REVIEW ARTICLE

Antithrombotic therapy in anticoagulated patients with atrial fibrillation presenting with acute coronary syndromes and/or undergoing percutaneous coronary intervention/stenting

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KEY WORDS

anticoagulation, atrial fibrillation, percutaneous coronary intervention, stenting

ABSTRACT

The management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting cannot be done according to a regimented common protocol, and stroke and bleeding risk stratification schema should be employed to individualize treatment options. A delicate balance is needed between the prevention of thromboembolism, against recurrent cardiac ischemia or stent thrombosis, and bleeding risk. New guidance from a consensus document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions on the management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting with Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary Intervention/Stenting has sought to clarify some of the major issues and problems surrounding this practice, and will allow clinicians to make much more informed decisions when faced with treating such patients.

Patients with atrial fibrillation (AF) and a moderate-high risk of thromboembolism are currently recommended long-term oral anticoagulation (OAC), which is usually in the form of the vitamin K antagonist warfarin.[1] Balancing the risk of bleeding and thromboembolism is crucial in the management of patients with AF, and this is never more apparent than when such AF patients require percutaneous coronary intervention (PCI). Coronary artery disease coexists in 20% to 30% of patients with AF, and it follows that many will require PCI at some stage.[2] The periprocedural management of anticoagulated patients is very important, but clinical practice varies widely between clinicians, hospitals, and countries, driven by a lack of data on which to draw guidance. Arguably, the 3 key issues appear to be whether or not to interrupt OAC for the procedure, how best to modify the procedure to ensure optimal safety, and finally, the choice of long-term antithrombotic therapy that follows PCI.

The much anticipated consensus document on this topic, from the European Society of Cardiology (ESC) Working Group on Thrombosis, endorsed by the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions, has been recently published and offers much needed direction.[3] Whilst acknowledging the relative lack of high-quality studies in this field, the document summarizes the most contemporary evidence based upon a systematic review of 18 studies and 3500 patients. The document offers practical recommendations for performing PCI in patients with AF requiring OAC, and these can be largely subdivided into what happens before, during, and after PCI.

The first key decision is whether to interrupt OAC before the procedure. This strategy exposes

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TABLE Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thromboembolic risk (in whom oral anticoagulation therapy is required)[3]

Hemorrhagic risk	Clinical setting	Stent implanted	Recommendations
low or intermediate	elective	BMS	**1 month:** triple therapy of warfarin (INR 2.0–2.5) + ASA ≤100 mg/day + clopidogrel 75 mg/day + gastric protection **lifelong:** warfarin (INR 2.0–3.0) alone
	elective	DES	**3 (-olimus group) to 6 (paclitaxel) months:** triple therapy of warfarin (INR 2.0–2.5) + ASA ≤100 mg/day + clopidogrel 75 mg/day **up to 12th month:** combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day[a] or ASA (100 mg/day) **lifelong:** warfarin (INR 2.0–3.0) alone
	ACS	BMS/DES	**6 months:** triple therapy of warfarin (INR 2.0–2.5) + ASA ≤100 mg/day + clopidogrel 75 mg/day **up to 12th month:** combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day[a] or ASA (100 mg/day) **lifelong:** warfarin (INR 2.0–3.0) alone
high	elective	BMS[b]	**2 to 4 weeks:** triple therapy of warfarin (INR 2.0–2.5) + ASA -100 mg/day + clopidogrel 75 mg/day **lifelong:** warfarin (INR 2.0–3.0) alone
	ACS	BMS[b]	**4 weeks:** triple therapy of warfarin (INR 2.0–2.5) + ASA ≤100 mg/day + clopidogrel 75 mg/day **up to 12th month:** combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day[a] or ASA (100 mg/day) **lifelong:** warfarin (INR 2.0–3.0) alone

a combination of warfarin (INR 2.0–3.0) + ASA = 100 mg/day (with PPI, if indicated) may be considered as an alternative
b DES should be avoided

Abbreviations: ACS – acute coronary syndrome, ASA – acetylsalicylic acid, BMS – bare-metal stents, DES – drug-eluting stents, INR – international normalized ratio, PPI – proton pump inhibitor

patients to the risks of thromboembolism and re-initiation may produce a temporary prothrombotic state due to protein C and S suppression.[4] Common practice is to offer "bridging" with either unfractionated or low-molecular-weight heparin, but this is not supported by any results from large randomized trials, and there are some suggestions that this increases the risks of periprocedural bleeding.[5] Until recently, concerns over increased bleeding from uninterrupted OAC have largely precluded this strategy for many clinicians, but recent findings suggest that in some circumstances, this is at least as safe as a strategy of interruption with heparin bridging, especially in patients who are deemed at high risk of thromboembolic complications.[3] Recognizing this, the consensus document highlights this as an alternative to interrupting OAC, especially in elective PCI. For patients admitted with acute coronary syndrome, the risk of bleeding vs. thromboembolism becomes more complex, as these patients often require bivalirudin (a direct thrombin inhibitor) or glycoprotein IIb/IIIa inhibitors (GPI). The consensus document suggests stopping the OAC on admission in this circumstance. Exception to this may be patients at a very high risk of thromboembolism, such as those with mechanical mitral valves or recurrent venous thromboembolism, where uninterrupted OAC may be preferable to the potential risk of bleeding with interruption and heparin bridging.

The procedure itself often requires modification in this patient group, especially if OAC is uninterrupted. The consensus document highlights a key role for radial access where possible, recognizing that the majority of major bleeds are related to the access site.[6] This is particularly relevant for patients undergoing primary PCI for acute myocardial infarction, where international normalized ratios (INRs) are often unknown and patients may require bivalirudin or a GPI. In PCI procedures where patients have an INR >2, these adjunctive anticoagulants should be used with caution, due to the increased risk of major bleeding.[7,8] Likewise, any periprocedural heparin dose should be adjusted to achieve a low-therapeutic activated clotting time.[3] The choice of stent should also be considered carefully for patients who are on long-term OAC, as they will require additional dual antiplatelet therapy (DAPT) for a duration that is dependent upon the choice of stent.[9] When drug-eluting stents (DES) are used, DAPT is often required for at least 3 months with a "-limus" DES, and for at least 6 months with a paclitaxel DES3, although some would advocate at least 12 months for both. This compares to the recommended 1-month DAPT duration with a bare-metal stent (BMS). DES should therefore be used as sparingly as possible, and reserved for circumstances where there is clear benefit, such as long lesion length and in patients with diabetes.

The choice of antithrombotic therapy following PCI is perhaps the most difficult decision for clinicians to make. Recommendations from the consensus document are shown in the TABLE. There is evidence that DAPT is superior

to the combination of acetylsalicylic acid (ASA) and warfarin in the prevention of stent thrombosis,[10] but OAC has clear superiority over DAPT in stroke prevention in patients with AF.[11] The major drawback from a triple therapy approach with DAPT and OAC arises from a 4.7% prevalence of major bleeding, most occurring within a month of PCI and half being fatal.[12] The consensus document has again reviewed the available data and concluded that in the absence of a very high bleeding risk, triple therapy should be considered for 1 month following BMS, and at least 6 months with DES. Subsequently, patients should continue on long-term OAC and clopidogrel (or alternatively, ASA plus gastric protection) for a year. In the absence of additional ischemia or an acute event by 12 months, OAC alone can be given long-term.

Despite the available guidance, one should recognize the paucity of randomized trials and the current dependence on small retrospective cohort analyses. The ongoing WOEST study is comparing triple therapy with a combination of warfarin plus clopidogrel in patients requiring OAC following PCI, and may further clarify the debate.[13] The development of novel antithrombotic agents is rapidly expanding, and in some respects, this may hinder attempts to form clear-cut guidelines for performing PCI for patients on OAC. Warfarin may well be superseded by the novel oral factor Xa inhibitors or direct thrombin inhibitors for patients with AF. These have the potential advantage of requiring no regular monitoring and having fewer drug and dietary interactions.[14,15] It is unclear, however, what implications this would have on bleeding and stent thrombosis when combined with DAPT. Furthermore, the constituents of DAPT are already changing, with the development of more potent antiplatelet agents such as prasugerel and ticagrelor. With this speed of change, it may ultimately be difficult to apply results from any randomized trials to contemporary clinical practice.

Performing PCI in patients who require OAC cannot be done according to a regimented common protocol, and stroke and bleeding risk stratification schema should be employed to individualize treatment options.[16,17] The guidance from the ESC consensus document has sought to clarify some of the major issues and problems surrounding this practice, and it will allow clinicians to make much more informed decisions when faced with treating such patients.[18,19]

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Terapia przeciwzakrzepowa u chorych z ostrymi zespołami wieńcowymi lub poddawanych przezskórnej interwencji wieńcowej/ stentowaniu tętnic wieńcowych leczonych przeciwkrzepliwie z powodu migotania przedsionków

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antykoagulacja, migotanie przedsionków, przezskórna interwencja wieńcowa, stentowanie

STRESZCZENIE

U pacjentów z migotaniem przedsionków, którzy zgłaszają się z powodu ostrych zespołów wieńcowych lub są poddawani przezskórnej interwencji wieńcowej/stentowaniu tętnic wieńcowych, nie można prowadzić terapii przeciwzakrzepowej z powodu migotania przedsionków według jednego wspólnego schematu. W celu zindywidualizowania leczenia trzeba uwzględnić ryzyko wystąpienia udaru mózgu oraz ryzyko powikłań krwotocznych. Należy uzyskać subtelną równowagę między zapobieganiem powikłaniom zakrzepowo-zatorowym, nawrotom niedokrwienia mięśnia sercowego lub wystąpieniu zakrzepicy w stencie a ryzykiem krwawienia.

W celu wyjaśnienia niektórych ważnych zagadnień i problemów związanych z tym postępowaniem opracowano wskazówki zawarte w uzgodnionym stanowisku European Society of Cardiology Working Group on Thrombosis poparte przez European Heart Rhythm Association i European Association of Percutaneous Cardiovascular Interventions. Pozwolą one lekarzom podejmować znacznie bardziej świadome decyzje podczas opieki nad takimi pacjentami.

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