Review of antiplatelet and oral anticoagulant use in patients with stable coronary artery disease


Stable coronary artery disease definition:

1. Patients having stable angina or other symptoms felt to be related to coronary artery disease

2. Patients previously symptomatic with known obstructive or non-obstructive CAD, who have become asymptomatic with treatment and need regular follow-up

3. Patients who report symptoms for the first time and are judged to already be in a chronic stable condition.

4. Stable coronary artery disease excludes situations in which coronary artery thrombosis dominates clinical presentation, in other words acute coronary syndromes.

1. WOEST trial indicated that therapy with vitamin K antagonist with clopidogrel, without aspirin, reduced bleeding complications in patients with indication for vitamin K antagonist undergoing percutaneous intervention.

2. In Danish registry there was no increased risk of recurrent coronary events on dual therapy relative to triple therapy and bleeding risk was nonsignificantly lower for vitamin K antagonist plus clopidogrel.

   - Above shows potential of combination of vitamin K antagonist and clopidogrel without aspirin to improve clinical outcomes in comparison with triple therapy. Vitamin K antagonist with clopidogrel is a reasonable alternative to triple therapy in patients on vitamin K antagonist for atrial fibrillation who undergo percutaneous intervention.

3. In patients on long-term vitamin K antagonist therapy who receive a coronary stent, how should we treat after clopidogrel is discontinued?
   - No randomized trials
   - Two registries: Danish registry and ORBIT-AF
     - Vitamin K antagonist with aspirin associated with increased bleeding without clear reduction of cardiac events

4. No data on combination of vitamin K antagonist with prasugrel or ticagrelor in patients with atrial fibrillation undergoing percutaneous intervention.

5. No data on use of new non-vitamin K antagonists in patients with atrial fibrillation undergoing percutaneous intervention.

1. In patients with acute coronary syndrome already on oral anticoagulation, retrospective studies have compared triple therapy with dual therapy and the results consistently show increase in bleeding with triple therapy.

2. In patients with atrial fibrillation on oral anticoagulation who undergo stent implantation, dual therapy with oral anticoagulation and clopidogrel may be considered as an alternative to triple therapy in patients at low risk of recurrent cardiac events.

3. The period of triple therapy should be as short as possible, followed by oral anticoagulation plus a single antiplatelet agent.

4. When clopidogrel is given in combination with clopidogrel and/or low dose aspirin, the INR target should be 2.0-2.5. (Class IIa, LOE C)

5. In patients with atrial fibrillation and stable vascular disease (no acute coronary syndrome or revascularization over last one year), oral anticoagulation alone, without concomitant antiplatelet therapy, should be pursued. (Class IIa, LOE B)

6. Prasugrel and Ticagrelor should not be part of triple therapy regimen in patients with atrial fibrillation. (Class III, LOE C)

7. In patients with coronary artery disease and atrial fibrillation undergoing percutaneous intervention for stable coronary artery disease, at low bleeding risk, triple therapy should be given for a minimum of for weeks. (Class IIa, LOE C)

    - If bleeding risk is increased, dual therapy with oral anticoagulant plus clopidogrel may be considered. (Class IIb, LOE C)

Class IIb

1. Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA2DS2-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin. (Level of Evidence: B)
Class I

1. Anticoagulation with a vitamin K antagonist is recommended in patients with a mechanical prosthesis. (Level of Evidence: A)

2. Aspirin 75-100 mg daily is recommended in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical prosthesis (Level of Evidence: A)

Class IIa

1. Aspirin 75-100 mg daily is reasonable in all patients with an aortic or mitral bioprosthesis. (Level of Evidence: B)

- Due to a favorable ratio between benefit and risk in patients with stable coronary artery disease, and its low cost, low-dose aspirin is the drug of choice in most cases.

- Dual antiplatelet therapy is the standard of care for patients with stable coronary artery disease who have undergo elective percutaneous intervention. For revascularized patients with stable coronary artery disease, aspirin is recommended indefinitely. Dual antiplatelet therapy is indicated after bare metal stent for at least one month. Dual antiplatelet therapy is indicated for six to twelve months after drug eluting stenting. Dual antiplatelet therapy may be continued beyond these recommendations only in selected patients with stable coronary artery disease that are at high risk of ischemic events (stent thrombosis, recurrent acute coronary syndrome on dual antiplatelet therapy, diffuse coronary artery disease), and low bleeding risk, but this is not recommended for all stable coronary artery disease patients. Duration of dual antiplatelet therapy may need to be decreased in patient with high bleeding risk, undeferrable surgery, or concomitant anticoagulant therapy.
Class I

1. P2Y12 inhibitor therapy should be given for one year to patients with ST elevation myocardial infarction who receive a stent, bare metal or drug eluting. (Level of evidence: B)

2. The duration of triple anti-thrombotic therapy with a vitamin K antagonist, aspirin, and P2Y12 receptor inhibitor should be minimized to prevent the risk of bleeding. (Level of evidence: C)

Class IIb

1. Targeting vitamin K antagonist therapy to an INR of 2.0-2.5 may be considered in patients with ST elevation myocardial infarction who are receiving dual antiplatelet therapy. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely. (Level of evidence: C)
Class I

1. Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with stable coronary artery disease. (Level of Evidence: A)

2. Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with stable coronary artery disease. (Level of Evidence: B)

Class IIb

1. Treatment with aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with stable coronary artery disease but data on specific subgroups is lacking. (Level of Evidence: B)

2. Aspirin in a dose of 75 to 162 mg daily is equally as effective as 325 mg in secondary prevention and is associated with a lower risk of bleeding.

Class I

1. Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis. (Level of evidence: B)

2. Oral anticoagulation is recommended lifelong for patients with bioprosthesis who have other indications for anticoagulation, such as atrial fibrillation. (Level of evidence: C)

Class IIa

1. The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease. (Level of evidence: C)

2. Low-dose aspirin should be considered for the first three months after the implantation of an aortic bioprosthesis. (Level of evidence: C)

- Combination of oral anticoagulants with antiplatelet drugs

In determining whether an antiplatelet agent should be added to anticoagulation in patients with prosthetic valves, it is important to distinguish between the possible benefits in coronary and vascular disease and those specific to prosthetic valves. Trials showing a benefit from antiplatelet drugs in vascular disease and in patients with prosthetic valves and vascular disease should not be taken as evidence that patients with prosthetic valves and no vascular disease will also benefit. When added to anticoagulation, antiplatelet agents increase the risk of major bleeding. They should, therefore, not be prescribed to all patients with prosthetic valves, but be reserved for specific indications, according to the analysis of benefit and increased risk of major bleeding. If used, the lower recommended dose should be prescribed (e.g. aspirin ≤100 mg daily). The addition of antiplatelet agents should be considered only after full investigation and treatment of identified risk factors and optimization of anticoagulation management. Addition of aspirin and a P2Y12 receptor blocker is necessary following intracoronary stenting, but increases the risk of bleeding. Bare-metal stents should be preferred over drug-eluting stents in patients with mechanical prostheses, to shorten the use of triple antithrombotic therapy to 1 month. Longer durations (3–6 months) of triple antithrombotic therapy should be considered in selected cases after acute coronary syndrome. During this period, close monitoring of INR is advised and any over-anticoagulation should be avoided. Finally, there is no evidence to support the use of antiplatelet agents beyond 3 months in patients with bioprostheses who do not have an indication, other than the presence of the bioprosthesis itself.

Class I

1. Aspirin to administered to unstable angina/non-ST elevation myocardial infarction patients and continued indefinitely in those who tolerate it. (Level of evidence: A)

2. In unstable angina/non-ST elevation myocardial infarction patients who undergo a non-invasive strategy, clopidogrel or ticagrelor should be added to aspirin and administered up to 12 months. (Level of evidence: B)

3. If the risk of morbidity because of bleeding outweighs the anticipated benefit by P2Y12 receptor inhibitor therapy, early discontinuation should be considered. (Level of evidence: C)
Class I

1. Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated. (Level of Evidence: A)

2. Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin. (Level of Evidence: B)

3. A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement. (Level of Evidence: A)

4. For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months. (Level of Evidence: A)

5. For patients undergoing coronary artery bypass grafting, aspirin should be started within 6 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for 1 year appear to be efficacious. (Level of Evidence: A)

6. Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other vitamin K antagonists to treat patients with atherosclerosis. (Level of Evidence: A)

   • If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75–81 mg daily) (Level of Evidence: A)

   • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.

Class Ila

1. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (eg, 12 months) is reasonable. (Level of Evidence: C) (Note: the risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.)

2. After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses. (Level of Evidence: B)
Class IIb

1. Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease. (Level of Evidence: B)

Class I

1. After PCI, use of aspirin should be continued indefinitely. (Level of evidence: A)

2. The duration of P2Y12 inhibitor therapy after stent implantation should generally be:

   - In patients receiving a stent, BMS or DES, during PCI for acute coronary syndrome, P2Y12 inhibitor therapy should be given for at least 12 months. (Level of evidence: B)
   - In patients receiving a DES for a non-acute coronary syndrome indication, clopidogrel should be given for at least 12 months if patients are not at high risk for bleeding. (Level of evidence: B)
   - In patients receiving a BMS for a non-acute coronary syndrome indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months, unless the patient is at increased risk for bleeding. (Level of evidence: B)

Class IIa

1. After PCI, it is reasonable to use aspirin 81mg daily in preference to higher doses. (Level of evidence: B)

2. If the risk of morbidity from bleeding outweighs the benefits by a recommended duration of P2Y12 inhibitory therapy after stent implantation, early discontinuation is reasonable. (Level of evidence: C)

Class I

1. If aspirin (100 mg to 325 mg daily) was not initiated preoperatively, it should be initiated within 6 hours postoperatively and then continued indefinitely to reduce the occurrence of SVG closure and adverse cardiovascular events. (Level of Evidence: A)
My conclusions:

- **Stable Coronary Artery Disease Alone**

1. In patients with stable coronary artery disease, low dose daily aspirin should be continued indefinitely in the absence of contraindications. Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.

- **Stable Coronary Artery Disease + ACS/PCI**

2. In patients with stable coronary artery disease with history of stent placement, drug eluting or bare metal, during percutaneous intervention for acute coronary syndrome, daily dual antiplatelet therapy should be given for at least 12 months. In patients who undergo a non-invasive strategy, daily clopidogrel or ticagrelor should be added to aspirin for up to 12 months.

3. In patients with stable coronary artery disease with a history of drug eluting stent placement for a non-acute coronary artery syndrome indication, daily dual antiplatelet therapy should be given for at least 12 months if not at high risk for bleeding.

4. In patients with stable coronary artery disease with a history of bare metal stent placement for a non-acute coronary artery syndrome indication, daily dual antiplatelet therapy should be given for at least 1 month and ideally up to 12 months, unless the patient is at increased risk for bleeding.

- **Stable Coronary Artery Disease + Valve Prosthesis**

5. In patients with stable coronary artery disease and a mechanical prosthesis, anticoagulation with a vitamin K antagonist is recommended. Additionally daily low dose aspirin is recommended.

6. In patients with stable coronary artery disease and a bioprosthesis, daily low dose aspirin is recommended. If atrial fibrillation is present, warfarin alone or warfarin plus low dose aspirin is reasonable.

7. In patients with stable coronary artery disease and a mechanical prosthesis, with a history of intracoronary stenting, bare metal stents should be preferred over drug-eluting stents to shorten the use of triple antithrombotic therapy to 1 month. During this period, close monitoring of INR is advised and any over-anticoagulation should be avoided.

- **Stable Coronary Artery Disease + Atrial Fibrillation**

8. In patients with stable coronary artery disease and atrial fibrillation, it is reasonable to use warfarin alone or warfarin plus low dose aspirin.

9. In patients with stable coronary artery disease and atrial fibrillation (CHA2DS2-VASc score of 2 or greater), with recent stent placement, it is reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin, based on individual thrombosis/bleeding risk.
Clinicians need to use judgment to personalize management to balance risks of ischemia, myocardial infarction, stent thrombosis, and thromboembolism with bleeding for each individual patient.