Atrial Fibrillation: Management with PCI

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Ain Shams University

Patient profile

Patient: A.N.

Personal Information

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68</td>
</tr>
<tr>
<td>Weight</td>
<td>70 kg</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>145/90 mmHg</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>110 bpm, irregular</td>
</tr>
<tr>
<td>Renal function</td>
<td>62 ml/min</td>
</tr>
</tbody>
</table>

Patient History

Medical History

- Arterial hypertension.
- Diabetes Mellitus

Medications

- Ramipril.
- Dabigatran.
- Metformin.

Presentation

- Abrupt retrosternal chest pain of 7 hours duration.
On Examination

• He was vitally stable, conscious, alert, oriented.
• Height 169 cm, body weight of 73 kg (BMI = 24)
• She was lying flat, BP 145/90 bilaterally, HR 110 bpm, irregular.
• Cardiac examination: apical short systolic murmur.
• PP felt with no lower limb oedema
Laboratory results: Cr 1.1 mg/dl- Cr Cl= 62 ml/min

ECG on admission

[ECG image]
An early interventional strategy reduces mortality. What about the arterial access site?

A) Radial artery.

B) Femoral artery.

- Anticoagulant doses adjusted to bodyweight and renal function, especially in women and elderly patients.
  - Radial approach preferred.
  - Proton pump inhibitors in patients on DAPT at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use, or two or more among age ≥65 years, dyspepsia, gastrooesophageal reflux disease, Helicobacter pylori infection, and chronic alcohol use).

- In patients on OAC
  - PCI performed without interruption of VKAs or NOACs.
  - In patients on VKAs, do not administer UFH if INR value >2.5.
  - In patients on NOACs, regardless of the timing of the last administration of NOACs, add additional low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg).
  - Aspirin indicated but avoid pretreatment with P2Y12 inhibitors.
  - GPIIb/IIa inhibitors only for bailout of periprocedural complications.
PCI

• RCA: showed a subtotal occlusion at its mid segment.

• LAD: showed a 95% ostial lesion.

• PCI followed by stenting to the RCA lesion was performed with a 3.0 x 38 mm DES with subsequent TIMI III flow, and the LAD was done using a 3.5 x 15 mm DES.
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and estimates suggest its prevalence is increasing.

If left untreated, AF increases the risk of stroke five-fold.

AF-related strokes are often more severe with higher morbidity and mortality, but are also preventable with effective management.
Epidemiology and AF and PCI

@ 1 Billion people in US and Europe

@ 20 Million with AF (1-2% of population)\(^1,2\)

@ 16 Million anticoagulation indicated (80%) \(^1,2\)

@ 4.8 Million have CAD as well (20%-45%) \(^1,2\)

@ 1-2 Million potential revasc (20%-25%)

24.9% of patients with AF enrolled in ARISTOTLE had prior PCI\(^4\)


There is an unmet need in the management of patients with AF undergoing PCI

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
30% with CAD therefore may require PCI

70% isolated AF or + other comorbidities

Which anti-coagulant to use???
- High protection against stroke
- Can be used safely if PCI is needed

Which anti-coagulant to use???
- High protection against stroke
- Best safety profile
- Broad use with different patient profiles

Guidelines*:
If NOAC is considered the lowest dose effective for stroke prevention in AF should be considered.


Antithrombotic therapy for atrial fibrillation and PCI

NVAF

PCI

NVAF and PCI

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

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

BOTH anticoagulant and dual antiplatelet therapy =
'triple therapy'

High bleeding risk

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Major bleeding in PCI is associated with an increase in mortality

| 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):

- **Major bleeding** was associated with a significant increase in in-hospital mortality, regardless of bleeding site.

  - In-hospital mortality rate:
    - **Non-bleeding**: 1.87% (95% CI: 1.66%–2.07%)
    - **Major bleeding**: 5.26% (95% CI: 4.93%–5.59%)

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

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Bleeding is the most common non-cardiac complication of PCI

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

- APT, antiplatelet therapy; PCI, percutaneous coronary intervention; Steg et al. Eur Heart J 2011
- Chhatriwalla et al. JAMA 2013
Even when warfarin is used, INR control is often suboptimal

**TTR in different world regions**

- **54%** (N. America)
- **67%** (W Europe)
- **59%** (E Europe)
- **47%** (M East)
- **34%** (India)
- **38%** (Asia)
- **44%** (S America)
- **67%** (W Europe)
- **59%** (E Europe)
- **36%** (China)

Based on three most recent INR values. TTR, time in therapeutic range (INR 2.0–3.0)
Healey et al. ESC 2011; session 711006
UK:DBG:151150a Aug 2015

Warfarin in Real World:
Poor INR control increases the risk of stroke

**Stroke survival in 37 907 AF patients**

- %TTR
- >70
- 61-70
- 51-60
- No warfarin
- 41-50
- <30
- 31-40

Patients without stroke (%)

Time after diagnosis (months)

UK General Practice Research Database: 27 458 warfarin users and 10 449 not treated with an antithrombotic.

TTR, time in therapeutic range

Warfarin in Real World: #1 cause of emergency hospitalisations due to adverse drug reactions in elderly patients in the US

Estimated rates of emergency hospitalisations in older adults

65% of emergency hospitalisations in older adults were due to unintentional drug overdoses

33% of these were associated with warfarin therapy

Adverse event data collected from 5,077 cases in the National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance project between 2007 and 2009

2016 ESC guidelines: NOAC is recommended in preference to a Vitamin K antagonist for patients who are eligible for a NOAC

Recommendations for stroke prevention in patients with atrial fibrillation

When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.

**4-trial Meta-analysis Full Dose NOAC in NVAF**

Pre-specified meta-analysis of all 71,683 patients

**Efficacy:** Stroke or Systemic Embolic events

**Safety:** Major Bleeding


NOAC, non vitamin K antagonist oral anticoagulant. NVAF, nonvalvular atrial fibrillation

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**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

For patients with AF, guidelines recommend initial triple therapy followed by dual therapy after PCI with stent.

When a NOAC is used, the lowest dose effective for stroke prevention in AF should be considered. Dabigatran 110 mg is the only reduced-dose NOAC to be fully tested for effectiveness in stroke prevention in AF.

Management of patients with AF undergoing PCI must balance stroke and bleeding risk.

ASA, acetylsalicylic acid; MACE, major adverse cardiac events; Adapted from Dewilde et al. J Am Coll Cardiol 2014; Cannon et al. Clin Cardiol 2016.
Post-procedural resumption of oral anticoagulation

- In stabilized patients (i.e. no recurrent ischaemia or need for other invasive treatment), anticoagulation can be restarted after parenteral anticoagulation is stopped.

- It is reasonable to restart the NOAC that the patient was taking before the ACS or elective procedure.

- There are no data to recommend switching to VKA (which may even be associated with higher bleeding and thrombo-embolic risks, especially in VKA-naive patients in whom the correct VKA dose is unknown), or to one particular NOAC.

- The same applies for AF patients after coronary bypass grafting.

*Heidbuchel et al., 2015*

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What was the design of the PIONEER AF - PCI trial?
**PIONEER AF-PCI compared regimens of rivaroxaban with single or dual antiplatelet therapy**

**Multicentre, randomized, open-label trial**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 15 mg /10 mg OD + clopidogrel</td>
<td>Rivaroxaban 2.5 mg BID + DAPT*</td>
<td>Rivaroxaban 15 mg/10 mg OD + low-dose ASA</td>
</tr>
<tr>
<td>VKA (INR 2.0–3.0) + DAPT*</td>
<td>VKA + low-dose ASA</td>
<td></td>
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</tbody>
</table>

**Primary endpoint: clinically-significant bleeding**

- Rivaroxaban 2.5 mg BID has not been tested or approved for stroke prevention in AF
- Rivaroxaban 15 mg OD regimen has been tested in 1474 patients with moderate renal dysfunction (ROCKET-AF)
- Rivaroxaban 15/10 mg OD regimen has been tested in 639 Japanese patients for stroke prevention in AF (J-ROCKET)

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**PIONEER AF-PCI primary endpoint**

**Occurrence of clinically significant bleeding, a composite of:**

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

**Adjudication**

- All major and minor bleeding events
- 15% of bleeds requiring medical attention (85% classified by algorithm)

**PIONEER AF-PCI is not sufficiently powered** to test efficacy for stroke prevention; it cannot be ruled out that patients were not protected from thrombotic events

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### PIONEER AF-PCI key inclusion and exclusion criteria

**Key inclusion criteria**
- Male or female patients with AF aged ≥18 years
- Paroxysmal, persistent, or permanent AF
- Undergone PCI (with stent placement)

**Key exclusion criteria**
- Active internal bleeding, clinically significant bleeding, or bleeding at non-compressible site
- Cardiogenic shock at randomization
- History of ICH
- Clinically significant GI bleeding in past 12 months
- History of stroke or TIA
- Severe renal impairment with CrCl <30 mL/min
- Suspected or documented stent thrombosis during index procedure or PCI with stent placement for previously stented lesion during the index procedure or within past 12 months

CrCl, creatinine clearance; ICH, intracranial haemorrhage; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; Gibson et al. N Engl J Med 2016

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### TIMI major bleeding
- Any symptomatic intracranial haemorrhage
- OR
- Clinically overt signs of haemorrhage (including imaging) associated with a drop in haemoglobin of ≥5 g/dL (or when haemoglobin concentration is not available, an absolute drop in haematocrit of ≥15%)

### TIMI minor bleeding
- Any clinically overt sign of haemorrhage (including imaging) that is associated with a fall in haemoglobin concentration of 3 to <5 g/dL (or, when haemoglobin concentration is not available, a fall in haematocrit of 9 to <15%)

### Bleeding requiring medical attention
- Any bleeding that requires medical or surgical treatment or laboratory evaluation, including:
  - Laboratory evaluation
  - CT or MRI
  - Nasal packing
  - Endoscopy / colonoscopy / cystoscopy / bronchoscopy
  - Compression
  - Ultrasound-guided closure of an aneurysm
  - Coil embolization
  - Pericardiocentesis
  - Ionotropic support
  - Stopping study medication
  - Reducing or removing antiplatelet therapies
  - Surgery

All major and minor bleeding events, and 15% of bleeds requiring medical attention were adjudicated

## PIONEER AF-PCI study design at a glance

<table>
<thead>
<tr>
<th></th>
<th>PIONEER AF-PCI</th>
</tr>
</thead>
</table>
| **Trial design** | Multicentre, randomized, open-label trial  
No formal hypothesis were tested |
| **Bleeding risk**| Excluded if any history of ICH or if GI bleeding in past year |
| **Stroke risk**  | Excluded if any prior stroke/TIA |
| **Primary endpoint** | Composite of major bleeding or minor bleeding according to TIMI criteria, or bleeding requiring medical attention |
| **Mean follow-up**| 12 months |
| **DAPT duration** | DAPT duration defined by investigator |


## PIONEER AF-PCI baseline characteristics

|                  | Group 1  
R15 mg + clopidogrel (n=709) | Group 2  
R2.5 + DAPT / R15 + ASA (n=709) | Group 3  
VKA + DAPT / VKA + ASA (n=706) |
|------------------|--------------------------------|
| **Mean age, years** | 70.4  
70.0  
69.9 |
| **Women, %**      | 25.5  
24.5  
26.6 |
| **Index event, %**| NSTEMI  
18.5  
12.3  
20.7 |
|                  | STEMI  
18.3  
13.8  
21.1 |
|                  | Unstable angina  
17.8  
10.7  
23.7 |
| **Type of stent, %**| DES  
65.4  
32.6  
2.0 |
|                  | BMS  
66.8  
31.2  
2.0 |
|                  | Both  
66.5  
31.8  
1.7 |
| **Comorbidities, %**| Heart failure  
25.4  
26.4  
24.8 |
|                  | Hypertension  
73.3  
73.2  
75.4 |
|                  | Previous MI  
19.8  
25.4  
22.2 |
|                  | Diabetes  
28.8  
28.1  
31.3 |

ASA, acetylsalicylic acid; BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; R2.5, rivaroxaban 2.5 mg; R15, rivaroxaban 15 mg; Gibson et al. N Engl J Med 2016
The primary endpoint of clinically significant bleeding is a composite of major bleeding or minor bleeding according to TIMI criteria, or bleeding requiring medical attention.
PIONEER AF-PCI demonstrated a lower rate of the primary endpoint in both rivaroxaban groups vs the triple therapy group.

Composite of bleeding events*

Group 1: 16.8%
Group 2: 18.0%
Group 3: 26.7%

Group 1 vs 2: HR: 0.59; 95% CI: 0.47–0.76; P<0.001
Group 2 vs 3: HR: 0.63; 95% CI: 0.50–0.80; P<0.001

*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention.
†Trial not powered to definitively establish superiority or noninferiority. TIMI, Thrombolysis in Myocardial Infarction; Gibson et al. N Engl J Med 2016

PIONEER AF-PCI: event rates for primary endpoint components across DAPT durations†

Guidelines recommend 1 month triple therapy in patients with AF undergoing elective PCI with stenting. Most patients in PIONEER AF-PCI received triple therapy for 6 months (37%) or 12 months (53%).

*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention.
†P<0.05 Group 2 vs Group 3; DAPT, dual antiplatelet therapy; Med att, medical attention; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; 1. Gibson et al. N Engl J Med 2016; 2. Kirchhof et al. Eur Heart J 2016
PIONEER AF-PCI showed similar rates of thromboembolic events across treatment groups, with low power to demonstrate efficacy

The study was not powered to show superiority or non-inferiority between treatments in efficacy endpoints

MACE, major adverse cardiac event (composite of CV death, MI, and stroke); Gibson et al. N Engl J Med 2016

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6.5</td>
<td>0.93 (0.59-1.48)</td>
<td>0.76</td>
</tr>
<tr>
<td>Group 2</td>
<td>5.6</td>
<td>1.08 (0.69-1.68)</td>
<td>0.75</td>
</tr>
<tr>
<td>Group 3</td>
<td>6.0</td>
<td>1.08 (0.69-1.68)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

PIONEER AF-PCI key points

1. PIONEER AF-PCI was an exploratory trial, comparing the safety of low-dose rivaroxaban regimens plus single or dual antiplatelet therapy vs warfarin-based triple therapy

2. The rate of bleeding events (composite endpoint) was lower in both rivaroxaban groups vs the triple therapy group

3. The rivaroxaban doses used have either not been approved for stroke prevention (2.5 mg BID) or have been tested in only a small number of patients with AF (15/10 mg OD in 639 Japanese patients in J-ROCKET)
What was the design of the RE-DUAL PCI trial?

RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin.

Patients with AF undergoing PCI with stenting

N=2725

Randomization ≤120 hours post-PCI

Dabigatran 150 mg BID + P2Y12 inhibitor

Dabigatran 110 mg BID + P2Y12 inhibitor

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

Primary endpoint: ISTH major or CRNM bleeding

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

RE-DUAL PCI was a multicentre, open-label trial following a prospective, randomized, open, blinded end-point design; *Study drug should be administered 6 hours after sheath removal and no later than 120 hours post-PCI (≤72 hours is preferable). †ASA discontinued after 1 month after bare-metal stent and 3 months after drug-eluting stent; ASA, acetylsalicylic acid; CRNM, clinically relevant non-major; R, randomization; Cannon et al. Clin Cardiol 2016; Cannon et al. N Engl J Med 2017
Study objective and design

RE-DUAL PCI tested the safety 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 event
- Formally tested endpoints included:
  - non-inferiority and superiority of 110 mg and 150 mg dual therapy in time to first ISTH major bleeding event or clinically relevant non-major bleeding event
  - time to first event of death, thromboembolic event (MI, stroke, systemic embolism) with and without unplanned revascularization
- 100% of outcome events were independently adjudicated by blinded external committee

**Patients were randomized based on age group and location, according to local label**

<table>
<thead>
<tr>
<th></th>
<th>&lt;80 years</th>
<th>≥80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide (except USA, Japan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For comparison of outcomes:

- N=763 vs N=764: Dabigatran 150 mg dual therapy vs Warfarin triple therapy (age-matched)
- N=981 vs N=981: Dabigatran 110 mg dual therapy vs Warfarin triple therapy

For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥80 years) and Japan (≥70 years) were excluded; Cannon et al. N Engl J Med 2017
RE-DUAL PCI key inclusion and exclusion criteria

**Inclusion**
- 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)

**Exclusion**
- Cardiogenic shock during current hospitalization
- Use of fibrinolytics within 24 hours 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; BMS, bare-metal stent; CAD, coronary artery disease; DES, drug-eluting stent; PCI, percutaneous coronary intervention; Cannon et al. Clin Cardiol 2016

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RE-DUAL PCI primary endpoint

**ISTH major bleeding event**
- Symptomatic bleeding in a critical area or organ*, and/or
- Bleeding associated with reduced haemoglobin ≥2 g/dL (1.24 mmol/L) or transfusion of ≥2 units of blood or packed cells† and/or
- Fatal bleed

**OR**

**ISTH CRNM bleeding event**
- Not meeting criteria for a major bleed but prompts ≥1 of:
  - Hospital admission
  - Physician-guided medical or surgical treatment
  - Physician-guided change, interruption (≥1 dose) or discontinuation of study drug

All primary and secondary endpoints were adjudicated by a treatment-blinded independent central committee

*E.g. intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; †Bleeding should be overt and haemoglobin drop should be considered due to and temporally related to bleeding event. CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; Cannon et al. Clin Cardiol 2016; Kaatz et al. J Thromb Haemost 2015; Schulman et al. J Thromb Haemost 2005
What were the results of the RE-DUAL PCI trial?

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>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 (USA, 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 (USA, 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>37.9</td>
<td>34.1</td>
<td>39.7</td>
</tr>
<tr>
<td>CHA2DS2-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 placed 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; ACS, acute coronary syndrome; DES, drug-eluting stent; PCI, percutaneous coronary intervention; Cannon et al. N Engl J Med 2017; Cannon et al. ESC 2017
Significantly lower rates of ISTH major bleeding or CRNMBE with dabigatran dual therapy

For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥80 years) and Japan (≥70 years) are excluded. Full analysis set presented CRNMBE, clinically relevant non-major bleeding event; ISTH, International Society on Thrombosis and Haemostasis; Cannon et al. ESC 2017; Cannon et al. N Engl J Med 2017

ARR, absolute risk reduction; Cannon et al. N Engl J Med 2017
ISTH and TIMI major bleeding: significantly lower rates for dabigatran dual therapy

ISTH major bleeding event

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with outcome event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D110-DT n=981</td>
<td>9.2%</td>
</tr>
<tr>
<td>W-TT n=981</td>
<td>5.0%</td>
</tr>
<tr>
<td>D150-DT n=763</td>
<td>8.4%</td>
</tr>
<tr>
<td>W-TT n=764</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

TIMI major bleeding event

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with outcome event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D110-DT n=981</td>
<td>3.7%</td>
</tr>
<tr>
<td>W-TT n=981</td>
<td>1.4%</td>
</tr>
<tr>
<td>D110-DT n=763</td>
<td>3.8%</td>
</tr>
<tr>
<td>W-TT n=764</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

HR: 0.52 (95% CI: 0.37–0.74) P<0.001
HR: 0.64 (95% CI: 0.43–0.94) P=0.02
HR: 0.37 (95% CI: 0.20–0.68) P=0.002
HR: 0.51 (95% CI: 0.28–0.93) P=0.03

TIMI major or minor bleeding: significantly lower rate for dabigatran dual therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients with outcome event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg dual therapy (n=981)</td>
<td>7.0%</td>
</tr>
<tr>
<td>Warfarin triple therapy (n=981)</td>
<td>3.0%</td>
</tr>
<tr>
<td>Dabigatran 150 mg dual therapy (n=763)</td>
<td>6.3%</td>
</tr>
<tr>
<td>Warfarin triple therapy (n=764)</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

HR: 0.41 (95% CI: 0.26–0.63) P<0.001
HR: 0.53 (95% CI: 0.33–0.85) P=0.009

TIMI major bleeding definition: fatal, ICH, clinically overt bleeding with fall in Hb ≥2 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; Cannon et al. N Engl J Med 2017
Intracranial haemorrhage: fewer events with dabigatran dual therapy

Dabigatran dual therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; Cannon et al. N Engl J Med 2017; Cannon et al ESC 2017
Secondary endpoint: time to death or thromboembolic event (death, MI, stroke or SE)

![Graph showing the comparison between Dabigatran and Warfarin for secondary endpoint]


There are no significant differences in efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>D110 DT vs warfarin TT</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</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</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>Stroke</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>Unplanned revascularization</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>MI</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>Stent thrombosis</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>

RE-DUAL PCI was not powered to show differences in individual thromboembolic endpoints

DT, dual therapy; TT, triple therapy; Cannon et al. N Engl J Med 2017; Cannon et al. ESC 2017
How do RE-DUAL PCI and PIONEER AF-PCI compare?

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

<table>
<thead>
<tr>
<th>Confirmatory trial</th>
<th>Exploratory trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-DUAL PCI</strong></td>
<td><strong>PIONEER AF-PCI</strong></td>
</tr>
</tbody>
</table>
| Dual therapy (dabigatran 110 or 150 mg BID + P2Y12 inhibitor) | Dual therapy (rivaroxaban 15/10 mg OD + P2Y12 inhibitor)  
| VS | VS |
| Triple therapy (warfarin + P2Y12 inhibitor + ASA)* | Triple therapy (warfarin 2.5 mg BID + P2Y12 inhibitor + ASA)†  
| OR | OR |
| Triple therapy (warfarin + P2Y12 inhibitor + ASA)‡ | Triple therapy (warfarin + P2Y12 inhibitor + ASA)† |

*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\(^1\)

and 150 mg BID was tested in 6076 patients\(^1\)

Both doses are approved for stroke prevention in patients with AF\(^2\)

**PIONEER AF-PCI**
SAFETY AND EFFICACY OF RIVAROXABAN DOSES

15/10 mg OD regimen was tested in 639 Japanese patients in an exploratory trial\(^5\)

2.5 mg BID has not been tested in a confirmatory trial for stroke prevention in patients with AF\(^2\)

2.5 mg BID is not approved for stroke prevention in patients with AF;\(^4\) the 15/10 mg OD regimen is not approved outside Japan

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

**RE-DUAL PCI**
PRIMARY SAFETY OUTCOMES

ISTH major bleeding

ISTH CRNM bleeding

OR

Primary endpoint is composed of well-established safety outcome parameters; 100% of events were adjudicated by an independent, blinded committee\(^1\)

**PIONEER AF-PCI**
PRIMARY SAFETY OUTCOMES

TIMI major bleeding

TIMI minor bleeding

Bleeding requiring medical attention

Composite primary endpoint; bleeding requiring medical attention is not commonly used but drove the results; 15% of these events were independently adjudicated\(^2\)

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.
In RE-LY, the effects of dabigatran 150 mg BID vs warfarin were consistent regardless of whether patients were taking antiplatelets.

**Dabigatran 150 mg BID**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/embolism</td>
<td>0.52 (0.38–0.72)</td>
<td>0.06</td>
</tr>
<tr>
<td>CV death</td>
<td>0.91 (0.73–1.13)</td>
<td>0.36</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.94 (0.78–1.15)</td>
<td>0.87</td>
</tr>
<tr>
<td>All bleeds</td>
<td>0.92 (0.85–1.00)</td>
<td>0.50</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0.36 (0.21–0.63)</td>
<td>0.53</td>
</tr>
<tr>
<td>Extracranial bleed</td>
<td>1.11 (0.90–1.38)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Favours dabigatran  
Favours warfarin

ASA, acetylsalicylic acid; Dans et al. Circulation 2013

---

In RE-LY, the effects of dabigatran 110 mg BID vs warfarin were consistent regardless of whether patients were taking antiplatelets.

**Dabigatran 110 mg BID**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/embolism</td>
<td>0.87 (0.66–1.15)</td>
<td>0.74</td>
</tr>
<tr>
<td>CV death</td>
<td>0.93 (0.75–1.16)</td>
<td>0.67</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.79 (0.64–0.96)</td>
<td>0.79</td>
</tr>
<tr>
<td>All bleeds</td>
<td>0.78 (0.72–0.85)</td>
<td>0.85</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0.35 (0.20–0.61)</td>
<td>0.37</td>
</tr>
<tr>
<td>Extracranial bleed</td>
<td>0.92 (0.74–1.15)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Favours dabigatran  
Favours warfarin

ASA, acetylsalicylic acid; Dans et al. Circulation 2013
Dabigatran is the only NOAC with a fully tested lower dose that is approved for use in patients receiving antiplatelets who are at increased bleeding risk

**Doses investigated in J-ROCKET in Japanese patients (n=1280)**

<table>
<thead>
<tr>
<th><strong>Rivaroxaban</strong></th>
<th><strong>Recommended dose</strong></th>
<th><strong>Patients with CrCl 15–49 mL/min</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg OD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In RE-LY, the pivotal trial comparing dabigatran vs warfarin for stroke prevention in AF, patients were randomized to dabigatran 150 mg BID (n=6076), dabigatran 110 mg BID (n=6015), or warfarin (n=6022), irrespective of clinical characteristics. ASA, acetylsalicylic acid; CrCl, creatinine clearance; 1. Pradaxa SPC, 2016; 2. Xarelto SPC, 2016; 3. Hori et al. Circ J 2012; 4. Connolly et al. N Engl J Med 2009
Praxbind®

Idarucizumab characteristics and mechanism of action
What are the characteristics of an ideal anticoagulation reversal agent?

- Widely available
- Specifically targets only the NOAC
- Acts immediately
- Complete reversal
- Easy to use
- No pro-coagulant effects
- Effect is sustained
- Predictable effects

Idarucizumab is a humanized monoclonal antibody fragment developed and produced by Boehringer Ingelheim

A monoclonal mouse antibody was developed with high dabigatran binding affinity

Idarucizumab is the humanized Fab fragment expressed directly in hamster cells and produced in-house by BI

Fab region
This is the part of the antibody that binds to dabigatran

Fc region removed
This is a structural element and interacts with the immune system
Non-specific binding is avoided by removal of the Fc region

Fab, fragments of antigen-binding; Fc, fragment crystallizable. Schiele et al. Blood 2013; van Ryn. AHA 2012
Re-administration of dabigatran 24 hours after idarucizumab fully restores anticoagulation

Idarucizumab effect does not last >24 hours

Idarucizumab reversed dabigatran anticoagulation

24 hours later, dabigatran was restarted (n=12)
Dabigatran anticoagulation restored to levels similar to baseline regardless of prior use of idarucizumab

RE-VERSE AD™: key results in a cohort of multi-morbid, elderly patients presenting with life-threatening emergencies:

1. 5 g of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation

2. Median time to cessation of extracranial bleeding in Group A was 3.5–4.5 hours after reversal, depending on anatomical location of the bleed

3. Median time to surgery after reversal was 1.6 hours, with 'normal' intraoperative haemostasis in 93% of Group B patients, and prompt restart of antithrombotic therapy post-procedure

4. No safety concerns identified to date
The White Paper provides guidance on when reversal of NOACs may be appropriate in line with the idarucizumab label

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Definite need for a reversal agent</th>
<th>Possible need for a reversal agent*</th>
<th>Reversal agent generally not needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening bleeding</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding in a closed space or critical organ</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent major bleeding despite local haemostatic measures</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of recurrent bleeding due to delayed NOAC clearance</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency surgery or intervention in patients at high risk for procedural bleeding</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for urgent surgery or intervention in patients with acute renal failure</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Elective surgery</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>GI bleeds that respond to supportive measures</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>High drug levels or excessive anticoagulation without associated bleeding</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Surgery or intervention that can be delayed until drug is cleared</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*Depended on patient; adapted from Ageno et al. Thromb Haemost 2016

For patients with AF undergoing PCI

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

2. Dabigatran dual therapy regimens, using full-dose anticoagulation at the 110 and even 150 mg doses, significantly reduced the risk of major bleeding

3. Dabigatran dual therapy provides an alternative for managing post-PCI patients with both doses approved for stroke prevention in atrial fibrillation

PCI, percutaneous coronary intervention
Thank You