Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation

Background:

Oral anticoagulation is indicated to prevent stroke in patients that suffer from atrial fibrillation, but does not help in preventing stent thrombosis in patients with PCI. Dual anti-platelet therapy (DAPT) has long been recommended for stent thrombosis and cardiac ischemia prophylaxis but doesn't assist in stroke prophylaxis in those without atrial fibrillation. Therapy with dual anti-platelet therapy and anticoagulation is associated with higher risk of bleeding.

There have been previous trials that have evaluated either standard or reduced dose of other direct oral anticoagulants (DOACs) in patients with atrial fibrillation who also underwent PCI and these were shown to have a lower incidence of bleeding with the DOACs without aspirin compared to warfarin plus aspirin. However, these trials weren't powered to detect if the difference was due to the lower dose of DOACs or the presence or absence of aspirin. This trial was designed to evaluate the safety and efficacy of apixaban versus warfarin and of low dose aspirin compared to placebo, on the background of P2Y12 inhibitor therapy for 6 months.

What they did:

This was a prospective, randomized, two by two factorial design conducted in 33 countries examining use of apixaban or a vitamin K antagonist with either aspirin or placebo in patients with atrial fibrillation who had acute coronary syndrome or PCI.

- First hypothesis was that apixaban would be at least non-inferior, and possibly superior to warfarin in regards to the primary outcome of major or clinically relevant non-major bleeding as defined by the International Society on Thrombosis and Hemostasis.
- Second hypothesis was that single antiplatelet therapy with a P2Y12 inhibitor would be superior to DAPT in regards to the primary outcome of major or clinically relevant non-major bleeding as defined by the International Society on Thrombosis and Hemostasis.

Patients were followed for 6 months following PCI with stent placement.

Definitions:

Major bleeding was defined as bleeding that resulted in death, occurred in a critical organ, or was associated with either a decrease in hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed RBC.

Ischemic events was defined as stroke, myocardial infarction, stent thrombosis, or urgent revascularization.

Outcomes:

Primary outcome was major or non-major clinically significant bleeding.

Secondary outcomes included death or hospitalization and a composite of ischemic events.

Inclusion:

18 years or older, diagnosed with atrial fibrillation (AF), with planned long term anticoagulation therapy

Also had recent ACS or PCI and planned P2Y12 inhibitor usage for at least 6 months

Exclusion:

Anticoagulation for another reason other than AF, such as mechanical valve or venous thromboembolism. Other exclusion criteria included severe renal insufficiency, a history of intracranial hemorrhage, recent or planned coronary-artery bypass graft surgery, coagulopathy or ongoing bleeding, and contraindication to any of the drugs being studied

Results:

Total randomized = 4614

Randomization 1 = apixaban (n=2306) vs warfarin (N=2308)

- Primary outcome of bleeding: 10.5% vs 14.7% HR 0.69 (95% CI 0.58-0.81) p<0.001
- Secondary outcomes
    - Death or hospitalization: 23.5% vs 27.4% HR 0.83 (95% CI 0.74-0.93) p= 0.002
    - Death or ischemic event: 6.7% vs 7.1% HR 0.93 (95% CI 0.75-1.16) p= non-significant
    - Death: 3.3% vs 3.2% Hr 1.03 (95% 0.75-1.42) p= not reported

Randomization 2 = Aspirin (N=2307) vs placebo (N=2307)

- Primary outcome of bleeding: 16.1% vs 9.0% HR 1.89 (95% CI 1.59-2.24) p<0.001
- Secondary outcomes
    - Death or hospitalization: 26.2% vs 24.7% HR 1.08 (95% CI 0.96-1.21) p= non-significant
    - Death or ischemic event: 6.5% vs 7.3% HR 0.89 (95% CI 0.71-1.11) p= non-significant
    - Death: 3.1% vs 3.4% HR 0.91 (95% CI 0.66-1.26)

Overall primary outcome of the rate of major or clinically relevant non-major bleeding as define by the International Society on Thrombosis and Hemostasis according to combination in event rate per 100 patient years:

- Warfarin and aspirin = 49.1
- Apixaban and aspirin = 33.6
- Warfarin and placebo = 26.7
- Apixaban and placebo = 16.8

Strengths:

- Large randomized study performed in multiple countries
- The dose of apixaban used has proven efficacy to prevent stroke in patients with atrial fibrillation
- It supports previous data that apixaban is a safe and effective option that is superior to warfarin in patients with atrial fibrillation that undergo PCI or have ACS
- Supports previous data that DAPT with ASA and a P2Y12 in conjunction with anticoagulation likely provides little antithrombotic benefit compared to single antiplatelet with P2Y12 with an oral anticoagulant

Limitations:

- Those in the warfarin group spent approximately 23% of times out of therapeutic range
- Follow up was short in duration as it only included 6 months post PCI or ACS event
- Even though it was well powered, there were not enough patients to detect differences in less common but important individual ischemic outcomes.
- A majority of the patients were treated with clopidogrel so there is limited applicability to the other P2Y12 agents.

Study Author Conclusions:

- In patients with atrial fibrillation who also undergo PCI or have ACS, apixaban plus a P2Y12 inhibitor is associated with less bleeding and fewer hospitalizations without increased ischemic events risk compared to those treated with warfarin, aspirin or both.

Our Take home point

- Unfortunately, there is not one drug that can be used to prevent cardioembolic strokes in atrial fibrillation and prevent stent thrombosis or ischemic attacks in patients with ACS or undergoing PCI.
- This study adds to previous literature in allowing us to safely assume dual antiplatelet therapy plus anticoagulation is unnecessary unless there is a huge thrombotic risk.
- Using a new oral anticoagulant, over warfarin, plus clopidogrel without additional aspirin provides safe and effective prevention of both events without significantly increasing bleeding risk.

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References:

- Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019;