Clinical recommendations for surgery and bleeding during treatment with oral antiplatelet agents

Published: 2015-04-29

These recommendations have been developed at the request of the Swedish Society of Cardiology and the Swedish Society on Thrombosis and Haemostasis

Swedish Society of Cardiology

Swedish Society on Thrombosis and Haemostasis

The legitimacy of these recommendations

This document has been sent to the following medical associations in Sweden
to offer them the opportunity of expressing their opinions:

Emergency Care, General Medicine, Anaesthesia and Intensive Care, Gastroenterology, Haematology, Internal Medicine, Cardiology, Surgery, Clinical Chemistry, Vascular Surgery, Neurology, Neurosurgery, Nephrology, Obstetrics and Gynaecology, Oncology, Orthopaedics, Plastic Surgery, Cardiothoracic Surgery, Transfusion Medicine, Urology, and Ear-Nose and Throat.

These recommendations are based on published scientific studies,
clinical experience and discussions seeking to arrive at a consensus.
In many of the situations described, no studies could be found on which to base recommendations

The Working Group consisted of:

Chairperson
Oscar Braun, MD, PhD
Department of Cardiology, Skåne University Hospital in Lund
Oscar.Braun@med.lu.se

David Erlinge, Senior Consultant, Professor
Department of Cardiology, Skåne University Hospital in Lund

Håkan Wallén, Senior Consultant, Professor
Department of Cardiology, Danderyd Hospital

Anders Jeppsson, Senior Consultant, Professor
Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg

Peter J. Svensson, Senior Consultant, Professor
Centre for Coagulation Disorders, Skåne University Hospital in Malmö

Anders Själander, Senior Consultant, Associate Professor
Umeå University, Department of Internal Medicine, Sundsvall Hospital

SWEDEN

AstraZeneca provided a small financial contribution for the translation and printing of these recommendations.
AstraZeneca has not in any way participated in, or been involved in,
the production of this document.

Contents

Background

The recommendations for the clinical situations described in this document are based on published scientific studies and the assessments and recommendations of the US Food and Drug Administration (FDA) and the European Medical Agency (EMA). We have also taken into consideration clinical experience and consensus reached through discussions in the working group, including consultation with colleagues in Sweden and other countries.

Few of these clinical situations are included in clinical studies, but are common in practical health care.

The recommendations presented here are expressed concisely so that they can be used in clinical practice. The bibliography provides background documentation. This document and the recommendations contained in it will be updated as and when new information becomes available.

Commonly accepted abbreviations are used.

The recommendations in this document cover the most common clinical situations. However, these recommendations do not apply to children, pregnant women or patients with severe liver or kidney disease. For advice in these cases we recommend that the coagulation specialist on call should be contacted.

Abbreviations and names of pharmaceuticals

Abbreviations

ACS – acute coronary syndrome
ASA – acetylsalicylic acid
ADP – adenosine diphosphate
APTT – activated partial thromboplastin time
BMS – bare metal stent
cAMP – cyclic adenosine monophosphate
COX-1 – cyclooxygenase-1
DAPT – dual antiplatelet therapy (with ASA and ADP receptor inhibitors)
DES – drug-eluting stent
ICP – intracranial pressure
LMWH – low-molecular-weight heparin
NOAC – non anti-vitamin-K (new) oral anticoagulants
PCC – prothrombin complex concentrate
PT (INR) – prothrombin time (internationalized normal ratio)

Pharmaceuticals

Generic name
acetylsalicylic acid
clopidogrel
prasugrel
ticagrelor
cilostazol
dipyridamole
desmopressin
tranexamic acid
vitamin K1
prothrombin complex concentrate

General information on antiplatelet agents

Platelets can be activated by a number of different stimuli. In order for a stable haemostatic clot to form, the activation of platelets must be enhanced by so-called positive feedback loops. A clinically important feedback loop is the transformation of arachidonic acid to thromboxane, which when it is released, activates the platelets via specific receptors. This process is dependent on the enzyme cyclooxygenase-1 (COX-1), which is irreversibly inhibited by acetylsalicylic acid (ASA). Another clinically important feedback loop is the release of adenosine diphosphate (ADP), which is found in the granulae of platelets. ADP can in turn activate the platelets by binding to ADP receptors. These are irreversibly inhibited by thienopyridines (clopidogrel and prasugrel), and reversibly by drugs such as ticagrelor.

Dipyridamole is not only a phosphodiesterase inhibitor, but also an adenosine reuptake inhibitor, and both effects can contribute to platelet inhibition. Cilostazol is a reversible selective phospho-diesterase-3 inhibitor, the effect of which on platelets is mediated by an increase in intracellular cyclic adenosine monophosphate (cAMP).

Platelets have a lifetime in the circulation of 5-9 days. This means that about 15% of platelets are replaced each day.

Table 1. Properties of common antiplatelet agents

	ASA	**Clopidogrel**	**Prasugrel**	**Ticagrelor**	**Dipyridamole**	**Cilostazol**
Bioavailability	70%	50%	80%	36%	70%	Not known
Time to maximum plasma concentration	120 minutes	45 minutes	30 minutes	90 minutes	120-180 minutes	120 minutes
Degree of platelet inhibition	+	+/++	+++	+++	(+)	(+)
Half-life of the active metabolite	2-4 hours	1-2 hours	2 hours	7-9 hours	3 hours	11-13 hours
Type of inhibition	irreversible	irreversible	irreversible	reversible	reversible	reversible
Influence of genetics	-	+++	-	-	-	-
Time to 100% recovery of platelet function*	7-9 days	7-9 days	7-9 days	5 days	1-2 days	4-6 days
Time to at least 50% recovery of platelet function*	4 days	5 days	7 days	3 days	1 day	2 days
Antidote (specific)	None	None	None	None	None	None
Reversal of effect	Desmopressin/ platelet concentrate	platelet concentrate	platelet concentrate	platelet concentrate	platelet concentrate can be considered	platelet concentrate can be considered

* **NOTE:** The times given here are not the recommended times for discontinuation prior to surgery or other procedures.

Current indications and duration of treatment

Description of platelet inhibition today

Single antiplatelet therapy

ASA is used in some cases as primary prophylaxis in patients with multiple risk factors for cardiovascular disease, but documentation of its use for primary prophylaxis is limited. Lifelong treatment is usually recommended for patients with coronary artery disease and/or following a heart attack or atherosclerotic ischaemic stroke. In cases of intolerance to ASA, clopidogrel is usually given.

In this document, single antiplatelet therapy thus refers to treatment with ASA *or* clopidogrel alone.

Dual antiplatelet therapy

Dual antiplatelet therapy, i.e. ASA plus an ADP receptor inhibitor, is used after stent implantation in coronary arteries and, in some cases, after the insertion of stents into carotid or intracranial arteries or after acute coronary syndrome (ACS). The period of treatment varies depending on the indication and local guidelines.

One year's treatment with dual antiplatelet therapy is recommended after ACS, regardless of the intervention, according to international standards. Dual antiplatelet therapy is recommended for patients with stable angina pectoris who have undergone coronary artery interventions and who have a bare metal stent (BMS). The recommended duration of treatment is at least four weeks; often longer. If a drug-eluting stent (DES) has been implanted, at least six month's dual antiplatelet therapy is recommended; often longer.

Triple therapy – Oral anticoagulants in combination with antiplatelet agents

Triple therapy involves treatment with a combination of oral anticoagulant agents (usually warfarin) and dual antiplatelet therapy. Common indications are recent ACS and concomitant atrial fibrillation, left ventricular thrombus, mechanical heart valve, or ongoing treatment for venous thromboembolism. The risk of bleeding is considerably increased in patients receiving triple therapy. The combination of warfarin + clopidogrel without ASA has been studied in an attempt to reduce the risk of bleeding. This combination appears to provide similar protection against ischaemic events, while reducing the risk of bleeding. Some centres also use a combination of warfarin and only ticagrelor in these cases. The general recommendation is to keep the duration of combined treatment with potent antiplatelet agents and warfarin as short as possible (preferably only a month), as long-term treatment with oral anticoagulants combined with antiplatelet agents leads to a clear increase in the risk of bleeding complications.

There is very little experience from the use of new oral anticoagulants (NOAC) in combination with dual antiplatelet therapy, but this can be applied in special cases. When bleeding complications arise from the use of NOAC in combination with antiplatelet agents, the coagulation specialist on call should be consulted.

All patients treated with oral anticoagulants in combination with antiplatelet agents should be carefully monitored at a specialised clinic and should be followed up regularly. The duration of treatment should be documented and adhered to.

Treatment with dipyridamole and cilostazol

Dipyridamole is used in secondary prevention of ischaemic stroke and transitory ischaemic attacks, in most cases in combination with ASA. Cilostazol is indicated for the improvement of walking distance in patients with severe intermittent claudication.

Principles for the treatment of bleeding

There are no specific antidotes to antiplatelet agents. The only way of regaining platelet function after treatment with irreversible oral agents (ASA, clopidogrel or prasugrel) is to wait until the whole circulating pool of platelets has been replaced. This normally takes 7-10 days. In the case of ticagrelor, which is a reversible agent, it is necessary to wait until the drug has been eliminated from the plasma, which normally takes 5 days.

Desmopressin increases the release of factor VIII and von Willebrand factor from endothelial cells and can increase platelet adhesion, but has no documented specific pharmacological effect on platelets. Desmopressin represses the haemorrhagic effect of ASA, while the effect on platelet function during ADP receptor inhibition therapy is less well documented.

Transfusion with platelet concentrate is a non-specific treatment that can be used to reverse the effect of antiplatelet agents. As long as the original substance or active metabolites of the anti-platelet agent remain in the circulation they can be expected to have an antiplatelet effect, and will probably also inhibit the transfused platelets, resulting in a reduction in haemostatic effect.

Tranexamic acid is a fibrinolysis inhibitor, and can be administered based on broad indications associated with bleeding, as indicated below. However, exceptions are macroscopic haematuria and during major urological surgery, due to the risk of clotting of ureters resulting in urine retention. Tranexamic acid has no documented effect on platelet function.

Surgery

Single therapy

As a rule, single treatment with ASA should not be discontinued before surgery, with the exception of intracranial interventions, surgery in the posterior chamber of the eye, and in some kinds of urological surgery, especially major prostate surgery. The same recommendations apply to the withdrawal of single therapy with clopidogrel. Note, that if there are strong indications for anti-platelet therapy, the specialists involved should discuss the treatment and base their decision on a benefit-risk analysis.

Single therapy with prasugrel or ticagrelor is exceptional. If this is the case, a coagulation specialist should be consulted before treatment is initiated, as these drugs have a stronger antiplatelet effect than ASA and clopidogrel, and the recommendations regarding single antiplatelet therapy given below are not applicable.

Dual antiplatelet therapy

	Clinical situation	Recommendation
1	Acute surgery	1. Check PT(INR), APTT, platelets and Hb. 2. Determine when the most recent dose of antiplatelet agents was given.* 3. Administer tranexamic acid: 10 mg/kg i.v. 4. Consider giving desmopressin: 0.3 µg/kg i.v. 5. Administer platelet transfusion in cases of clinically significant bleeding. The effect will be reduced if there are active drugs in the circulation. Suggested starting dose: 2 units in the case of ongoing treatment. Can be repeated if necessary. Re-instate antiplatelet therapy as soon as possible postoperatively. Possibly ASA and LMWH initially postoperatively. Avoid LMWH/heparin in combination with DAPT.
2	Subacute surgery	1. Surgery should be delayed as long as is justifiable, bearing in mind the risks of thrombosis and bleeding. About 15% new platelets are formed per day. 2. Check PT(INR), APTT, platelets and Hb. 3. Determine when the most recent dose of antiplatelet agents was given.* 4. Administer tranexamic acid: 10 mg/kg i.v. 5. Consider administering desmopressin: 0.3 µg/kg i.v. 6. Administer platelet transfusion in cases of clinically significant bleeding. The effect will be reduced if there are active drugs in the circulation. Suggested starting dose: 2 units in the case of ongoing treatment. Can be repeated if necessary. Re-instate antiplatelet therapy as soon as possible postoperatively. Possibly ASA and LMWH initially postoperatively. Avoid LMWH/heparin in combination with DAPT.

3	Elective surgery	Elective surgery should, if possible, be delayed until the planned DAPT period is completed. If this is not possible, treatment with antiplatelet agents should be discussed with a cardiologist. In many cases, it is appropriate to continue treatment with ASA. If ADP receptor inhibitors are to be discontinued, this should be done according to the appropriate guidelines. Number of days before surgery antiplatelet agents should be discontinued: clopidogrel: 5 days prasugrel: 7 days ticagrelor: 5 days

*Information on the time of the most recent dose is valuable as it can be used to estimate the degree of antiplatelet effect and/or the expected effect of antiplatelet agents on transfused platelets (see Table 1).

Triple therapy

	Clinical situation	Recommendation
1	Acute surgery	1. Check PT(INR), APTT, creatinine, platelets and Hb. 2. Reverse the effects of warfarin with PCC, and give vitamin K1: 10 mg i.v. 3. Determine when the most recent dose of antiplatelet agents was given. 4. Administer tranexamic acid: 10 mg/kg i.v. 5. Consider giving desmopressin: 0.3 µg/kg i.v. 6. Administer platelet transfusion in cases of clinically significant bleeding. The effect will be reduced if there are active drugs in the circulation. Suggested starting dose: 2 units in the case of ongoing treatment. Can be repeated if necessary. Re-instate antiplatelet treatment as soon as possible postoperatively. Possibly ASA and LMWH initially. Avoid LMWH/heparin in combination with DAPT.
2	Subacute surgery	1. Check PT(INR), APTT, creatinine, platelets and Hb. 2. Administer vitamin K1: 1-10 mg i.v., depending on the initial PT(INR), recheck PT(INR). 3. Surgery should preferably be delayed until the PT(INR) is acceptable. 4. Determine when the most recent dose of antiplatelet agents was given. 5. Administer tranexamic acid: 10 mg/kg i.v. 6. Consider giving desmopressin: 0.3 µg/kg i.v. 7. Administer platelet transfusion in cases of clinically significant bleeding. The effect will be reduced if there are active drugs in the circulation. Suggested starting dose: 2 units in the case of ongoing treatment. Can be repeated if necessary. Re-instate antiplatelet treatment as soon as possible postoperatively. Possibly ASA and LMWH initially. Avoid LMWH/heparin in combination with DAPT

3	Elective surgery	Elective surgery should, if possible, be delayed until the planned triple therapy is completed. If this is not possible, treatment with warfarin should be temporarily discontinued while continuing treatment with ASA. After consultation with the cardiologist, antiplatelet agents should be discontinued several days before surgery: clopidogrel: 5 days prasugrel: 7 days ticagrelor: 5 days Warfarin should be discontinued according to standard practices.

Minor surgery/Dental surgery

	Clinical situation	Recommendation
1	Endoscopies with or without biopsy	**Single therapy** No measures need be taken. **DAPT** Without biopsy: no measures need be taken. With biopsy: discontinue clopidogrel and ticagrelor 5 days, and prasugrel 7 days, before the intervention. **Triple therapy** Discontinue warfarin temporarily before the intervention, according to standard practices. Antiplatelet treatment should be discontinued as described above for DAPT. ERCP – high-risk interventions: as for DAPT/triple therapy with biopsy.
2	Punctures, skin biopsies, i.m./i.a. injections , central vein catheter and portal catheter insertion	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. **Triple therapy** Discontinue warfarin temporarily before the intervention according to standard practices.
3	Dental plaque removal and similar procedures	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. **Triple therapy** Discontinue warfarin temporarily before the intervention according to standard practices.
4	Major dental surgery (including extractions)	See surgery.

Anaesthesia

	Clinical situation	Recommendation
1	Regional anaesthesia	**Single therapy** See surgery above. **DAPT** See surgery above. **Triple therapy** See surgery above.
2	Spinal/epidural anaesthesia	**Single therapy** See elective surgery above.* **DAPT** Do not perform the procedure, or see elective surgery above. **Triple therapy** Do not perform the procedure, or see elective surgery above.

* Swedish Association for Anaesthesiology (SFAI) recommends that ASA is temporarily withdrawn on the day of the procedure

Various medical procedures

	Clinical situation	Recommendation
1	Acupuncture	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.
2	Angiography	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. Radial approach recommended. **Triple therapy** No measures need be taken if PT is therapeutic. Radial approach recommended.
3	Botox or hyaluronic acid injections	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.
4	Crista biopsy	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure, or see surgery above. **Triple therapy** Do not perform the procedure, or see surgery above.
5	Partial-thickness skin grafts	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure, or see surgery above. **Triple therapy** Do not perform the procedure, or see surgery above.
6	Electroconvulsive therapy (ECT)	**Single therapy** No measures need be taken. **DAPT** Avoid the procedure if possible. **Triple therapy** Do not perform the procedure.

7	Electromyography (EMG)	**Single therapy** No measures need be taken. **DAPT** Avoid the procedure if possible. **Triple therapy** Do not perform the procedure.
8	Cardiac catheterization	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. **Triple therapy** Discontinue warfarin temporarily before the intervention, according to standard practices.
9	Skin excision	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.
10	Cataract removal	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. **Triple therapy** Discontinue warfarin temporarily before the intervention, according to standard practices.
11	Liver biopsy	**Single therapy** Discontinue 5 days before the procedure. **DAPT** Do not perform the procedure, or see elective surgery above (if possible also discontinue ASA 5 days before the procedure). **Triple therapy** Do not perform the procedure, or see elective surgery above (if possible also discontinue ASA 5 days before the procedure).
12	Lumbar puncture	**Single therapy** See elective surgery above. **DAPT** Do not perform the procedure, or see elective surgery above. **Triple therapy** Do not perform the procedure, or see elective surgery above.

13	Renal biopsy	**Single therapy** Discontinue 5 days before the procedure. **DAPT** Do not perform the procedure, or see elective surgery above (if possible also discontinue ASA 5 days before the procedure). **Triple therapy** Do not perform the procedure, or see elective surgery above (if possible also discontinue ASA 5 days before the procedure).
14	Implantation of a pacemaker or event recorders	**Single therapy** No measures need be taken. **DAPT** Discuss with the surgeon. **Triple therapy** If clinically indicated, discontinue warfarin before the procedure, according to standard practices.
15	Thoracentesis	**Single therapy** No measures need be taken. **DAPT** Avoid the procedure if possible. **Triple therapy** If clinically indicated, discontinue warfarin before the procedure, according to standard practices.
16	Prostate biopsy	**Single therapy** ASA - no measures need be taken. If clopidogrel - discuss with the urologist **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.
17	Tattooing	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.
18	Transoesophageal ECG/ultrasound	**Single therapy** No measures need be taken. **DAPT** No measures need be taken. **Triple therapy** No measures need be taken if PT is therapeutic.

19	Eyelid surgery	**Single therapy** No measures need be taken. **DAPT** Do not perform the procedure. **Triple therapy** Do not perform the procedure.

Stroke and cerebral haemorrhage

	Clinical situation	Recommendation
1	Embolic ischaemic stroke	Consider measuring the patient's degree of platelet inhibition to establish whether he or she is taking their medication as prescribed.
2	Thrombolysis in combination with acute ischaemic stroke	**Single therapy** No measures need be taken. Thrombolysis can be carried out using standard practices. **DAPT** The combination of ASA and clopidogrel appears to increase the risk of bleeding in thrombolysis. There is no reliable documentation on more potent antiplatelet agents, but it is likely that the risk of bleeding will be increased further. **NOTE:** There are no studies supporting thrombolysis during ongoing DAPT. Indications for thrombolysis should be weighed against the risk of bleeding. If catheter intervention is possible, this should be considered instead of thrombolysis. **Triple therapy** Refrain from thrombolysis during ongoing triple therapy and therapeutic PT. **NOTE:** If catheter intervention is possible, this can be considered.
3	Intracranial haemorrhage	**Single therapy and DAPT** 1. Assess the risk of bleeding in relation to the most recent dose of antiplatelet agent(s). 2. Administer tranexamic acid: 10 mg/kg i.v. 3. Consider administration of desmopressin: 0.3 µg/kg i.v. **NOTE:** Risk of increased ICP 4. Administer platelet transfusion. The effect will be reduced if there are active drugs in the circulation. Suggested dose: 2-4 units. Can be repeated if necessary. 5. Contact a coagulation specialist if the above treatment does not give the intended effect. **Triple therapy** 1. Reverse the effect of warfarin with PCC and administer vitamin K1: 10 mg i.v. 2. Determine the time of the most recent dose of antiplatelet agent(s). 3. Administer tranexamic acid: 10 mg/kg i.v. 4. Consider administering desmopressin: 0.3 µg/kg i.v. **NOTE:** Risk of increased ICP 5. Administer platelet transfusion. The effect will be reduced if there are active drugs in the circulation. Suggested dose: 2-4 units. Can be repeated if necessary. 6. Contact a coagulation specialist if the above treatment does not give the intended effect.

Bleeding/Risk of bleeding

In cases of severe gastrointestinal bleeding consider acute/subacute gastroscopy with surgical intervention (clips, instillation of vasoconstrictive agents, etc.).

	Clinical situation	Recommendation
1	Acute, severe bleeding	**Single therapy and DAPT** 1. Determine Hb, platelet count, APTT, PT(INR), fibrinogen and take other tests according to local practice. Do not await the results in acute situations, but follow the procedure below. 2. Administer desmopressin: 0.3 µg/kg i.v. **NOTE:** Monitor ICP in cases of intracranial bleeding. 3. Administer tranexamic acid: 10 mg/kg i.v. 4. Administer platelet transfusion. The effect will be reduced if there are active drugs in the circulation. Suggested starting dose: 2-4 units. Can be repeated. 5. Contact blood bank early. **Triple therapy** 1. Determine Hb, platelet count, APTT, PT(INR), fibrinogen and take other tests according to local practice. Do not await the results in acute situations, but follow the procedure below 2. Reverse the effect of warfarin with PCC and administer vitamin K1: 10 mg i.v. 3. Administer desmopressin: 0.3 µg/kg i.v. **NOTE:** Monitor ICP in cases of intracranial bleeding. 4. Administer tranexamic acid: 10 mg/kg i.v. 5. Administer platelet transfusion. The effect will be reduced if there are active drugs in the circulation. Suggested dose: 2-4 units. Can be repeated. 6. Contact blood bank early.
2	Slight bleeding from regions that can easily be treated mechanically, e.g. minor nosebleeds (which can be stopped within a few minutes by compression), small wounds or single occasions of blood in urine	**Single therapy and DAPT** No measures need be taken. **Triple therapy** No measures need be taken.

3	Anaemia	**Single therapy and DAPT** No measures need be taken. **Triple therapy** Discontinue warfarin but maintain antiplatelet agents. If there are strong indications for warfarin, administer short-acting LMWH (from prophylactic to therapeutic doses, depending on the situation). In cases of more severe anaemia consider treatment according to item 1 in this table
4	Severe trauma to the head or large muscles where there is a risk of thoracic or abdominal compart-ment syndrome	**Single therapy, DAPT and triple therapy** The patient should undergo a medical examination. Consider appropriate imaging. Consider interruption of treatment.

Determination of platelet function

The patient's medical history and status provide information on whether his/her medication will lead to an increased risk of bleeding or not. Measurement of bleeding time does not provide reliable information. A number of methods of measuring the degree of platelet inhibition are available. The results obtained with these methods show considerable variation, and none of them has been sufficiently validated for the determination of the risk of bleeding resulting from treatment with antiplatelet agents. Examples of these methods are VerifyNow®, Multiplate®, PlateletWorks® and PLT VASP/P2Y12 (Biocytex).

Bibliography

Hamm, CW. et al., 2011. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*, 32(23), pp. 2999–3054.

Wijns, W. et al., 2010. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, 31(20), pp. 2501–2555.

Korte, W. et al., 2011. Peri-operative management of antiplatelet therapy in patients with coronary artery disease: joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (ÖGARI) and the working group on thrombosis of the European Society for Cardiology (ESC). In Thrombosis and Haemostasis. pp. 743–749.

Steg, P.G. et al., 2012. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*

The European Medicines Agency Summary of Product Characteristics for Brilique

The European Medicines Agency Summary of Product Characteristics for Efient

The European Medicines Agency Summary of Product Characteristics for Plavix