Guidelines for mono, double and triple antithrombotic therapy

Renate C A E van Uden,1,2 Ilse Houtenbos,3 Anita Griffioen-Keijzer,3 Diego A M Odekerken,4 Patricia M L A van den Bemt,5 Matthijs L Becker 1,2

ABSTRACT
Guidelines for antithrombotic therapy are complex, especially if a patient has several indications that require antithrombotic therapy. In general, no patient should receive lifelong double or triple antithrombotic therapy. In this overview, we outline the most common indications for mono, double and triple antithrombotic therapy; the preferred antithrombotic therapy and the recommended duration of therapy. Both antiplatelet therapy and therapeutic anticoagulation therapy with vitamin K antagonists or direct oral anticoagulants were included. European guidelines were used or, if no European guidelines were available, the Dutch guidelines were used.

BACKGROUND OF THROMBOSIS
Formation of a thrombus is a complex physiological process caused by multiple factors. Three factors together known as Virchow’s triad are important in the pathophysiology of thrombosis: damage to the endothelial lining of the vessel wall, a hypercoagulable state and stasis of blood flow.

Venous thrombosis
Venous thrombi develop in veins, especially in areas with a diminished blood flow, for instance, around vein valves. These valves promote blood flow through the venous system, but are also a potential location for venous stasis. Venous thrombosis consists of fibrin and can cause venous thromboembolism, that is, deep venous thrombosis or a pulmonary embolism. Low-molecular-weight heparins (LMWHs), vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), are used for the prevention and treatment of venous thrombosis. VKAs and DOACs are part of the group of oral anticoagulants (OACs). LMWHs inhibit coagulant factor II and X and are mostly used temporarily, for instance, for bridging VKA therapy or as a temporary replacement for a VKA or DOAC. VKAs inhibit the carboxylation of vitamin K-dependent coagulation factors II, VII, IX and X in the liver and inhibit the coagulation process indirectly. The DOACs apixaban, edoxaban and rivaroxaban inhibit activated coagulation factor X. The inhibition of factor Xa interrupts the intrinsic and extrinsic routes of the coagulation cascade. The DOAC dabigatran inhibits activated factor II (thrombin) and prevents the conversion of fibrinogen to fibrin and prevents the formation of thrombi.

Arterial thrombosis
Plaque formation in the arterial wall is the initiating factor for the occurrence of arterial thrombosis. Arterial thrombi consist mostly of thrombocytes. Therefore, antiplatelet therapy is indicated for the prevention of arterial thrombosis. Acetylsalicylic acid (ASA) inhibits the synthesis of thromboxane A2, in thrombocytes by acetylating cyclooxygenase 1, thus inhibiting thrombocyte aggregation. Carbasalate calcium is the calcium salt of ASA and is not mentioned separately in this article. P2Y12 inhibitors such as clopidogrel, ticagrelor and prasugrel inhibit the P2Y12-ADP receptor on the surface of thrombocytes, causing the inhibition of thrombocyte aggregation.

It is important for healthcare providers to be familiar with the guidelines for antithrombotic therapy. This article aims to provide an overview of the indications for mono, double and triple antithrombotic therapy; the preferred antithrombotic therapy and the recommended duration of therapy. The guidelines for the non-acute treatment with antithrombotics are presented. With the information in this overview, healthcare providers can assess whether the prescribed antithrombotic therapy for a patient is adequate or whether the medication should be adjusted.
The bleeding risk in patients at the time of percutaneous coronary intervention (PCI) can be assessed using the Academic Research Consortium for High Bleeding Risk tool or using the PRECISE-DAPT score. In patients with a high bleeding risk, a shorter duration of DAPT may be considered, while in patients with a lower bleeding risk standard duration of DAPT may be considered. After 12 months of uneventful treatment, the DAPT score can be calculated and might be helpful to consider whether treatment with DAPT should be prolonged after 12 months. The PRECISE-DAPT score and the DAPT score are different risk scores and are calculated by

Types and combinations of antithrombotic therapy

Antithrombotic therapy can be divided into several classes depending on the number and class of drugs used. Single antiplatelet therapy (SAPT) is therapy with one platelet inhibitor, and dual antiplatelet therapy (DAPT) is therapy with two platelet inhibitors. Double therapy consists of one platelet inhibitor and an OAC, and triple therapy consists of DAPT with an OAC. The bleeding risk increases with the number of antithrombotics. A Danish study found that the incidence of major bleedings per 100 patient-years was 2.6 for SAPT, 2.3 for OAC, 3.8 for DAPT, 4.7 for double therapy and 10.2 for patients using triple therapy.

Risk stratification

The antithrombotic regimen should be tailored based on the patients’ ischaemic and bleeding risk profile. Depending on the indication, several tools were developed to assess the bleeding and ischaemic risk. The CHA2DS2-VASc score can be calculated to estimate the risk of stroke in patients with atrial fibrillation. Patients without clinical stroke risk factors do not need an OAC while patients with stroke risk factors that is, CHA2DS2-VASc score of ≥1 or more for men and ≥2 or more for women, are likely to benefit from an OAC.

The HAS-BLED score is a scoring system developed to assess the risk of major bleeding in patients using a VKA for atrial fibrillation. The HAS-BLED score can be used to identify treatable factors, such as hypertension.

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different risk factors. For instance, the DAPT score includes myocardial infarction at presentation, smoking status and diabetes mellitus. Whereas the PRECISE-DAPT score does not include these factors, but includes for instance renal function and prior bleeding.\textsuperscript{13}

Klok and Huisman describe the different risk stratification schemes for major bleeding in patients with venous thromboembolism (VTE).\textsuperscript{24} The ACCP risk table, the VTE-BLEED, RIEETE and HAS-BLED could be used in patients with a VTE. Klok and Huisman advise to screen for modifiable and treatable risk factors for major bleeding, for instance, hypertension and drug adherence. They also advise to identify patients with a low bleeding risk in whom long-term treatment with an OAC should be considered.\textsuperscript{24}

### Racial differences

Ethnicity-related differences should be considered when starting antithrombotic therapy. The concept of the East Asian paradox states that East Asian patients have a lower risk of thrombosis and a higher risk of bleeding.\textsuperscript{25,26} Therefore, a different target of the international normalised ratio (INR) in East Asians has been proposed for treating non-valvular atrial fibrillation (INR 1.6–2.6) compared with the European Guidelines (INR 2.0–3.0).\textsuperscript{27} When comparing patients with a similar INR range, more intracranial bleedings occurred in the East Asian population compared with the Caucasian population.\textsuperscript{28} Considering the increased bleeding risk the advised dose of the platelet inhibitor prasugrel in Japanese guidelines is 3.75 mg once daily compared with 10 mg once daily in Western guidelines.\textsuperscript{29} The advised

## Table 2  Dual antiplatelet therapy (DAPT)

| Indication                                      | Therapy                        | Duration of therapy | Guideline                                                                 |
|------------------------------------------------|--------------------------------|---------------------|---------------------------------------------------------------------------|
| Minor non-cardioembolic ischaemic stroke <21 days ago, who did not receive IV alteplase | Clopidogrel+ASA               | 21 days, followed by lifelong clopidogrel\footnote{\textsuperscript{14}}.  | 2019 FMS Herseninfarct en hersenbloeding (Cerebral infarction and cerebral haemorrhage) |
| Acute coronary syndrome (NSTE, STEMI, IAP)     | DAPT+ (ASA+P2Y12 inhibitor)   | 3–36 months\footnote{\textsuperscript{15}} In general 12 months, followed by lifelong SAPT*\footnote{\textsuperscript{16}}.  | 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease\footnote{\textsuperscript{17}}. |
| PCI in stable CAD setting                      | Clopidogrel+ASA               | 1–30 months\footnote{\textsuperscript{18}} In general 6 months followed by lifelong SAPT*\footnote{\textsuperscript{19}}.  | 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease\footnote{\textsuperscript{17}}. |
| TAVI (without high bleeding risk)             | Clopidogrel+ASA               | 3–6 months after, TAVI. Followed by lifelong SAPT*\footnote{\textsuperscript{20}}.  | 2017 ESC/EACTS Guidelines for the management of valvular heart disease\footnote{\textsuperscript{21}}. |
| Below the knee bypass with a prosthetic graft  | Clopidogrel+ASA               | At least 1 year. Not clearly indicated in guideline for which period. Followed by SAPT*.  | 2017 ESVS/ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases\footnote{\textsuperscript{22},\textsuperscript{23}}. |
| Carotid artery stenting                        | Clopidogrel+ASA               | At least 1 month, optimal duration is not known. In studies/research setting till 6 months. Followed by lifelong SAPT*.  | 2011 Society for vascular surgery Guidelines for management of extracranial carotid disease\footnote{\textsuperscript{24}}. |
| Revascularisation percutaneous in patients with lower extremity artery disease  | Clopidogrel+ASA               | At least 1 month, in research setting till 12 months. Followed by lifelong SAPT*.  | 2017 ESVS/ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases\footnote{\textsuperscript{25},\textsuperscript{26}}. |

\footnote{\textsuperscript{14}} Lifelong indication, unless patients develop an indication for a therapeutic anticoagulation therapy. In these cases, the antithrombotic therapy for patients must be evaluated in terms of whether antplatelet therapy is still indicated.

\footnote{\textsuperscript{15}} Depending on indication and treatment choice (medically managed, PCI or CABG, bleeding risk, PRECISE-DAPT score or DAPT score. (2017 ESC focused update on dual antiplatelet therapy in coronary artery disease).\textsuperscript{13}

\footnote{\textsuperscript{16}} Depending on bleeding risk (PRECISE-DAPT).

\footnote{\textsuperscript{17}} ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EACTS, European Society of Cardio-Thoracic Surgery; ESC, European Society of Cardiology; ESVS, European Society of Vascular Surgery; FMS, Federation of Medical Specialists; IAP, unstable angina pectoris; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

## Table 3  Therapeutic anticoagulation therapy (OAC)

| Indication                                      | Therapy | Duration of therapy | Guideline                                                                 |
|------------------------------------------------|---------|---------------------|---------------------------------------------------------------------------|
| Non-valvular atrial fibrillation or atrial flutter with CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥2 | DOAC or VKA | Lifelong | 2016 ESC Guidelines for the management of atrial fibrillation.\textsuperscript{14} |
| Atrial fibrillation >48 hours existing for which cardioversion is indicated and CHA\textsubscript{2}DS\textsubscript{2}-VASc <2 | DOAC or VKA | At least 3 weeks prior to cardioversion until 4 week after cardioversion | 2016 ESC Guidelines for the management of atrial fibrillation.\textsuperscript{14} |
| Venous thromboembolism                         | DOAC or VKA | 3 months to lifelong | 2016 FMS Antithrombotisch beleid (Antithrombotic policy)\textsuperscript{15} |
| Mechanical valve                               | VKA     | Lifelong            | 2017 ESC Guidelines for the management of valvular heart disease.\textsuperscript{12} |
| Biological mitral of tricuspid valve <3 months (implantation or reconstruction) | VKA | 3 months, followed by lifelong SAPT | 2017 ESC/EACTS Guidelines for the management of valvular heart disease.\textsuperscript{16} |

**ECATS, European Society of Cardio-Thoracic Surgery; ESC, European Society of Cardiology; FMS, Federatie Medisch Specialists; VKA, vitamin K antagonists.**
### Table 4

| Indication | Therapy | Duration of double therapy | Guideline |
|------------|---------|----------------------------|-----------|
| Indication for therapeutic anticoagulation and ACS <1 year after ACS*†, followed by OAC therapy‡ | At least 1–2 months after ACS*†, followed by OAC therapy* | 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease.9 |
| Indication for therapeutic anticoagulation and PCI <1 year | OAC+ASA 6–12 months after PCI*†, followed by OAC therapy‡ | 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease.9 |
| Indication for therapeutic anticoagulation and PCI <1 year | OAC+ASA 3–6 months, followed by OAC therapy†* | 2018 ESC/EACTS Guidelines on myocardial revascularisation.17 |
| Indication for therapeutic anticoagulation and valve repair or valve replacement <3 months ago | OAC+ASA At least 1 year | 2011 Society for vascular surgery Guidelines for management of extracranial carotid disease.13 |
| Indication for therapeutic anticoagulation and carotid artery stenting <1–6 months ago | OAC+ASA | 2017 ESC/EACTS Guidelines on myocardial revascularisation.17 |
| Indication for therapeutic anticoagulation and endovascular revascularisation (stent/graft) | OAC+ASA | 2017 ESVS/ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases.11,12 |

*Footprint may be extended in patients with high ischaemic risk and in patients with mechanical prostheses and aortic valve implantation.
†Shorter duration may be considered in patients with high bleeding risk.
‡Followed by OAC therapy only.

Antithrombotic therapy is a moving target. A lot of studies are now being conducted to find the optimal antithrombotic regimen for various indications. We will highlight the results of three recently published trials of which the results have not been adopted yet in the guidelines, but are expected to be so in due time.

The COMPASS trial was a double-blind randomised clinical trial in 27,000 patients with stable atherosclerotic vascular disease (CAD and/or PAD).12 Patients were randomised to receive either rivaroxaban two times a day 2.5 mg in combination with ASA 100 mg, rivaroxaban two times a day 3 mg or ASA 100 mg. The primary outcome was a composite of cardiovascular death, stroke or myocardial infarction. The primary outcome occurred significantly less in patients in the rivaroxaban plus ASA group (4.1%) compared with the ASA group (5.4%). There was no statistical significant difference between the rivaroxaban monotherapy group (4.9%) and the ASA monotherapy group (5.4%).

FUTURE DIRECTIONS

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In the rivaroxaban plus ASA group significantly more major bleedings occurred (3.1%) compared with the ASA monotherapy group (1.9%). Rivaroxaban two times a day 2.5 mg in combination with ASA is currently registered for prevention of atherothrombotic complications in patients with CAD and in patients with symptomatic PAD.

The TWILIGHT trial was a double-blind randomised clinical trial in 7119 post-PCI patients at high risk for bleeding or ischaemic events. 33 These patients received DAPT (ticagrelor plus ASA) for 3 months and were then randomised to receive ticagrelor or ticagrelor plus ASA. In the ticagrelor alone group significantly less bleeding events occurred (4.0%) than in the ticagrelor plus ASA group (7.1%). There was no difference in ischaemic end points (3.9% for both groups).

The POPular Genetics trial was a randomised clinical trial in PCI patients in which patients were randomised to a genotype-guided strategy for selection of a P2Y12 inhibitor or standard treatment with ticagrelor or prasugrel.34 Patients with a genetic variation in CYP2C19*2 and CYP2C19*3 received ticagrelor or prasugrel, because in these patients clopidogrel is probably less effective. Patients without a genetic variation of CYP2C19 received clopidogrel. Over 2400 patients were included. In the

| Indication | Therapy | Duration of triple therapy | Guideline |
|------------|---------|----------------------------|-----------|
| Atrial fibrillation, NSTEMI and PCI <1 week | OAC+ASA+clopidogrel | 1 week after PCI† Followed by OAC+SAPT for 12 months after PCI, followed by OAC therapy lifelong† | 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.18 |

*Longer duration till 6 months can be considered in patients with a high ischaemic risk or patients with a mechanical valve.

†Unless the therapeutic anticoagulation therapy is stopped, in which case ASA or clopidogrel should be started.

‡Longer duration till 1 month can be considered in patients with a high ischaemic risk.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; ESC, European Society of Cardiology; NSTEMI, non-ST-elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

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genotype-based group, the occurrence of thrombotic events was comparable (5.1%) with the standard treatment group (5.9%) and in the genotype-based group significant less bleeding events occurred (9.8%) compared with the standard treatment group (12.5%).

Advice for daily practice
When is double therapy indicated?
Double therapy is indicated, if a patient should be treated with an OAC and has had an acute coronary event or PCI in the past year. Other indications are a recent aortic bioprosthesis or valve sparing surgery less than 3 months or transcatheter aortic valve implantation (TAVI) less than 3–6 months ago; or having an indication for an OAC and with recent stenting of the carotid artery or endovascular revascularisation (table 4).

When is triple therapy indicated?
Triple therapy is indicated, if a patient should be treated with a therapeutic anticoagulation therapy and has had a PCI in the past week in case of an NSTEMI and a month in case of STEMI. If patients have a high bleeding risk, a physician can choose to give double therapy instead of triple therapy. During the period of double or triple therapy, a physician can consider to reduce the dosage of rivaroxaban to 15 mg every day and the dosage of dabigatran to 110 mg two times a day or target the INR in the lower part of the recommended target range in case of a VKA (table 5).

Stopping SAPT when starting OAC
For patients who start with OAC and are already on SAPT, our experience is that the antiplatelet therapy is frequently not evaluated. If an OAC is started for a patient who uses SAPT, the rule of thumb is that the antiplatelet agent can be stopped, unless the patient has had an ACS or PCI in the past year, a recent CVA/TIA, TAVI, valve surgery, carotid artery stenting or endovascular revascularisation.

Antiplatelet agent in double or triple therapy
Only clopidogrel and ASA should be combined with an OAC. P2Y12 inhibitors other than clopidogrel are not recommended, because of a higher bleeding risk.

Thrombosis prophylaxis combined with antithrombetics?
Patients who use SAPT or DAPT and have an indication for thrombosis prophylaxis should receive thrombosis prophylaxis as any other patient. Patients who use an OAC should not receive

Main messages
▶ Treatment schedules for combined antithrombotic therapy in guidelines are complex, especially if a patient has several indications that require multiple antithrombetics. The risk of inadvertent prolonged continuation of antithrombotic therapy exists.
▶ An overview of the most common indications for mono, double and triple antithrombotic therapy; the preferred antithrombotic therapy, and the recommended duration of the therapy is provided in this article.
▶ With this information, healthcare providers can assess whether the prescribed antithrombotic therapy for a patient is adequate or whether the medication regimen should be adjusted.
▶ Antithrombotic therapy is a moving target. A lot of studies are now being conducted to find the optimal antithrombotic regimen for various indications.

Current research questions
▶ To what extent is guideline-based combination antithrombotic therapy prescribed in daily practice?
▶ What is the optimal antithrombotic regimen when more than one antithrombotic agent is indicated?
▶ How can guideline-based prescription of antithrombotic therapy be improved in patients who use more than one antithrombotic agent?

Self-Assessment questions
1. A patient is diagnosed with a pulmonary embolism in August 2020. In 2015, this patient had a cerebrovascular accident. What is the adequate antithrombotic therapy for this patient?
   A. Clopidogrel plus acetylsalicylic acid.
   B. Clopidogrel plus therapeutic anticoagulation therapy.
   C. Therapeutic anticoagulation therapy.
   D. Dipyridamole + therapeutic anticoagulation therapy.
2. A patient is admitted in August 2020 and is diagnosed with atrial fibrillation. In May 2020, he underwent percutaneous coronary intervention after a non-STEMI. What is the adequate antithrombotic therapy for this patient?
   A. Therapeutic anticoagulation therapy and one antiplatelet agent.
   B. Therapeutic anticoagulation therapy and two antiplatelet agents.
   C. Therapeutic anticoagulation therapy.
   D. Two antiplatelet agents (DAPT).
3. A patient receives a prophylactic dosage of a low-molecular-weight heparin after surgery. The physician restarts the DOAC. When can the thrombosis prophylaxis be stopped?
   A. Immediately.
   B. After 1 day.
   C. After 2 days.
   D. When an adequate INR is reached.
4. How much higher is the bleeding risk for a patient who uses the combination of a vitamin K antagonist plus a antiplatelet agent compared with a patient who uses only a vitamin K antagonist?
   A. Same bleeding risk.
   B. Two times as high.
   C. Three times as high.
   D. Four times as high.
5. A patient with atrial fibrillation had a STEMI and underwent a percutaneous coronary intervention. The cardiologist wants to start triple therapy. What is an adequate therapy?
   A. Therapeutic anticoagulation therapy plus acetylsalicylic acid and clopidogrel.
   B. Therapeutic anticoagulation therapy plus acetylsalicylic acid and ticagrelor.
   C. Therapeutic anticoagulation therapy plus acetylsalicylic acid and prasugrel.
   D. Therapeutic anticoagulation therapy plus acetylsalicylic acid and dipyridamole.
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ORCID iD
Matthijs J Becker http://orcid.org/0000-0003-0054-7498

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**Answers**

1. C
2. A
3. A
4. B
5. A