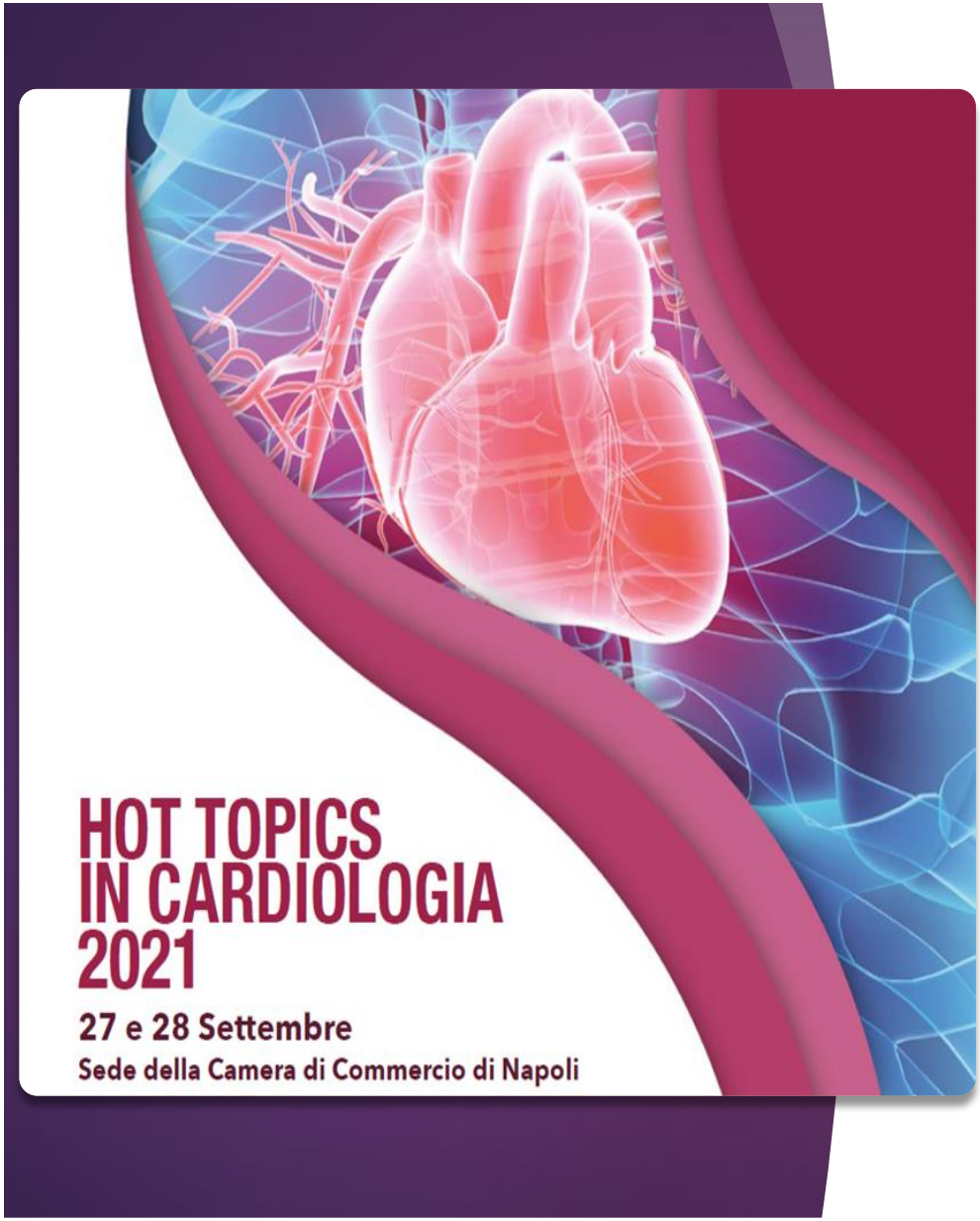

TITOLO: RE-DUAL

RELATORE: Giuseppe Stabile

Antithrombotic therapy for atrial fibrillation and PCI

NVAF + **PCI** = **NVAV + PCI**

Anticoagulant therapy

Anticoagulation superior to antiplatelet therapy

Antiplatelet therapy

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

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EDITORIAL COMMENT

Going Polymer Free and Dual Antiplatelet Free Earlier

The Coevolution of Stent and Pharmacotherapy*

C. Michael Gibson, MD

FIGURE 2 Combinations of Antiplatelet Agents and Antithrombotic Agents in Treating Patients With Atrial Fibrillation and Stent Placement

Dosing Strategies in the ACS Patient with Atrial Fibrillation

• ASA Dose: Low High None • ASA Duration (mos): 1 3 6 12	2 X 4 = 8 + None = 9 ASA
• Thienopyridine: None Clop Ticlid Pras Ticag • Thienopyridine duration (mos): 1 3 6 12	4 X 4 = 16 + None = 17 Thienopyridine
• AC: None Warf 2-3 Warf 2-2.5 Dabi 110 Dabi 150 Riva 20 Riva 15 Apix 10 Apix 5 Edox 60 Edox 30	11 Anticoagulants

Combination of Single, Dual or Triple Therapy as *Early Initial Therapy* (0-1,0-3,0-6 mos) following ACS: 12 X 20 X 11 = 1,683

Combinations of Single or Dual Therapy *Late After Early Therapy (1-12,3-12,6-12, all 12 mos)* following ACS = 1,683

Total Combinations *throughout one year:* 2.8 Million

Shown here are the combinations of aspirin (ASA), thienopyridines, anticoagulants (AC), and the durations of all of the above that can be used to manage the patient with atrial fibrillation who undergoes stent placement. ACS = acute coronary syndrome; Apix = apixaban; Clop = clopidogrel; Dabi = dabigatran; Edox = edoxaban; Pras = prasugrel; Riva = rivaroxaban; Ticag = ticagrelor; Ticlid = ticlopidine; Warf = warfarin.

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Table 12 Classification of elective surgical interventions according to bleeding risk

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)
Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account, and be discussed with the operating physician.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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

Study objective and design

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

- The primary endpoint was time to first ISTH major or clinically relevant non-major bleeding
- Formally tested and powered endpoints included:
  - Non-inferiority of 110 mg and 150 mg dual therapy groups on time to first ISTH major or clinically relevant non-major bleeding event.
  - Non-inferiority of both dual therapy groups combined on time to first event of death, thromboembolic event (MI, stroke, systemic embolism) or unplanned revascularization
  - Superiority testing of the bleeding endpoints
- 100% of outcome events were independently adjudicated by blinded external committee

ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction Non-inferiority testing (margin1.38)

Inclusion and exclusion criteria

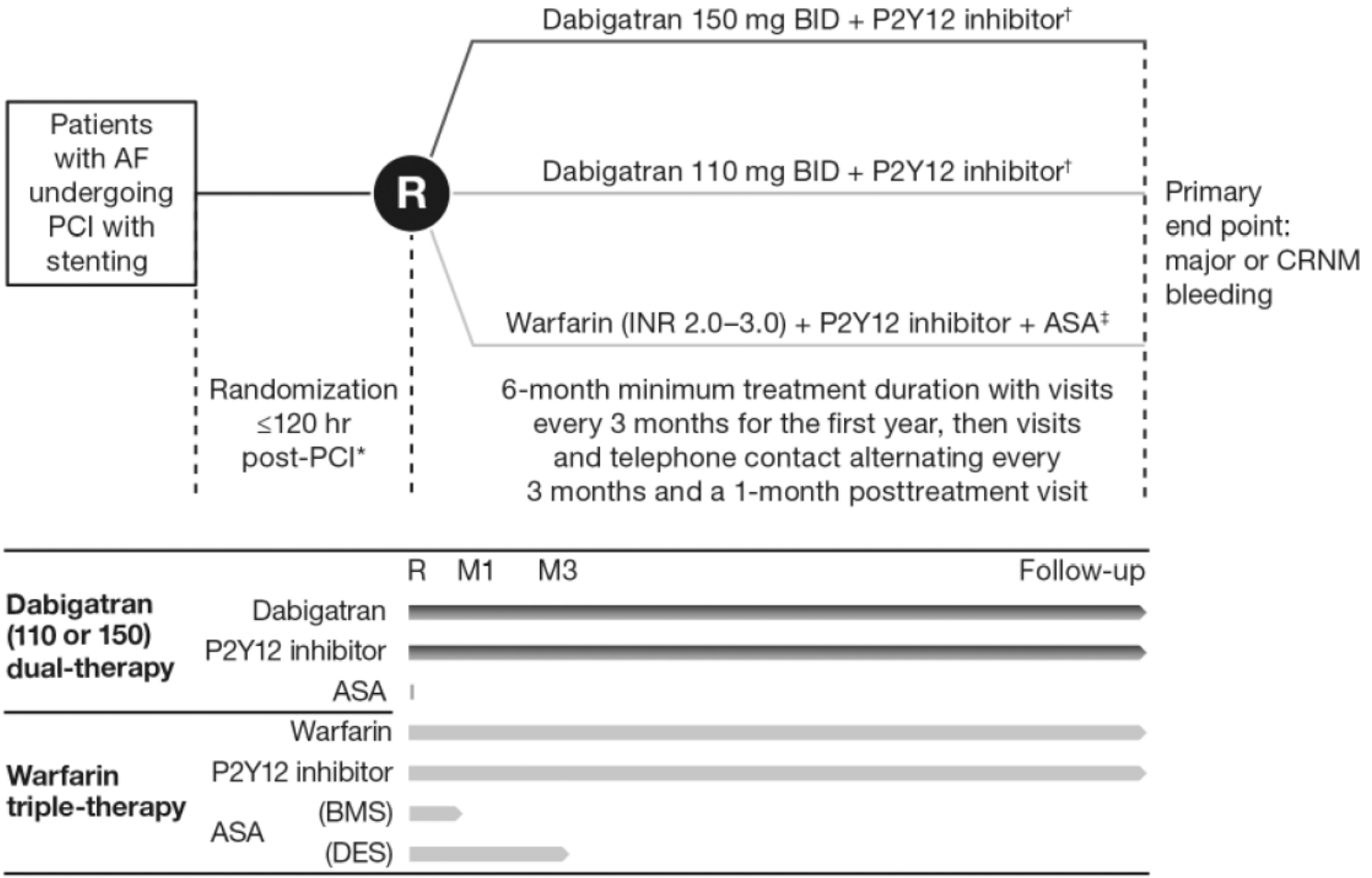
Key inclusion criteria

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

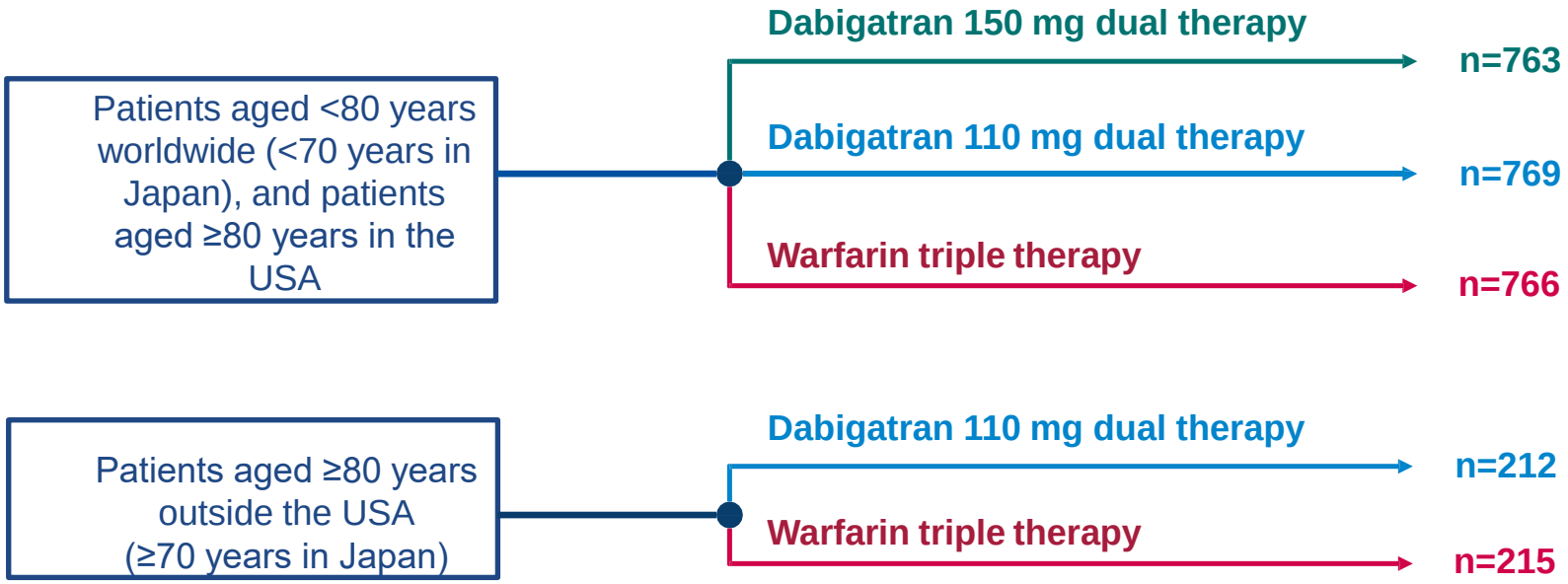
Key exclusion criteria

- Cardiogenic shock during current hospitalization
- Use of fibrinolytics within 24 hrs of randomization that, in the investigator's opinion, will put patient at high risk of bleeding
- Stroke or major bleeding event within 1 month prior to screening visit
- Severe renal impairment (CrCl <30mL/min)

ACS, acute coronary syndrome; CAD, coronary artery disease; CrCl, creatinine clearance


Dabigatran 150 mg BID + P2Y12 inhibitor†
Patients with AF undergoing PCI with stenting
R
Dabigatran 110 mg BID + P2Y12 inhibitor†
Primary end point: major or CRNM bleeding
Warfarin (INR 2.0–3.0) + P2Y12 inhibitor + ASA‡
Randomization ≤120 hr post-PCI*
6-month minimum treatment duration with visits every 3 months for the first year, then visits and telephone contact alternating every 3 months and a 1-month posttreatment visit
R
M1
M3
Follow-up
Dabigatran (110 or 150) dual-therapy
Dabigatran
P2Y12 inhibitor
ASA
Warfarin triple-therapy
Warfarin
P2Y12 inhibitor
ASA
(BMS)
(DES)

Patients were randomized based on age group and location



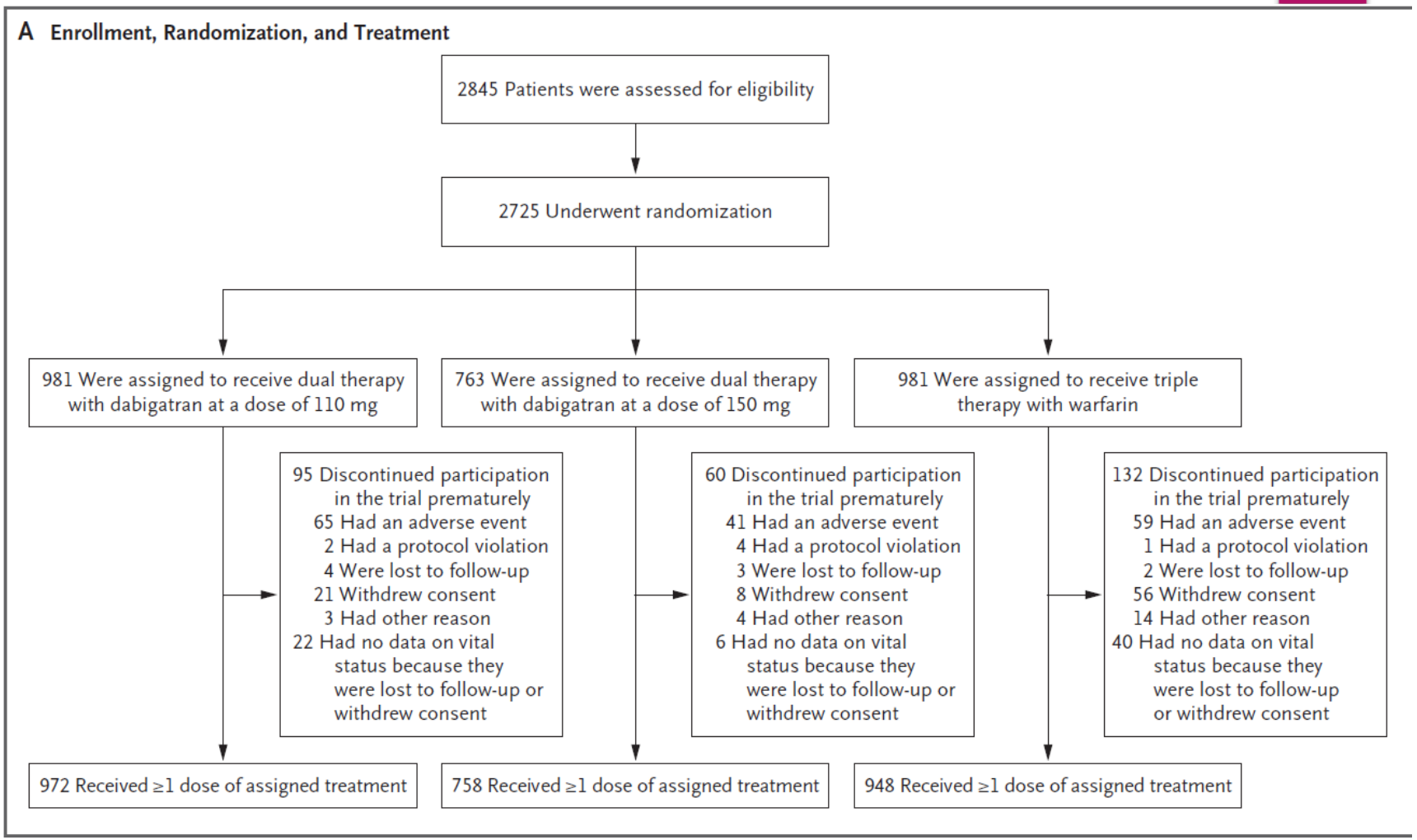
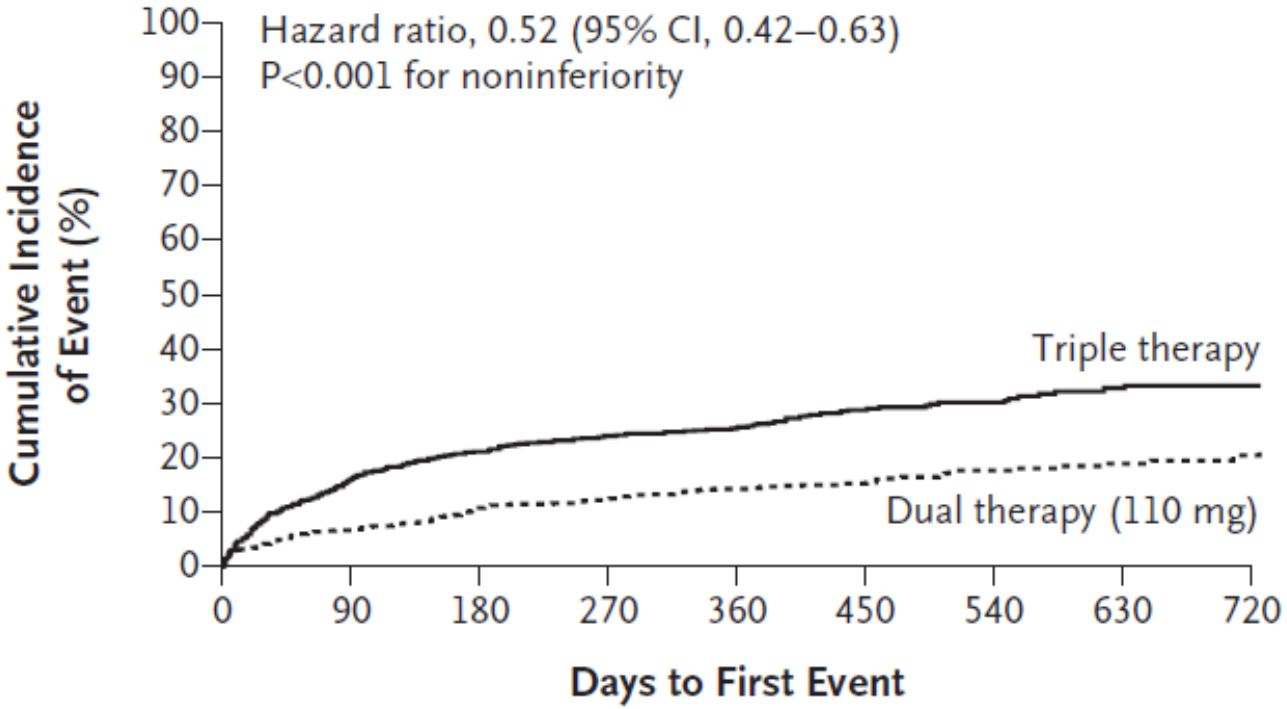

A Enrollment, Randomization, and Treatment
2845 Patients were assessed for eligibility
2725 Underwent randomization
981 Were assigned to receive dual therapy with dabigatran at a dose of 110 mg
763 Were assigned to receive dual therapy with dabigatran at a dose of 150 mg
981 Were assigned to receive triple therapy with warfarin
95 Discontinued participation in the trial prematurely
65 Had an adverse event
2 Had a protocol violation
4 Were lost to follow-up
21 Withdrew consent
3 Had other reason
22 Had no data on vital status because they were lost to follow-up or withdrew consent
60 Discontinued participation in the trial prematurely
41 Had an adverse event
4 Had a protocol violation
3 Were lost to follow-up
8 Withdrew consent
4 Had other reason
6 Had no data on vital status because they were lost to follow-up or withdrew consent
132 Discontinued participation in the trial prematurely
59 Had an adverse event
1 Had a protocol violation
2 Were lost to follow-up
56 Withdrew consent
14 Had other reason
40 Had no data on vital status because they were lost to follow-up or withdrew consent
972 Received ≥1 dose of assigned treatment
758 Received ≥1 dose of assigned treatment
948 Received ≥1 dose of assigned treatment

Table 1. Baseline Characteristics of the Patients.*

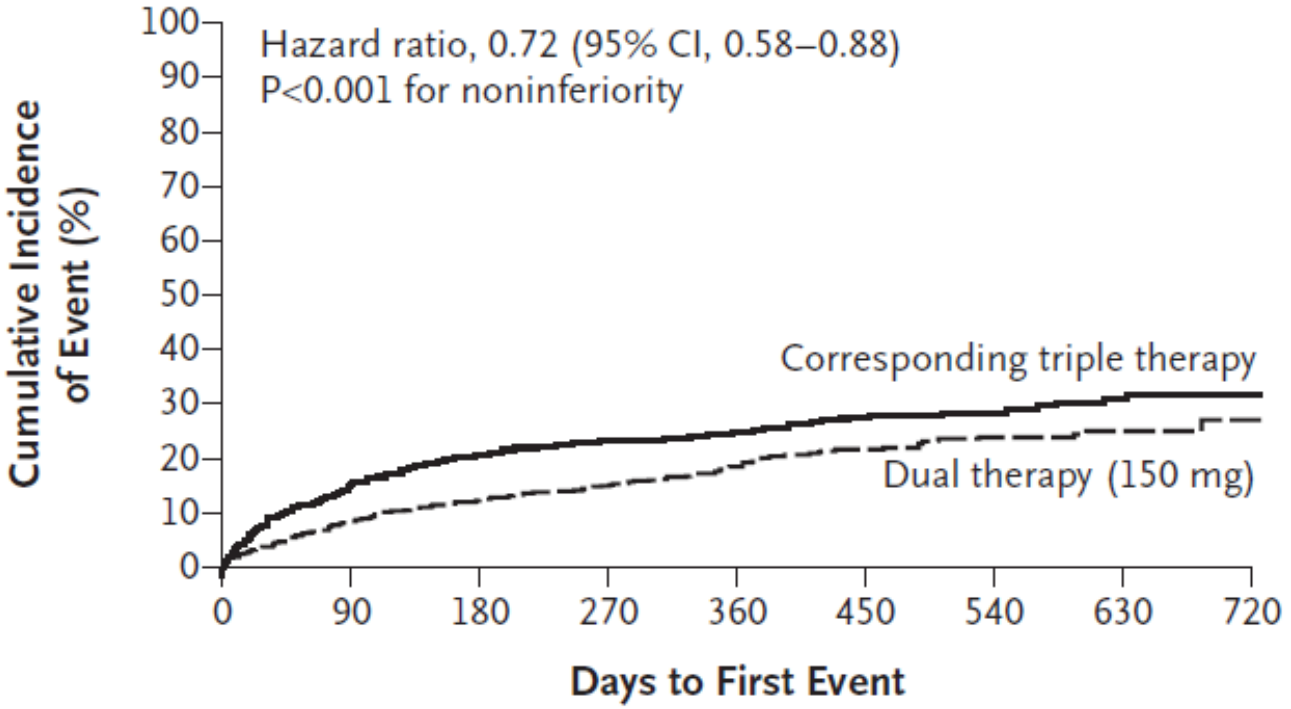
Characteristic	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin† (N=764)
Age — yr	71.5±8.9	71.7±8.9	68.6±7.7	68.8±7.7
Elderly age group — no. (%)‡	225 (22.9)	225 (22.9)	8 (1.0)	8 (1.0)
Male sex — no. (%)	728 (74.2)	750 (76.5)	592 (77.6)	594 (77.7)
Diabetes mellitus — no./total no. (%)	362/981 (36.9)	371/980 (37.9)	260/763 (34.1)	303/763 (39.7)
Previous stroke — no./total no. (%)	74/981 (7.5)	100/980 (10.2)	52/763 (6.8)	77/763 (10.1)
CHA_2DS_2-VASc score§	3.7±1.6	3.8±1.5	3.3±1.5	3.6±1.5
HAS-BLED score¶	2.7±0.7	2.8±0.8	2.6±0.7	2.7±0.8
Creatinine clearance — ml/min‖	76.3±28.9	75.4±29.1	83.7±31.0	81.3±29.6
Previous myocardial infarction — no. (%)	237 (24.2)	268 (27.3)	194 (25.4)	211 (27.6)
Previous PCI — no./total no. (%)	326/981 (33.2)	347/980 (35.4)	239/763 (31.3)	272/763 (35.6)
Previous CABG — no./total no. (%)	97/981 (9.9)	111/980 (11.3)	79/763 (10.4)	87/763 (11.4)
Type of atrial fibrillation — no./total no (%)				
Persistent	174/981 (17.7)	178/980 (18.2)	132/763 (17.3)	149/763 (19.5)
Permanent	320/981 (32.6)	318/980 (32.4)	250/763 (32.8)	238/763 (31.2)
Paroxysmal	487/981 (49.6)	484/980 (49.4)	380/763 (49.8)	376/763 (49.3)
Indication for PCI — no. (%)				
Stable angina or positive stress test	433 (44.1)	429 (43.7)	320 (41.9)	339 (44.4)
Acute coronary syndrome	509 (51.9)	475 (48.4)	391 (51.2)	369 (48.3)
Staged procedure	156 (15.9)	168 (17.1)	138 (18.1)	134 (17.5)
Other	43 (4.4)	62 (6.3)	65 (8.5)	50 (6.5)
Type of stent — no./total no. (%)				
Drug-eluting	804/979 (82.1)	826/976 (84.6)	621/762 (81.5)	638/759 (84.1)
Bare-metal	148/979 (15.1)	133/976 (13.6)	123/762 (16.1)	107/759 (14.1)
Drug-eluting and bare-metal	19/979 (1.9)	12/976 (1.2)	10/762 (1.3)	9/759 (1.2)
Other	8/979 (0.8)	5/976 (0.5)	8/762 (1.0)	5/759 (0.7)

A **Primary End Point in Dual-Therapy Group (110 mg) vs. Triple-Therapy Group**



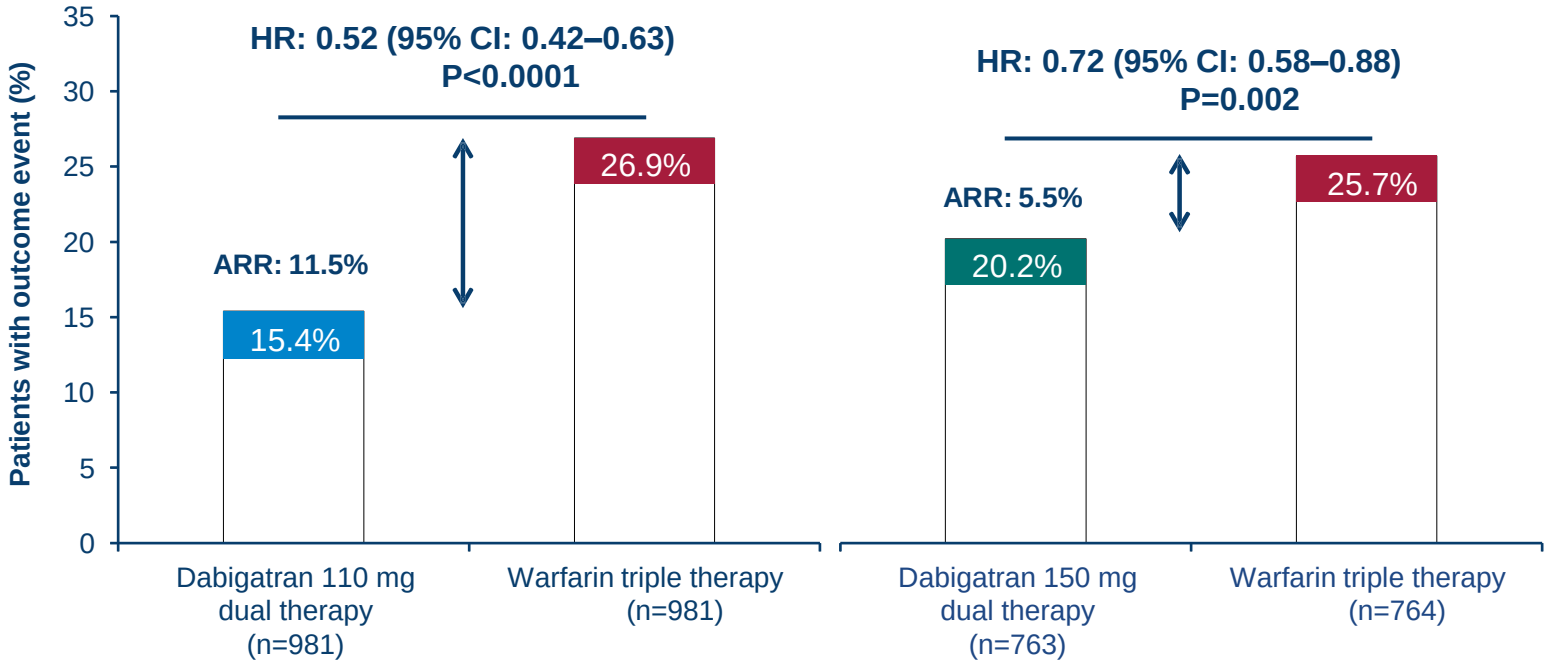
No. at Risk									
Dual therapy (110 mg)	981	898	834	671	538	384	258	162	86
Triple therapy	981	800	719	580	453	302	205	124	63

B **Primary End Point in Dual-Therapy Group (150 mg) vs. Triple-Therapy Group**



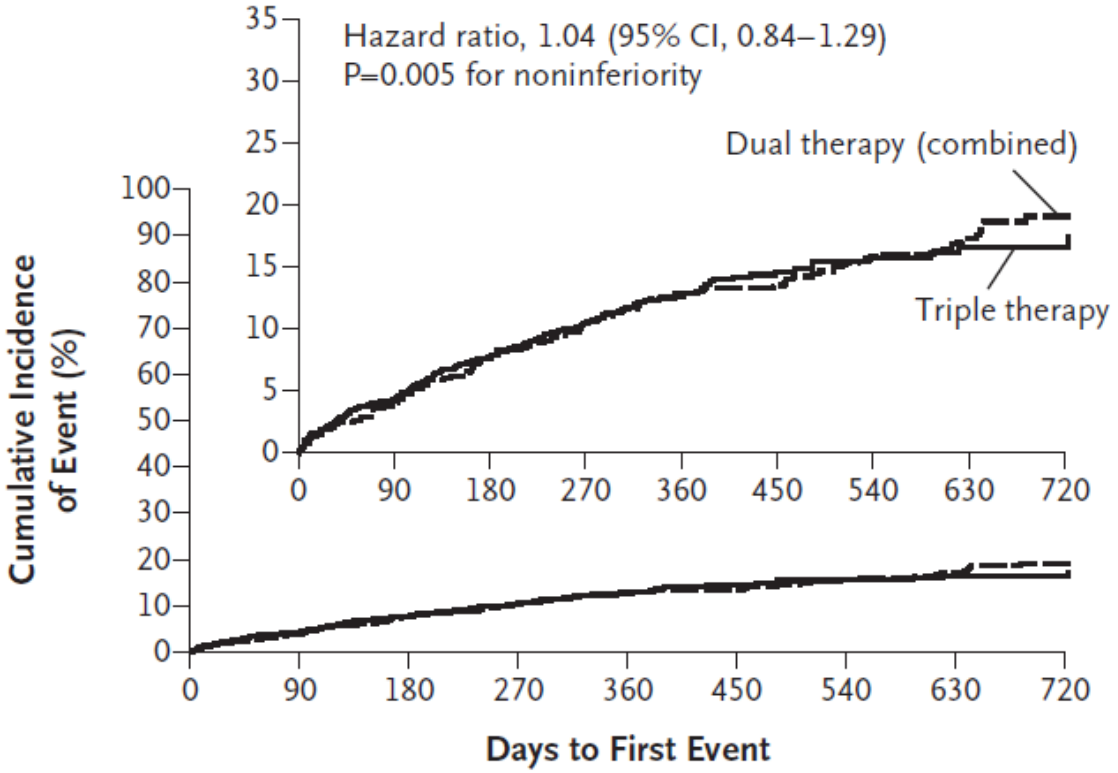
No. at Risk									
Dual therapy (150 mg)	763	694	640	514	404	278	182	113	65
Corresponding triple therapy	764	630	562	446	349	222	152	88	47

Primary endpoint: ISTH major or clinically relevant non-major bleeding event



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

C Secondary Efficacy End Point in Dual-Therapy Groups (Combined) vs. Triple-Therapy Group



No. at Risk

Dual therapy (combined)	1744	1660	1561	1257	1003	720	481	295	161
Triple therapy	981	921	854	700	548	383	259	161	81

Table 2. Safety End Points.*

End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

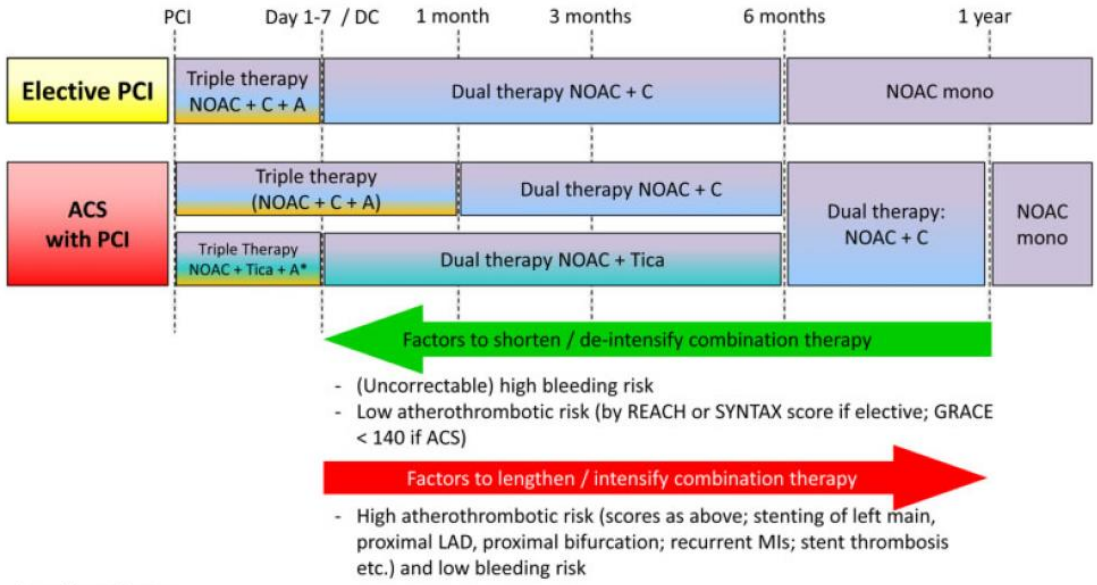
Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
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
Myocardial infarction					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
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
Definite 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

The RE-DUAL PCI trial showed that, among patients with atrial fibrillation who had undergone PCI, two different regimens of full-dose anticoagulation therapy with dabigatran (either 110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) resulted in a risk of major or clinically relevant nonmajor bleeding events that was significantly lower than the risk with triple therapy with warfarin; in addition, dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the composite efficacy end point of thromboembolic events, death, or unplanned revascularization. For

ESC European Society of Cardiology Europace (2021) 00, 1–65 doi:10.1093/europace/euab065
POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation



In all patients:

- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

Figure 17 Anticoagulation therapy after elective PCI or ACS in patients with AF. 'Shorten/de-intensify': e.g. discontinuing Aspirin or P_2Y_{12} inhibitor at an earlier stage. 'Lengthen/intensify': e.g. continuing triple combinations longer, or continuing P_2Y_{12} inhibitor longer. A: aspirin 75–100 mg QD; C: clopidogrel 75 mg QD; Tica: Ticagrelor 90 mg BID. *If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data). ACS, acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; QD, once daily.

ESC European Society of Cardiology
Europace (2021) 00, 1–65
doi:10.1093/europace/euab065
POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

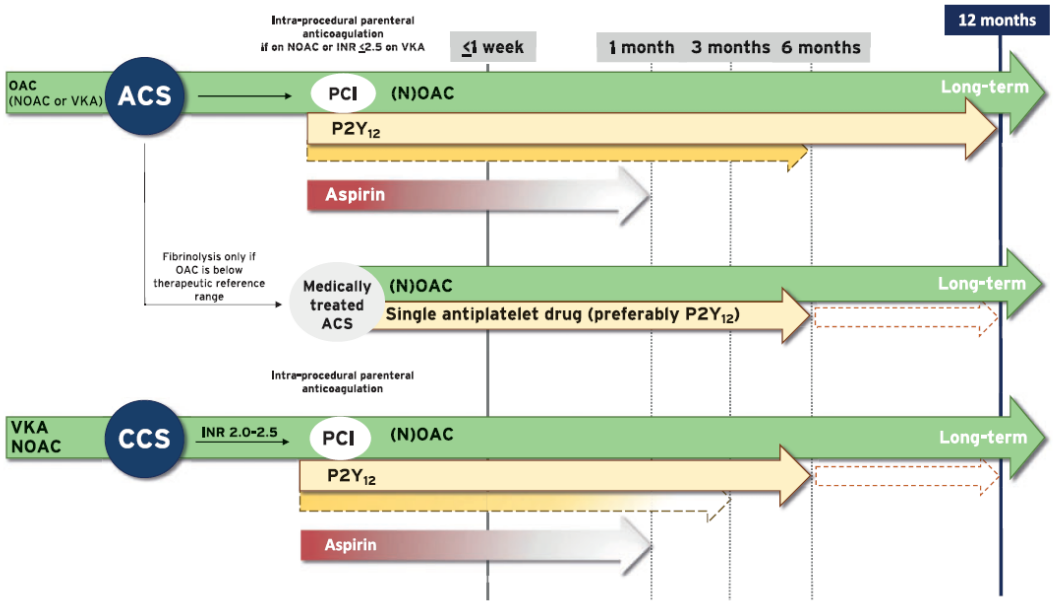
NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban[244]	5 mg BID	Dose reduction as for SPAF
Dabigatran[247]	150 mg BID or 110 mg BID	110mg as for SPAF[403]
Edoxaban[245]	60 mg QD	Dose reduction as for SPAF
Rivaroxaban[246]	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

ESC European Society of Cardiology
European Heart Journal (2020) 00, 1–125
doi:10.1093/eurheartj/ehaa612
ESC GUIDELINES

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)



THROMBOTIC RISK FACTORS

- Diabetes mellitus requiring therapy
- Prior ACS/recurrent myocardial infarction
- Multivessel CAD
- Concomitant PAD
- Premature CAD (occurring at age of <45 y) or accelerated CAD (new lesion within 2 years)
- CKD (eGFR <60 mL/min)
- Clinical presentation (ACS)
- Multivessel stenting
- Complex revascularisation (left main stenting, bifurcation lesion stenting, chronic total occlusion intervention, last patent vessel stenting)
- Prior stent thrombosis on antiplatelet treatment
- Procedural factors (stent expansion, residual dissection, stent length, etc.)

BLEEDING RISK FACTORS

- Hypertension
- Abnormal renal or liver function
- Stroke or ICH history
- Bleeding history or bleeding diathesis (e.g., anaemia with haemoglobin <110 g/L)
- Labile INR (if on VKA)
- Elderly (>65 years)
- Drugs (concomitant OAC and antiplatelet therapy, NSAIDs), excessive alcohol consumption

STRATEGIES TO REDUCE BLEEDING ASSOCIATED WITH PCI

- Radial artery access
- PPIs in patients taking DAPT who are at increased risk of bleeding (e.g., the elderly, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use)
- Non–administration of unfractionated heparin in patients on VKA with INR >2.5
- Pre-treatment with aspirin only, add a $P2Y_{12}$ inhibitor when coronary anatomy is known or if STEMI
- GP IIb/IIIa inhibitors only for bailout or periprocedural complications
- Shorter duration of combined antithrombotic therapy

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575
ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

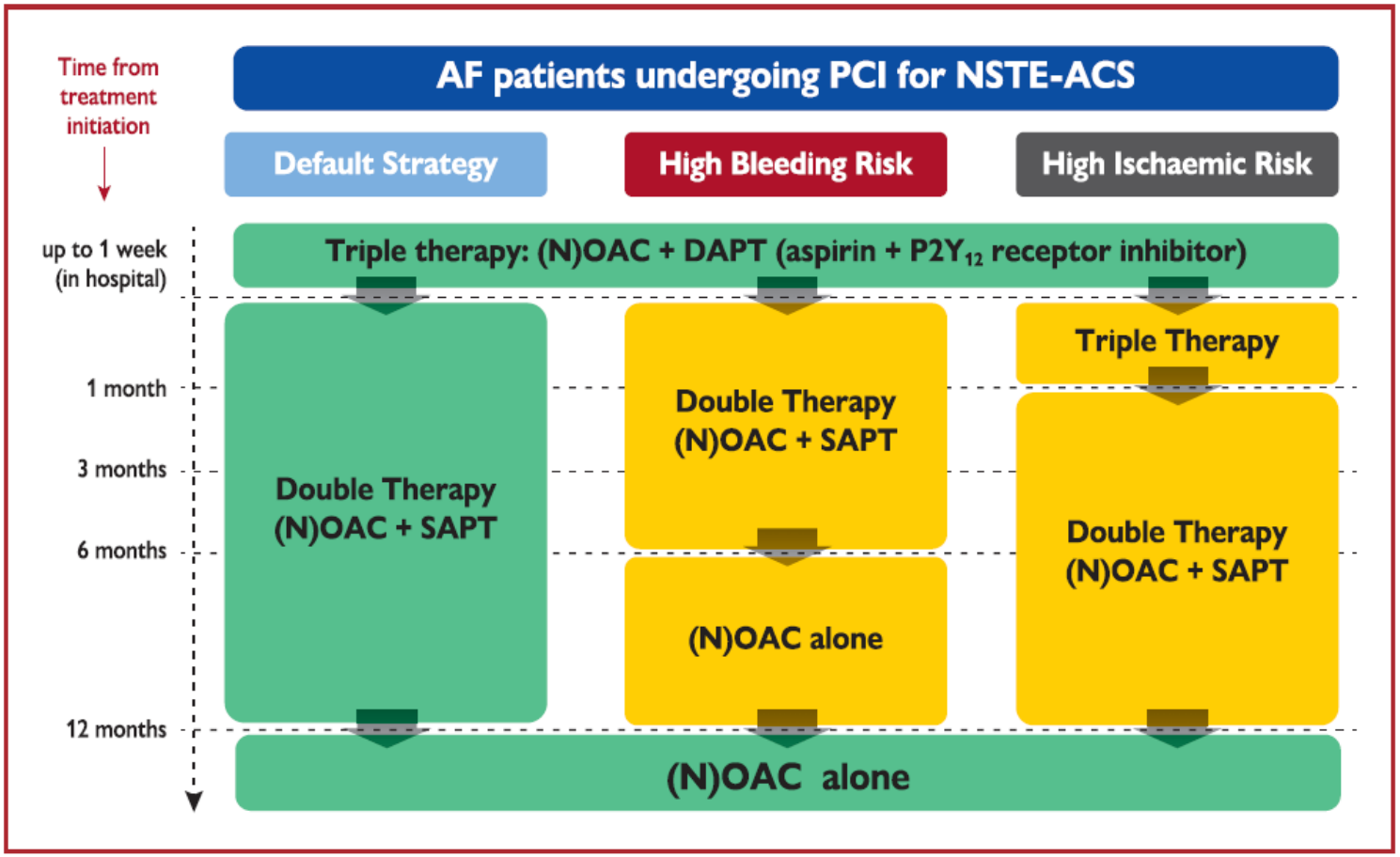


Table 7 **Major and minor criteria for high bleeding risk according to the Academic Research Consortium for High Bleeding Risk at the time of percutaneous coronary intervention (bleeding risk is high if at least one major or two minor criteria are met)**

Major	Minor
• Anticipated use of long-term OAC[a]	• Age ≥ 75 years
• Severe or end-stage CKD (eGFR <30 mL/min)	• Moderate CKD (eGFR 30–59 mL/min)
• Haemoglobin <11 g/dL	• Haemoglobin 11–12.9 g/dL for men or 11–11.9 g/dL for women
• Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	• Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
• Moderate or severe baseline thrombocytopenia[b] (platelet count <100 × 10^9/L)	• Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
• Chronic bleeding diathesis	• Any ischaemic stroke at any time not meeting the major criterion
• Liver cirrhosis with portal hypertension	
• Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	
• Previous spontaneous intracranial haemorrhage (at any time) • Previous traumatic intracranial haemorrhage within the past 12 months • Presence of a brain arteriovenous malformation • Moderate or severe ischaemic stroke[d] within the past 6 months	
• Recent major surgery or major trauma within 30 days prior to PCI • Non-deferrable major surgery on DAPT	

CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; OAC = oral anticoagulation/anticoagulant; PCI = percutaneous coronary intervention.

[a]This excludes vascular protection doses.[162]

[b]Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

[d]National Institutes of Health Stroke Scale score >5.