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Review of Anticoagulation Therapy in Unprovoked Pulmonary Embolism

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Abstract

The purpose of this research was to identify the best course of action in response to a diagnosis of unprovoked pulmonary embolism.

- The evidence demonstrates non-inferiority status of new direct oral anticoagulants (DOAC) when indirectly compared to conventional warfarin therapy.
- Aspirin was also found effective in mitigating the risk of recurrence, but to a lesser extent than both DOAC agents and warfarin.
- DOACs are reasonable alternatives to conventional therapy. Attention to individual comorbidities may allow providers to find advantage with one therapy over another.
- The research, thus far, has not been able to identify a universally safe and an effective agent for all patients experiencing a first-time unprovoked pulmonary embolism.
- Additional research is needed to evaluate the duration of therapy and generate more robust data to recommend a specific therapeutic agent for all patients.

Introduction

- Secondary prevention of pulmonary embolism has generated a tremendous amount of interest and debate in recent years.
- The development of Direct Thrombin Inhibitors (DTI), and Factor Xa Inhibitors (FXI) collectively known as the direct oral anticoagulation drugs (DOAC), have become replacement agents for conventional therapy.
- Traditional anticoagulation agent, Warfarin, a vitamin K antagonist (VKA) has an increased bleeding risk
- Acetylsalicylic acid or Aspirin (ASA) has been used as an alternative to VKA, which provides only a fraction of the benefit while marginally mitigating the bleeding risk.
- Another consideration is the duration of therapy, as termination of therapy places patients back into a high-risk category.

Statement of the Problem

First-time unprovoked pulmonary embolism presents a difficult choice for recurrence prevention. Etiology of the insult is unknown, and prevention of recurrence is of utmost importance, but with treatment comes increased risk, primarily bleeding episodes. A provider must address each unprovoked PE patient on an individual basis and evaluate risk/benefit individually. This research is designed to help providers choose the best course of action for PE recurrence prevention while mitigating risk

Research Question

Does drug choice and treatment duration impact morbidity and mortality for first-time unprovoked pulmonary embolism?

Literature Review

- Preliminary data suggest DOACs net benefit threshold deserves to be lower than warfarin in lifelong therapy consideration
- DOACs are considered reasonable alternatives to conventional warfarin therapy with reported 0.4-1.2% for recurrence in treatment arms and 5.6-8.8% in the placebo arms
- **DOACs**
  - Apixaban was shown to be the safest DOAC evaluated
  - Dabigatran demonstrates equal efficacy to warfarin; 1.3% reported recurrence in the warfarin group and 1.8% in the dabigatran group, p= 0.01
  - Dabigatran was found to be safer than conventional therapy in patients over the age of 60, p=0.0099.
  - Dabigatran also demonstrated protection up to one after discontinuing therapy
  - Rivaroxaban was shown to be more effective at 10mg and 20 mg doses than placebo and daily aspirin; 4.4% recurrence rate whereas rivaroxaban reported recurrence at 1.5% and 1.2% in 10 mg and 20 mg respectively, p< 0.001
- **Warfarin**
  - 8.8% reduction per year in treatment groups over placebo.
  - The same study showed a 1.3% increase in bleeding risk in the treatment over placebo
  - 8.6% increase in bleeding risk at a four-year follow-up in the treatment group over control.
  - Warfarin reports higher rates of clinically relevant bleeding dabigatran
- **Aspirin**
  - Potential cardioprotective component of daily aspirin therapy, 34% reduction in reported major cardiovascular events, p=0.01
  - Aspirin showed no statistically significant differences in recurrence when compared to placebo 4.8% versus 6.5% respectively, p= 0.09.

Discussion

- Most studies did not exclusively evaluate first-time pulmonary embolism patients.
- Limited data for extended and indefinite therapy
- Very strict inclusionary criteria in DOAC studies
- Fragile patients were not included in the DOAC studies
- Heterogenous lead-in therapy in the DOAC studies
- Only one study directly compared warfarin to DOAC
- Aspirin was least efficacious agent but did not have as stringent contraindications.

TABLE 5 Main Results of Phase III Studies With NOACs for Extended Treatment of VTE

NOAC (Ref. #)	Study	N	Treatment	Duration (months)	Efficacy Outcome	Safety Outcome
Dabigatran (85)	RE-MEDY	2,856	Dabigatran 150 mg bid vs. warfarin (INR 2-3)	18-36	Recurrent VTE: 1.8% with dabigatran, 1.3% with warfarin	Major bleeding: 0.9% with dabigatran, 1.8% with warfarin
	RESONATE	1,343	Dabigatran 150 mg bid vs. placebo	6	Recurrent VTE: 0.4% with dabigatran, 5.6% with warfarin	Major bleeding: 0.3% with dabigatran, 0 with placebo
Rivaroxaban (39)	EINSTEIN-extension	602	Rivaroxaban 20 mg daily vs. placebo	6 or 12	Recurrent VTE: 1.3% with rivaroxaban, 7.1% with placebo	Major bleeding: 0.7% with rivaroxaban, 0 with placebo
Apixaban (86)	AMPLIFY-extension	2,486	Apixaban 2.5 mg bid vs. placebo	12	Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo	Major bleeding: 0.2% with apixaban, 0.5% with placebo
			Apixaban 5 mg twice daily vs. placebo		Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo	Major bleeding: 0.1% with apixaban, 0.5 % with placebo

RESONATE = Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; other abbreviations as in Tables 1 and 3.

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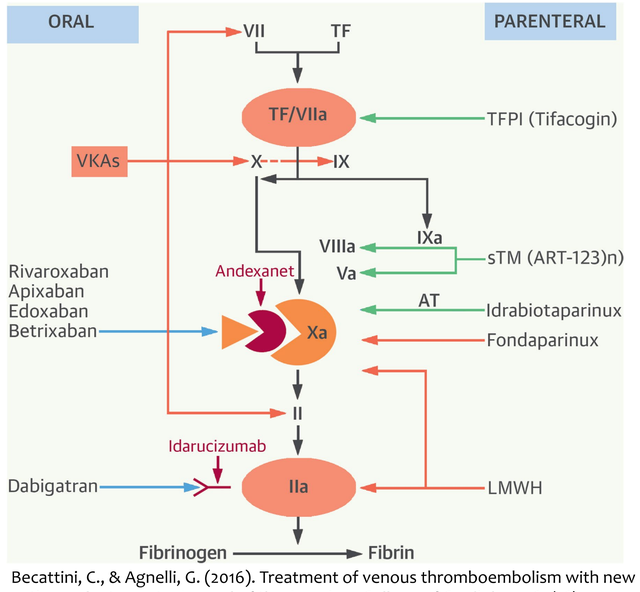

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Applicability to Clinical Practice

- More alternatives present more tailored care
- Providers must continually monitor and reassess risk
- More research is needed to determine optimal agent and duration of treatment.
- Continued shared decision-making
- Providers must remain diligent in keeping current on changes to anticoagulation therapy

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