Indicators for Triple Therapy

Patients with atrial fibrillation and who have a CHA2DS2-VASc score of ≥1 are indicated for chronic oral anticoagulation with warfarin for stroke prevention. About 30% of these patients also have coronary artery disease (CAD), which may require percutaneous coronary intervention (PCI), a procedure used to open blocked coronary arteries.

In patients undergoing PCI, therapy with aspirin and clopidogrel to prevent stent thrombosis and other thromboembolic events was recommended by the 2010 European guidelines. This often results in triple therapy because the patient needs dual antiplatelet therapy post-PCI and is most likely receiving oral anticoagulation for atrial fibrillation. However, the 2014 North American guidelines recommend dual therapy with warfarin and clopidogrel only.

Risks of Triple Therapy

The use of triple therapy with warfarin, aspirin, and clopidogrel produces a high annual bleeding risk of up to 45% and has been associated with major bleeding events, the need for blood transfusion, and an increased risk of mortality. With the population of patients that have both atrial fibrillation and CAD increasing, the risks of using triple therapy must be weighed against the potential benefit.

Allegheny County, PA, and Beyond

Prevalence of Atrial Fibrillation and Warfarin Therapy

- It was estimated that there were 2.7-3.1 million people in the United States that had atrial fibrillation in 2010 and that over 12 million people will be affected by 2030.
- Around 30% of people with atrial fibrillation also have CAD.
- In patients with atrial fibrillation, CAD accounts for 22% of early deaths (within the first four months of diagnosis of atrial fibrillation) and 15% of later deaths.
- An estimated 2.3 million patients start taking warfarin for the first time each year.
- The rate of age-adjusted coronary heart disease deaths is 14.7 out of every 100,000 people.

Risk Factors: Pennsylvania and Allegheny County

- In 2013, 21% of PA residents over the age of 18 reported smoking daily or some days.
- 49.3% of Allegheny County residents reported smoking 100+ cigarettes in their life time from 2005-2009.
- Prevalence of obesity in PA was 38-39% of the population in 2014.
- In Allegheny County, 62% of adults were found to be overweight or obese in 2018.

Risk Factors for Cardiovascular Disease

- Cigarette smoking
- High Blood Pressure
- High Cholesterol
- Physical Inactivity
- Being Overweight or Obese

Standard Therapies

Clopidogrel is a less potent agent than other P2Y12 antiplatelet agents like prasugrel and ticagrelor. It has a lesser risk of intracranial hemorrhage, which is important when choosing therapy in patients on an anticoagulant.

A low-dose aspirin is the other component of the dual antiplatelet therapy. Duration is recommended as indefinitely by the AHA Guidelines, but clinical judgment also has a strong influence.

The Vitamin K Antagonist warfarin is still the most common choice for lifelong anticoagulation in atrial fibrillation patients for stroke prevention. However, the direct thrombin inhibitor dabigatran is FDA-approved for treatment in these patients based on the RE-LY trial. Dabigatran was superior to warfarin in stroke reduction but both had similar rates of major bleeding events. There is still a lack of data for direct acting oral anticoagulants in general.

Direct Comparison: Triple vs. Dual Antithrombotic Therapy

- **WORST trial**: There was a significant reduction in major bleeding events in the dual therapy arm (warfarin and clopidogrel only), but direct thrombin events were not increased. Major bleeding events were numerically lower in the dual arm, but did not show statistical significance.
- **Danish group registry study**: Supports the data presented in the WORST trial and suggests that dual therapy without aspirin is insufficient to reduce the risk of thromboembolic events.
- **Study by Heri CN et al**: Bleeding requiring hospital readmission was significantly higher with triple therapy (17.8% vs. 11.9%).
- **Study by Kim JY et al**: For second-generation drug-eluting stents, there is no additional survival benefit of triple therapy.

Data

Weighing Bleeding Risk and Stroke Risk

- "No firm recommendations can be made at this time concerning triple therapy with dabigatran given the absence of safety and efficacy data in patients undergoing PCI." (Patson et al)

Blurring risk and bleeding risk should be considered when making clinical decisions about antithrombotic therapy. As shown here, HAS-BLED score is an indicator of bleeding risk, while the CHA2DS2-VASc score indicates the risk for stroke in patients with atrial fibrillation.

These scores influence the choice and duration of therapy. Dual therapy achieved by the discontinuation of aspirin immediately after PCI can replace triple therapy.

Pharmacists’ Role

Pharmacists can play a crucial role in decreasing the bleeding risk in patients on dual and triple therapies. Most importantly, pharmacists should be a patient advocate, working to create individualized care plans while also following current guidelines and recommendations.

Implications

It is important that atrial fibrillation patients post-PCI are receiving the current standard of care:
- Low-dose aspirin is defined as less than or equal to 100 mg daily
- Clopidogrel is less potent than prasugrel and ticagrelor in terms of intracranial hemorrhage
- Initiation of a proton pump inhibitor, such as lansoprazole, could aid in prevention of gastrointestinal bleeding

Other factors to consider:
- Patient population is generally older and have other co-morbidities
- Discontinuing an oral anticoagulant prior to the procedure as well as bridging before and after the procedure increases risk of complications and bleeding
- What to do after clopidogrel is discontinued
- The role of novel oral anticoagulants such as dabigatran

Patient Counseling:
- Ensure patient is taking low-dose aspirin if aspirin cannot be discontinued
- Discontinue NSAIDs if possible
- Discuss possible implementation of PPI to combat GI bleeding
- Counsel on signs and symptoms of bleeding

Make Recommendations:
- Lowest possible dose of aspirin
- Consider clopidogrel rather than prasugrel or ticagrelor

Implement Interventions:
- Utilize technology to employ a flagging system to bring attention to high risk patients
- Patients on triple therapy should be flagged