NOACs and the interventional cardiologist: what’s new?

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Red Cross Hospital
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Conflict of interest

• Speaker Honoraria from Boehringer Ingelheim
Anticoagulation in patients with AF is usually lifelong and they may undergo multiple procedures during this time.
The safety and efficacy of dabigatran was established in the RE-LY trial.

<table>
<thead>
<tr>
<th>Efficacy endpoints (ITT set)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.89</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.76</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>1.13</td>
<td>0.31</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.85</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.90</td>
<td>0.21</td>
</tr>
<tr>
<td>MI</td>
<td>1.27</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety endpoints (safety set)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0.94</td>
<td>0.41</td>
</tr>
<tr>
<td>ICH</td>
<td>0.80</td>
<td>0.003</td>
</tr>
<tr>
<td>ICH</td>
<td>0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bold values indicate statistical significance. ICH, intracranial haemorrhage; ITT, intention-to-treat; SE, systemic embolism

In a post hoc RE-LY analysis, patients on the recommended dabigatran dose showed meaningful clinical benefits vs warfarin.

Data are from EU label simulated dabigatran treatment analysis: patients received dabigatran 150 mg BID or 110 mg BID according to EU label recommendations.

**Efficacy endpoints (ITT set):**
- Stroke/SE: HR 0.74 (0.60–0.91)
- CV mortality: HR 0.80 (0.68–0.95)
- MI: HR 1.14 (0.83–1.55)

**Safety endpoints (safety set):**
- Major bleeding: HR 0.85 (0.73–0.98)
- ICH: HR 0.28 (0.17–0.45)

Based on recommendations and considerations of the EU label information at time of publication: recommended dose of dabigatran 110 mg BID in the following patients: age ≥80 years, or on concomitant verapamil, or high risk of bleeding. All other patients should receive dabigatran 150 mg BID. Lip et al. Thromb Haemost 2014.
RE-CIRCUIT showed a lower risk of major bleeding during and after ablation with uninterrupted dabigatran vs warfarin.

Major bleeding events during and up to 8 weeks after ablation

Patients with ISTH major bleeding (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with bleeds (n)</th>
<th>Absolute risk difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg BID (n=317)</td>
<td>5</td>
<td>-5.3% (P&lt;0.001)</td>
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<tr>
<td>Warfarin (n=318)</td>
<td>22</td>
<td>77.2%</td>
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</tbody>
</table>
Incidence of Atrial Fibrillation in PCI Patients

5 to 21%

Acute or stable Coronary Syndrome

PCI + Afib

Atrial Fibrillation
Management of patients with AF who have undergone PCI must balance the risk of bleeding with risk of thrombosis.

ACS, acute coronary syndrome
Lip et al. Thromb Haemost 2010
Cumulative incidence of death after an ischemic event and after a bleeding event is about the same.

Cumulative incidence of death was 0.5% after an ischemic event and 0.3% after a bleeding event.
Possible mechanisms linking bleeding with increased mortality

Increased hospitalizations. Nosocomial infections or other adverse sequelae hospitalization can cause major morbidity, including of a cardiovascular nature.

Low 2,3-diphosphoglyceric acid activity.
For patients who underwent PCI, major bleeding was associated with a significant increase in in-hospital mortality, regardless of bleeding site.

In the CathPCI registry, analysing data from 3.3 million PCI procedures (2004–11):

- **1.87%** in-hospital mortality rate: non-bleeding
- **5.26%** in-hospital mortality rate: major bleeding

Risk difference = 3.39%
(95% CI: 3.20–3.59)
P<0.001

Bleeding is the most common non-cardiac complication of PCI.

Antithrombotic therapy that minimizes the risk of bleeding complications might therefore be expected to result in better short- and long-term clinical outcomes after PCI.

Chhatriwala et al. JAMA 2013
Bleeding means longterm mortality

Eikelboom et al Circulation. 2006;114:774-782
Research focus for OACs: antithrombotic therapy in patients with NVAF after PCI/post-ACS

WOEST: dual therapy with VKA + clopidogrel (excluding ASA) reduces bleeding risk vs triple therapy without compromise on efficacy

573 patients receiving OAC (any indication, 69% for AF/atrial flutter) and undergoing PCI in open-label, randomized WOEST trial

ASA, acetylsalicylic acid; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; TVR, target vessel revascularization

Dewilde et al. Lancet 2013
Pre-Randomization Choice of Duration of DAPT & Thienopyridine: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

XARELTO® 15 mg qd*
 Clopi 95%, Ticag 4%, Prasugrel 1%

1 mo: 16%
6 mos: 35%
12 mos: 49%

XARELTO® 2.5 mg bid
 Clopi 95%, Ticag 4%, Prasugrel 1%
 Aspirin 75-100 mg qd‡

1 mo: 16%
6 mos: 35%
12 mos: 49%

VKA (target INR 2.0-3.0)
 Clopi 95%, Ticag 4%, Prasugrel 1%
 Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)
 Aspirin 75-100 mg qd
 TTR 65%

Gibson et al. AHA 2016
◆ 2100 patients with NVAF
◆ Coronary stenting
◆ No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30
PIOINER AF-PCI showed reduced bleeding with NOAC-based dual therapy vs VKA triple therapy

Primary endpoint: 
clinically significant bleeding*

- TIMI major bleeding
- TIMI minor bleeding
- Bleeding requiring medical attention

Total number of events
393
46
27
334

Favours R15/10 + clopidogrel  
Favours VKA triple therapy

Favours R2.5 + DAPT  
Favours VKA triple therapy

Any bleeding requiring medical or surgical treatment or laboratory evaluation

Primary endpoint of major bleeding or minor bleeding according to TIMI criteria, or bleeding requiring medical attention. DAPT, dual antiplatelet therapy; R2.5, rivaroxaban 2.5 mg BID; R15/10, rivaroxaban 15/10 mg OD
Adapted from Gibson et al. N Engl J Med 2016
Management of patients with AF who have undergone PCI must balance the risk of bleeding with risk of thrombosis.

Combination of OAC and antiplatelets increases bleeding risk, which in turn drives poor outcome, so as well as preventing thrombotic events, a low major bleeding rate is a key treatment target.
WOEST and PIONEER AF-PCI were not designed to provide confirmatory data for efficacy outcomes

**Incidence of any bleeding**

- **WOEST**
  - N=573
- **PIONEER AF-PCI**
  - N=2124

**Death, MI, TVR, stroke, and ST**

- **WOEST**
  - N=573
- **PIONEER AF-PCI**
  - N=2124

*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention. R15, rivaroxaban 2.5 mg BID; R15/10, rivaroxaban 15/10 mg OD; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization. Dewilde et al. Lancet 2013; Gibson et al. N Engl J Med 2016; Gibson et al. AHA 2016*
CONCLUSIONS

Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events.
RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin

Multicentre, randomized, open-label trial following a PROBE design

Patients with AF undergoing PCI with stenting
N=2725
Inclusion if:
• Successful PCI
• AF
Excluded if:
• Stroke/ major surgery/ major bleeding within 1 month
• CrCl <30mL/min

Primary endpoint: ISTH major or CRNM bleeding

Dabigatran 150 mg BID + P2Y12 inhibitor

Dabigatran 110 mg BID + P2Y12 inhibitor

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

Dabigatran (110 or 150 mg) + P2Y12 inhibitor

Warfarin + P2Y12 inhibitor

≤120 hours post-PCI

6-month minimum treatment duration, maximum treatment duration 30 months (mean follow-up 14 months)

*Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable). Elderly patients outside the USA (≥80 years) and Japan (≥70 years) were randomized to either dabigatran 110 mg BID or warfarin arm; †ASA discontinued after 1 month after BMS and 3 months after DES. BMS, bare-metal stent; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; PROBE, prospective, randomized, open label, blinded endpoint; R, randomization. Cannon et al. Clin Cardiol 2016; Cannon et al. N Engl J Med 2017
Dabigatran dual therapy: significantly lower rates of ISTH major bleeding or clinically relevant non-major bleeding

HR: 0.52 (95% CI: 0.42–0.63)
Non-inferiority P<0.001
Superiority P<0.001

HR: 0.72 (95% CI: 0.58–0.88)
Non-inferiority P<0.001
P=0.002

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 years 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. Full analysis set presented. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional hazard model (alpha=0.05); Cannon et al. N Engl J Med 2017
Dabigatran dual therapy had fewer TIMI major bleeding events than warfarin triple therapy.

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%
- Warfarin triple therapy (n=981): 3.8%
- Dabigatran 150 mg dual therapy (n=763): 2.1%
- Warfarin triple therapy (n=764): 3.9%

HR: 0.37 (95% CI: 0.20–0.68)  
P=0.002

HR: 0.51 (95% CI: 0.28–0.93)  
P=0.03
Dabigatran dual therapy had fewer ICH events than warfarin triple therapy

HR: 0.30 (95% CI: 0.08–1.07)  
$P=0.06$

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

Wald two-sided $P$ value from (stratified) Cox proportional hazard model (alpha=0.05).  
ICH, intracranial haemorrhage.  
Dabigatran dual therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint.

HR: 1.04 (95% CI: 0.84–1.29)
Non-inferiority P=0.005

Non-inferiority P value is one sided (alpha=0.025). Results presented are a pre-defined testing of non-inferiority for dabigatran dual therapy (combined doses) vs. warfarin triple therapy in death or thromboembolic event and unplanned revascularization (statistical power: 83.6%); Cannon et al. N Engl J Med 2017
Time to first ISTH major or CRNM bleeding event in relation to ticagrelor or clopidogrel

Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 years in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 vs warfarin comparison, an unstratified model is used, elderly patients outside the United States 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).

CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.
Is dropping ASA safe in the context of dual therapy with dabigatran for patient with ACS?
RE-DUAL PCI subanalysis: no interaction between treatment and patients with or without ACS in bleeding endpoints

The index indication for PCI was an ACS in ~50% of patients enrolled in RE-DUAL PCI.

<table>
<thead>
<tr>
<th></th>
<th>P interaction</th>
<th>D110-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
<th>P interaction</th>
<th>D150-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTH major/</td>
<td>0.34</td>
<td>75/509 (14.7)</td>
<td>132/475 (27.8)</td>
<td>0.57</td>
<td>80/391 (20.5)</td>
<td>100/369 (27.1)</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td></td>
<td>76/472 (16.1)</td>
<td>132/505 (26.1)</td>
<td></td>
<td>74/372 (19.9)</td>
<td>96/394 (24.4)</td>
</tr>
<tr>
<td>ISTH major</td>
<td>0.14</td>
<td>26/509 (5.1)</td>
<td>55/475 (11.6)</td>
<td>0.39</td>
<td>25/391 (6.4)</td>
<td>40/369 (10.8)</td>
</tr>
<tr>
<td>bleeding</td>
<td></td>
<td>23/472 (4.9)</td>
<td>35/505 (6.9)</td>
<td></td>
<td>18/372 (4.8)</td>
<td>24/394 (6.1)</td>
</tr>
<tr>
<td>TIMI major</td>
<td>0.30</td>
<td>7/509 (1.4)</td>
<td>23/475 (4.8)</td>
<td>0.47</td>
<td>9/391 (2.3)</td>
<td>19/369 (5.1)</td>
</tr>
<tr>
<td>bleeding</td>
<td></td>
<td>7/472 (1.5)</td>
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</tr>
</tbody>
</table>

Oldgren et al. AHA 2017
RE-DUAL PCI subanalysis: no interaction between treatment and patients with or without ACS in thromboembolic endpoints

Oldgren et al. AHA 2017
Is ticagrelor an option for patients on dabigatran dual therapy?
RE-DUAL PCI subanalysis: no interaction between treatment and P2Y12 inhibitor in bleeding endpoints

Most patients (~88%) received clopidogrel in addition to their randomized OAC regimen in RE-DUAL PCI

<table>
<thead>
<tr>
<th></th>
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<th>D110-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
<th>P interaction</th>
<th>D150-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTH major/CRNM bleeding</td>
<td>0.69</td>
<td>28/104 (21.2) 34/91 (37.4)</td>
<td>123/849 (14.5) 230/890 (25.8)</td>
<td>0.53</td>
<td>24/104 (23.1) 25/73 (34.2)</td>
<td></td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>0.75</td>
<td>11/132 (8.3) 15/91 (16.5)</td>
<td>38/849 (4.5) 75/890 (8.4)</td>
<td>0.37</td>
<td>8/104 (7.7) 12/73 (14.6)</td>
<td></td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>0.39</td>
<td>3/132 (2.3) 9/91 (9.9)</td>
<td>11/849 (1.3) 28/890 (3.1)</td>
<td>0.17</td>
<td>2/104 (1.9) 7/73 (9.6)</td>
<td></td>
</tr>
</tbody>
</table>

*58 patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup; †93 patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup. Oldgren et al. Presented at AHA 2017.
RE-DUAL PCI subanalysis: no interaction between treatment and P2Y12 inhibitor in thromboembolic endpoints

*58 patients who received ticagrelor + clopidogrel are included in the ticagrelor subgroup; †93 patients who received neither clopidogrel nor ticagrelor are included in the clopidogrel subgroup. Oldgren et al. Presented at AHA 2017
Bleeding events: BMS vs DES

<table>
<thead>
<tr>
<th></th>
<th>D110-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISTH Major/CRNM Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>19/148 (12.8)</td>
<td>35/133 (26.3)</td>
</tr>
<tr>
<td>DES</td>
<td>127/804 (15.8)</td>
<td>288/826 (27.6)</td>
</tr>
<tr>
<td><strong>ISTH Major Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>4/148 (2.7)</td>
<td>13/133 (9.8)</td>
</tr>
<tr>
<td>DES</td>
<td>44/804 (5.5)</td>
<td>77/826 (9.3)</td>
</tr>
<tr>
<td><strong>TIMI Major Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>0/148 (0.0)</td>
<td>8/133 (6.0)</td>
</tr>
<tr>
<td>DES</td>
<td>13/804 (1.6)</td>
<td>29/826 (3.5)</td>
</tr>
</tbody>
</table>

P interaction: 0.52

<table>
<thead>
<tr>
<th></th>
<th>D150-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
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<tbody>
<tr>
<td><strong>ISTH Major/CRNM Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>18/123 (14.6)</td>
<td>27/107 (25.2)</td>
</tr>
<tr>
<td>DES</td>
<td>133/621 (21.4)</td>
<td>168/638 (26.3)</td>
</tr>
<tr>
<td><strong>ISTH Major Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>8/123 (6.5)</td>
<td>10/107 (9.3)</td>
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<tr>
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<tr>
<td>DES</td>
<td>12/621 (1.9)</td>
<td>23/638 (3.6)</td>
</tr>
</tbody>
</table>

P interaction: 0.31

BMS, bare-metal stent; CRNM, clinically relevant non-major; D, dabigatran; DES, drug-eluting stent; DT, dual therapy; ISTH, International Society on Thrombosis and Haemostasis; TIMI, thrombolysis in myocardial infarction; TT, triple therapy.
## Death and thromboembolic events: BMS vs DES

<table>
<thead>
<tr>
<th></th>
<th>D110 dual-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
<th>D150-DT n/N (%)</th>
<th>Warfarin-TT n/N (%)</th>
<th>P interaction</th>
<th>DTE or Unplanned Revascularization</th>
<th>P interaction</th>
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<tbody>
<tr>
<td><strong>DTE or Unplanned Revascularization</strong></td>
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<td>BMS</td>
<td>25/148 (16.9)</td>
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<td>0.72</td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>DES</td>
<td>118/804 (14.7)</td>
<td>108/826 (13.1)</td>
<td>73/621 (11.8)</td>
<td>81/638 (12.7)</td>
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<tr>
<td><strong>Myocardial Infarction</strong></td>
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<tr>
<td>BMS</td>
<td>9/148 (6.1)</td>
<td>4/133 (3.0)</td>
<td>3/123 (2.4)</td>
<td>2/107 (1.9)</td>
<td>0.66</td>
<td></td>
<td>0.96</td>
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<tr>
<td>DES</td>
<td>35/804 (4.4)</td>
<td>24/826 (2.9)</td>
<td>23/621 (3.7)</td>
<td>19/638 (3.0)</td>
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<tr>
<td><strong>All-cause Death</strong></td>
<td></td>
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<td></td>
<td>0.85</td>
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<td>0.20</td>
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<td>BMS</td>
<td>7/148 (4.7)</td>
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<td>8/123 (6.5)</td>
<td>4/107 (3.7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DES</td>
<td>43/804 (5.3)</td>
<td>41/826 (5.0)</td>
<td>22/621 (3.5)</td>
<td>30/638 (4.7)</td>
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BMS, bare-metal stent; D, dabigatran; DES, drug-eluting stent; DT, dual therapy; DTE, death or thromboembolic event (myocardial infarction, stroke or systemic embolism); TT, triple therapy.
2017 ESC focused update on dual antiplatelet therapy in coronary artery disease (2018 Revasc update)

*Based on HAS-BLED score
Valgimigli et al. Eur Heart J 2018
2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA)

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1. Periprocedural administration of aspirin and dipyridamole during PCI is recommended irrespective of the treatment strategy; as dual therapy, potent P2Y12 inhibitors (ticagrelor) may be combined with dabigatran.

2. High ischaemotherombotic risk (For Elective PCI, use SYNTAX score; for ACS, GRACE score >140; scoring of the left main, proximal LAD, proximal bifurcation, recurrent MI; acute coronary syndrome etc.) and low bleeding risk

3. Bleeding risk can be estimated using the HAS-BLED score; correct modifiable bleeding risk factors
Management of NOACs in patients who underwent elective and ACS PCI

While awaiting the results of trials with apixaban and edoxaban, the 150 mg dabigatran dual therapy appears to be the preferred choice over triple therapy for the majority of patients based on both the results from RE-LY\textsuperscript{28} and RE-DUAL PCI\textsuperscript{141}; dual therapy using 110 mg dabigatran or rivaroxaban 15 mg (10 mg in renal insufficiency) appears as a viable alternative for patients with estimated high bleeding risk—provided that dabigatran or rivaroxaban per se appear as a good choice for this individual patient based on age (see chapter \textbf{18.1}), comorbidities (e.g. renal insufficiency; see chapter \textbf{6}), interactions (see chapter \textbf{5}), and others.

Figure 10 Acute management of elective percutaneous coronary intervention or acute coronary syndrome in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulant.

Management of NOACs in patients who underwent elective and ACS PCI

Figure 11 Long-term treatment of patients on non-vitamin K antagonist oral anticoagulant therapy after elective percutaneous coronary intervention or acute coronary syndrome. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach to each and every single patient. This figure wants to create a “backbone” as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD; Tica: Ticagrelor 90 mg BID. If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data).
Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention
A North American Perspective–2018 Update

ABSTRACT: The optimal antithrombotic treatment regimen for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation represents a challenge in clinical practice. In 2016, an updated opinion of selected experts from the United States and Canada on the treatment of patients with atrial fibrillation undergoing percutaneous coronary intervention was reported. After the 2016 North American consensus statement on the management of antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention, results of pivotal clinical trials assessing the type of oral anticoagulant agent and the duration of antiplatelet treatment have been published. On the basis of these results, this focused update on the antithrombotic management of patients with atrial fibrillation undergoing percutaneous coronary intervention recommends that a non–vitamin K antagonist oral anticoagulant be preferred over a vitamin K antagonist as the oral anticoagulant of choice. Moreover, a double-therapy regimen (oral anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor) by the time of hospital discharge should be considered for most patients, whereas extending the use of aspirin beyond hospital discharge (i.e., triple therapy) should be considered only for selected patients at high ischemic/thrombotic and low bleeding risks and for a limited period of time. The present document provides a focused update on the rationale for the new expert consensus–derived recommendations on the antithrombotic management of patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention.

OAC:
- A NOAC should be preferred in most patients and used at established stroke prevention doses; lower doses are not recommended unless specifically tested.
- If VKA is chosen, maintain INR at the lower end of the therapeutic range (e.g., 2.0–2.5).
- Maintain OAC lifelong.

APT:
Aspirin in the peri-PCI phase and continued through hospital discharge.
Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be a reasonable alternative in high ischemic and low bleeding risk patients; avoid prasugrel.
Discontinue SAPT at 1 year in most patients; consider earlier SAPT discontinuation (e.g., 6 months) in patients at low ischemic or high bleeding risks and prolonging SAPT (>1 year) for select patients with high ischemic and low bleeding risks.

Strategy (double vs triple therapy):
- A double-therapy regimen (OAC plus P2Y12 inhibitor) immediately after hospital discharge for most patients.
- Consider triple-therapy by extending aspirin use for a limited period of time (e.g., 1 month) only in patients at high ischemic and low bleeding risks.
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- A NOAC should be preferred in most patients and used at established stroke prevention doses; lower doses are not recommended unless specifically tested.
- If VKA is chosen, maintain INR at the lower end of the therapeutic range (e.g., 2.0 – 2.5).
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APT:
- Aspirin in the peri-PCI phase and continued through hospital discharge.
- Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be a reasonable alternative in high ischemic and low bleeding risk patients; avoid prasugrel.
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- Consider triple-therapy by extending aspirin use for a limited period of time (e.g., 1 month) only in patients at high ischemic and low bleeding risks.
Default strategy

Patients at high ischemic/thrombotic and low bleeding risks

Patients at low ischemic/thrombotic or high bleeding risks

**OAC**: prefer a NOAC over VKA if no contraindications

**SAPT**: prefer a P2Y₁₂ inhibitor over aspirin

Clopidogrel is the P2Y₁₂ inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel

Consider SAPT in addition to OAC after >12 mo. only in select patients at high ischemic/thrombotic and low bleeding risks
### Case 1#

Patient details have been altered to protect patient confidentiality.

<table>
<thead>
<tr>
<th>Personal information</th>
<th>Patient history</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td><strong>Medical history</strong></td>
</tr>
<tr>
<td>Male</td>
<td>• Hypertension (2002)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>• Type 2 diabetes mellitus (2003)</td>
</tr>
<tr>
<td>85 years</td>
<td>• Peripheral artery disease</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>• Renal insufficiency (GFR = 55 mL/min)</td>
</tr>
<tr>
<td>161/89 mmHg</td>
<td>• TIA (2011)</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td>• Paroxysmal NVAF (diagnosed 2011; CHA\textsubscript{2}DS\textsubscript{2}-VASc: 7)</td>
</tr>
<tr>
<td>69 bpm</td>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td><strong>Oxygen saturation</strong></td>
<td>• Beta blocker</td>
</tr>
<tr>
<td>97%</td>
<td>• Statin</td>
</tr>
<tr>
<td></td>
<td>• ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>• Antidiabetics</td>
</tr>
<tr>
<td></td>
<td>• NOAC since 2013 (because of labile INR/low TTR)</td>
</tr>
<tr>
<td></td>
<td><strong>Presentation</strong></td>
</tr>
<tr>
<td></td>
<td>• Heavy chest pain (40 min, previous night)</td>
</tr>
<tr>
<td></td>
<td>• Pain-free at presentation</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; TIA, transient ischaemic attack; TTR, time in therapeutic range
ECG and lab results at admission

Lab results:
- GFR 55
- Normal Hb, TnT 0.067 (rise and fall)
- CK-max 290/20 (N 175/15)

ECG:
- ST depression

Diagnosis:
- NSTEMI
- GRACE 139, CRUSADE 41, HAS-BLED 4

Scheduled for coronary angiography next day

CK, creatine kinase; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; GRACE: Global Registry of Acute Cardiac Events; NSTEMI: non-ST segment elevation myocardial infarction; TnT: troponin T
Our patient: coronary angiography

- NOAC continued during Coronography*
- Low-dose ASA started; P2Y12-inhibitor withheld
- Radial coronary angiography next day with additional low-dose UFH
- Clopidogrel 600mg loading dose
- PCI was performed with 2nd-generation DES for long LAD stenosis in patient with diabetes mellitus

Outcome:
- PCI successful
- Patient with CHA₂DS₂-VASc = 7 and high bleeding risk

*Please note that patients on dabigatran undergoing surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran (Pradaxa SPC, 2018)

CAG, coronary angiogram; DES, drug-eluting stent; LAD, left anterior descending
Case patient:

Based on WOEST, PIONEER, RE-DUAL PCI discharge on:

- NOAC dual therapy: dabigatran 110 mg BID, clopidogrel (12 months)
- Pantoprazole, beta blocker, statin, ACE inhibitor (ASA during PCI but then discontinued)
Case 2#

- Male
- 65 years hypertensive
- Positive stress test
- Paroxysmal nVAF – VKA
- Diabetes type II
- Radial procedure
- HAS-BLED 2
Pci left main
Discharge (high ischemic risk, low haemorhagic risk)

- NOAC Triple therapy
- Dabigatran 150mgx2
- Clopidogrel
- Aspirin
- PPI

- He is planned for six months triple therapy and then double therapy for ..
Case 3#

- Male
- 75 yrs, hypertensive
- Nstemi
- History of bladder cancer
- COPD
- Paroxysmal AF
- Radial procedure
- HAS-BLED 3
Pci left main, lad
Discharge (high hemorrhagic- high ischemic risk) (based in RE-Dual PCI)

- NOAC double therapy for 12 months
- Dabigatran 110mg x2
- Brilique 90mg x2
- PPI
- Individualized treatment
Why is first month important?

Ischemic / bleeding risks
Evolution after ACS

Thrombosis

M1

Thrombotic risk > Bleeding Risk

Bleeding Risk > Thrombotic risk
“Medtronic Announces One-Month DAPT Clinical Study in the U.S. and Japan with Resolute Onyx DES in High Bleeding Risk Patients"
The Greek AntiPlatElet Atrial Fibrillation (GRAPE-AF) registry

• 18 PCI centers

INCLUSION CRITERIA
  - PCI with stent implantation
  - Non-valvular AF (paroxysmal, persistent or permanent) with indication for anticoagulation
  - Written informed consent

EXCLUSION CRITERIA
  - Any clinically significant bleeding (BARC ≥2) at the time of screening or within the previous month
  - Prior intracranial bleeding
  - Dialysis or calculated creatinine clearance <30 mL/min at screening
  - Known significant liver disease
  - Life expectancy of less than 12 months
  - Incomplete staged PCI procedure (once the completion of the staged procedure has occurred, the final PCI may become the index event and is allowed)
  - Planned CABG
  - Contraindications to the use of clopidogrel or ticagrelor or NOAC
The Greek AntiPlatElet Atrial Fibrillation (GRAPE-AF) registry

- **The primary safety end point** will be the occurrence of clinically significant bleeding (BARC ≥2) by the end of 12 months, between the 2 groups (VKA vs NOACs).

- **Secondary end points** will be:
  MACEs (cardiovascular death, ischemic stroke, myocardial infarction, systemic embolism and unplanned coronary revascularization) by the end of 12 months, between the 2 groups (VKA vs NOACs).

The net clinical endpoint MACEs+BARC ≥2 bleedings by the end of 12 months, between the 2 groups (VKA vs NOACs).
Antithrombotic regimens for patients with AF following PCI: a new era

Key learnings

► Antithrombotic treatment with dabigatran dual therapy following PCI offers clinicians a new treatment option, with two SPAF-approved doses available

► Individualized approach by patient’s characteristics

► RE-DUAL PCI subgroup analyses have demonstrated that findings for high-risk patients were consistent with the main results for primary safety and composite efficacy endpoints

► A new era has begun