Atrial Fibrillation: Management with PCI

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Patient profile

Patient: A.N.

Personal Information	
Sex	Male
Age	68
Weight	70 kg
Blood Pressure	145/90 mmHg
Heart Rate	110 bpm, irregular
Renal function	62 ml/min

ECG: electrocardiogram; AF: atrial fibrillation

Patient History	
Medical History	• Arterial hypertension. • Diabetes Mellitus
Medications	• Ramipril. • Dabigatran. • Metformin.

Presentation

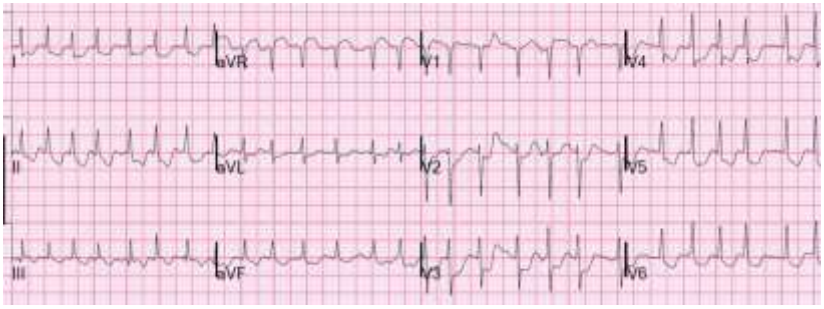
- Abrupt retrosternal chest pain of 7 hours duration.

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



An early interventional strategy reduces mortality. What about the arterial access site?

A) Radial artery.

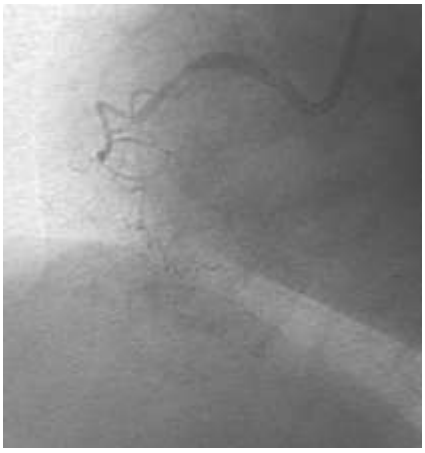
B) Femoral artery.

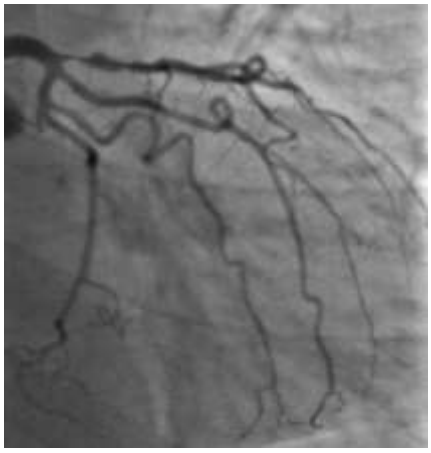
- Anticoagulant doses adjusted to bodyweight and renal function, especially in women and elderly patients.
- Radial approach preferred.
- Proton pump inhibitors in patients on DAPT at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant 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 $P2Y_{12}$ inhibitors.
  - GPIIb/IIIa inhibitors only for bailout of periprocedural complications.

PCI

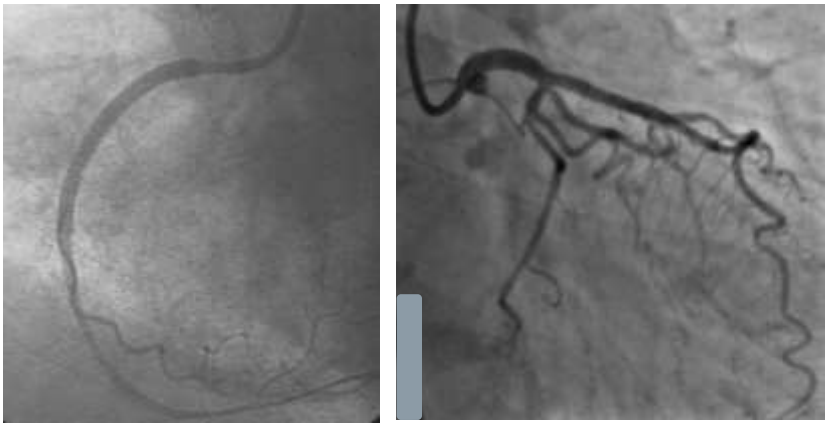
- RCA: showed a subtotal occlusion at its mid segment.
- LAD: showed a 95% ostial lesion.
- PCI followed by stenting to the RCA lesion was performed with a 3.0 x 38 mm DES with subsequent TIMI III flow, and the LAD was done using a 3.5 x 15 mm DES.

LESIONS





FINAL RESULT



Introduction

- 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.

JACC. 2014; 64(21): e1-76.

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]

1. The AFFIRM Investigators. *Am Heart J* 2002;143:991–1001;
2. Carpodanno D *et al*, *Circ Cardiovasc Interv* 2014;7:113–124;
3. Kralev S *et al*, *PLoS One* 2011;6:e24964;
4. Bahit MC *et al*, *Int J Cardiol* 2013;170:215–220

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

13

Message

PEACE OF MIND

AF patients

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.

*percutaneous coronary intervention. Kirchhof et al. Eur Heart J 2016

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 =

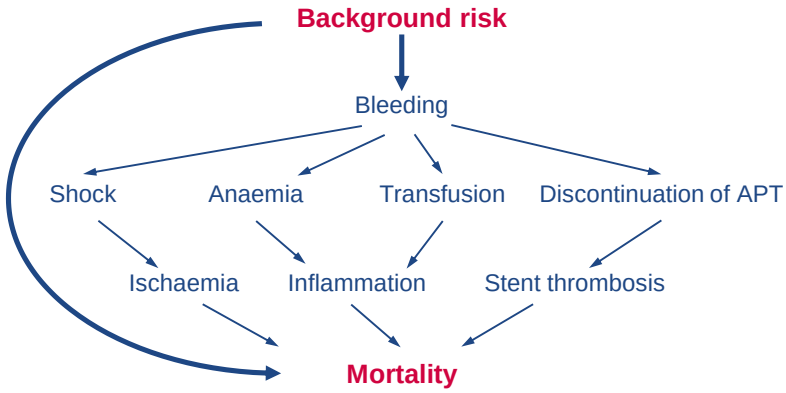
'triple therapy'

High bleeding risk

?

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention

Major bleeding in PCI is associated with an increase in mortality



Compared with patients without bleeding, patients who experience bleeding are more likely to die, not only early (in hospital) but also late (after discharge)

APT, antiplatelet therapy; PCI, percutaneous coronary intervention; Steg et al. Eur Heart J 2011

16

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

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

5.26%
in-hospital mortality rate:
major bleeding

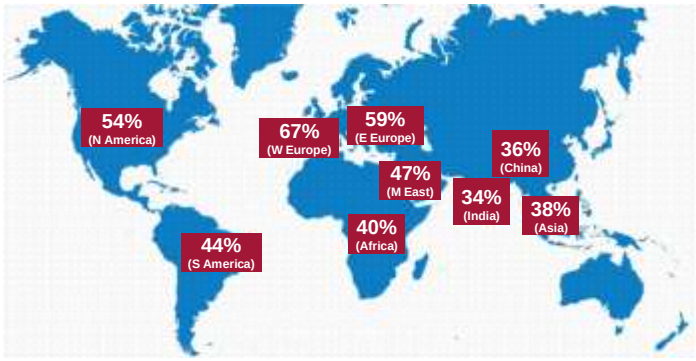
Bleeding is the most common non-cardiac complication of PCI
Antithrombotic therapy that minimizes the risk of bleeding complications therefore might be expected to result in better short- and long-term clinical outcomes after PCI

PCI, percutaneous coronary intervention; Chhatriwalla et al. JAMA 2013

17

Even when warfarin is used, INR control is often suboptimal

TTR in different world regions

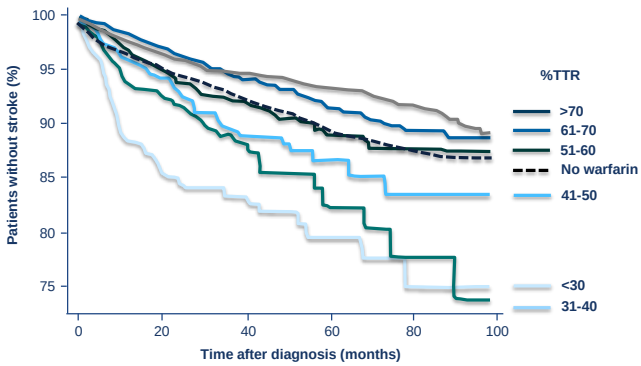


Based on three most recent INR values. TTR, time in therapeutic range (INR 2.0–3.0)
Healey et al. ESC 2011; session 711006

UK/DBG-151106a Aug 2015

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

Stroke survival in 37 907 AF patients



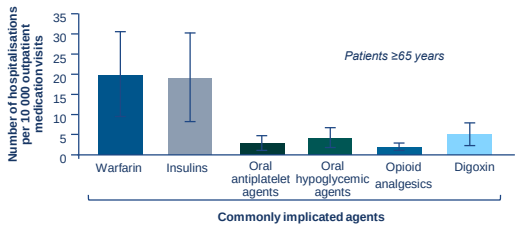
UK General Practice Research Database: 27 458 warfarin users and 10 449 not treated with an antithrombotic.

TTR, time in therapeutic range

1- Gallagher AM, Setakis E, Plumb JM, et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;106(5):968-77.

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

1- Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med.* 2011;365(21):2002-12.

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

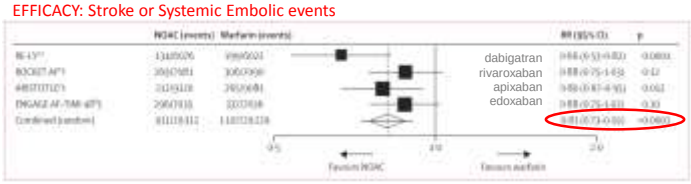
Recommendations for stroke prevention in patients with atrial fibrillation	Class	Level
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A

1. Paulus Kirchhof et al. *European Heart Journal* doi:10.1093/eurheartj/ehw210

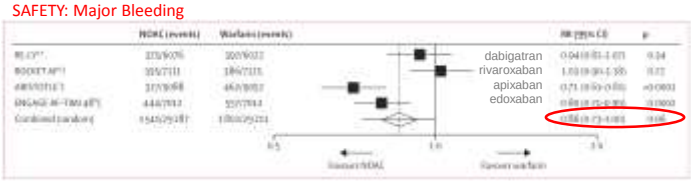
4-trial Meta-analysis Full Dose NOAC in NVAF

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

EFFICACY: Stroke or Systemic Embolic events



SAFETY: Major Bleeding



From Ruff C et al. Lancet 2014; 383: 955–62 NOAC, non vitamin K antagonist oral anticoagulant. NVAF, nonvalvular atrial fibrillation

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?

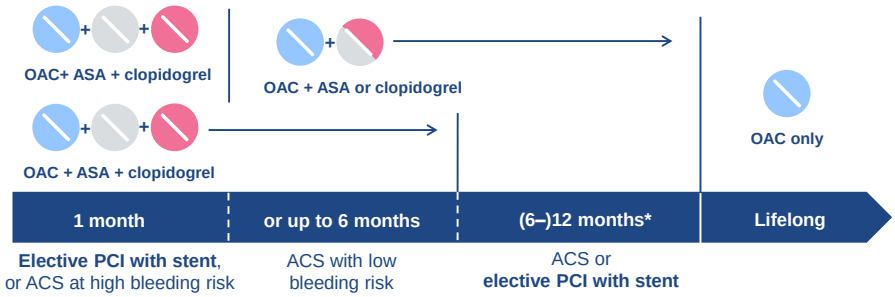
OR

TRIPLE THERAPY: anticoagulant and dual antiplatelet therapy?

ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Kirchhof et al. Eur Heart J 2016; Lip et al. Eur Heart J 2014

23

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



Elective PCI with stent, or ACS at high bleeding risk

ACS with low bleeding risk

ACS or **elective PCI with stent**

When a NOAC is used, **the lowest dose effective for stroke prevention in AF† should be considered.**

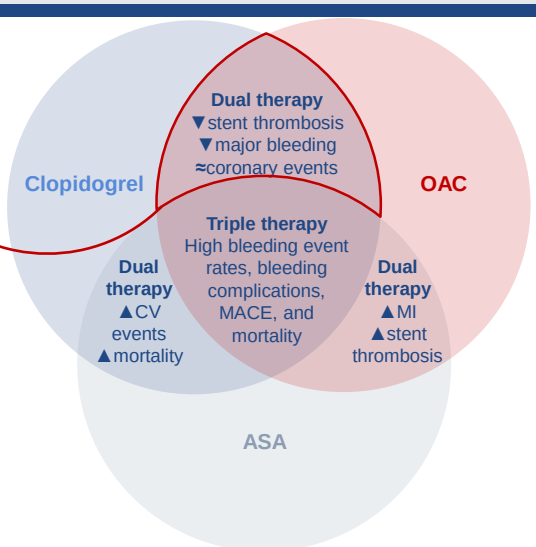
Dabigatran 110 mg is the only reduced-dose NOAC to be fully tested for effectiveness in stroke prevention in AF.

*6 months after elective PCI in patients with high bleeding risk; †Dabigatran 110 mg BID, rivaroxaban 15 mg OD, or apixaban 2.5 mg BID according to selected study population in pivotal studies; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention. Kirchhof et al. Eur Heart J 2016

24

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

RE-DUAL PCI assessed safety of this combination



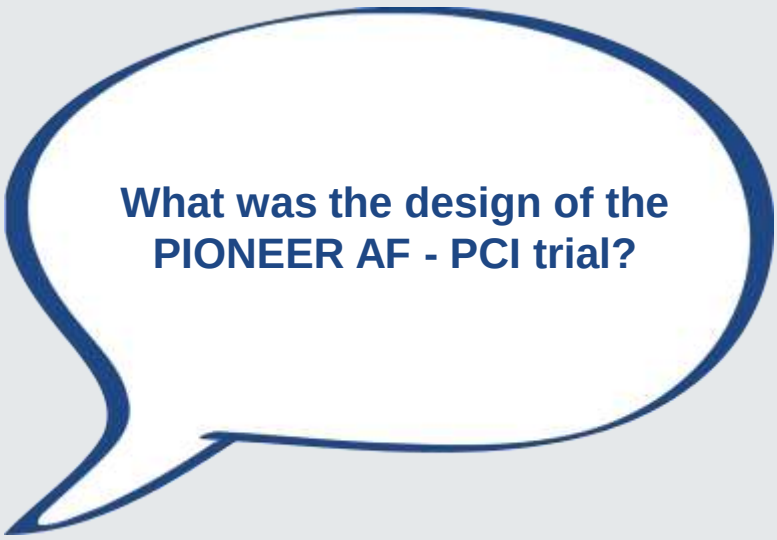
ASA, acetylsalicylic acid; MACE, major adverse cardiac events; Adapted from Dewilde et al. J Am Coll Cardiol 2014; Cannon et al. Clin Cardiol 2016

25

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.

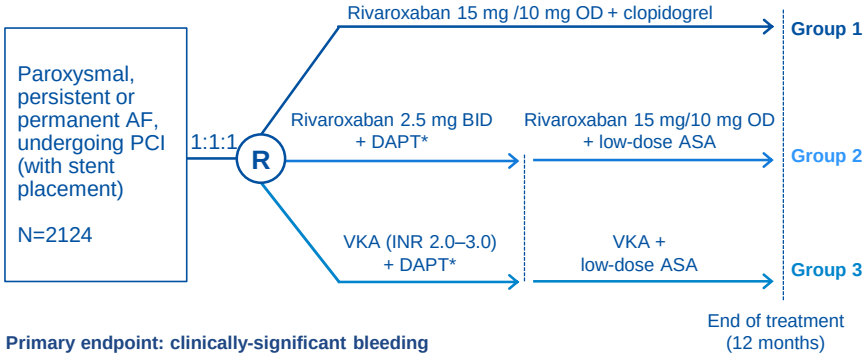
Heidbuchel et al., 2015



27

PIONEER AF-PCI compared regimens of rivaroxaban with single or dual antiplatelet therapy

Multicentre, randomized, open-label trial



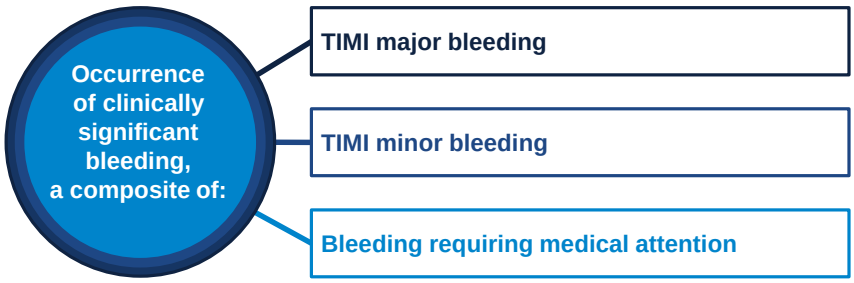
Primary endpoint: clinically-significant bleeding

- 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 in 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)

*DAPT duration 1, 6 or 12 months (physician choice); ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; R, randomization; Gibson et al. Am Heart J. 2015; Gibson et al. N Engl J Med 2016; Fox et al. Eur Heart J 2011; Hori et al. Circ J 2012

28

PIONEER AF-PCI primary endpoint



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

TIMI, Thrombolysis in Myocardial Infarction; Gibson et al. Am Heart J 2015; Gibson et al. N Engl J Med 2016

29

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

30

PIONEER AF-PCI bleeding definitions

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

TIMI, Thrombolysis in Myocardial Infarction; Gibson et al. N Engl J Med 2016

31

PIONEER AF-PCI study design at a glance

	PIONEER AF-PCI
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

DAPT, dual antiplatelet therapy; ICH, intracranial haemorrhage; TIA, transient ischaemic attack; TIMI, Thrombolysis in Myocardial Infarction; Gibson et al. N Engl J Med 2016; Hori et al. Circ J 2012

32

PIONEER AF-PCI baseline characteristics

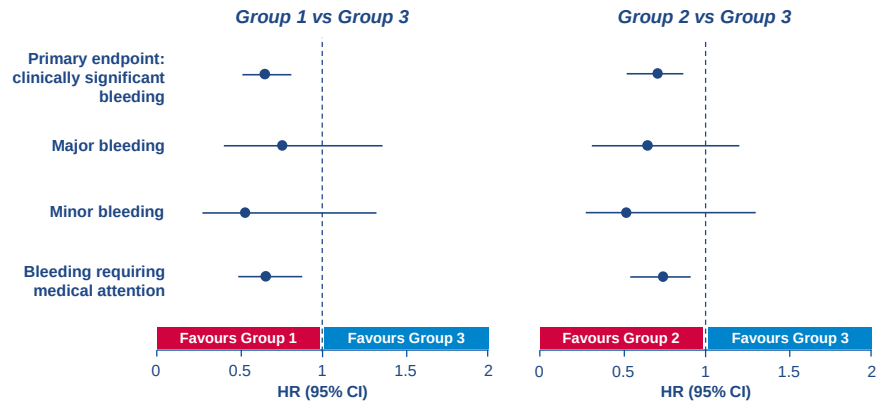
	Group 1 R15 mg + clopidogrel (n=709)	Group 2 R2.5 + DAPT / R15 + ASA (n=709)	Group 3 VKA + DAPT / VKA + ASA (n=706)
Mean age, years	70.4	70.0	69.9
Women, %	25.5	24.5	26.6
Index event, %			
NSTEMI	18.5	18.3	17.8
STEMI	12.3	13.8	10.7
Unstable angina	20.7	21.1	23.7
Type of stent, %			
DES	65.4	66.8	66.5
BMS	32.6	31.2	31.8
Both	2.0	2.0	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

33

PIONEER AF-PCI: primary safety endpoint results

Group 1: R15/10 + clopidogrel **Group 2:** R2.5 + DAPT **Group 3:** Triple therapy



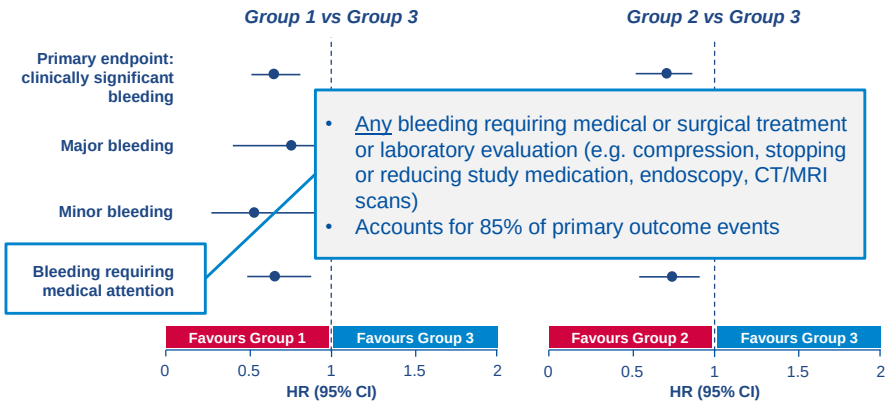
The primary endpoint of clinically significant bleeding is a composite of major bleeding or minor bleeding according to TIMI criteria, or bleeding requiring medical attention

TIMI, Thrombolysis in Myocardial Infarction; Adapted from Gibson et al. N Engl J Med 2016

34

PIONEER AF-PCI: primary safety endpoint results

Group 1: R15/10 + clopidogrel **Group 2:** R2.5 + DAPT **Group 3:** Triple therapy



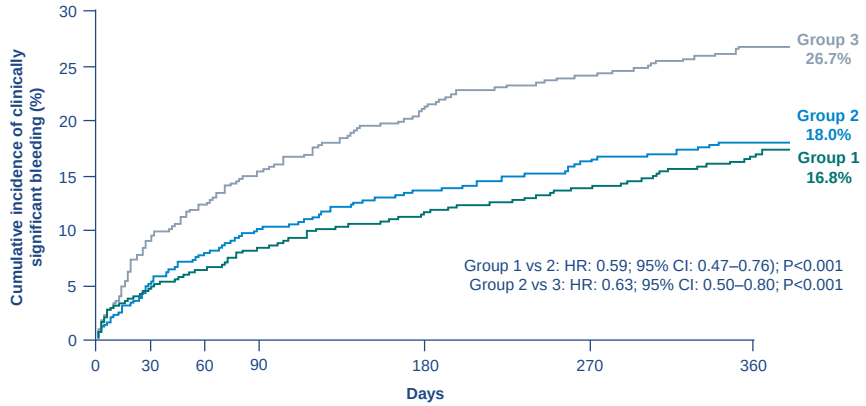
The primary endpoint of clinically significant bleeding is a composite of major bleeding or minor bleeding according to TIMI criteria, or bleeding requiring medical attention

TIMI, Thrombolysis in Myocardial Infarction; Adapted from Gibson et al. N Engl J Med 2016

35

PIONEER AF-PCI demonstrated a lower rate of the primary endpoint in both rivaroxaban groups vs the triple therapy group

Composite of bleeding events*

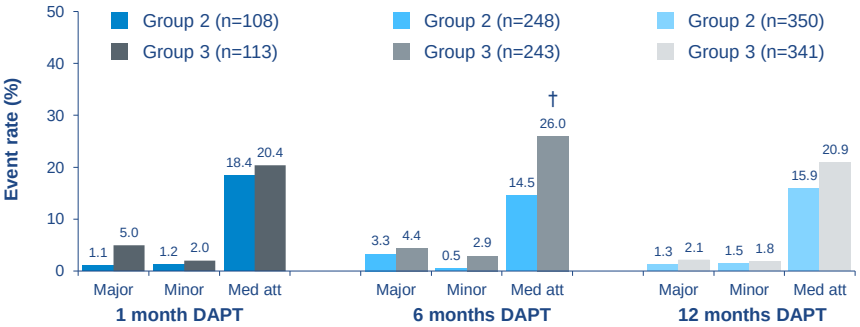


*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention;
†Trial not powered to definitively establish superiority or noninferiority. TIMI, Thrombolysis in Myocardial Infarction;
Gibson et al. N Engl J Med 2016

36

PIONEER AF-PCI: event rates for primary endpoint components across DAPT durations[1]

Composite of bleeding events*

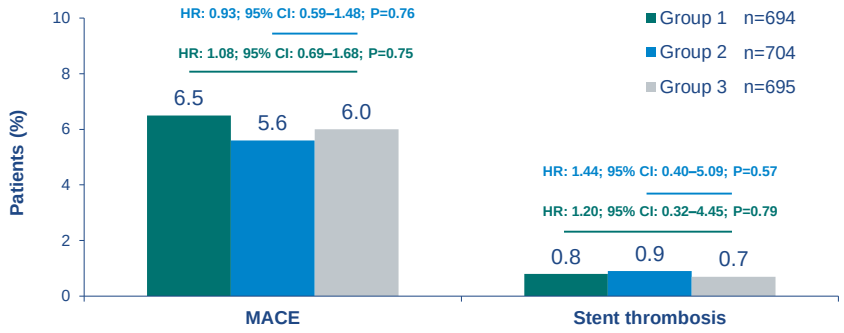


Guidelines recommend 1 month triple therapy in patients with AF undergoing elective PCI with stenting[2]
Most patients in PIONEER AF-PCI received triple therapy for 6 months (37%) or 12 months (53%)[1]

*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

37

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

38

PIONEER AF-PCI key points

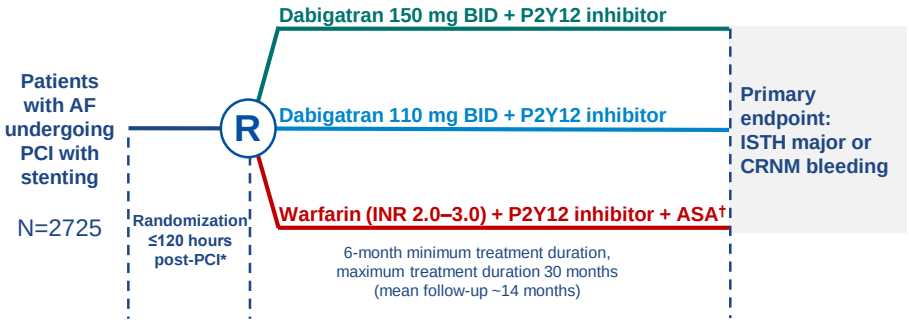
1. **PIONEER AF-PCI was an exploratory trial, comparing the safety of low-dose rivaroxaban regimens plus single or dual antiplatelet therapy vs warfarin-based triple therapy**
2. **The rate of bleeding events (composite endpoint) was lower in both rivaroxaban groups vs the triple therapy group**
3. **The 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)**

39

What was the design of the RE-DUAL PCI trial?

40

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



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

41

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

ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction. Cannon et al. N Engl J Med 2017

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

For comparison of outcomes:

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

43

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

44

RE-DUAL PCI primary endpoint

RE-DUAL PCI primary safety endpoint: time to first…

…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

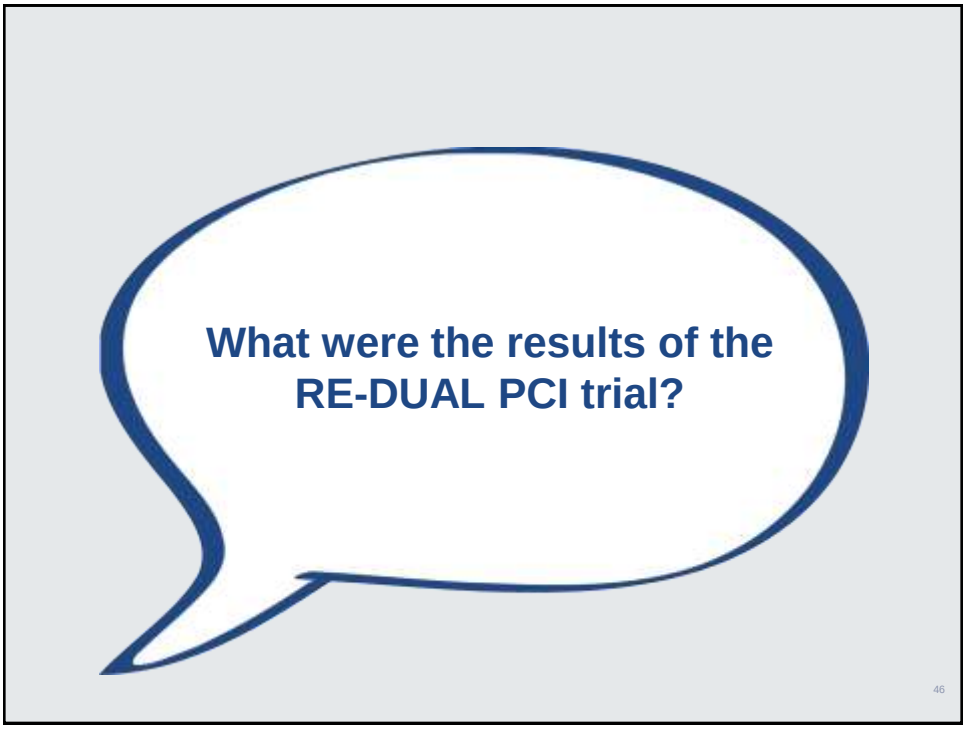
Not meeting criteria for a major bleed but prompts ≥1 of:

- 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

45



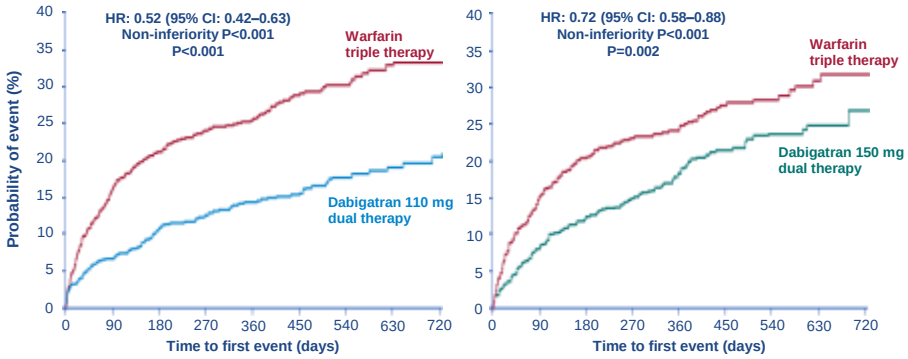
Baseline characteristics

	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (USA, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (USA, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83.7	81.3
Diabetes mellitus, %	36.9	37.9	34.1	39.7
CHA_2DS_2–VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES placed only, %	82.0	84.2	81.4	83.5

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

47

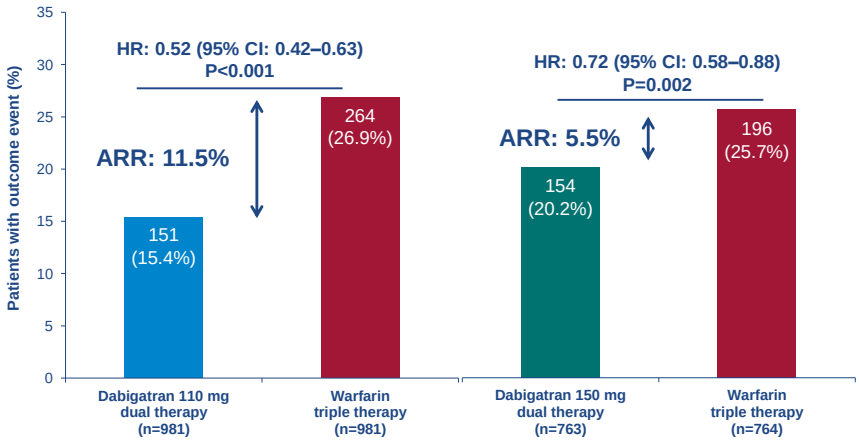
Significantly lower rates of ISTH major bleeding or CRNMBE with dabigatran dual therapy



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

48

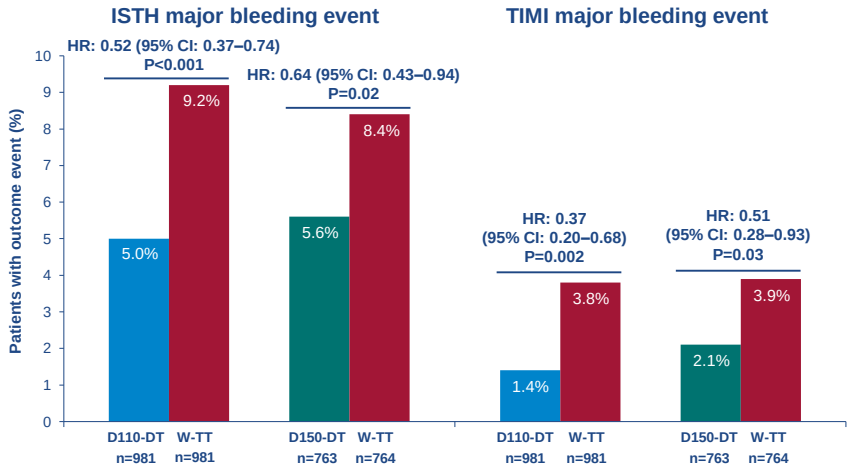
Significantly lower rates of ISTH major bleeding or CRNMBE with dabigatran dual therapy



ARR, absolute risk reduction; Cannon et al. N Engl J Med 2017

49

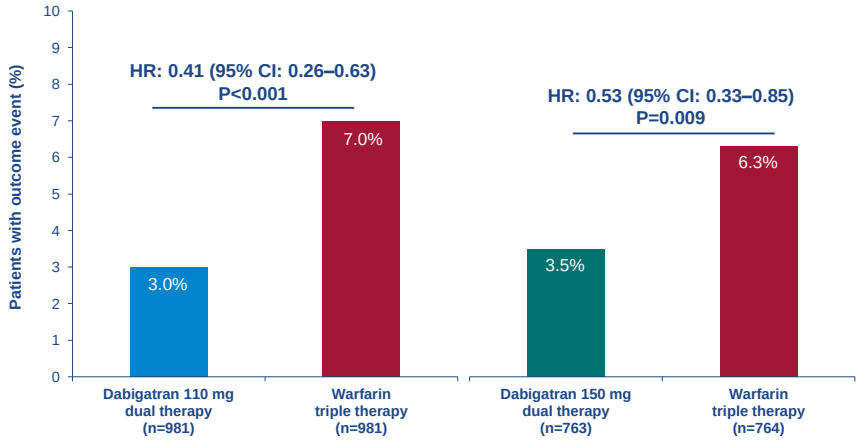
ISTH and TIMI major bleeding: significantly lower rates for dabigatran dual therapy



ISTH major bleeding definition: fatal, critical organ (including ICH), clinically overt bleeding with fall in Hb ≥2 g/dL; TIMI major bleeding definition: fatal, ICH, clinically overt bleeding with fall in Hb ≥5 g/dL. D110/150-DT, dabigatran 110 mg/150 mg dual therapy; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction; W-TT, warfarin triple therapy; Cannon et al. N Engl J Med 2017

50

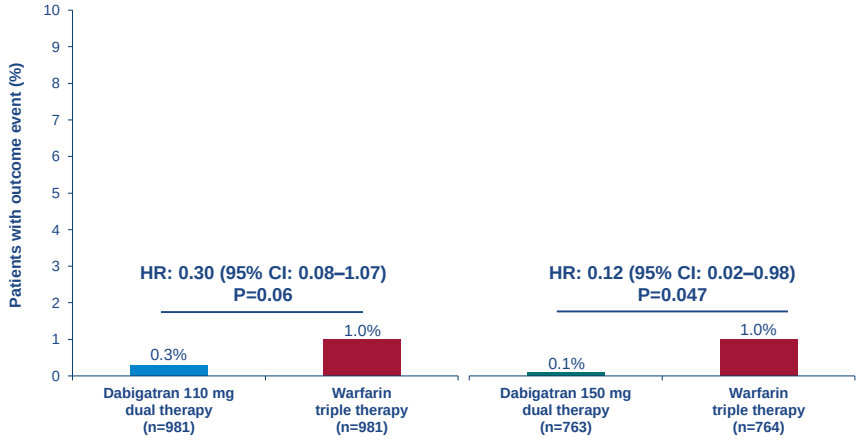
TIMI major or minor bleeding: significantly lower rate for dabigatran dual therapy



TIMI major bleeding definition: fatal, ICH, 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; Cannon et al. N Engl J Med 2017

51

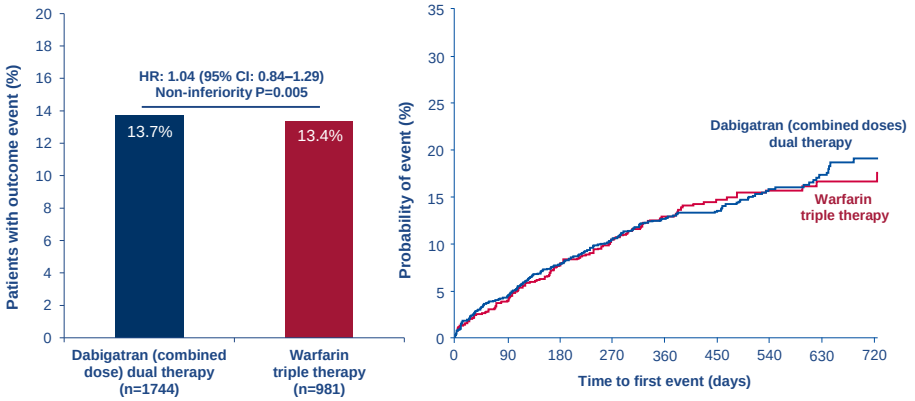
Intracranial haemorrhage: fewer events with dabigatran dual therapy



Cannon et al. N Engl J Med 2017

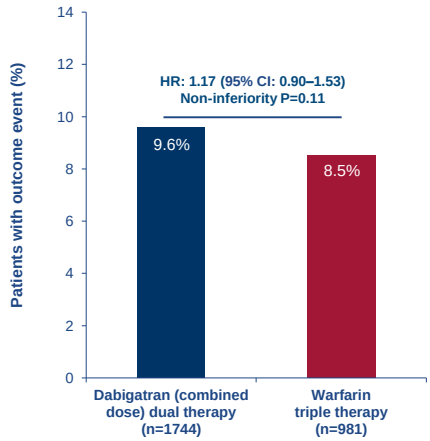
Dabigatran dual therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)



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)



Cannon et al. N Engl J Med 2017

54

There are no significant differences in efficacy outcomes

	Dabigatran 110 mg dual therapy (n=981) n (%)	Warfarin triple therapy (n=981) n (%)	D110 DT vs warfarin TT HR (95% CI)	D110 DT vs warfarin TT P value	Dabigatran 150 mg dual therapy (n=763) n (%)	Warfarin triple therapy (n=764) n (%)	D150 DT vs warfarin TT HR (95% CI)	D150 DT vs warfarin TT P value
All-cause death	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Stroke	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Unplanned revascularization	76 (7.7)	69 (7.0)	1.09 (0.79–1.51)	0.61	51 (6.7)	52 (6.8)	0.96 (0.65–1.41)	0.83
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

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

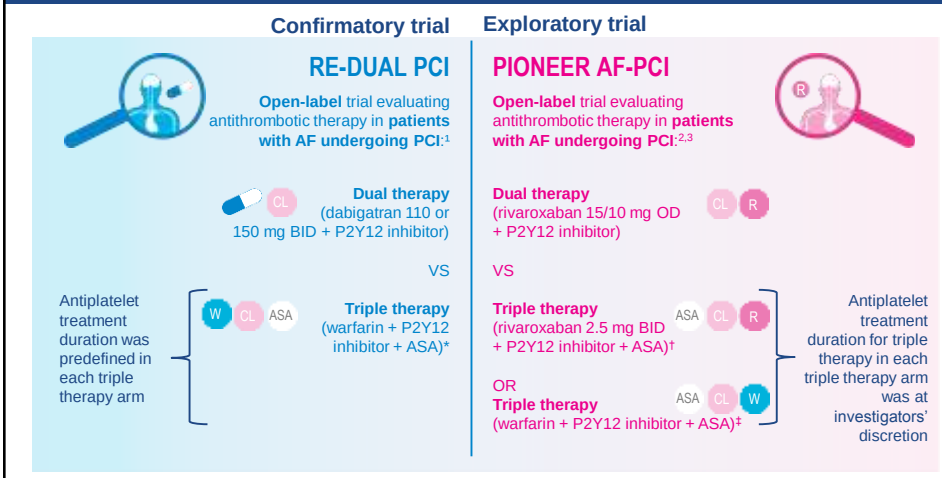
DT, dual therapy; TT, triple therapy; Cannon et al. N Engl J Med 2017: Cannon et al. ESC 2017

55

How do RE-DUAL PCI and PIONEER AF-PCI compare?

56

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



*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;

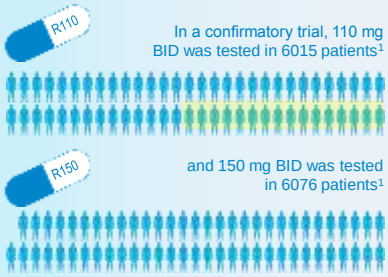
1. Cannon et al. Clin Cardiol 2016; 2. Gibson et al. Am Heart J 2015; 3. Gibson et al. N Engl J Med 2016

57

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[3§]

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

2.5 mg BID is **not approved** for stroke prevention in patients with AF;[4] the 15/10 mg OD regimen is **not approved outside Japan**

§Rivaroxaban 15 mg OD was also tested in an exploratory manner in ROCKET AF[5]

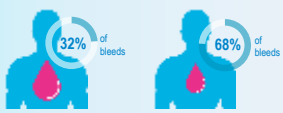
1. Connolly et al. N Engl J Med 2009; 2. Pradaxa SPC 2017; 3. Hori et al. Circ J 2012; 4. Xarelto SPC 2017; 5. Patel et al. N Engl J Med 2011

58

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

RE-DUAL PCI

PRIMARY SAFETY OUTCOMES



ISTH major bleeding

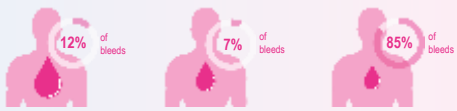
ISTH CRNM bleeding

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

Composite primary endpoint; bleeding requiring medical attention is not commonly used but drove the results; **15% of these events were independently adjudicated**[2]

CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction; 1. Cannon et al. Clin Cardiol 2016; 2. Gibson et al. N Engl J Med 2016

59

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

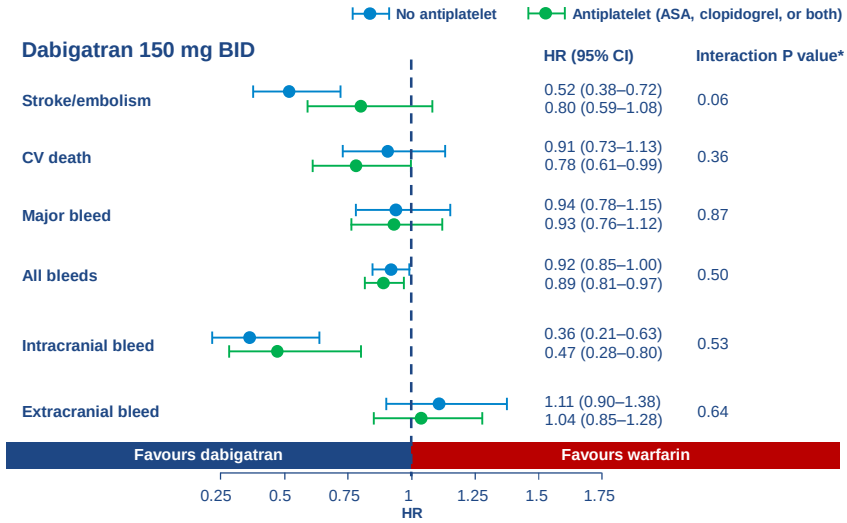
PCI, percutaneous coronary intervention

62

Dual Therapy VS Triple Therapy

65

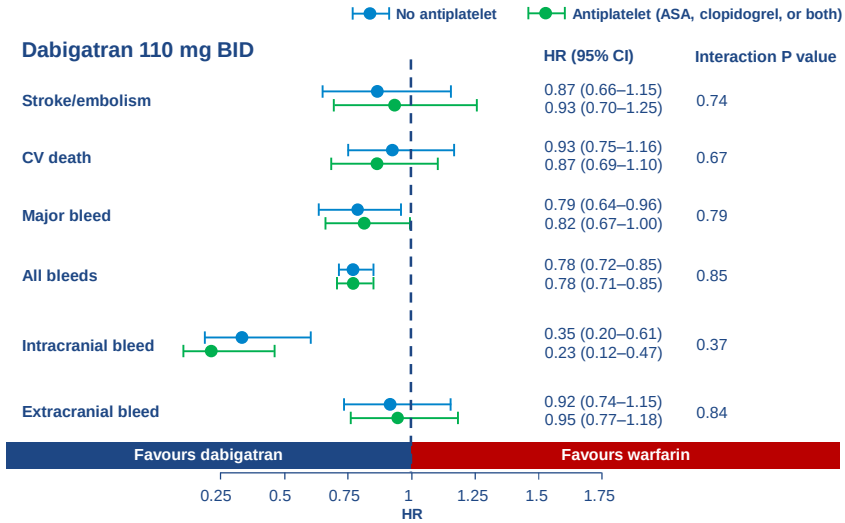
In RE-LY, the effects of dabigatran 150 mg BID vs warfarin were consistent regardless of whether patients were taking antiplatelets



ASA, acetylsalicylic acid; Dans et al. Circulation 2013

66

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



ASA, acetylsalicylic acid; Dans et al. Circulation 2013

67

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

Dabigatran[1]	150 mg BID	Recommended dose	Individual thromboembolic and bleeding risk assessment in patients with: • Age 75–80 years • Moderate renal impairment • Gastritis, oesophagitis, gastro-oesophageal reflux • **Increased risk of bleeding (e.g. receiving concomitant ASA/clopidogrel)**
	110 mg BID	Patients ≥80 years, or concomitant verapamil	

Rivaroxaban[2]	20 mg OD	Recommended dose
	15 mg OD	Patients with CrCl 15–49 mL/min

Doses investigated in J-ROCKET in Japanese patients (n=1280):[3]

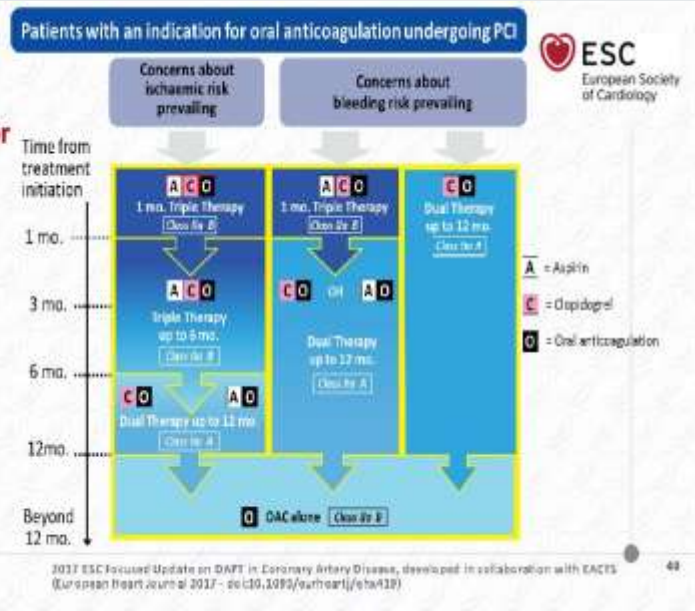
Rivaroxaban	15 mg OD	Recommended dose
	10 mg OD	Patients with CrCl 30–49 mL/min

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[4]

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

68

Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



www.escardio.org/guidelines

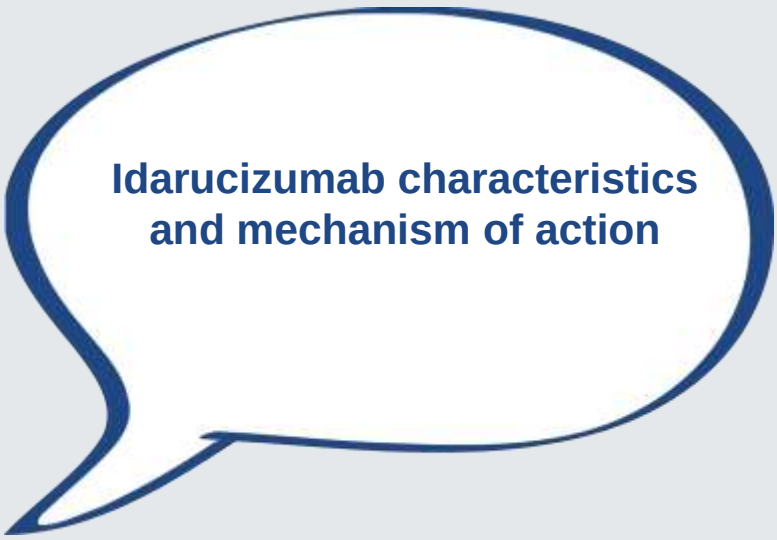
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

49

Praxbind®

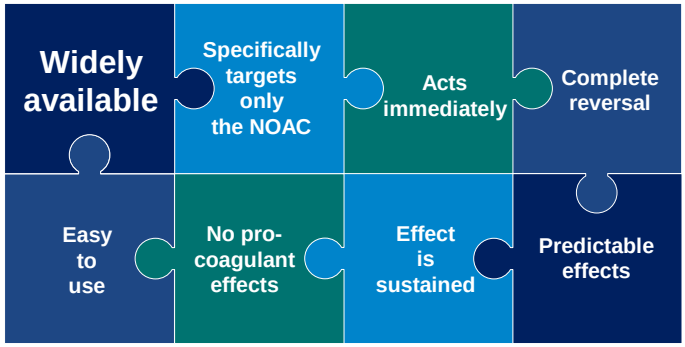
Boehringer Ingelheim

74



75

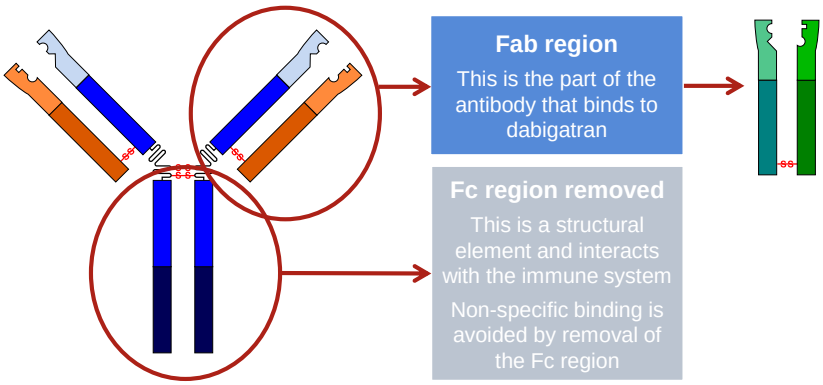
What are the characteristics of an ideal anticoagulation reversal agent?



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

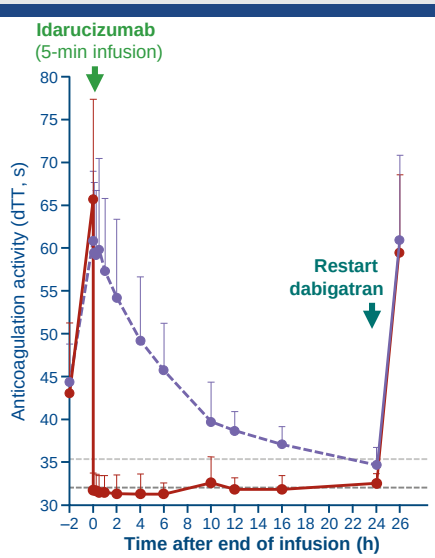
Fc region removed

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 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

Idarucizumab effect does not last >24 hours

- **45–64 years**, dabigatran etexilate 220 mg
- + Idarucizumab 5 g
- Upper limit of normal
- Mean baseline

Glund et al. J Am Coll Cardiol 2016; Glund et al. ASH 2014

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

Pollack et al. AHA 2016

The White Paper provides guidance on when reversal of NOACs may be appropriate in line with the idarucizumab label

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

*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

81

Thank You