Cardiovascular Disease

1. More target specific oral anticoagulants (TSOAC)
2. Vorapaxar (Zonivity)
3. Continued noise about a “polypill”
4. WATCHMAN
"Take an aspirin every day, but before you swallow it, take it out for a five-mile walk."

CLINICAL PERSPECTIVE

Vonaparin is a first-in-class inhibitor of the platelet prothrombin-activated receptor-1 pathway that is activated by thrombin. Vonaparin is established to be effective for the secondary prevention of thromboembolism, similar to other parenteral antithrombotics, decreases bleeding. The findings from the analysis of the TRAP-PLUS-50 show that, in high-risk patients with diabetes mellitus, the addition of vonaparin to standard therapy significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke with a favorable effect on net clinical outcomes. Although the relative benefit of vonaparin was similar in patients with or without diabetes mellitus, there was a greater absolute risk reduction in cardiovascular events with vonaparin in patients with diabetes mellitus, such that only 20 patients needed to be treated to prevent one occurrence of cardiovascular death, myocardial infarction, or stroke over the period of follow-up (1 year). The use of vonaparin in clinical practice should weigh the potential reductions in ischemic events with the concomitant risk of bleeding. These findings indicate that patients with diabetes mellitus have a particularly favorable balance between the risk of bleeding and reduction in thrombotic events with vonaparin.
Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis.

Abstract

Objective: Treatment with aspirin and a P2Y12-inhibitor is currently standard in patients with cardiovascular disease. The overall effect of more prolonged duration of dual antiplatelet therapy on clinical outcomes is not clear. Therefore we performed a systematic review to summarize the available evidence examining the association between the duration of dual antiplatelet therapy and corresponding clinical outcomes.

Methods: Studies were identified by searching the MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases. Studies were included if they compared the outcomes of patients treated with dual antiplatelet therapy for a duration of at least 12 months. Clinical outcomes assessed included all-cause mortality, cardiovascular death, myocardial infarction (MI), all-cause and cardiovascular hospitalization, and urgent coronary artery revascularization. Pooled estimates were calculated using random-effects meta-analysis.

Results: Twenty studies with a total of 14,199 patients were included in the analysis. A total of 3,402 patients were treated with aspirin and a P2Y12-inhibitor for a duration of at least 12 months. The pooled incidence of all-cause mortality was 3.4% (95% confidence interval [CI] 2.3% to 4.6%). The pooled incidence of cardiovascular death was 2.3% (95% CI 1.6% to 3.1%). The pooled incidence of MI was 4.4% (95% CI 2.9% to 6.4%). The pooled incidence of all-cause hospitalization was 21.5% (95% CI 19.6% to 23.4%). The pooled incidence of cardiovascular hospitalization was 13.5% (95% CI 11.6% to 15.4%). No differences were observed between patients treated with aspirin and a P2Y12-inhibitor for at least 12 months as compared with those treated with aspirin alone for the clinical outcomes assessed.

Conclusion: Dual antiplatelet therapy with aspirin and a P2Y12-inhibitor for a duration of at least 12 months was not associated with differences in all-cause mortality, cardiovascular death, MI, all-cause or cardiovascular hospitalization, or urgent coronary artery revascularization as compared with aspirin alone.
Left Atrial Appendage Closure Device (Watchman)
Apixaban

**Apixaban in Acute Coronary Syndrome**
- APPRAISE
  - Apixaban increased number of major bleeding events
  - Apixaban showed no significant reduction of recurrent ischemic events

**Apixaban in Atrial Fibrillation**
- ARISTOTLE
  - Apixaban superior to warfarin in preventing stroke or systolic embolism
  - Apixaban caused less bleeding resulting in lower mortality
Apixaban in Atrial Fibrillation

- **AVERROES**

  - Apixaban reduced the risk of stroke or systemic embolism
    - Without significantly increasing the risk of major bleeding or intracranial hemorrhage

Apixaban for DVT/PE Treatment

- **AMPLIFY**

  - Noninferior to conventional therapy for treatment of acute venous thromboembolism
    - Associated with significantly less bleeding

Apixaban for DVT/PE Treatment

- **Botticelli**

  - The attractive fixed dose combination of this compound may meet the demand to simplify anticoagulant treatment in patients with established venous embolism
### Apixaban for DVT PPx Hip

**ADVANCE-3**

- Thromboprophylaxis with apixaban (as compared with enoxaparin) was associated with lower rates of venous thromboembolism without increased bleeding.

### Apixaban for DVT PPx Knee

**ADVANCE-1**

- Compared with enoxaparin for efficacy of thromboprophylaxis after knee replacement apixaban did not meet the pre-specified statistical criteria for noninferiority.
  - Associated with lower rates of clinically relevant bleeding and had a similar adverse event profile.

### Apixaban Renal Dosing

- DVT/PE treatment: no dosage adjustment necessary.
- Nonvalvular AF:
  - Do not reduce dose if SCR < 1.5 if no factors present
  - Reduce dose to 2.5 mg BID if SCR < 1.5 mg/dL with **both** of the following:
    - Age ≥ 80 years
    - Body weight ≤ 60 kg
  - Reduce dose to 2.5 mg BID if SCR ≥ 1.5 mg/dL with **just one** of the following:
    - Age ≥ 80 years
    - Body weight ≤ 60 kg
- ESRD requiring hemodialysis:
  - Reduce dose to 2.5 mg BID with **just one** of the following:
    - Age ≥ 80 years
    - Body weight ≤ 60 kg
- Postoperative (hip or knee replacement) DVT PPx: no dosage adjustment necessary.
Dabigatran

**Dabigatran in Acute Coronary Syndrome**

- **RE-DEEM**

- Dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation activity in patients with a recent myocardial infarction.

**Dabigatran in Atrial Fibrillation**

- **RE-LY**

- Dabigatran at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.

- Dabigatran at a dose of 150mg (compared with warfarin) was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.
Dabigatran for DVT/PE Treatment

- RE-MEDY
- RE-SONATE

Dabigatran was effective in the extended treatment of venous thromboembolism and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.

Dabigatran DVT PPx Hip

- RE-NOVATE

Oral dabigatran was as effective as enoxaparin in reducing the risk of venous thromboembolism after total hip replacement surgery, with a similar safety profile.

Dabigatran for DVT PPx Knee

- RE-MOBILIZE

Dabigatran, effective compared to once daily enoxaparin, showed inferior efficacy to the twice-daily North American enoxaparin regimen.
Dabigatran Renal Dosing

- **DVT/PE Treatment**
  - CrCl > 30 mL/min and **no** P-gp Inhibitors: no dosage adjustment necessary
  - CrCl > 30 mL/min and P-gp inhibitors **PRESENT**: avoid co-administration
  - CrCl ≤ 30 mL/min

- **Nonvalvular AF**
  - CrCl > 55 mL/min: no dosage adjustment necessary
  - CrCl 30 – 50 mL/min and **no** Dronedarone or oral ketoconazole
    - No dosage adjustment necessary
  - CrCl 30 – 50 mL/min **with** Dronedarone or oral ketoconazole
    - Reduce dose to 75mg BID
  - CrCl 15 – 30 mL/min and **no** P-gp inhibitor: 75mg BID
  - CrCl 15 – 30 mL/min **with** P-gp Inhibitor: Avoid concurrent use
  - CrCl < 15 mL/min: avoid use

Edoxaban

Edoxaban in Atrial Fibrillation

- ENGAGE AF-TIMI 48

- Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes
Edoxaban for DVT/PE Treatment

• Hokusai

• Edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism.

Edoxaban DVT PPx Hip

• Takeshi F, Satoru F, Yohko K et al.

• Compared to subcutaneous enoxaparin 2000 IU twice daily, oral edoxaban 30mg once daily demonstrated similar safety and efficacy in the prevention of thromboembolic events in Japanese patients undergoing hip fracture surgery.

Edoxaban DVT PPx Knee

• STARS E-3

• Edoxaban 30mg once daily is more effective for thromboprophylaxis and associated with a similar incidence of bleeding in Japanese and Taiwanese patients undergoing TKA compared with subcutaneous enoxaparin 2000 IU twice daily.
Edoxaban Renal Dosing

- DVT/PE Treatment
  - CrCl >50 mL/min: no dosage adjustment necessary
  - CrCl 15 – 50 mL/min: 30 mg daily
  - CrCl < 15 mL/min: avoid use

- Nonvalvular atrial fibrillation
  - CrCl >95 mL/min: Avoid use
  - CrCl 51 – 95 mL/min: no dosage adjustment recommended
  - CrCl 15 – 50 mL/min: 30 mg daily
  - CrCl <15: Avoid use

Rivaroxaban

Rivaroxaban in Atrial Fibrillation

- ROCEKT AF

- In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
Rivaroxaban for DVT and PE Treatment

- EINSTEIN

- Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation.

Rivaroxaban for DVT PPx Hip

- RECORD-1

- A once-daily, 10-mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than once-daily, 40-mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. The two drugs had similar safety profiles.

Rivaroxaban DVT PPx Knee

- RECORD-3

- Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.
Rivaroxaban Renal Dosing

- **DVT/PE Treatment**
  - CrCl ≥ 30 mL/min: No dosage adjustment necessary
  - CrCl < 30 mL/min: Avoid use

- **Nonvalvular AF**
  - CrCl > 50 mL/min: No dosage adjustment necessary
  - CrCl 15 – 50 mL/min: 15mg daily with evening meal
  - CrCl <15 mL/min: Avoid use

- **DVT PPFx Hip and Knee**
  - CrCl ≥ 30 mL/min: No dosage adjustment necessary
  - CrCl < 30 mL/min: Avoid use

---

**Vorapaxar**

Vorapaxar is a first-in-class inhibitor of the platelet protease-activated receptor-1 pathway that is activated by thrombin. Vorapaxar is established to be effective for the secondary prevention of ischemic stroke in patients who have experienced a transient ischemic attack or minor stroke. The results from the VORTEX study showed that, as compared to patients with diabetes mellitus, the addition of vorapaxar to standard therapy significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke with a favorable effect on net clinical outcomes. Although the relative benefit of vorapaxar was similar in patients with or without diabetes mellitus, there was a greater absolute risk reduction in cardiovascular events with vorapaxar in patients with diabetes mellitus such that only 25 patients needed to be treated to prevent one occurrence of cardiovascular death, myocardial infarction, or stroke over the period of follow-up (1 year). The use of vorapaxar in clinical practice should weigh the potential reductions in ischemic events with the concomitant risk of bleeding. These findings indicate that patients with diabetes mellitus may have a particularly favorable balance between the risk of bleeding and reduction in thrombotic events with vorapaxar.
"Yes! That was very loud Sir, but I said I wanted to hear your HEART!"