ΔΙΑΧΕΙΡΙΣΗ ΑΣΘΕΝΩΝ ΜΕ ΣΤΕΦΑΝΙΑΙΑ ΚΑΡΔΙΟΠΑΘΕΙΑ ΚΑΙ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ: ΚΙΝΔΥΝΟΙ ΚΑΙ ΟΦΕΛΗ ΔΙΠΛΗΣ ΚΑΙ ΤΡΙΠΛΗΣ ΘΕΡΑΠΕΙΑΣ

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Epidemiology: AF and PCI

• Concomitant AF and CAD is common owing to the strong association of both conditions with ageing and overlapping risk factors
  – CAD is estimated to occur in 20–45% of patients with AF\textsuperscript{1,2}
  – Owing to an aging population, patient numbers are set to increase globally over the coming decades

• The literature indicates that 20–45% of patients with AF and CAD require coronary revascularization by PCI or CABG\textsuperscript{3,4}
  – In a prospective study, 34% of patients with AF also had CAD, of whom 21% required PCI or CABG\textsuperscript{3}
  – 24.9% of patients with AF enrolled in ARISTOTLE had prior PCI\textsuperscript{4}

• ~1–2 million patients with AF indicated for anticoagulation in the US and Europe are candidates for coronary revascularization\textsuperscript{2}

2007 Guidelines Recommended
Prolonged Triple Therapy

ACC/AHA 2007 Guidelines for management of patients with NSTE-ACS

UA/NSTEMI patient groups at discharge with indication for anticoagulation

Drug-eluting stent group

- ASA*
  - 162–325 mg/day for at least 3–6 months, then 75–162 mg/day indefinitely
  - Clopidogrel#
    - 75 mg/day for at least 1 year
- Warfarin‡
  - When added to ASA plus clopidogrel an INR of 2.0–2.5 is recommended

Bare-metal stent group

- ASA*
  - 162–325 mg/day for at least 1 month, then 75–162 mg/day indefinitely
  - Clopidogrel#
    - 75 mg/day for at least 1 month and ideally up to 1 year
- Warfarin‡
  - When added to ASA plus clopidogrel an INR of 2.0–2.5 is recommended

*For ASA allergic patients, use clopidogrel alone (indefinitely), or try desensitization; #for clopidogrel allergic patients, use ticlopidine 250 mg by mouth twice daily; ‡continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as AF
Antiplatelet Therapy Alone Does Not Provide Adequate Protection from AF-Related Stroke

A randomized trial for DAPT (n=3,335) vs VKA (n=3,371) for prevention of vascular events in patients with AF demonstrated superiority of OAC therapy

RR=1.44 (95% CI 1.18–1.76)  
\( p=0.0003 \)

*Composite of stroke, non-CNS embolus, MI and vascular death

ESC Guidelines for the Management of AF and PCI: ‘Minimize Triple Therapy Duration’

• Guidelines recommend the following in patients with AF after PCI:

- Elective PCI with stent\(^1,2\):
  - 0 months: Triple therapy OAC+A+C
  - 1 month: Triple therapy OAC+A+C
  - 6 months: Dual therapy OAC+A or C
  - 12 months: OAC monotherapy

- Urgent PCI after ACS\(^1,3\):
  - 0 months: Triple therapy OAC+A+C
  - 1 month: Triple therapy OAC+A+C
  - 6 months: Dual therapy OAC+A or C
  - 12 months: OAC monotherapy

High bleeding risk/low atherothrombotic risk:
- Shorten dual therapy

High atherothrombotic risk/low bleeding risk:
- Lengthen triple therapy

• In selected patients, dual therapy may be considered instead of triple therapy\(^1\)
• European guidelines suggest that NOACs may be used in triple/dual therapy,\(^1–3\) whereas US guidelines recommend a VKA\(^4,5\)

Canadian Cardiovascular Society Guidelines Recommend OAC + single AP after Elective PCI

For patients with AF and recent elective PCI

- Age <65 and \( \text{CHADS}_2 = 0 \):
  - ASA plus clopidogrel for 12 months
  - ASA alone after 12 months

- Age ≥65 or \( \text{CHADS}_2 ≥ 1 \):
  - OAC* plus clopidogrel for 12 months
  - OAC* alone after 12 months

*A NOAC is preferred over warfarin for patients with NVAF

Triple Therapy with a VKA Reduces Thromboembolic Events but Increases Bleeding after PCI in AF Patients

Danish registry data (2000–2009; N=11,480 patients)

Crude incidence rates (events per 100 person-years ± SE)

- CV death plus MI plus ischaemic stroke
- Fatal and non-fatal bleeding

Lamberts M et al, Circulation 2012;126:1185–1193
Treating AF with Concomitant ACS Is a Balancing Act

**Thromboembolic risk**
Patients with ACS and AF are at risk of both a second myocardial infarction\(^1\) and a stroke\(^2\).

**Bleeding risk**
Risk of bleeding increases with the number of antithrombotic agents\(^3\).

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The WOEST trial: Is ASA Necessary in Triple Therapy?

• Small-scale, open-label WOEST study (N=573) compared safety outcomes with triple therapy (VKA plus clopidogrel plus ASA) vs dual therapy (VKA plus clopidogrel): 69% of WOEST patients had AF

Use of dual therapy was associated with significantly lower rates of bleeding and overall mortality vs triple therapy, with similar rates of thrombotic events

*p<0.05

PIONEER AF-PCI: FirstProspective Study in Patients with AF Undergoing PCI Taking a NOAC

In an area of limited evidence, rivaroxaban is the first and currently only NOAC (versus VKA) to provide data from a dedicated RCT for patients with AF undergoing PCI.
Study objective: To assess the safety of two rivaroxaban treatment strategies compared with the current standard of care in patients with paroxysmal, persistent or permanent NVAF undergoing PCI with stent placement

Gibson CM et al, Am Heart J 2015;169:472–478e5
Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

**Design:** An open-label, randomized, controlled phase IIIb safety study

### Population:
Patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

- Rivaroxaban 15 mg OD*# plus single antiplatelet‡
- Rivaroxaban 2.5 mg BID# plus DAPT§
- Rivaroxaban 15 mg OD* plus low-dose ASA

### Decision for DAPT duration:
1, 6 or 12 months

- Rivaroxaban 15 mg OD*# plus single antiplatelet‡
- Rivaroxaban 2.5 mg BID# plus DAPT§
- Rivaroxaban 15 mg OD* plus low-dose ASA

### DAPT duration
(1 or 6 months)

- End of treatment (12 months)

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*CrCl 30–49 ml/min: 10 mg OD; †first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

**PIONEER AF-PCI**

**Rationale for Dual and Triple Therapy Arms**

<table>
<thead>
<tr>
<th>Study group 1</th>
<th>Study group 2</th>
<th>Study group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>1, 6 or 12 months</td>
<td>1, 6 or 12 months</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg OD plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Rivaroxaban 2.5 mg BID plus ASA plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>VKA plus ASA plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

The WOEST study showed oral anticoagulation in combination with clopidogrel was associated with significantly lower bleeding than triple therapy with no increase in thrombotic events.<sup>1</sup> This strategy has not yet been tested in a large study.

Where US guidelines recommend triple therapy with a VKA,<sup>2,3</sup> recent European guidelines suggest that a NOAC may be used in triple and dual therapy after PCI.<sup>4,5</sup>

Triple therapy with a VKA plus DAPT followed by dual therapy with VKA plus ASA is the standard of care for patients with AF and ACS, as recommended by US guidelines.<sup>2,3</sup>

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PIONEER AF-PCI
Rationale for Anticoagulant Dose Selection

**Study group 1**
- 12 months
- Rivaroxaban 15 mg OD plus P2Y\textsubscript{12}

**Study group 2**
- 1, 6 or 12 months
- Rivaroxaban 2.5 mg BID plus ASA plus P2Y\textsubscript{12}

**Study group 3**
- 1, 6 or 12 months
- VKA plus ASA plus P2Y\textsubscript{12}

**ATLAS ACS TIMI 46**: rivaroxaban 15 mg OD was associated with lower bleeding rates than 20 mg OD when taken in combination with antiplatelets\textsuperscript{1}

**J-ROCKET AF**: rivaroxaban 15 mg OD showed similar efficacy and safety compared with warfarin, with a trend towards a lower incidence of stroke/SE\textsuperscript{2}

**ATLAS ACS 2 TIMI 51** trial\textsuperscript{3} demonstrated the safety of the rivaroxaban 2.5 mg BID dose in combination with DAPT was selected because this is the recommended INR for stroke prevention in patients with AF\textsuperscript{4}

PIONEER AF-PCI
Rationale for Selection of ASA or P2Y$_{12}$ Inhibitor

**Study group 1**
- 12 months
- Rivaroxaban 15 mg OD plus P2Y$_{12}$

**Study group 2**
- 1, 6 or 12 months
- Up to 12 months
- Rivaroxaban 2.5 mg BID plus ASA plus P2Y$_{12}$

**Study group 3**
- 1, 6 or 12 months
- Up to 12 months
- VKA plus ASA plus P2Y$_{12}$
- VKA plus ASA

WOEST showed that combining an OAC (VKA) and clopidogrel was safe and effective\(^1\)
Prasugrel and ticagrelor were permitted at the discretion of the investigator as they are recommended in ACS guidelines\(^2,3\)

In Groups 2 and 3, a period of triple therapy was followed by dual therapy using an OAC plus **low-dose ASA**.
ASA was selected over clopidogrel because it is used for long-term therapy after PCI (guidelines from the ACCF/AHA/SCAI for the management of PCI recommend continuing therapy with ASA indefinitely)\(^4\)

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Primary safety outcomes

- TIMI clinically significant bleeding:
  - Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

- Time to the first event in the composite outcome
Secondary safety and efficacy outcomes

- Components of the clinically significant bleeding outcome
  - TIMI major
  - TIMI minor
  - Bleeding requiring medical attention

- Composite and components of major adverse CV events:
  - CV death
  - MI
  - Stroke

- Stent thrombosis

- Time to the first event in the composite outcome or components
## PIONEER AF-PCI
### Key Inclusion and Exclusion Criteria

#### Key inclusion criteria
- Medical history of paroxysmal, persistent or permanent NVAF
- Undergone PCI with stent placement for primary atherosclerotic disease
- INR ≤2.5 at randomization

#### Key exclusion criteria
- Contraindication for anticoagulant or antiplatelet therapy or unacceptable risk of bleeding*
- History of stroke or TIA
- CrCl <30 ml/min at screening

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*Including, but not limited to, platelet count <90,000/µl at screening, history of ICH, 12-month history of clinically significant GI bleeding, non-VKA-induced elevated PT at screening, anaemia of unknown cause with a haemoglobin level <10 g/dl (<6.21 mmol/l) or significant liver disease or liver function test abnormalities

More Patients in the VKA Group Discontinued Treatment Early than in Either Rivaroxaban Group

Primary reason for early discontinuation from treatment period

- Group 3 (VKA plus DAPT) (n=697)
- Group 2 (rivaroxaban 2.5 mg BID plus DAPT) (n=706)
- Group 1 (rivaroxaban 15 mg OD plus single antiplatelet) (n=696)

Early discontinuations were highest in the VKA plus DAPT group; discontinuation due to patient decision was significantly higher in this group vs both rivaroxaban groups.

There were no patients lost to follow up.

*p=0.016; **p<0.001

Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

Design: An open-label, randomized, controlled phase IIIb safety study

Population: patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

- Rivaroxaban 15 mg OD**# plus single antiplatelet‡
  - 12 mos: 100%
- Rivaroxaban 2.5 mg BID# plus DAPT§
  - 1 mo: 16%
  - 6 mos: 35%
  - 12 mos: 49%
- Rivaroxaban 15 mg OD* plus low-dose ASA
  - 1 mo: 16%
  - 6 mos: 35%
  - 12 mos: 49%

Decision for DAPT duration: 1, 6 or 12 months

- DAPT duration (1 or 6 months)
- End of treatment (12 months)

- N=2,124

*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); †first dose 12–72 hours after sheath removal

Time in Therapeutic Range When Receiving VKA plus DAPT Was High Across All Participating Regions

- Average TTR (INR 2.0–3.0) was 65%

Both Rivaroxaban Strategies was Associated With Significantly Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001

Primary Safety Endpoint: Reduced with Rivaroxaban Strategies vs VKA

Both rivaroxaban strategies associated with significant reduction in incidence of clinically significant bleeding vs the VKA plus DAPT strategy

*p=0.002 vs Group 3; **p<0.001 vs Group 3; #composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

ISTH Major Bleeding Significantly Reduced with Rivaroxaban Strategies vs VKA

Both rivaroxaban strategies associated with significant reduction in ISTH major and clinically relevant non-major bleeding vs the VKA plus DAPT strategy

* *p<0.05 vs Group 3
Efficacy was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints
Comparative Efficacy with Rivaroxaban Strategies vs VKA plus DAPT

**Composite endpoint**

- Incidence of major adverse CV events was comparable between all three treatment strategies; however, the trial was not powered for efficacy

*Composite of CV death, MI and stroke

Rivaroxaban Strategies Show Significantly Improved Safety and Comparable Efficacy vs VKA plus DAPT

Both rivaroxaban strategies were associated with a significant reduction in incidence of the primary safety endpoint with comparable incidence of major adverse CV events vs the VKA plus DAPT strategy (trial not powered for efficacy)

## Significantly Reduced Bleeding* with Rivaroxaban 15 mg Strategy Across Subgroups vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td><strong>Age</strong></td>
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<td></td>
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</tr>
<tr>
<td>&lt;75 years</td>
<td>0.56</td>
<td>0.41–0.77</td>
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<td>&lt;0.001</td>
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<tr>
<td>≥75 years</td>
<td>0.62</td>
<td>0.42–0.90</td>
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<td>0.011</td>
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<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.63</td>
<td>0.47–0.84</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.51</td>
<td>0.32–0.80</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Type of stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-eluting</td>
<td>0.64</td>
<td>0.47–0.86</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Bare metal</td>
<td>0.54</td>
<td>0.36–0.82</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Both</td>
<td>0.20</td>
<td>0.02–1.82</td>
<td></td>
<td>0.115</td>
</tr>
<tr>
<td><strong>Type of P2Y₁₂ inhibitor</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.59</td>
<td>0.46–0.76</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Prasugrel</td>
<td>1.16</td>
<td>0.22–6.03</td>
<td></td>
<td>0.857</td>
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<tr>
<td>Ticagrelor</td>
<td>0.33</td>
<td>0.11–1.01</td>
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<td>0.039</td>
</tr>
</tbody>
</table>

*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

Re-hospitalization Due to CV Events and Bleeding Were Both Reduced with the Rivaroxaban Strategies

Adverse events leading to hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes; Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Gibson CM et al, Circulation 2016; doi:10.1161/CIRCULATIONAHA.116.025783

Group 1 vs Group 3:
CV
HR=0.68; (95% CI 0.54–0.85); p<0.001
ARR=8.1%; NNT=13

Bleeding
HR=0.61; (95% CI 0.41–0.90); p=0.012
ARR=4.0%; NNT=25

Group 2 vs Group 3:
CV
HR=0.73 (95% CI 0.58–0.91); p=0.005
ARR=8.1%; NNT=13

Bleeding
HR=0.51 (95% CI 0.34–0.77); p=0.001
ARR=5.1%; NNT=20
Limitations

**Power**
- Trial was not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints
  - Power to detect a $\geq 15\%$ risk reduction for major adverse CV events was 11.4%.
  - Assuming a 90% power to detect a 15% relative difference between the treatment groups, a superiority trial would require 13,598 participants/arm.

**DAPT stratification**
- Stratification of patients in Groups 2 and 3 according to duration of DAPT (1, 6 or 12 months) was determined by the attending physician.
  - This resulted in imbalances in patient characteristics between treatment strategies within each stratum.
Both rivaroxaban dose strategies significantly reduced rates of clinically significant bleeding vs the VKA strategy
  - Rivaroxaban 15 mg OD plus single antiplatelet: RRR=41%
  - Rivaroxaban 2.5 mg BID plus DAPT: RRR=37%

Rates of CV death, MI and stroke were comparable between all three groups; however, the trial was not powered to definitively demonstrate either superiority or non-inferiority for efficacy
  - 360-day Kaplan–Meier estimates for the composite endpoint were 6.5% (Group 1), 5.6% (Group 2) and 6.0% (Group 3)

Post hoc analysis showed a reduction in mortality or recurrent hospitalization with both rivaroxaban strategies vs the VKA strategy
  - Rivaroxaban 15 mg OD plus single antiplatelet: RRR=21%
  - Rivaroxaban 2.5 mg BID plus DAPT: RRR=25%
Conclusions

• Administration of either rivaroxaban 15 mg OD plus a single antiplatelet for 1 year, or rivaroxaban 2.5 mg BID plus 1, 6 or 12 months of DAPT reduced the risk of clinically significant bleeding compared with a standard VKA plus DAPT strategy.

• Although the study was not powered to detect differences in efficacy endpoints, both rivaroxaban strategies demonstrated similar efficacy compared with a standard VKA plus DAPT strategy.

• Both rivaroxaban strategies showed a reduced risk of recurrent hospitalization.

## Comparable Efficacy with Rivaroxaban Strategies vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse CV events*</td>
<td>1.08</td>
<td>0.69–1.68</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>CV death</td>
<td>1.29</td>
<td>0.59–2.80</td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>MI</td>
<td>0.86</td>
<td>0.46–1.59</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.07</td>
<td>0.39–2.96</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.20</td>
<td>0.32–4.45</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse CV events*</td>
<td>0.93</td>
<td>0.59–1.48</td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>CV death</td>
<td>1.19</td>
<td>0.54–2.62</td>
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<td>0.66</td>
</tr>
<tr>
<td>MI</td>
<td>0.75</td>
<td>0.40–1.42</td>
<td></td>
<td>0.37</td>
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<tr>
<td>Stroke</td>
<td>1.36</td>
<td>0.52–3.58</td>
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<td>0.53</td>
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<tr>
<td>Stent thrombosis</td>
<td>1.44</td>
<td>0.40–5.09</td>
<td></td>
<td>0.57</td>
</tr>
</tbody>
</table>

*Composite of CV death, MI and stroke


Incidence of major adverse CV events was comparable between all three treatment strategies; however the trial was not powered for efficacy.
RE-DUAL PCI: dual antithrombotic therapy with dabigatran after percutaneous coronary intervention in patients with atrial fibrillation

Christopher P. Cannon

On behalf of the steering committee and RE-DUAL PCI investigators
Antithrombotic therapy for atrial fibrillation and PCI

**Anticoagulant therapy**
- Low shear stress thrombosis in left atrium
- Anticoagulation superior to antiplatelet therapy

**Antiplatelet therapy**
- High shear stress thrombosis mediated in the arteries
- Dual antiplatelet therapy superior to ASA alone

**BOTH anticoagulant and dual antiplatelet ‘triple therapy’**
- High bleeding risk

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Study Design: Multicenter, randomized, open-label trial following a PROBE design

Patients with AF undergoing PCI with stenting

Randomization ≤120 hours post-PCI

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
Patients were randomized based on age group and location.

Patients aged <80 years worldwide (<70 years in Japan), and patients aged ≥80 years in the USA.

Patients aged ≥80 years outside the USA (≥70 years in Japan).

- **Dabigatran 150 mg dual therapy**
  - n=763

- **Dabigatran 110 mg dual therapy**
  - n=769
    - **Warfarin triple therapy**
      - n=766

- **Dabigatran 110 mg dual therapy**
  - n=212
    - **Warfarin triple therapy**
      - n=215
## 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)

ACS, acute coronary syndrome; CAD, coronary artery disease; CrCl, creatinine clearance
Study objective and design

RE-DUAL PCI tests the safety and efficacy of two regimens of dual therapy with dabigatran without aspirin vs triple therapy with warfarin

- 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)
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>Dabigatran 150 mg dual therapy (n=763)</th>
<th>Corresponding Warfarin triple therapy (n=764)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean</td>
<td>71.5</td>
<td>71.7</td>
<td>68.6</td>
<td>68.8</td>
</tr>
<tr>
<td>≥80 (US, ROW), ≥70 (Japan), %</td>
<td>22.9</td>
<td>22.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;80 (US, ROW), &lt;70 (Japan), %</td>
<td>77.1</td>
<td>77.1</td>
<td>99.0</td>
<td>99.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>74.2</td>
<td>76.5</td>
<td>77.6</td>
<td>77.7</td>
</tr>
<tr>
<td>Baseline CrCl, mL/min, mean</td>
<td>76.3</td>
<td>75.4</td>
<td>83.7</td>
<td>81.3</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36.9</td>
<td>37.8</td>
<td>34.1</td>
<td>39.7</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2}−VASc score (mean)</td>
<td>3.7</td>
<td>3.8</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Modified HAS-BLED score at baseline (mean)</td>
<td>2.7</td>
<td>2.8</td>
<td>2.6</td>
<td>2.7</td>
</tr>
<tr>
<td>ACS indication for PCI, %</td>
<td>51.9</td>
<td>48.4</td>
<td>51.2</td>
<td>48.3</td>
</tr>
<tr>
<td>DES only, %</td>
<td>82.0</td>
<td>84.2</td>
<td>81.4</td>
<td>83.5</td>
</tr>
</tbody>
</table>

ROW, rest of world
Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

HR: 0.52 (95% CI: 0.42–0.63)  
Non-inferiority  
P<0.0001  P<0.0001

Warfarin triple therapy

HR: 0.72 (95% CI: 0.58–0.88)  
Non-inferiority  
P<0.0001  P=0.002

Warfarin triple therapy

Dabigatran 150 mg dual therapy

Dabigatran 110 mg dual therapy

Time to first event (days)

Probability of event (%)
Primary endpoint: ISTH major or clinically relevant non-major bleeding event

HR: 0.52 (95% CI: 0.42–0.63)  
P<0.0001

ARR: 11.5%

15.4%  

Dabigatran 110 mg dual therapy (n=981)

26.9%

Warfarin triple therapy (n=981)

HR: 0.72 (95% CI: 0.58–0.88)  
P=0.002

ARR: 5.5%

20.2%

Dabigatran 150 mg dual therapy (n=763)

25.7%

Warfarin triple therapy (n=764)

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05).  
ARR, absolute risk reduction
Rates of ISTH major bleeding

HR: 0.52 (95% CI: 0.37–0.74)  
P=0.0003

HR: 0.64 (95% CI: 0.43–0.94)  
P=0.022

Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ISTH major bleeding definition: fatal, critical organ (including intracranial haemorrhage), clinically overt bleeding with fall in Hb ≥2 g/dL. Hb, haemoglobin
Rates of TIMI major or minor bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dabigatran 110 mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>Dabigatran 150 mg dual therapy (n=763)</th>
<th>Warfarin triple therapy (n=764)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (%)</td>
<td>3.0%</td>
<td>7.0%</td>
<td>3.5%</td>
<td>6.3%</td>
</tr>
<tr>
<td>HR</td>
<td>0.41 (95% CI: 0.26–0.63)</td>
<td>P&lt;0.0001</td>
<td>0.53 (95% CI: 0.33–0.85)</td>
<td>P=0.009</td>
</tr>
<tr>
<td>ARR (%)</td>
<td>4%</td>
<td></td>
<td>2.8%</td>
<td></td>
</tr>
</tbody>
</table>

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; TIMI minor bleeding definition: clinically overt bleeding (including imaging), resulting in Hb drop of 3 to >5 g/dL. TIMI, thrombolysis in myocardial infarction.
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% (95% CI: 0.20–0.68) P=0.0015
  - ARR: 2.4%
  - HR: 0.37 (95% CI: 0.20–0.68)

- **Warfarin triple therapy (n=981)**: 3.8%
  -ARR: 1.8%
  -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

HR: 0.12 (95% CI: 0.02–0.98)  
P=0.047
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.
### Additional individual thromboembolic endpoints

<table>
<thead>
<tr>
<th></th>
<th>mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>D110 DT vs warfarin TT HR (95% CI)</th>
<th>P value</th>
<th>Dabigatran 150 mg dual therapy (n=763)</th>
<th>Warfarin triple therapy (n=764)</th>
<th>D150 DT vs warfarin TT HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 (5.6)</td>
<td>48 (4.9)</td>
<td>1.12 (0.76–1.65)</td>
<td>0.56</td>
<td>30 (3.9)</td>
<td>35 (4.6)</td>
<td>0.83 (0.51–1.34)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>17 (1.7)</td>
<td>13 (1.3)</td>
<td>1.30 (0.63–2.67)</td>
<td>0.48</td>
<td>9 (1.2)</td>
<td>8 (1.0)</td>
<td>1.09 (0.42–2.83)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Unplanned revascularization</strong></td>
<td>76 (7.7)</td>
<td>69 (7.0)</td>
<td>1.09 (0.79–1.51)</td>
<td>0.61</td>
<td>51 (6.7)</td>
<td>52 (6.8)</td>
<td>0.96 (0.65–1.41)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>44 (4.5)</td>
<td>29 (3.0)</td>
<td>1.51 (0.94–2.41)</td>
<td>0.09</td>
<td>26 (3.4)</td>
<td>22 (2.9)</td>
<td>1.16 (0.66–2.04)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Stent thrombosis</strong></td>
<td>15 (1.5)</td>
<td>8 (0.8)</td>
<td>1.86 (0.79–4.40)</td>
<td>0.15</td>
<td>7 (0.9)</td>
<td>7 (0.9)</td>
<td>0.99 (0.35–2.81)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Subgroup analysis: age and ticagrelor use at baseline

Time to first ISTH MBE or CRNMBE

**Age**

<table>
<thead>
<tr>
<th></th>
<th>Pts (n)</th>
<th>Pts with event (%)</th>
<th>Interaction P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D110-DT</td>
<td>225</td>
<td>22.2</td>
<td>Not. eval*</td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT</td>
<td>225</td>
<td>31.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D150-DT</td>
<td>8</td>
<td>87.5</td>
<td>P=0.0089</td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT†</td>
<td>8</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-elderly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D110-DT</td>
<td>13.</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>756</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D150-DT</td>
<td>25.0</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT†</td>
<td>5</td>
<td>19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>755</td>
<td>25.0</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT†</td>
<td>7</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ticagrelor use at baseline (12% Pts)**

<table>
<thead>
<tr>
<th></th>
<th>Pts (n)</th>
<th>Pts with event (n)</th>
<th>Interaction P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D110-DT</td>
<td>849</td>
<td>14.5</td>
<td>P=0.69</td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT</td>
<td>890</td>
<td>25.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D150-DT</td>
<td>659</td>
<td>19.7</td>
<td>P=0.53</td>
<td></td>
</tr>
<tr>
<td>Warfarin-TT†</td>
<td>691</td>
<td>24.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not evaluable: for age-stratified model, the interaction P value is not derived. †For the comparison with D150-DT, elderly patients outside the USA are excluded. Age category is determined IVRS, interactive voice response system; MBE, major bleeding event; CRNMBE, clinically relevant non-major bleeding event; Pts, patients

Missing/not applicable categories not shown and removed prior to calculation of interaction P values.
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.
## Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

<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, <strong>rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d.</strong></td>
<td>IIIB</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>

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www.escardio.org/guidelines | 2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)

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2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)
<table>
<thead>
<tr>
<th>Strategies to avoid bleeding complications in patients treated with oral anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.</td>
</tr>
<tr>
<td>• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.</td>
</tr>
<tr>
<td>• Consider the use of NOACs instead of VKA when NOACs are not contraindicated.</td>
</tr>
<tr>
<td>• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. &gt;65–70%) when VKA is used.</td>
</tr>
<tr>
<td>• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.</td>
</tr>
<tr>
<td>• Clopidogrel is the P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor of choice.</td>
</tr>
<tr>
<td>• Use low-dose (≤100 mg daily) aspirin.</td>
</tr>
<tr>
<td>• Routine use of PPIs.</td>
</tr>
</tbody>
</table>

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ΕΥΧΑΡΙΣΤΩ