envolve
Pharmacy Solutions

Drug Class Review Monograph – GPI Class 83 – Anticoagulants

Review Time Frame: January November 11/2015 – 01/January 2017

Previous Class Review: 02/2016

6

Background:

Anticoagulants are agents that prevent the formation of blood clots, by affecting blood coagulation factors. The mechanism of action of anticoagulation varies depending on the agent. They are used to prevent or to treat thrombotic and thromboembolic disease such as stroke, myocardial infarction, deep vein thrombosis (DVT), and pulmonary embolism (PE). The anticoagulant classes include:

- Heparins and heparin-like agents - exerts its anticoagulant action by accelerating the activity of antithrombin III (ATIII) to inactivate thrombin.
- Coumadin aAnticoagulants - inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S.
- Thrombin inhibitors - prevent thrombin-induced platelet aggregation and the development of a thrombus by preventing the thrombin-mediated conversion of fibrinogen into fibrin during the coagulation cascade.
- Direct fFactor Xa Iinhibitors - inhibits fFactor Xa that is both free and bound to clots and as well asalso inhibits prothrombinase activity.

New Ttreatment guideline recommendations pertaining to anticoagulants:

- The American Society of Clinical Oncology Clinical Practice guideline 2014 update recommends patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low-molecular weight heparin (LMWH) or low-dose aspirin.
- Those undergoing major surgery should receive prophylaxis starting before surgery and continuing for a minimum of 7 to 10 days. For those undergoing major abdominal or pelvic surgery with high-risk features, extending prophylaxis for up to 4 weeks should be considered.
- LMWH is recommended for the initial 5 to 10 days of treatment for deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis of at least 6 months.
- The American College of Chest Physicians (CHEST) guideline and expert panel report 2016 updated recommendations include:
  - In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
  - In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest low molecular weight heparin (LMWH) over VKA therapy (Grade 2B), dabigatran (Grade2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).
  - In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).

Formatted: Space After: 10 pt
Formatted: Font: 12 pt, Not Italic
Formatted: Font: 12 pt, Not Italic
Formatted: Font: 12 pt, Not Italic
Formatted: Font: 12 pt, Not Italic
Formatted: Space After: 10 pt
Formatted: Font: Not Bold
Formatted: Font:
Formatted: Font:
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font:
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font: Not Bold

Formatted: Right

- In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B).
- In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent post-thrombotic syndrome (PTS) (Grade 2B).
- In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C) or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).
- In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (e.g., after the first 5 days of treatment) (Grade 2B).
- In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).
- In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).
- In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter-directed thrombolysis (CDT) (Grade 2C).
- In selected patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).
- In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).
- In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

- The American Congress of Obstetricians and Gynecologists' District II Safe Motherhood Initiative's Venous thromboembolism bundle on risk assessment and prophylaxis for obstetric patients update in 2015 recommends:
  - All patients require VTE risk assessment at multiple time points in pregnancy and postpartum.
  - All patients undergoing cesarean delivery require mechanical prophylaxis, early ambulation, and adequate hydration.
  - Women with additional risk factors for VTE after delivery will benefit from pharmacologic prophylaxis.
  - Empiric pharmacologic prophylaxis is a reasonable option for:
    - All women undergoing cesarean delivery
    - All antepartum hospital admissions >72 hours
- The 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation was created to provide

Formatted

guidance statements on initiation, timing, maintenance, and restarting anticoagulation for patients with nonvavular atrial fibrillation going through procedures.

Newly approved drugs:
- None identified

Newly approved formulations:
- None identified

Newly approved generics:
- None identified

- None identified

FDA Safety Alert/black box warnings:
- ~~None Identified~~05/2016: FDA Safety Labeling Changes to Xarelto (Rivaroxaban) tablets: addition of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors as drugs that can cause additive bleeding when taken together (refer to page 4 for full detail).

Pipeline alerts:

Agents pending FDA approval include:
- Betrixaban is an oral, once-daily factor Xa inhibitor whose NDA is currently being reviewed by the FDA with priority review for the indication of extended-duration prophylaxis of venous thromboembolism in acute medically ill patients with risk factors for VTE.
- Tecarfarin is an oral vitamin K antagonist currently in phase III trials for the indication of reducing the risk of stroke. The drug is being developed to address the unmet need of a vitamin K antagonist with potentially fewer adverse and fatal drug interactions with improved stability in maintaining a therapeutic INR level. The trial population focused on patients who had a history of difficult INR control utilizing warfarin, defined as maintaining within the target INR less than 45% of the time.

~~**Summary/Recommendation:**~~

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2015. URL: http://www.clinicalpharmacology-ip.com/. Updated February 2017.
2. WWW.FDA.GOV.
3. Antithrombotic Therapy for VTE Disease: Chest Guideline and Expert Panel Report 2016. CHEST. 2016; 149 (2):315-352.
4. Maternal Safety Bundle for Venous Thromboembolism. The American Congress of Obstetricians and Gynecologists. Revised November 2015. Accessed February 2017. Available at: https://www.acog.org/-/media/Districts/District-II/Public/SMI/v2/VTESlideSetNov2015.pdf?dmc=1&ts=20170206T1609192410
5. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force.

Formatted: Right

Formatted: Default, Indent: Left: 0", Bulleted + Level: 1 + Aligned at: 0.25" + Indent at: 0.5", Adjust space between Latin and Asian text, Adjust space between Asian text and numbers

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Bold

Formatted: Tab stops: 4.28", Left + 5.06", Left

Formatted: Tab stops: 5.19", Left

Journal of the American College of Cardiology; 2017. Accesed February 2017. Available at: file:///C:/Users/a086474/Downloads/j.jacc.2016.11.024.full.pdf

6. Pharmacy & Therapeutics Management [database online]. Bay Harbor Islands, FL: IPD Analytics, LLD. Accessed February 2017. Available at:www.ipdanalytics.com.

FDA Drug Safety Labeling Update: FDA adds selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors to the paragraph beginning with Concomitant use of other drugs in the warning and precautions section under risk of bleeding. [May 2016]

In addition, safety labeling regarding "Use in Patients with Renal Impairment" in nonvalvular atrial fibrillation was changed to "Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation of Xarelto in patients who develop acute renal failure while on Xarelto." In patients with end-stage renal disease on dialysis, information was added regarding "Clinical efficacy and safety studies with Xarelto did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of Xarelto 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF."

~~*generic availability~~

Formatted: Right

Formatted: No bullets or numbering, Tab stops: 5.19", Left

Formatted: Font: Bold

Formatted: No bullets or numbering, Tab stops: 5.19", Left

Formatted: Font: Bold

Formatted: Font color: Auto

Formatted: Font: 12 pt, Font color: Auto

Formatted: Normal, Pattern: Clear (White)

Formatted: Font: 12 pt, Font color: Auto

Formatted: Font: Times New Roman, 12 pt, Font color: Auto

Formatted: Font: Times New Roman, 12 pt, Font color: Auto

Formatted: Font: Times New Roman, 12 pt, Font color: Auto

Formatted: Font: (Default) Helvetica, 10.5 pt, Not Bold, Not Italic