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Review article

Antithrombotic therapy after percutanous coronary intervention with stenting

Summary

Background. Patients with stent thrombosis have a serious prognosis and a high mortality rate. Insufficient blood platelet inhibition may be the cause of the condition. This article gives an overview of long-term treatment effects of blood platelet inhibition in patients with coronary artery stents.

Material and methods. The article is based on own experience and publications retrieved through a non-systematic search of Pubmed.

Results. Stent thrombosis is frequently associated with premature discontinuation of acetylsalicylic acid and/or clopidogrel and with non-cardiac surgery shortly after stenting. When possible, blood platelet inhibitors should not be discontinued during elective non-cardiac surgery. Surgery should be delayed for at least 6 weeks after insertion of bare metal stents and for at least 6 months after drug-eluting stents. Bare metal stents are preferred in patients who need anticoagulation. Antithrombotic treatment of these patients should consist of a combination of warfarin, acetylsalicylic acid and clopidogrel.

Conclusion. It is important to adequately inform patients, physicians and pharmacies about correct antithrombotic drug use, thereby preventing stent thrombosis and acute myocardial infarction.

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Acetylsalicylic acid and thienopyridines (clopidogrel and ticlopidine) are used to avoid thromboembolic complications after insertion of an intracoronary stent during percutaneous coronary interventions (PCI). Stent thrombosis most commonly occurs in the first weeks, but it can occur years after insertion of drug-eluting stents (1, 2). Common causes of stent thrombosis are drug intolerance, self-discontinuation of antithrombotic medication or premature discontinuation in connection with surgery or dental treatment (1).

Anticoagulation with warfarin alone does not adequately protect against stent thrombosis (as with acetylsalicylic acid and thienopyridines) and is not a good enough alternative to blood platelet inhibition (3). A combination of warfarin and blood platelet inhibition may be indicated in patients with mechanical heart valves, previous systemic or venous thromboembolism, thrombus in the left ventricle, pulmonary emboli or atrial fibrillation. Additional treatment with acetylsalicylic acid and clopidogrel to patients who already use anticoagulation will increase the risk of bleeding, and inadequate platelet inhibition will increase the risk of stent thrombosis (4, 5). Patients who need both anticoagulation and blood platelet inhibition can be a great therapeutic challenge, and the risk of bleeding must be balanced with that of thromboembolism and stent thrombosis.

The aim of this article is to provide an overview of documented effects of platelet inhibition as long-term treatment in patients with coronary artery stents. Advice on treatment is given in connection with non-cardiac surgery, and for patients who need both anticoagulation and platelet inhibition or are allergic to clopidogrel.

Material and methods

The article is based on own experience and publications retrieved through a non-systematic search of PubMed.

Risk of stent thrombosis and bleeding

Stent thrombosis most commonly occurs shortly after insertion of a stent and the incidence the first 30 days is 0.5–1.5 % for both bare metal and drug-eluting stents (acute/subacute stent thrombosis) (1, 2, 6). Late stent thrombosis (at least 30 days after insertion) occurs mainly with drug-eluting stents and can present after several years (2). The incidence of late stent thrombosis is not known and depends on the presence of predisposing factors (tab 1), (1, 7). An incidence of 0.6 % has been reported in unselected patients with drug-eluting stents with three years of follow-up (2). It is not known how long this increased risk remains. Late stent thrombosis often presents itself as acute myocardial infarction, i.e., with ST segment elevations in the ECG and has a high mortality rate (16–45 %) in observational studies (1, 8–10).

Both blood platelet inhibitors and warfarin increase the risk of bleeding. In more than 12 000 patients with acute coronary syndrome, the incidence of serious bleeding was 1.1 % with acetylsalicylic acid alone and 1.7 % with the combination of acetylsalicylic acid and clopidogrel (11). Adding clopidogrel to acetylsalicylic acid did not increase the incidences of fatal haemorrhage or cerebral infarction. Combination therapy

Main message

- Acetylsalicylic acid and clopidogrel provide the best drug combination with regard to preventing stent thrombosis.
- Premature discontinuation of blood platelet inhibitors is a common cause of stent thrombosis.
- Non-cardiac surgery should be postponed for at least six weeks with bare metal stents and for at least 6 months with drug-eluting stents.
- Bare metal stents should be preferred in anticoagulated patients to shorten the treatment period with triple antithrombotic therapy.

of warfarin, acetylsalicylic acid and clopidogrel increased the risk of bleeding, but this risk depended on several factors; such as the degree of anticoagulation, duration of treatment, comorbidity and the dosing of acetylsalicylic acid (4, 12, 13).

Guidelines for antithrombotic treatment after PCI

Guidelines developed by the European Society of Cardiology advise therapy with a combination of acetylsalicylic acid (75–160 mg daily) and clopidogrel (75 mg daily) for 3–4 weeks after insertion of a bare metal stent and for 6 to 12 months after insertion of a drug-eluting stent (14). If the patient has a history of acute coronary syndrome, treatment with clopidogrel is advised for 9 to 12 months irrelevant of stent type (14). Furthermore, life-long treatment with acetylsalicylic acid is advised.

The American treatment guidelines suggest that acetylsalicylic acid and clopidogrel are used for at least three months with drug-eluting stents with sirolimus (Cypher-stent) and for six months with drug-eluting stents with paclitaxel (Taxus-stent) (15), with reference to the documentation provided by the industry financed studies that formed the basis for their approval (15). But they also stated that in the absence of a high bleeding risk, the optimal treatment duration should be 12 months with blood platelet inhibition using two drugs (15). Based on reports of an increased risk of late stent thrombosis with drug-eluting stents, the guidelines have recently been revised (16). The revised optimal treatment is 12 months with both acetylsalicylic acid and clopidogrel (16).

Treatment of patients who have had late stent thrombosis

Stents that are not sufficiently covered by endothelial cells are a common finding in autopsy studies (17). A lesser effect of acetylsalicylic acid on blood platelet function has been shown in patients who have had late stent thrombosis (18). No studies or international guidelines are available for antithrombotic therapy after late stent thrombosis. It is common practice to give patients without a known cause for late stent thrombosis (such as premature discontinuation of blood platelet inhibitors or incomplete stent expansion), long-term treatment with both acetylsalicylic acid and clopidogrel for several years irrelevant of stent type.

Elective surgery after insertion of stent

5 % of patients treated with stents have been estimated to need non-cardiac surgery the following year (19). These patients will have an increased risk of stent thrombosis peri and postoperatively, and increased risk of bleeding if they use antithrombotic therapy (16, 19, 20). The risk of stent thrombosis is greatest if platelet inhibitors have been discontinued, but is also higher than normal with continuous use (20, 21). The reasons for this can be enhanced coagulation and platelet function through the operative trauma and perioperative stress (20–22). Bleeding itself can also cause a fall in blood pressure with coronary hypoperfusion, which in turn increases the risk of stent thrombosis.

Table 1 Predictors for late stent thrombosis in patients with drug-eluting stents (1, 7)

Angiographic	Clinical
Long stent	Premature discontinuation of platelet inhibitors
Overlapping stents	Self-discontinuation
Stent in bifurcation	Dental treatment
Stent in small artery	Minor bleeding
Suboptimal stent result	Non-cardiac surgical intervention
Inadequate expansion of the stent	Excessive physical activity
Small stent diameter	Acute coronary syndrome
	Reduced function of left ventricle
	Diabetes mellitus
	Renal failure

No studies have prospectively compared different antithrombotic treatment regimes during non-cardiac surgery in patients with coronary stents. Based on observational studies, it seems important to avoid surgery shortly after stent insertion. Kaluza and collaborators found that the perioperative mortality was 32 % in patients who had an operation less than two weeks after insertion of a bare metal stent (23). Heparin or low molecular heparin do not adequately inhibit blood platelet function, and are not documented to provide sufficient prophylaxis against stent thrombosis during operations (16). Increased frequency of stent thrombosis is detected during the first weeks after discontinuation of blood platelet inhibitors (7, 24) and surgery should if possible be avoided shortly after discontinuation of clopidgrel. Patients with stents for whom operations are planned, should be seen by a cardiologist for assessment of the risk associated with the procedure and possible adjustment of the antithrombotic treatment. It is important to document the type of stent (bare metal stent or drug-eluting stent), time after stenting, if there is a coronary lesion with an inherent increased risk of thrombosis and the size of the artery's supply area. The greater the risk of stent thrombosis, the stronger the need to delay the intervention until the advised treatment period of dual antiplatelet therapy is over (16). Box 1 shows our recommendations for antithrombotic therapy after stent insertion. The early period after stent insertion is associated with a greater risk of stent thrombosis for both stent types. Continuous therapy with dual blood platelet inhibitors is strongly advised during the operation in this period (16). In patients for whom a surgical intervention is needed shortly after stenting, it is advised that the operation is performed in hospitals with PCI facilities.

Dental treatment after stenting

In several observational studies premature discontinuation of clopidogrel in association with dental treatment has led to stent thrombosis (2, 16). Many of these procedures can be undertaken with low risk of serious bleeding (16). If dental treatment and dental surgical interventions cannot be done without discontinuation of the dual platelet therapy, the intervention should be delayed until this treatment has been discontinued (Box 1).

Warfarin in combination with blood platelet inhibition

Close to 10 % of patients treated with PCI with stenting use warfarin or have an indication for anticoagulation therapy (4). Anticoagulated patients who undergo PCI with stenting have a worse prognosis than others irrespective of the treatment regime, due to underlying disease, extensive comorbidity and problems related to the antithrombotic therapy (4, 25). The risk of bleeding, embolic cerebral infarctions, stent thrombosis and myocardial infarctions is greater than normal (4, 25, 26). The risk of cerebral infarction is greater if warfarin is discontinued after stenting (4, 27).

Several randomised studies have shown that warfarin combined with acetylsalicylic acid is not as effective as thienopyridines and acetylsalicylic acid for prevention of stent thrombosis and myocardial infarction (3). Patients without thienpyridines in the combination treatment (but with warfarin and acetylsalicylic acid) have an especially increased risk of stent thrombosis (4). Observational studies have shown that 6–9 % of those patients on triple treatment (warfarin, acetylsalicylic acid and clopidogrel) annually have serious bleeding complications (13, 25). The more serious bleedings occur in connection with PCI or with long-term treatment beyond one month (25). The risk of bleeding complications is closely related to the degree of anticoagulation (12). In patients with INR > 3.0 after PCI, the

Box 1

Guidelines for antithrombotic treatment after PCI with insertion of stent

General

- *Bare metal stent:* Clopidogrel for 3–4 weeks and life-long treatment with acetylsalicylic acid.
- *Drug-eluting stent:* Clopidogrel for 9 to 12 months and life-long treatment with acetylsalicylic acid.
- *Acute coronary syndrome:* Clopidogrel for 9 to12 months and life-long treatment with acetylsalicylic acid irrelevant of stent type.

After late stent thrombosis

- Acetylsalicylic acid and clopidogrel for several years if cause of the stent thrombosis has not been identified and treated.

Elective non-cardiac surgery

- *Bare metal stent:* Delay surgery for at least 6 weeks. No discontinuation of acetylsalicylic acid.
- *Drug-eluting stent and low risk of bleeding:* Delay surgery for at least 6 months. Continuous treatment with acetylsalicylic acid and clopidogrel.
- *Drug-eluting stent and a great risk of bleeding:* Delay surgery for 9 to 12 months after stent implantation. Acetylsalicylic acid should be continued perioperatively.

Dental treatment

- No premature discontinuation of blood platelet inhibitors. With great risk of bleeding, delay dental treatment for at least 6 weeks with bare metal stents and for 9 to 12 months with drug-eluting stents. Acetylsalicylic acid should be continued perioperatively.

Warfarin in combination with blood platelet inhibition

- *Strong indication for anticoagulation:* Warfarin in combination with acetylsalicylic acid and clopidogrel.
- *Weaker indication for anticoagulation:* Acetylsalicylic acid and clopidogrel. Warfarin is discontinued during the period with dual platelet inhibition. Use warfarin and acetylsalicylic acid after the treatment period with dual blood platelet inhibitors.

Skin rash after stenting

- Ticlopidine, 250 mg two times daily, with the same treatment duration as for clopidogrel.

risk of bleeding was more than three times higher than for patients with INR ≤ 3 (12). With less degree of anticoagulation (INR 2.0–2.5) and combined with acetylsalicylic acid, an increase in relation to acetylsalicylic acid alone has only been found for less serious bleedings (28). Extensive treatment with unfractionated or low molecular weight heparin, leads to more bleeding complications than the combination of warfarin and platelet inhibitors (4).

No international guidelines are currently available for platelet inhibition treatment in anticoagulated patients with stents. The treatment must be tailored for each patient and the indication for anticoagulation, the patients age and comorbidity must be taken into account (5). For most patients with a strong indication for warfarin treatment, continuous anticoagulation and dual platelet inhibition is the best treatment regime; e. g. those with mechanical heart valves, recent pulmonary emboli and systemic emboli (Box 1). It is advisable to use low dose acetylsalicylic acid (75–100 mg), clopidogrel (75 mg) and to reduce INR to the lower therapeutic area (3.0–2.5) to prevent bleeding. Radial access during PCI will reduce the risk of bleeding in the early phase, and the PCI procedure can usually be performed without discontinuing the anticoagulation therapy (29). With bare metal stents, the treatment time for anticoagulation combined with two blood platelet inhibitors can be reduced to 3–4 weeks (25). After discontinuation of clopidogrel one should continue with low dose long-term treatment with warfarin and acetylsalicylic acid. INR should optimally be reduced by 0.5 when warfarin is combined with blood platelet inhibitors. In anticoagulated patients with a relatively low thromboembolic risk (e.g. rate controlled non-valvular atrial fibrillation or dilated left ventricle) treatment with warfarin can be discontinued while the patient is treated with acetylsalicylic acid and clopidogrel (Box 1). After completion of treatment with dual platelet inhibitors the patient should continue on low dose acetylsalicylic acid in combination with warfarin.

Skin rash after stenting

It is important that blood platelet inhibition should not be discontinued in connection with skin rash, which often occurs in the early and dangerous phase for stent thrombosis. Drug-eluting stents, X-ray contrast media and blood platelet inhibitors may cause skin rash after stent insertion, but the most common cause is allergic reactions triggered by clopidogrel. The patient has often used acetylsalicylic acid over a longer period of time before PCI, and the skin rash usually occurs 1–2 weeks after start of clopidogrel treatment. Ticlopidine is an alternative to clopidogrel (Box 1) but it may cause haematologic complications and blood status must be monitored. Cross allergy between clopidogrel and ticlopidine is rare, but has been reported (30).

Conclusion

It is important to adequately inform patients, doctors and pharmacies about the risk associated with discontinuation of clopidogrel and acetylsalicylic acid. Self-discontinuation of these drugs is associated with a high risk of stent thrombosis. Discontinuation of platelet inhibitors after stenting due to risk of bleeding during non-cardiac surgery, dental treatment, small bleeding from the skin or need for anticoagulation therapy, will increase the patients' risk of stent thrombosis and acute myocardial infarction.

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