

Atrial Fibrillation on Non-vitamin K Antagonist Oral Anticoagulant Undergoing Elective Percutaneous Coronary Intervention for Stable Effort Angina

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2.1 Case Presentation

2.1.1 Baseline Characteristics

- Gender: male.
- Age: 68 years.
- Cardiovascular risk factors: type 2 diabetes mellitus (insulin treated), hypertension, hyperlipidemia, and current cigarette smoker (approximately 1 pack/day).
- Associated diseases: stage 3 chronic kidney disease (Table 2.1) (www.kdigo.org) (estimated glomerular filtration rate [eGFR] according to Cockcroft-Gault formula 46 ml/min), peripheral neuropathy, hypothyroidism, and gastroesophageal reflux disease.

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- Previous history: approximately 2.5 years earlier, inferior ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) with early-generation drug-eluting stent (DES) (TAXUS Express, Boston Scientific, 3.0×18 mm) in the midportion of the right coronary artery (RCA). Mild depression of left ventricular function (ejection fraction approximately 45 %) subsequently developed. Atrial fibrillation (AF) subsequently developed, and a rate-control strategy (with a beta-blocker) was selected along with oral anticoagulation (OAC) with non-vitamin K-antagonist oral anticoagulant (NOAC) dabigatran 150 mg twice daily.
- Current history: after a prolonged period of clinical stability, with no cardiological symptoms during ordinary activity, dyspnea (NYHA class II) and angina on exertion (CCS II) developed over the previous 2 months, thereby prompting hospitalization for coronary angiography/intervention (CORO/PCI). Upon admission, the patient was asymptomatic, the electrocardiogram (ECG) was negative for ongoing myocardial ischemia (as well as for previous infarction) (Fig. 2.1), and cardiac-specific troponin levels were in the normal range. Blood pressure was 180/100 mmHg, whereas other vital signs and oxygen saturation were within normal limits. Ongoing medications included dabigatran 150 mg twice daily, aspirin 100 mg/day, carvedilol 6.25 mg twice daily, amlodipine 5 mg once daily, isosorbide mononitrate 20 mg three times daily, lisinopril 10 mg once daily, simvastatin 20 mg once daily, allopurinol 100 mg once daily, L-thyroxine 25 mcg once daily, metformin 850 mg twice daily, and insulin.
- Based on the history and clinical presentation, the probability of coronary artery disease was deemed high, and the patient was referred directly for CORO/PCI, with no preliminary noninvasive testing.

Table 2.1 Stages of chronic kidney disease (www.kdigo.org)

CKD stage	Description	GFR (ml/min per 1.73 m ²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decreased GFR	60–89
3	Moderate decreased GFR	30–59
4	Severe decreased GFR	15–29
5	Kidney failure	<15 (or dialysis)

CKD chronic kidney disease, GFR glomerular filtration rate

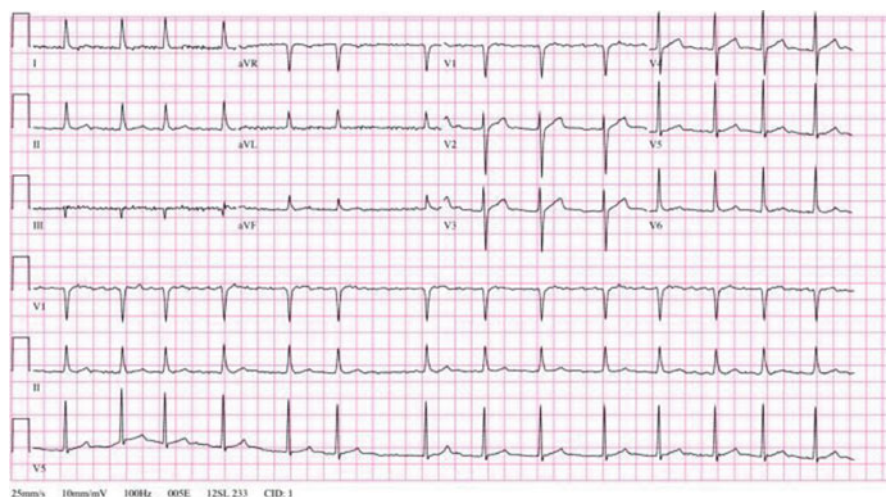


Fig. 2.1 Electrocardiogram (ECG) on admission

2.2 Periprocedural Issues

Because of the increased risk of bleeding and/or vascular complications in patients undergoing elective CORO/PCI on aggressive antithrombotic therapy, including dabigatran (or other NOACs) and antiplatelet agents, measures aiming to minimize such risk, while not increasing at the same time the risk of thromboembolic/thrombotic complications, need to be implemented [1–3].

Regarding OAC, timely discontinuation of dabigatran (or other NOACs) is the preferable option [1–3] (Table 2.2). Owing to the rapid offset (as well as onset) of action of dabigatran (or other NOACs) (Table 2.3), withdrawing treatment 24–48 h in advance, depending on the patient's renal function, would generally be sufficient for performing CORO/PCI during low exposure to the drug (Table 2.4) [3]. Taking into account that the half-life of dabigatran (as well as of other NOACs) is approximately 12 h (Table 2.3), after 24 and 48 h from interruption, the drug concentration, and therefore the pharmacological effect, is expected to be 1/4 and 1/16, respectively, of the initial [3]. Conversely, continuation of dabigatran in elective patients has been shown not to provide sufficient suppression of coagulation activation during and after PCI, as indicated by a consistent increase in the levels of prothrombin fragment 1+2 and thrombin-antithrombin III complex plasma levels in comparison to standard unfractionated heparin (UFH) [4]. This might not be true for uninterrupted OAC with rivaroxaban, since the suppression of the above markers of thrombin generation and coagulation activity in a small group of patients undergoing elective PCI was reported comparable to standard UFH [5]. For now, however, pre-procedural NOAC interruption should be regarded as the standard

Table 2.2 Periprocedural management recommendations

Issue	Recommendations
Anticoagulation	Discontinuation ^a
Vascular access site	Radial/femoral
Antiplatelet therapy	Low-dose ASA ^{b, c} + clopidogrel PO ^d

NOAC non-vitamin K-antagonist oral anticoagulant, ASA aspirin, PO orally

^a24 to 48–72 h in advance (depending on the patient renal function and NOAC used), with no heparin bridging

^b75–100 mg/day

^cMay be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

^d600 (or 300 mg) front-loading

Table 2.3 Main pharmacological properties of warfarin and non-vitamin K-antagonist oral anticoagulants

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factors II, VII, IX, X	Factor IIa (thrombin)	Factor Xa		
Prodrug	No	Yes	No	No	No
Bioavailability	100 %	6 %	66 ^a /100 % ^b	50 %	62 %
Plasma protein binding	97 %	35 %	93 %	87 %	50 %
Time to peak	4–5 days	1.5–2 h	2–3 h	2–3 h	1–2 h
Elimination half-life	36–42 h	12–17 h	5–9 ^c /11–13 ^d hours	12 h	10–14 h
Route of clearance	Multiple	80 % renal	35 % renal	27 % renal	50 % renal

^aWithout food

^bWith food

^cIn the young

^dIn the elderly

Table 2.4 Recommended last drug intake before elective surgical/invasive procedure

	Dabigatran		Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	
	Low risk ^a	High risk ^b	Low risk ^a	High risk ^b
CrCl ≥ 80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 ml/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 ml/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 ml/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl < 15 ml/min	No official indication for use			

From Heidbuchel et al. [3]

Note: when no important bleeding risk and/or adequate local hemostasis possible, perform procedure at trough level (i.e., ≥12 or 24 h after the last intake)

Note: there is no need for bridging with low-molecular-weight/unfractionated heparin

CrCl creatinine clearance

^aWith a low frequency of bleeding and/or minor impact of a bleeding

^bWith a high frequency of bleeding and/or important clinical impact

of treatment, regardless of the ongoing NOAC [1–3]. Effective ongoing anticoagulation with dabigatran (or other NOACs) would also preclude the use, if needed, of glycoprotein IIb/IIIa inhibitors, as they have been shown (in patients however on therapeutic OAC with warfarin) to largely increase the occurrence of major bleeding complications [6]. In addition, the lack of the possibility to reliably measure the intensity of OAC with dabigatran (as well as of other NOACs) would also make cumbersome the use of additional anticoagulants, such as unfractionated heparin (UFH), in the event that a thrombotic complication (e.g., acute stent/vessel occlusion) occurs. As an alternative to timely interruption of dabigatran (or other NOACs), consideration may be given to perform CORO/PCI at the drug trough level (i.e., ≥ 24 –48 h from last intake), provided however that the bleeding risk is low and adequate hemostasis is possible (i.e., the procedure is performed by the radial approach) (Table 2.4) [3]. Given the short pre-procedural interruption of OAC with dabigatran (or other NOACs) and therefore the associated low risk of thromboembolic events, bridging with other anticoagulants, generally represented by low-molecular-weight heparins (LMWHs), should be considered virtually in no case [3]. In patients on warfarin either because of AF or other indications, in whom perioperative interruption of anticoagulation is generally rather long (on average 5 days), forgoing bridging anticoagulation with LMWH has been recently shown to be as effective as and safer than perioperative bridging with LMWH [7–9].

Regarding oral antiplatelet therapy, front-loading with aspirin and clopidogrel (if not ongoing) is generally performed in patients referred for elective CORO/PCI. Because of the timely interruption of dabigatran before the procedure, effective OAC should be waning at the time of clopidogrel administration, which therefore can be performed with either 300 or 600 mg loading dose (Table 2.2) [2]. Of note, newer P2Y₁₂-receptor inhibitors, including prasugrel and ticagrelor, are not approved in this clinical setting [10], regardless of whether or not they are going to be combined with OAC and should therefore not be used [1, 2, 10].

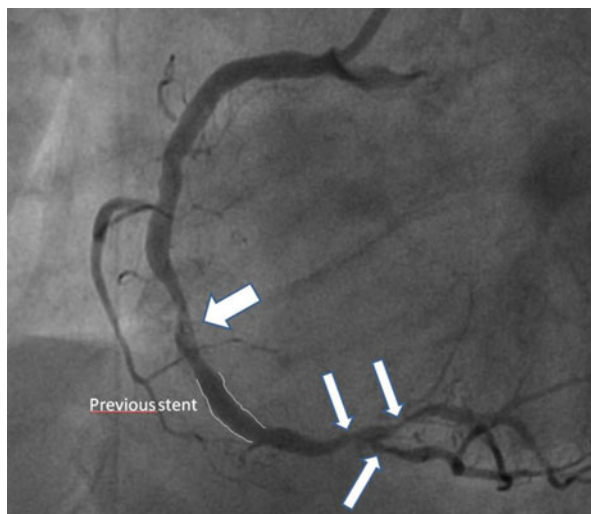
Regarding the vascular access site, radial approach should generally be preferred because of the dramatic decrease in bleeding and/or vascular complications reported in general population [11], as well as in a small group of patients on OAC with warfarin [12] (Table 2.2). Given, however, that the effect of dabigatran (or other NOACs) should be minimal when timely interrupted, the choice of the radial as compared to femoral approach may not be as important as for patients undergoing PCI on ongoing therapeutic (i.e., international normalized ratio [INR] ≥ 2.0) OAC with warfarin.

2.2.1 Periprocedural Management

- Coronary angiography was scheduled 48 h after the last intake of dabigatran 150 mg.
- No periprocedural LMWH bridging anticoagulation was arranged after dabigatran interruption.

- Front-loading with 600 mg of clopidogrel orally was performed the evening before the procedure.
- Ongoing aspirin treatment was continued at the dose of 100 mg once daily.
- Right radial access site was selected.
- An intravenous (IV) bolus of 4,000 IU (about 50 IU/kg) of UFH was given through the arterial sheath at the beginning of procedure to prevent radial artery occlusion.
- CORO was carried with conventional JL and JR 6 F diagnostic catheters and showed a right dominant system with severe (>70%) stenosis proximal to the DES previously implanted in the mid-RCA, severe (>70%) ostial stenosis of posterior descending artery, and a proximal, severe (90%) stenosis of the right posterolateral branch (Fig. 2.2). No significant lesions were detected in the left coronary system.

Fig. 2.2 Diagnostic angiography of right coronary artery (RCA) (LAO view). LAO left anterior oblique



2.3 Procedural Issues

To prevent thrombosis at the PCI hardware and/or at the atherosclerotic plaque disrupted by balloon traumatism, effective anticoagulation is required throughout elective PCI. Once dabigatran (or other NOACs) has been timely interrupted, intra-procedural UFH administration should be carried out as per usual practice (Table 2.5) [1–3]. Therefore, a standard IV bolus of UFH at the dose of 70–100 IU/kg should be given upon the start of procedure [2]. Even though specific data are not available, also glycoprotein IIb/IIIa inhibitors might likely be used safely, should the indication arise (e.g., high thrombus burden or acute stent/vessel occlusion) [1–3].

Table 2.5 Procedural management recommendations

Additional intra-procedural IV UFH	Yes
Dose of additional intra-procedural IV UFH	Standard ^a
Type of stent	New-generation DES ^b
Adjunct IV GPI	Provisional ^c

IV intravenous, *UFH* unfractionated heparin, *DES* drug elutin stent, *GPI* glycoprotein IIb/IIIa inhibit, *BMS* bare metal stent
^a70–100 U/kg
^bBMS may be considered in patients at high risk of bleeding or when unavoidable surgery is planned within 3–6 months
^cIn high-risk lesions, large thrombus burden, no reflow/slow flow, threatened vessel closure

Table 2.6 Academic Research Consortium (ARC) definitions of stent thrombosis [13]

Event certainty	(a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis
	(b) Probable:
	(i) Unexplained death within 30 days of stent implantation without autopsy (ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation
Time frame	(a) Early:
	(i) Acute – within 24 h of stent implantation
	(ii) Subacute – between 24 h and 30 days of stent implantation
	(b) Late: between 30 days and 1 year of stent implantation
	(c) Very late: after 1 year of stent implantation

Regarding the type of stent to be implanted, it has been extensively proven that DESs are more effective than bare-metal stents (BMSs) in preventing restenosis and associated clinical *sequelae*, at the price however of a possibly increased incidence of late/very late (i.e., >30 days from implantation) stent thrombosis (Table 2.6) [10, 13]. For this reason, dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂-receptor inhibitor, including clopidogrel, ticagrelor, and prasugrel (these latter two only in acute coronary syndromes), has been recommended for 1 month after BMS implantation and 6–12 months after DES implantation [10]. Based on several and increasing data showing that new-generation DESs, with both durable and bioabsorbable polymer coatings (Table 2.7), are associated with minimal, and likely not substantially different, incidence of stent thrombosis compared to BMSs, most recent recommendations reduce the suggested duration of DAPT to 6 months only [10]. Further, even durations as short as 1 month may possibly be considered after the implantation of zotarolimus and everolimus, durable polymer DES, as well as of a polymer-free, biolimus A9-DES, given the apparent lack of an increase in stent thrombosis with the interruption of one of the two antiplatelet agents after the first 4 weeks of treatment [14–16]. At present, however, standard prescription of 6-month DAPT may generally be preferable even with these stents, with the option however of more safely interrupt DAPT in the event that a need arises (e.g., bleeding complication) [1, 2]. Based on the above, the stent to be preferably implanted in an AF patient on dabigatran (or other NOACs) should generally be either a BMS or a new-generation DES, to be chosen taking into account the individual risk of restenosis, stent thrombosis, and bleeding

Table 2.7 General classification of coronary stents/scaffolds

BMS		(a) Stainless steel (b) Non-stainless steel, cobalt- or platinum-chrome alloy
DES	Early generation	(a) Durable polymer: sirolimus, paclitaxel eluting
	New generation	(a) Durable polymer: zotarolimus, everolimus eluting (b) Biodegradable polymer: biolimus A9 and everolimus eluting (c) Polymer-free: biolimus A9, amphilius eluting
BAS		(a) Diamond-like carbon coated, titanium nitric oxide coated (b) Endothelial progenitor cell capturing
BVS		(a) Nondrug eluting (b) Everolimus, myolimus, sirolimus eluting

BMS bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

(Table 2.5) [1–3]. The recently introduced bioresorbable vascular scaffolds (BVSs) appear at the moment not to have a specific role in AF patients on OAC given that DAPT is warranted at least until the start of BVS degradation, which occurs not earlier than 6 months from implantation [17]. Similarly, no specific role is currently apparent for drug-eluting balloons (DEBs). Given the indication for a short duration of DAPT (i.e., 1–3 months) [18], they may nonetheless represent a valuable option when treating conditions, like in-stent restenosis and small vessel disease, which represent commonly accepted indications for these devices are present.

2.3.1 Procedural Management

- An additional IV bolus of 2.000 IU of UFH was given upon the start of PCI to obtain a total dose of about 70 IU/kg.
- A new-generation, bioabsorbable polymer DES (BioMatrix Flex, Biosensors, 3.0×11 mm) was implanted in the mid-RCA proximal to the previous stent without overlap.
- Two additional new-generation, bioabsorbable polymer DESs were implanted (T-stenting technique) on distal RCA-proximal right posterolateral branch (BioMatrix Flex, Biosensors, 2.5×18 mm) and on posterior descending branch (BioMatrix Flex, Biosensors, 2.75×18 mm).

- An excellent angiographic result was obtained, with no residual stenosis (Fig. 2.3).
- The radial sheath was immediately removed upon completion of PCI and a local compression device applied (RadiStop, St. Jude Medical).
- Stratification of both the risk of stroke and bleeding was performed: CHA₂DS₂-VASc score 4 (Table 2.8) and HAS-BLED score 3 (Table 2.9).

Fig. 2.3 Final angiography after multiple stenting of RCA (LAO view). *LAO* left anterior oblique



Table 2.8 CHA₂DS₂-VASc score and associated risk of stroke/year [19]

	Condition	Points	Total score	Stroke risk/year (%)
C	Congestive heart failure (or left ventricular ejection fraction $\leq 35\%$)	1	0	0
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1	2	1.3
A ₂	Age ≥ 75 years	2	2	2.2
D	Diabetes mellitus	1	3	3.2
S ₂	Prior stroke or TIA or thromboembolism	2	4	4.0
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1	5	6.7
A	Age 65–74 years	1	6	9.8
Sc	Sex category (i.e., female sex)	1	7	9.6
			8	6.7
			9	15.2

TIA transient ischemic attack

Table 2.9 HAS-BLED score and associated risk of major bleeding/year [19]

	Condition	Points	Total score	Risk of major bleeding/year (%)
H	Hypertension (uncontrolled blood pressure above 160/90 mmHg)	1	0	<1
A	Renal (dialysis, transplant, creatinine >2.6 mg/dL or >200 μ mol/L) and/or liver (cirrhosis, bilirubin >2 \times normal or AST/ALT/AP >3 \times normal) disease	1 or 2	1–2	2–3
S	Stroke	1	≥ 3	4–12
B	Bleeding (previous or predisposition to)	1		
L	Labile INR (unstable/high or TTR <60 %)	1		
E	Elderly (i.e., age >65 years)	1		
D	Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥ 8 drinks a week)	1 or 2		

INR international normalized ratio, TTR time in therapeutic range, NSAID nonsteroidal anti-inflammatory drug AST aspartate aminotransferase, ALT alanine aminotransferase, AP alkaline phosphatase

2.4 Post-procedural Issues

Following PCI with stent implantation, combined OAC and antiplatelet therapy is warranted. DAPT with aspirin and clopidogrel is in fact inferior to OAC with warfarin for prevention of stroke in AF [20], and OAC with warfarin is inferior to DAPT for prevention of stent thrombosis and major adverse cardiac events (MACEs), including death, myocardial infarction, and repeat revascularization, after PCI with stent implantation [21]. Given, however, the lack of conclusive data on the optimal antithrombotic regimen and the general weakness of available evidence, some options should be considered, carefully taking into account the individual risk of stroke, stent thrombosis, MACEs, and bleeding (Fig. 2.4). In the presence of a high stroke risk, as expressed by a CHA₂DS₂-VASc score ≥ 2 , OAC is warranted [22] (Table 2.8). In general, OAC should be given in conjunction with DAPT of aspirin and clopidogrel [1–3, 10, 23] (Fig. 2.4), as such so-called triple therapy (TT) has been generally shown to be the most effective antithrombotic regimen for the prevention of MACEs, stent thrombosis, and (especially) stroke. In patients at increased risk of bleeding, such as those with HAS-BLED score ≥ 3 (Table 2.9), and concomitant low risk of stent thrombosis and MACEs, such as those undergoing elective PCI with stent implantation in the context of stable coronary artery disease (CAD), dual therapy (DT) of OAC and clopidogrel may be considered [1–3, 10]. Available, yet suboptimal, data suggest in fact that DT may be significantly safer than TT, in terms of reduced incidence of (total) bleeding, while not being associated with reduced efficacy (i.e., incidence of MACEs, stent thrombosis, and stroke) [24, 25]. Based on historical data showing that DT of OAC and aspirin is largely insufficient to protect against MACEs and (especially) stent thrombosis, such combination has at present virtually no indication [1, 2, 23].

A relevant question is whether ongoing dabigatran (or other NOACs) should be confirmed or either another NOAC or warfarin should be preferred instead

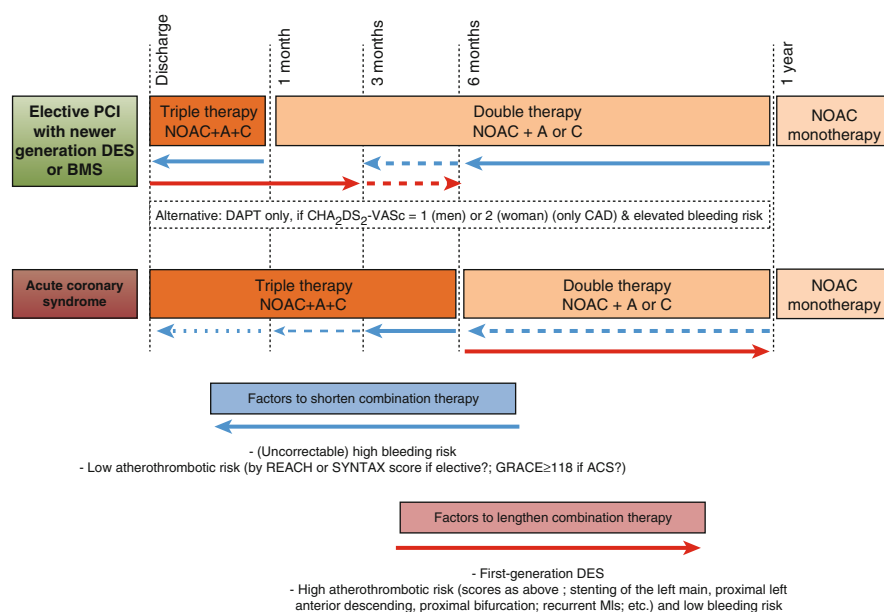


Fig. 2.4 Management suggestions for antithrombotic therapy (Reproduced with permission from [3]). *PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *NOAC* non-vitamin K-antagonist oral anticoagulant, *A* aspirin, *C* clopidogrel, *ACS* acute coronary syndrome, *MI* myocardial infarction

following PCI with stent implantation. According to available, albeit limited, data, efficacy and safety of dabigatran when combined with (either single or dual) antiplatelet therapy appear comparable to that of warfarin [26]. Thus, there is apparently no reason to switch to warfarin, given also the superior convenience and safety on intracranial bleeding of dabigatran (and other NOACs) (Table 2.10) [2, 31]. The issue of anticoagulation reversal currently appears also to be overcome given the development of specific antidotes to NOACs, like idarucizumab for dabigatran [32] and andexanet alfa for factor Xa inhibitors [33] (Table 2.10). Their availability, together with nonspecific reversal agents, like prothrombin complex concentrates, recombinant factor VII and fresh frozen plasma, and short half-life of NOACs (i.e., approximately 12 h), is expected to allow safe management of relevant bleeding in the event it occurs [34]. Because of the lack of specific data with other NOACs and the apparent similar effect on the risk of bleeding compared to DAPT of the various NOACs [31], there is also no apparent reason to switch to a NOAC different from the one ongoing.

In patients at intermediate risk of stroke, as expressed by a CHA₂DS₂-VASc score 1 (Table 2.8) [22], while either TT or DT might indeed be considered (Fig. 2.4), temporary (i.e., 1–6 months, depending on whether a BMS or new-generation DES has been implanted) withdrawal of OAC appears the preferable option [1–3]. Given the low absolute risk of stroke in such category, especially in the short period, as well as some protection against stroke (i.e., approximately

Table 2.10 Efficacy and safety of non-vitamin K-antagonist oral anticoagulants vs warfarin in clinical trials (hazard ratio, 95 % confidence intervals) [27–30]

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Rivaroxaban 20 mg ^a OD	Apixaban 5 mg ^b BID	Edoxaban 30 mg BID	Edoxaban 60 mg BID
Stroke or systemic embolism	0.91 ^c (0.74–1.11)	0.66 ^d (0.53–0.82)	0.88 ^c (0.74–1.03)	0.79 ^d (0.66–0.95)	1.07 ^c (0.87–1.31)	0.79 ^c (0.63–0.99)
Major bleeding	0.80 ^c (0.69–0.93)	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 ^c (0.60–0.80)	0.47 ^c (0.41–0.55)	0.80 ^c (0.71–0.91)
Intracranial bleeding	0.31 ^c (0.20–0.47)	0.40 ^c (0.27–0.60)	0.67 ^c (0.47–0.93)	0.42 ^c (0.30–0.58)	0.30 ^c (0.21–0.43)	0.47 ^c (0.34–0.63)
Gastrointestinal bleeding	1.10 (0.86–1.41)	1.50 ^c (1.19–1.89)	1.60 ^c (1.29–1.98)	0.89 (0.70–1.15)	0.67 ^c (0.53–0.83)	1.23 ^c (1.02–1.50)

BID twice daily, *OD* once daily

^a15 mg OD in patients with creatinine clearance 30–50 ml/min

^b2.5 mg BID in patients with two of the following three features: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 ml/min

^cSignificant for non-inferiority

^dSignificant for superiority

^eStatistically significant

30% relative risk reduction compared to placebo) provided by DAPT [35], it appears more prudent to abstain from OAC in order to limit the incidence of bleeding, which, in turn, may offset the benefit in reducing the risk of stroke (Table 2.5) [1, 2].

Whatever combination of antithrombotic agents is chosen, that is, either TT or DT, dabigatran (or other NOACs) can be restarted soon after PCI with stent implantation has been completed, given the short time to the onset of the pharmacological effect (i.e., a few hours) of dabigatran (and other NOACs) (Table 2.3) [3]. The dose of dabigatran (and other NOACs) should generally be reduced to the lower tested in clinical trials [1–3]. Either when evaluated prospectively or adjusted according to the characteristics of the patients, the reduced NOAC doses appeared consistently safer than warfarin, with no substantial reduction in efficacy (Table 2.10) [27–30].

Regarding the antiplatelet therapy to be combined with dabigatran (or other NOACs), DAPT of aspirin and clopidogrel should generally be given (Table 2.2) [1–3]. Both data from clinical trials comparing clopidogrel to newer agents prasugrel and ticagrelor, albeit in the specific context of acute coronary syndrome [36, 37], and small data from a single-center cohort where prasugrel was used instead of clopidogrel in combination with OAC with VKA and aspirin show that the risk of bleeding may largely be increased. In patients also on VKA, such increase in bleeding appears not accompanied by any substantial advantage in preventing MACEs, stent thrombosis, and stroke [38]. Whether, on the other hand, combination with OAC and single antiplatelet therapy with prasugrel or ticagrelor may have a favorable efficacy and safety profile is being investigated in clinical trials, including PIONEER AF-PCI with rivaroxaban [39] and RE-DUAL PCI with dabigatran [40]. Initial, observational, and very limited data in patients with acute coronary syndrome suggest, however, that this might possibly be a safe and effective option [41].

2.4.1 Post-procedural Management

- Following the procedure, dabigatran was restarted, at the reduced dose of 110 mg twice daily, the evening (i.e., about 6 h after) of the day of the procedure.
- DAPT of aspirin at the dose of 100 mg once daily and clopidogrel 75 mg once daily was confirmed.
- Pantoprazole 20 mg once daily was added for gastric protection.
- Remaining therapies, including carvedilol 6.25 mg twice daily, amlodipine 5 mg once daily, isosorbide mononitrate 20 mg three times daily, lisinopril 10 mg once daily, simvastatin 20 mg once daily, allopurinol 100 mg once daily, L-thyroxine 25 mcg once daily, metformin 850 mg twice daily, and insulin, were confirmed.

2.5 Medium- to Long-Term Issues

While having consistently been shown that TT is the most effective antithrombotic combination for the prevention of MACEs, stent thrombosis, and (especially) stroke, this comes at the price of an increased incidence of total/major bleeding (approximately 2.5-fold that of either DAPT or OAC alone) [1, 2, 23, 31]. Even though such finding appears not to unbalance the favorable benefit-to-risk ratio of TT, the increased risk of bleeding requires nonetheless the careful implementation of measure aiming to reduce bleeding (Table 2.11). These should include the shortest possible duration of TT (given that the risk of bleeding apparently increases with the prolongation of the exposure), the reduction of the intensity of OAC (given the superior safety of both an international normalized ratio [INR] of 2.0–2.5 and of the lower dose of NOAC), and the extensive use of proton pump inhibitors (PPIs) [1–3, 23] (Table 2.11). All the above measures are of special importance in the presence of an increased risk of bleeding, as expressed by a HAS-BLED score ≥ 3 (Table 2.9) [22], which per se, however, should not be a reason to withhold TT [42]. The dose reduction might be especially appropriate for dabigatran and rivaroxaban, which at the higher dose may increase the risk of gastrointestinal bleeding (Table 2.11).

Table 2.11 Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

Issue	Recommendations
Initial antithrombotic treatment	Triple therapy (NOAC + aspirin ^{a,b} + clopidogrel)
Duration of triple therapy	BMS in elective setting: 1 month DES in elective setting: 3–6 months ^c Either BMS or DES in ACS setting: 3–6 months ^d
Intensity of OAC throughout triple therapy	Reduced ^e
Special care throughout triple therapy	Frequent laboratory monitoring (CrCl, CBC, Hgb) ^f Routine gastric protection ^g
Subsequent antithrombotic treatment ^h	NOAC ⁱ + clopidogrel (or ASA) ^j

PCI percutaneous coronary intervention, NOAC non-vitamin K-antagonist oral anticoagulant, BMS bare-metal stent, DES drug-eluting stent, ACS acute coronary syndrome, OAC oral anticoagulation, CrCl creatinine clearance, CBC complete blood count, Hgb hemoglobin, ASA aspirin, PPI proton-pump inhibitors, BID twice daily, OD once daily, TT triple therapy

^a75–100 mg once daily

^bMay be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

^cOne month only may be considered when the risk of bleeding is high, and new-generation DES has been implanted

^dOne month only may be considered when the risk of bleeding is high, and either a BMS or a new-generation DES has been implanted

^eLower dose of NOAC: dabigatran 110 mg BID, rivaroxaban 15 mg OD, and apixaban 2.5 mg BID (and, possibly, edoxaban 30 mg OD)

^fEvery two weeks

^gPreferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

^hAfter the initial course of 1 to 3–6 months of TT has been completed

ⁱLow-dose NOAC (dabigatran 110 mg BID, rivaroxaban 15 mg OD, and apixaban 2.5 mg BID (and edoxaban 30 mg BID) should likely be maintained to keep minimizing the risk of bleeding)

^jDepending on the individual risk of bleeding, especially gastrointestinal, and stent thrombosis

The duration of TT, namely, clopidogrel, after PCI with stent implantation in the context of stable CAD is driven by the type of stent (i.e., BMS or DES) implanted [3, 10] (Table 2.11) (Fig. 2.4). Thus, either after 1 or 6 months, respectively, clopidogrel or aspirin (preferably) should be interrupted, and a single antiplatelet agent only continued in conjunction with OAC (Table 2.11) [1–3, 23].

Throughout such combination therapy, the ongoing reduced-dose dabigatran (or other NOACs) should generally be maintained in order to minimize the risk of bleeding (which is approximately 1.6-fold higher compared to OAC alone). In the absence of conditions increasing the risk of bleeding, such as moderate renal insufficiency (i.e., creatinine clearance 30–50 ml/min), low body weight (i.e., <60 kg), and advanced age (i.e., >80 years) alone or in combination, the full dose of rivaroxaban and apixaban should be reinstituted instead, given the uncertain efficacy of the lower dose in patients without the above characteristics [2]. Renal function should be periodically (i.e., every 1–3 months) checked during combined therapy with dabigatran (or other NOACs) and antiplatelet agents [1–3].

Because most of bleeding events in patients on TT occur from the gastrointestinal tract, extensive use of gastric protection, preferably with PPIs not interfering with the metabolism of clopidogrel (e.g., pantoprazole), is generally warranted during combined OAC and antiplatelet therapy [1–3]. This is especially true when TT includes a NOAC as the anticoagulant, given the consistent increase in gastrointestinal bleeding compared to warfarin reported with these agents [43].

2.5.1 Medium- to Long-Term Management

- The patient was discharged with the recommendations to (a) continue TT of dabigatran 110 mg twice daily and DAPT for 1 month and then withdraw aspirin while continuing clopidogrel 75 mg once daily up to 12 months in combination with dabigatran 110 mg twice daily; (b) continue gastric protection with pantoprazole 20 mg once daily for 12 months (as long as combination therapy of dabigatran and DAPT or single antiplatelet therapy was ongoing); and (c) check renal function (i.e., creatinine clearance) periodically, the first time after 2 weeks from discharge.

2.6 Long-Term Issues

After 1 year from the index procedure and in the absence of further cardiac events, ongoing single antiplatelet therapy should generally be interrupted, and dabigatran (or other NOACs) only continued lifelong (Table 2.12) [1–3] (Fig. 2.4). Although data on effective secondary prevention after an acute coronary syndrome were reported with VKAs [44, 45] and specific evidence with NOACs is currently lacking, there appears no reason why these agents would not be effective in such regard.

Table 2.12 Long-term (i.e., >12 months after PCI, in the absence of recurrent events) management recommendations

Issue	Recommendation
Antithrombotic treatment	NOAC monotherapy ^a
Intensity of OAC	Standard ^b

PCI percutaneous coronary intervention, *NOAC* non-vitamin K-antagonist oral anticoagulant, *ASA* aspirin, *BID* twice daily, *OD* once daily *OAC* oral anticoagulation

^aIndefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal, and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low

^bThat is, dabigatran 150 mg BID, rivaroxaban 20 mg OD, apixaban 5 mg BID, and edoxaban 60 mg BID, unless other indications for reduced dose are present *CAD* coronary artery disease

In the presence, however, of high risk of recurrent cardiac events, such as in patients with a history of stent thrombosis or with diffuse coronary artery disease, especially if not amenable of revascularization and associated with diabetes, or in conditions where stent thrombosis might have catastrophic consequence, such as in left main or last remaining vessel stenting, combination of dabigatran (or other NOACs) and single antiplatelet therapy may be continued long term [1–3]. Albeit in the different contexts of patients with no indication for OAC, long-term combination therapy of OAC and single antiplatelet appears, however, associated with a relevant incidence of bleeding, without apparent benefit on MACEs [46] and therefore should not be considered routinely [1–3].

Unless reasons for keeping the lower dose of dabigatran (or other NOACs) are present, initial full dose of the drug should be resumed and the management of OAC carried out as per usual recommendations (Table 2.12) [1–3].

2.6.1 Long-Term Management

- Upon completion of the 1-year combined therapy of OAC and DAPT or single antiplatelet therapy, ongoing clopidogrel 75 m once daily was discontinued and dabigatran, after increasing of the dose to the initial 150 mg twice daily (given that conditions mandating the use of low dose, including age ≥80 years and/or concomitant use of P-glycoprotein inhibitors, like verapamil, amiodarone, or quinidine, were not present), prescribed lifelong.

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