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# The Role of Novel Oral Anticoagulants and Antiplatelet Therapy after Percutaneous Coronary Intervention: Individualizing Therapy to Optimize Outcomes

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## ABSTRACT

The number of patients undergoing percutaneous coronary intervention (PCI) who mandate additional oral anticoagulant therapy has been increasing. Dual antiplatelet therapy (DAPT) is associated with reduced ischemic events including stent thrombosis, myocardial infarction and stroke following PCI. However, the tradeoff is an increased risk for bleeding while on DAPT. The addition of a novel oral anticoagulant (NOAC) further increases the likelihood of bleeding while on antiplatelet therapy. Thus, the overall risks and benefits for each patient undergoing PCI on NOAC must be assessed and therapy individualized to ensure optimal therapy for each unique situation. Patients on NOAC undergoing PCI should undergo routine assessment with intravascular imaging as the role of high-risk lesion-related features have increased importance prior to determining optimal duration of treatment with DAPT. We review the best practices for the pharmacologic management of patients requiring anticoagulation with NOAC who are treated with PCI and require antiplatelet therapy.

**Keywords:** Antiplatelet therapy; Oral anticoagulant; Non-vitamin K antagonist oral anticoagulants; Percutaneous coronary intervention

## INTRODUCTION

Contemporary percutaneous coronary intervention (PCI) involves placement of a stent in the vast majority of cases. This necessitates pharmacotherapy with dual antiplatelet therapy (DAPT) following stent implantation. The number of patients undergoing PCI who mandate additional oral anticoagulant therapy following stent implantation has been on the rise. The addition of oral anticoagulation often requires modification of the antiplatelet regimen to optimize patient outcomes by balancing the risk of bleeding with the risk for ischemic events. We herein review the current best practices for the pharmacologic management of patients requiring anticoagulation with novel oral anticoagulants (NOAC) who are treated with PCI.

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## POPULATION OF INTEREST

The use of NOAC in patients treated with PCI comprise several indications and occurs in approximately 7% of all procedures.[1] The most commonly encountered indication for anticoagulation is for the prevention of stroke in the setting of atrial fibrillation (AF) with an elevated $CHA_2DS_2$-VASc score. In 2010, AF affected over 6 million Americans, with estimates predicting that by 2050, over 12 million adults in the United States will have AF.[2][3] Encounters for patients on NOAC in the cardiac catheterization laboratory also occur in patients requiring treatment and prevention of venous thromboembolism including deep vein thrombosis and pulmonary embolism. Off-label use of NOAC also has been reported for the treatment of patients with left ventricular thrombus and for prophylaxis in patients with hereditary hypercoagulable disorders.[4][5]

## NOVEL ORAL ANTICOAGULANTS

NOAC has become widely adopted since initial approval. They represent a class of drugs that have two unique mechanisms of action; both directly inhibit a single coagulation factor with the distinction between individual types of agents occurring based on the coagulation factor that is inhibited. Apixaban, edoxaban and rivaroxaban each inhibit factor Xa, whereas the direct thrombin inhibitor dabigatran inhibits factor IIa (thrombin).

An overview of the pivotal NOAC trials in patients with non-valvular AF are summarized in **Table 1**. In the Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) trial, dabigatran was compared to warfarin in 18,113 patients with results first published in 2009.[6] In 2011, results were published from the pivotal Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF (ROCKET-AF) trial of 14,246 patients comparing rivaroxaban to warfarin.[7] The Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) trial compared apixaban to warfarin and assessed outcomes in 18,201 patients.[8] Effective Anticoagulation with Factor Xa Next Generation in AF (ENGAGE-AF) compared edoxaban to warfarin in 21,105 patients with results reported in 2013.[9]

The introduction and rise of NOAC were in response to numerous limitations and challenges with the pre-existing therapy of vitamin K antagonists (VKA), which requires frequent monitoring and has numerous drug and dietary interactions. NOAC provides a potent and

**Table 1.** Pivotal randomized trials comparing NOAC's with warfarin for patients with non-valvular atrial fibrillation

| Trial | Study drug | No. | Mean $CHA_2DS_2$-VASc score | Outcome |
|---|---|---|---|---|
| RE-LY[6] | Dabigatran | 18,113 | 2.2 | Lower rates of stroke and systemic embolism with dabigatran but similar rates of major hemorrhage |
| ROCKET AF[7] | Rivaroxaban | 14,246 | 3.5 | Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism<br>There was no difference in the risk of major bleeding; intracranial and fatal bleeding however occurred less frequently in the rivaroxaban group |
| ARISTOTLE[8] | Apixaban | 18,201 | 2.1 | Apixaban was superior to warfarin in preventing stroke or systemic embolism, and caused less bleeding and was associated with lower mortality |
| ENGAGE AF[9] | Edoxaban | 21,105 | 2.8 | Edoxaban was noninferior to warfarin with respect to the prevention of stroke or systemic embolism and was associated with lower rates of bleeding and death from cardiovascular causes |

ARISTOTLE = apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation; ENGAGE AF= effective anticoagulation with factor Xa next generation in atrial fibrillation; NOAC = novel oral anticoagulants; RE-LY= Randomized Evaluation of Long-term anticoagulant therapY; ROCKET AF = rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation.


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a predictable therapeutic effect with comparatively minimal routine laboratory monitoring required. The class of drugs that comprise NOAC has been alternatively termed direct oral anticoagulants as well as a number of other acronyms including target-specific oral anticoagulants, oral direct inhibitors, non-VKA oral anticoagulants, and specific oral direct anticoagulants. Despite the numerous acronyms proposed, NOAC is the acronym that has been favored in society guideline statements.[10)11)]

## HIGH-BLEEDING RISK

While triple therapy with a NOAC and DAPT offers efficacy in the reduction of ischemic events, this combination comes at the risk of increased bleeding. A number of clinical features contribute to increased bleeding risk. The use of triple therapy on its own increases the risk of bleeding, and the duration of triple therapy should be minimized whenever possible. Prior history of bleeding, age ≥75 years, heart failure, stroke, abnormal kidney or liver function, chronic steroid use, alcohol abuse and malignancy all predispose patients to an increased bleeding risk and should all be considered for individualized tailoring of the optimal treatment regimen. Additionally, gender, body mass and ethnic differences can impact the risk for bleeding on NOAC therapy and may impact the appropriate dose selection.[12-14)]

Multiple risk prediction scores have been introduced to assist in the assessment and stratification of bleeding risk. The hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) score is among the most commonly used scores for bleeding risk stratification and is used to assess bleeding risk in patients with AF. A patient with a HAS-BLED score ≥3 is considered to be at high-risk for bleeding.[15)] The use of the HAS-BLED score specifically for patients on concomitant DAPT however has not been validated. The PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent (PRECISE)-DAPT score was introduced to assess bleeding risk for patients on DAPT. A longer duration of DAPT is associated with significantly increased bleeding in patients at high PRECISE-DAPT risk (score≥25).[16)] Data support an ischemic benefit of DAPT only in patients with a PRECISE-DAPT score <25.[16)] Both bleeding risk prediction models have utility for predicting future significant bleeding events in patients taking an oral anticoagulants (OAC) and undergoing PCI.[17)]

## BLEEDING AFTER STENT IMPLANTATION

The risk of bleeding in patients on DAPT following PCI remains low but can be significant when it occurs. Approximately 4.8% of patients following discharge for PCI required bleeding-related readmission in a large analysis from the HMO Research Network-Stent (HMORN-Stent) Registry.[18)] In the Assessment of DAPT with Drug-Eluting Stents (ADAPT-DES) study, post-discharge bleeding occurred in 6.2% of patients following PCI.[19)] Significant bleeding following PCI is associated with worse long-term clinical outcomes including increased mortality.[1)18)20)] Important racial differences may impact the risk for bleeding with DAPT. In a landmark meta-analysis of 7 randomized controlled trials with patient-level data for 16,518 patients with varying durations of DAPT following PCI, East Asians had a higher probability of bleeding versus ischemia when compared with non-East Asians.[14)]


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## PATIENT-RELATED RISK OF ISCHEMIA

Patient-related risk factors may predispose to major adverse cardiac ischemic events following PCI. One of the most critical factors contributing to the necessary minimum duration of DAPT and the risk of future ischemic events includes the clinical presentation that necessitated the PCI. Patients presenting with ST-elevation-myocardial infarction (MI) and acute coronary syndrome typically require DAPT of at least 1 year, whereas PCI for stable angina can often be safely managed with DAPT for at least 6 months.

## LESION-RELATED ISCHEMIC RISK

It has been standard practice to include patient-level risk for bleeding in the equation of decision making for optimal pharmacotherapy regimen. However, it is equally important to weigh the risk for ischemic events not just on patient-level risk factors such as diabetes, chronic kidney disease and prior stent thrombosis, but also for lesion specific risk factors including the anatomical location of the stent, number of stents implanted, total stent length, lesion complexity and procedural outcome (**Figure 1**).

While in 1 analysis of 6 randomized controlled trials, reference vessel diameter was the only predictor of target lesion failure, there are several other high-risk lesion-related features which have been associated with worse clinical outcomes.[21] Stent underexpansion, edge dissection and residual reference segment disease play a significant role in the occurrence of future ischemic events including stent thrombosis.[22] Identification of these risk factors is essential to appropriately tailor the optimal duration of DAPT. These features are best identified by intravascular imaging, highlighting its importance in any patient being considered for early termination of DAPT.[23]

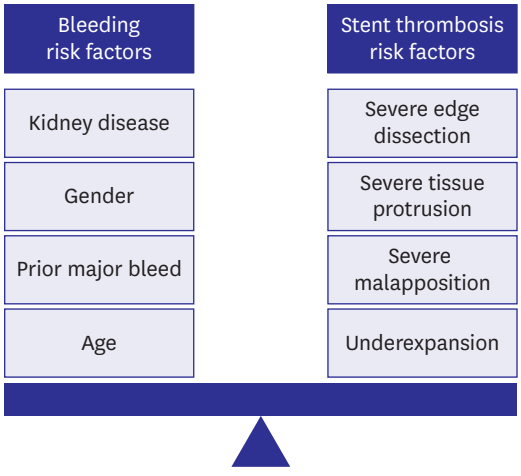


**Figure 1.** Risk-benefit assessment for individualized approach to pharmacotherapy following PCI.
PCI = percutaneous coronary intervention.


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## STENT SELECTION

There is wide variation in practice patterns for antiplatelet therapy and stent selection for PCI in patients treated with NOAC's. In a survey of 38 European centers in 2015, just 12% preferentially prescribed NOAC in patients with non-valvular AF undergoing PCI.[24] Furthermore, in elective PCI for patients with non-valvular AF and high bleeding risk, the majority of respondents favored bare-metal stents (BMS) for stent implantation.

In the Polyzene-F (PzF) SHIELD trial, the novel cobalt-chromium coronary stent with specialized PzF coating (COBRA PzF coronary stent; CeleNova Biosciences, San Antonio, TX, USA) is associated with favorable target vessel failure at 9-months following 1 month of DAPT with no stent thrombosis.[25] In the ongoing COBRA REDUCE trial, 996 patients with high bleeding risk are being randomized to commercially approved DES with 3 or 6 months of DAPT or PCI with COBRA PzF and 14 days of DAPT (NCT02594501).

In the SENIOR trial, 1,200 elderly patients age ≥75 years were randomized to bioresorbable polymer DES or BMS. In patients with a similar duration of DAPT, DES reduced the occurrence of major adverse cardiac events suggesting even in patients with a high bleeding risk, there is limited benefit with BMS.[26]

The common practice is to use BMS to be used for patients requiring long-term systemic anticoagulation. Currently, it is believed that in patients at high-risk of bleeding, the duration of DAPT necessary with contemporary DES is short enough so that DES may be used as the primary stent almost universally. This is supported by the 2018 European Society of Cardiology (ESC) and the European Association of Cardiovascular Surgery guidelines on myocardial revascularization which recommend that new-generation DES should "be considered as the default stent type for PCI regardless of clinical presentation, lesion subtype, concomitant therapies, or comorbidities" (class I, level of evidence A).[27]

While bioresorbable vascular scaffolds (BVS) and drug-coated balloons (DCB) offer potential future alternatives to the implantation of DES in patients at high-risk for bleeding to minimize necessary post-procedural DAPT, the present data are not sufficient to support routine use of BVS or DCB in favor of DES.

## DURATION OF DUAL ANTIPLATELET THERAPY

There is wide variation in the duration of required DAPT based on a number of features that include balancing patient risk of bleeding and ischemic events, lesion-related risk of ischemic events, and stent type. Additionally, significant variation in practice patterns exist worldwide. The duration for DAPT can be as short as 2 weeks following stent implantation, as is the case with stents such as the COBRA PzF, ranging to as long as lifelong DAPT in patients in whom have had vascular brachytherapy. The risk of ischemic events following stent implantation is highest immediately after PCI and in the initial weeks afterward. However, the risk of bleeding related to DAPT remains relatively constant with time. Therefore, minimizing DAPT duration has advantages following the initial post-PCI period. Data supporting shorter duration of DAPT (≤6 months) have been increasing.[28] Initial results of the short and optimal duration of DAPT after everolimus-eluting cobalt-chromium stent-2 (STOPDAPT-2) trial suggests that 1-month of DAPT was noninferior to 12-months of DAPT at preventing


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major adverse ischemic events and superior to 12-months of DAPT at preventing significant bleeding.[29] Notably, in STOPDAPT-2 intravascular imaging was used almost universally in this randomized clinical trial of 3,045 patients.

The GLOBAL LEADERS randomized trial assessed the impact of discontinuation of aspirin after 1-month following PCI, followed by antiplatelet monotherapy with ticagrelor compared with standard DAPT in 15,991 patients. The investigators reported the experimental single antiplatelet therapy arm with ticagrelor alone failed to show superiority for the primary endpoint at 2-year follow-up.[30] While failing to demonstrate superiority for its primary endpoint, the GLOBAL LEADERS study demonstrated the feasibility and safety of an early discontinuation of aspirin strategy following PCI, ushering in the way for future studies. This will also be investigated in the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial (NCT02270242) of approximately 9,000 randomized patients comparing the use of ticagrelor alone versus ticagrelor and aspirin together. The impact of these various antiplatelet regimens on bleeding and ischemic events at 1-year will be reported. Prolonged DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care however due to the increased risk of MI with 6-month DAPT based on data from the SMART-DATE randomized trial of 2,712 patients in Korea.[31]

Numerous ongoing pivotal trials are assessing the role of short DAPT therapy following DES implantation that will inform optimal practice. In the XIENCE 90 study the safety of 3-month DAPT in approximately 2,000 patients at high-risk of bleeding is being evaluated (NCT03218787). The XIENCE 28 global study will evaluate the safety of 1-month DAPT in 960 high bleeding risk patients (NCT03355742). Similarly, the Onyx ONE Clear trial is evaluating 1 month of DAPT treatment following stent implantation in 800 high bleeding risk patients (NCT03647475). There is growing evidence that DAPT is required for increasingly shorter periods with contemporary DES, and numerous clinical trials are assessing the impact of shorter durations of therapy.

## ANTIPLATELET AGENT

Aspirin dosing should be low-dose only (≤100 mg daily) for all patients on aspirin therapy following PCI.[32] Significant variation exists in platelet reactivity for patients on clopidogrel. Nearly one-third of patients on clopidogrel have high on-treatment platelet reactivity (HTPR) predisposing them to increased ischemic events.[33-35] Due to low clinical event rates in the Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety (GRAVITAS) trial, routine platelet function testing fell out of favor.[36][37] This however may have increased importance when considering discontinuation of aspirin and using monotherapy with clopidogrel.

In the Evaluation of Platelet Inhibition in Patients Having A VerifyNow Assay (EPIPHANY) trial, patients undergoing PCI on maintenance DAPT had platelet function assessed with VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) at the time of PCI. Patients not on prior thienopyridine therapy were randomized to clopidogrel or prasugrel and underwent P2Y12 platelet function testing. HTPR with P2Y12 reaction units >230 occurred in 51% of patients on maintenance clopidogrel (n=192), and 37% of patients that were randomized to be loaded with clopidogrel (n=90).[38] The EPIPHANY trial highlights the frequency of

HTPR in patients treated with PCI, suggesting routine screening in patients who are to be considered for antiplatelet monotherapy with clopidogrel alone. Furthermore, the EPIPHANY trial supports the role of prasugrel in clopidogrel non-responders.[38)39)]

There are important ethnic variations in response to antiplatelet agents. In Korean patients presenting with acute coronary syndrome, a prospective, observational study of 4,421 patients from the Korea Acute MI Registry-National Institute of Health, found that after propensity score matching, there was significantly higher in-hospital bleeding complications without a reduction in ischemic events with prasugrel compared with clopidogrel.[40)] Antiplatelet therapy in a Korean population with potent antiplatelet agents may still be safe, however may require dose adjustment. In the PRASugrel compared to clopidogrel For Japanese PatIenTs with ACS undergoing PCI (PRASFIT-ACS) study, reduced dosages of prasugrel was associated with lower ischemic events without increased bleeding complications compared to clopidogrel.[41)] The ethnic variation observed with antiplatelet agents highlights that a universal recommendation has significant limitations, and optimal treatment regimens should be individualized based on the best available data and patient specific factors.

## CLINICAL EVIDENCE

The PIONEER AF-PCI trial and the RE-DUAL trial both compared a NOAC plus single antiplatelet therapy with triple therapy with a VKA plus DAPT. Both pivotal trials reported significantly lower bleeding with the dual antithrombotic regimen compared with triple therapy.[42-44)] In the RE-DUAL trial, dabigatran compared to triple therapy with VKA in 2,725 randomized patients was associated with a significant reduction of bleeding events at both 150 mg and 110 mg twice daily dosing with dabigatran.[42)43)] Due to a concern for potential increased risk for ischemic events with the lower dabigatran dose (110 mg twice daily),150 mg twice daily dosing with dabigatran is preferred with single antiplatelet therapy. The PIONEER AF-PCI trial randomized 2,124 patients with nonvalvular AF treated with PCI to receive 1 of 3 treatment strategies of antiplatelet therapy and OAC. The investigators reported that the use of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT was associated with lower clinically significant bleeding compared with VKA plus DAPT.[44)]

The AUGUSTUS trial reported the impact of apixaban with and without aspirin in 4,614 patients with AF and an acute coronary syndrome or PCI. The use of a P2Y12 inhibitor and apixaban without aspirin resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events compared with drug regimens that included a vitamin K antagonist, aspirin, or both.[45)] Edoxaban is currently being studied as part of a triple therapy regimen in the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With AF Undergoing PCI (ENTRUST-AF) trial (NCT02866175).

## ROLE OF INTRAVASCULAR IMAGING WITH PERCUTANEOUS CORONARY INTERVENTION

Studies assessing the impact of intravascular ultrasound (IVUS) on clinical outcomes following PCI have consistently demonstrated significant benefit and a reduction in events with intravascular imaging.[46-49)] Ischemic events following PCI can be minimized with intravascular imaging, potentially reducing the likelihood of negative impact from interruption in DAPT.


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Intravascular imaging with either IVUS or optical coherence tomography offers potential benefit in this patient population both pre- and post- stent implantation. Pre-PCI intravascular imaging is useful for stent sizing and the determination for need for lesion preparation to ensure maximal stent expansion.[50)51)] Post-PCI intravascular imaging can exclude complications pre-disposing to ischemic events that may be otherwise not appreciated by angiography alone including significant edge dissection, stent underexpansion, and residual disease.[52-56)] In patients in whom a short duration of DAPT is being considered, it is increasingly important for procedural optimization with intravascular imaging with final assessment.

## GUIDELINE RECOMMENDATIONS

The 2016 American College of Cardiology/American Heart Association (ACC/AHA) focused update on duration of DAPT in patients with coronary artery disease guideline recommendations for patients at high bleeding risk treated with PCI supports clopidogrel as the P2Y12 inhibitor of choice in patients on OAC therapy.[57)] The duration of DAPT recommended by the ACC/AHA guidelines is based on the indication for PCI. In patients with stable coronary artery disease, discontinuation of the P2Y12 inhibitor at 3-months is recommended, whereas for patients treated for acute coronary syndrome, P2Y12 inhibitors should be continued for at least 6 months.[57)]

The 2018 ESC guidelines similarly recommend clopidogrel as the P2Y12 inhibitor of choice, with low dose (≤100 mg daily) aspirin, however recommend keeping the duration of triple therapy as short as possible.[27)] ESC guidelines recommend triple therapy with aspirin, clopidogrel and OAC for 1 month, and up to 6 months in patients at higher ischemic risk due to acute coronary syndrome or procedural characteristics that outweigh bleeding risk (class IIa, level of evidence B).[27)] When a NOAC is added to either aspirin or clopidogrel, the lowest approved effective dose for stroke prevention tested in AF trials should be considered (class IIa, level of evidence C).[27)] The ESC cautions that the use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC (class III, level of evidence C).[27)]

## ALGORITHMIC APPROACH

Our recommendation based on current evidenced-based medicine, best practices, clinical experience and available pharmacologic therapies is summarized in **Figure 2**. Prognosis is worse in those experiencing an adverse event whether it is an ischemic or bleeding event following PCI, so efforts are needed to balance these competing risks.[58)] Aspirin therapy should be limited to low-dose aspirin, and DES should be used as the default choice of stent. NOAC's offer significant advantages to VKA including less drug and dietary interactions, less routine monitoring of blood work, and greater time in therapeutic range. Potent thienopyridine therapy should be used following stent implantation in the absence of routine P2Y12 testing prior to initiating antiplatelet monotherapy.

## CONCLUSION

DAPT is associated with reduced ischemic events including stent thrombosis, MI and stroke. The tradeoff however is an increased risk for bleeding on DAPT. The addition of a NOAC


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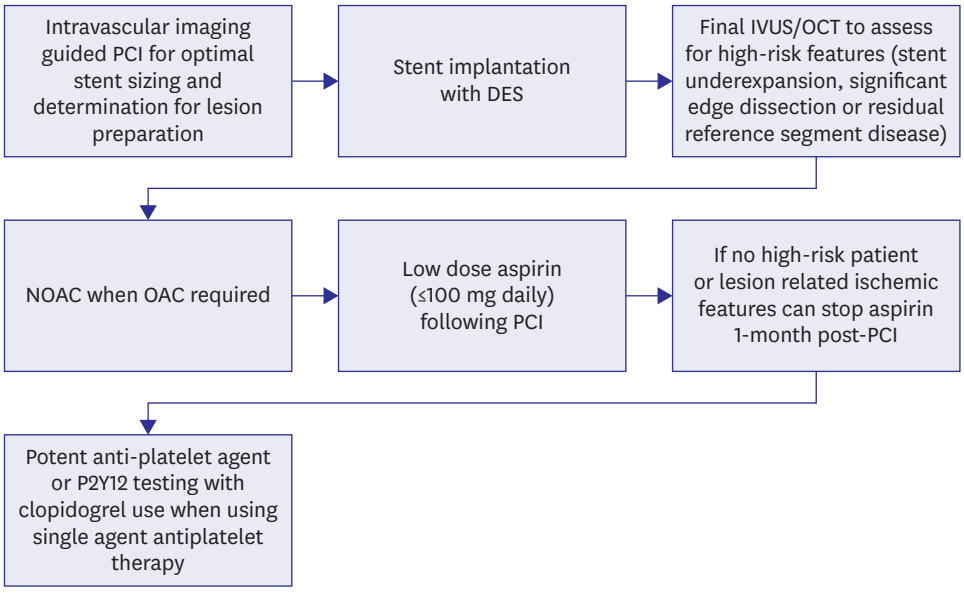


**Figure 2.** Approach to patients requiring PCI on oral anticoagulant therapy.
DAPT = dual antiplatelet therapy; DES = drug-eluting stent; IVUS = intravascular ultrasound; NOAC = novel oral anticoagulant; OAC = oral anticoagulant; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

further increases the likelihood of bleeding while on antiplatelet therapy. Thus, the overall risks and benefits for each patient undergoing PCI on NOAC's must be assessed and therapy individualized to ensure optimal therapy for each unique clinical situation.

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