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Intensification of antithrombotic therapy for chronic atherosclerosis

OPINIONS

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Intensification of antithrombotic therapy can reduce morbidity and mortality in patients with established atherosclerosis. The treatment strategy ought to be incorporated into Norwegian guidelines.

Atherosclerosis causes a weakening or stenosis of the arterial walls and is a pathophysiological cause of many cardiovascular diseases. Erosion or rupture of atherosclerotic lesions, with coagulation factor and blood platelet activation, can result in further stenosis with thrombus formation and peripheral embolisation (1).

In 2016, more than one in five people in Norway used drugs to treat or prevent cardiovascular disease (2). Although the incidence of cardiovascular diseases is declining, an increase in the proportion of the population living with these conditions is anticipated. This is a result of improved survival and an ageing population (3).

Elevated cardiovascular risk

Established preventive measures against cardiovascular disease are lifestyle interventions, antidiabetic drugs, blood pressure-regulating and cholesterol-lowering drugs, as well as revacularisation treatment if indicated (4, 5). Secondary prophylaxis includes antithrombotic medication for coronary artery disease, carotid stenosis or symptomatic peripheral artery disease.

Patients with established cardiovascular disease are considerably exposed to serious cardiovascular events (cardiovascular death, myocardial infarction and stroke), even with effective treatment and good compliance (1). The risk has been estimated at as much as 20 % after 3–4 years (1, 6).

In patients with coronary artery disease, peripheral artery disease is a known risk marker for a serious outcome, and patients with this disease have an elevated risk of serious cardiovascular events (7). Patients with peripheral artery disease are also considerably exposed to major adverse limb events (acute ischaemia, amputation and surgical revascularisation) (5).

New trials of antithrombotic regimens

A number of trials of different antithrombotic regimens for patients with cardiovascular disease have been published, but total benefit viewed in relation to risk has often been unfavourable, for reasons including an increase in intracranial and/or fatal haemorrhaging (4, 6). Two recently published trials showed different results.

PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction) (8, 9) included 21 162 patients with a history of myocardial infarction. Dual antiplatelet therapy with ticagrelor 60 mg twice daily plus acetylsalicylic acid 75 mg daily resulted in a significant reduction in serious cardiovascular events (HR 0.84, p = 0.004) compared with acetylsalicylic acid as monotherapy. In the ticagrelor group, the number of major haemorrhages doubled but there was no significant increase in fatal or intracranial haemorrhages. There was a significant reduction in mortality for patients with peripheral arterial disease in the group that received 60 mg ticagrelor (HR 0.52, p = 0.007).

«Intensified antithrombotic therapy resulted in a marked reduction in systemic ischaemic complications in patients with cardiovascular disease»

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) (10, 11) included 27 395 patients with stable atherosclerosis, coronary and/or peripheral. Acetylsalicylic acid plus 2.5 mg rivaroxaban resulted in significantly fewer serious cardiovascular events (HR 0.76, $p < 0.001$) and a significant reduction in mortality (HR 0.82, $p = 0.01$) compared to acetylsalicylic acid as monotherapy. Major haemorrhages increased significantly (3.1 % vs 1.9 %, $p < 0.001$), but intracranial or fatal haemorrhages did not. Major adverse limb events were halved in the subgroup with peripheral artery disease (HR 0.54, $p = 0.005$). An independent safety committee terminated the COMPASS trial early due to a clear intervention effect.

Assessment

In the studies mentioned, intensified antithrombotic therapy resulted in a marked reduction in systemic ischaemic complications in patients with cardiovascular disease, and it even improved survival. The treatment regiments may consequently improve prognosis for a patient population that is particularly exposed to risk. The benefit was especially notable in patients with peripheral artery disease. Intensified antithrombotic medication invariably increases the risk of haemorrhage and must be included in the risk-benefit assessment.

On the basis of these trials, the Norwegian Medicines Agency has expanded the indications for drug therapy. The long-term treatments have now been included in the drug reimbursement scheme.

European guidelines for coronary artery disease, published in January 2020, state that in cases of high/moderate risk of an ischaemic event, the addition of an antithrombotic drug to acetylsalicylic acid therapy should/may be considered (4).

In light of the above, we believe that the findings from the trials should be incorporated into Norwegian guidelines. Patients with established coronary disease or symptomatic peripheral artery disease and who are at high risk of an ischaemic event, without a high risk of haemorrhage, should be assessed for supplementary therapy with rivaroxaban or ticagrelor (after myocardial infarction). The patients should be involved in the risk-benefit discussion and in the decision on treatment strategy.

LITERATURE

1. Fox KAA, Metra M, Morais J et al. The myth of 'stable' coronary artery disease. Nat Rev Cardiol 2020; 17: 9–21. [PubMed][CrossRef]

2. Folkehelseinstituttet. Statistikk fra Reseptregisteret. http://www.reseptregisteret.no/Prevalens.aspx Accessed 4.5.2020.

3. Folkehelserapporten. Hjerte- og karsykdommer i Norge. https://www.fhi.no/nettpub/hin/ikke-smittsomme/Hjerte-kar/ Accessed 4.5.2020.

4. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020; 41: 407–77. [PubMed][CrossRef]

5. Aboyans V, Ricco JB, Bartelink MEL et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases. Eur Heart J 2018; 39: 763–816. [PubMed][CrossRef]

6. Fox KAA, Eikelboom JW, Anand SS et al. Anti-thrombotic options for secondary prevention in patients with chronic atherosclerotic vascular disease: what does COMPASS add? Eur Heart J 2019; 40: 1466–71. [PubMed][CrossRef]

7. Lewis BS, Atar D. Peripheral arterial disease and limb salvage: a new arena for the cardiologist. Eur Heart J Cardiovasc Pharmacother 2018; 4: 136–7. [PubMed][CrossRef]

8. Bonaca MP, Bhatt DL, Cohen M et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791–800. [PubMed][CrossRef]

9. Bonaca MP, Bhatt DL, Storey RF et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol 2016; 67: 2719–28. [PubMed][CrossRef]

10. Anand SS, Bosch J, Eikelboom JW et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018; 391: 219–29. [PubMed][CrossRef]

11. Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377: 1319–30. [PubMed][CrossRef]

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