE-DUAL PCI vs PIONEER AF-PCI: study treatments

Confirmatory trial

**RE-DUAL PCI**
- Open-label trial evaluating antithrombotic therapy in patients with AF undergoing PCI.
- Dual therapy: dabigatran 110 or 150 mg BID + P2Y12 inhibitor
- VS
- Triple therapy: warfarin + P2Y12 inhibitor + ASA

Exploratory trial

**PIONEER AF-PCI**
- Open-label trial evaluating antithrombotic therapy in patients with AF undergoing PCI.
- Dual therapy: rivaroxaban 15/10 mg OD + P2Y12 inhibitor
- VS
- Triple therapy: rivaroxaban 2.5 mg BID + P2Y12 inhibitor + ASA
- OR
- Triple therapy: warfarin + P2Y12 inhibitor + ASA

Antiplatelet treatment duration was predefined in each triple therapy arm.

*ASA was discontinued 1 month after bare-metal stent or 3 months after drug-eluting stent; †If P2Y12 inhibitor was discontinued after 1 or 6 months (as prespecified by physician), the rivaroxaban regimen switched to 15/10 mg OD for the remainder of the treatment period; ‡If P2Y12 inhibitor was discontinued after 1 or 6 months (as prespecified by physician), patients continued on warfarin plus ASA for the remainder of the treatment period.

Are the NOAC doses tested in these studies also approved for stroke prevention in AF?

**RE-DUAL PCI**

**SAFETY AND EFFICACY OF DABIGATRAN DOSES**

- In a confirmatory trial, 110 mg BID was tested in 6015 patients.
- And 150 mg BID was tested in 6076 patients.

Both doses are approved for stroke prevention in patients with AF.

**PIONEER AF-PCI**

**SAFETY AND EFFICACY OF RIVAROXABAN DOSES**

- 15/10 mg OD regimen was tested in 639 Japanese patients in an exploratory trial.

- 2.5 mg BID has not been tested in a confirmatory trial for stroke prevention in patients with AF.

- 2.5 mg BID is not approved for stroke prevention in patients with AF; the 15/10 mg OD regimen is not approved outside Japan.

---

6 Rivaroxaban 15 mg OD was also tested in an exploratory manner in ROCKET AF.

How reliable are the primary outcome measures in these open-label trials?

**RE-DUAL PCI**

**PRIMARY SAFETY OUTCOMES**

- ISTH major bleeding: 32% of bleeds
- ISTH CRNM bleeding: 68% of bleeds

**OR**

Primary endpoint is composed of well-established safety outcome parameters; 100% of events were adjudicated by an independent, blinded committee.

**PIONEER AF-PCI**

**PRIMARY SAFETY OUTCOMES**

- TIMI major bleeding: 12% of bleeds
- TIMI minor bleeding: 7% of bleeds
- Bleeding requiring medical attention: 85% of bleeds

**COMPOSITE**

Composite primary endpoint; bleeding requiring medical attention is not commonly used but drove the results; 15% of these events were independently adjudicated.

RE-DUAL PCI vs PIONEER AF-PCI summary

1. RE-DUAL PCI (a confirmatory study) and PIONEER AF-PCI (an exploratory trial) evaluated the use of dual therapy with a NOAC + P2Y12 inhibitor in patients with AF undergoing PCI.

2. There are significant differences in study design between RE-DUAL PCI and PIONEER AF-PCI which prevent meaningful comparisons between the trials.

3. RE-DUAL PCI's robust study design makes it applicable to clinical practice, and both of the studied dabigatran doses are approved for stroke prevention in AF.
so how to proceed?