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Direct Factor Xa Inhibitors Versus Warfarin in Non-Valvular Atrial Fibrillation: Efficacy, Safety, Cost, and Reversibility

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Applicability to Clinical Practice

- Direct factor Xa inhibitors are effective in preventing stroke and have similar or reduced bleeding risks when compared to warfarin.
- Direct factor Xa inhibitors decrease the risk of intracranial hemorrhage.
- Direct factor Xa inhibitors have favorable pharmacokinetics and pharmacodynamics when compared to warfarin.
- Cost is a concern for direct factor Xa inhibitors, but the risk of intracranial hemorrhage is far exceeding that of warfarin.
- Despite no reversal agent, direct factor Xa inhibitors cause less bleeding deaths when compared with warfarin.

References

Amsbaugh PA. (2016). Direct Factor Xa Inhibitors Versus Warfarin in Non-Valvular Atrial Fibrillation: Efficacy, Safety, Cost, and Reversibility. Cary D. Jacobs, PA-S, DC Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences Grand Forks, ND 58202-9037

Abstract

Atrial fibrillation is a common cause for stroke. Vitamin K antagonists such as warfarin are an effective prophylactic medication to prevent stroke in patients with atrial fibrillation. Warfarin, however, has a narrow therapeutic index, requires patient education, increases bleeding risks, and requires frequent monitoring. New medications have been developed to prevent clot formation while avoiding the negative effects of warfarin. The purpose of this study was to compare direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) versus warfarin in stroke prevention, safety, and cost.

The review of literature analyzed studies comparing warfarin and direct factor Xa inhibitors in patients with atrial fibrillation. Study outcomes included stroke prevention, safety, and cost. Analysis on anticoagulation/reversal agents were also examined.

Direct factor Xa inhibitors decreased stroke compared with warfarin with an odds reduction of 0.81 and decreased intracranial hemorrhages with an odds reduction of 0.56 (Bruins & Berge, 2013). Direct factor Xa inhibitors were more cost effective, but with higher out of pocket expenses. Direct factor Xa inhibitors have no reversal agent. Despite no antidote, research showed lower rates of fatal bleeding deaths associated with direct factor Xa inhibitor use compared to warfarin.

Introduction

Atrial fibrillation is a common abnormal heart rhythm leading to clot formation and stroke risk. Eckman (2016) states:

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is also the most powerful common risk factor for stroke: about 15% of all strokes in the U.S. are attributable to AF. (p. 234)

Vitamin K antagonists have long been used as an effective prophylactic medication to prevent thrombus formation in patients with atrial fibrillation. According to Santapag, Curcio, Sibilio, and Indolfi (2015), warfarin’s effectiveness is proven by 64% relative risk reduction of stroke compared with placebo, and it also shows superior results to aspirin and to aspirin plus clopidogrel (p. 914). Warfarin, while effective at preventing thrombi, has several drawbacks associated with its use. The direct factor Xa inhibitors have been developed in an attempt to effectively anticoagulate patients while waiting the negative aspects of warfarin.

Statement of the Problem

Warfarin is an effective anticoagulant but has several drawbacks to its use including a narrow therapeutic index, reaction with foods containing vitamin K, variable pharmacokinetics/pharmacodynamics and increased intracranial hemorrhage. These factors led to the development of new medications such as the direct factor Xa inhibitors.

Research Questions

In patients with atrial fibrillation, do direct factor Xa inhibitors decrease the risk of stroke and bleeding, and are the direct factor Xa inhibitors cost effective when compared to warfarin? Are direct factor Xa inhibitors reversible?

Literature Review

An online database search of PubMed and Cochran was performed for scholarly articles related to direct factor Xa inhibitor use versus warfarin in nonvalvular atrial fibrillation. Specific searches included efficacy of factor Xa inhibitors versus warfarin for stroke prevention, safety, cost, and reversibility.

Atrial fibrillation is a risk factor for stroke and a commonly used grading scale to assess stroke risk in atrial fibrillation is the CHA2DS2-VASc score.

Stroke Prevention:
- Bruins and Berge (2013) completed a systematic review and found a statistically significant reduction of all types of strokes for the factor Xa inhibitors compared to warfarin (odds ratio 0.78, 95% CI, 0.07 to 0.87, P = 0.003).
- Granger et al. (2011) demonstrated apixaban and warfarin in stroke prevention. Results demonstrated 1.60% had stroke or systemic embolism on warfarin compared to 1.27% on apixaban (hazard ratio for apixaban, 0.79, 95% CI, 0.66 to 0.95, P < 0.001); noninferiority).
- Patel et al. (2011) compared rivaroxaban and warfarin in stroke prevention. Results demonstrated rivaroxaban had a stroke or systemic embolism occurrence rate of 1.7% per year compared to 2.2% on warfarin (hazard ratio for rivaroxaban group, 0.79, 95% CI, 0.66 to 0.96, P < 0.001). (noninferiority).
- Giugliani et al. (2013) compared edoxaban and warfarin for stroke risk. Edoxaban was associated with comparable stroke and non-dose esoxaban and warfarin had an equal ischemic stroke risk of 1.25% per year (hazard ratio 1.00, 95% CI, 0.83 to 1.19, P = 0.97).

Bleeding Risks:
- Bruins and Berge (2013) found factor Xa inhibitors decreased intracranial hemorrhage when compared to warfarin (odds ratio 0.51, 95% CI, 0.41-0.65, P < 0.001). Factor Xa inhibitors decreased bleeding risks versus warfarin with high heterogeneity (odds ratio 0.89, 95% CI, 0.81-0.98, P = 0.011).
- Million, Grand, Shemyen, Filion, and Eisenhower (2012) demonstrated the new oral anticoagulants reduced rates of intracranial hemorrhage (RR=0.49, 95% CI, 0.36-0.66). Rivaroxaban had similar major bleeding events while apixaban had less major bleeding risks when compared to warfarin (RR=0.88, 95% CI, 0.71-1.09). Rivaroxaban had a non-significant risk for major bleeding (RR=0.98, 95% CI, 0.91-1.17).
- Giugliani et al. (2013) demonstrated warfarin had a major bleeding occurrence rate of 4.3% per year while apixaban had major bleeding occurrence rate of 2.75% per year (hazard ratio, 0.80, 95% CI, 0.71-0.91, P<0.001). High dose esoxaban was associated with higher rates of gastrointestinal bleeding (5.14% versus 1.23% in the warfarin group) (hazard ratio, 2.13, 95% CI, 1.02-1.50, P Value =0.03).

Cost:
- Amin et al. (2014) demonstrated cost savings with the direct factor Xa inhibitors apixaban ($493) and rivaroxaban ($359) for stroke prevention. In cost avoidance, excluding intracranial hemorrhage, apixaban saved $752 while rivaroxaban cost more than warfarin by $502.
- Out of pocket expenses depend on insurance coverage. With no insurance, the cost of rivaroxaban is $347 for 20 mg tabs, $342 for 5 mg apixaban tabs, and $290 for 60 mg edoxaban tabs. The cost of warfarin is $13 for 5 mg tabs (Anticoagulants, 2015).

Discussion

Direct factor Xa inhibitors are efficacious at preventing both ischemic and hemorrhagic stroke. Apixaban is superior to warfarin in stroke prevention while rivaroxaban and edoxaban are non-inferior to warfarin. All three direct factor Xa inhibitors cause less intracranial hemorrhage. Apixaban had less bleeding risks associated with its use compared to warfarin. Rivaroxaban had similar bleeding risks as warfarin but increased gastrointestinal bleeding. Edoxaban demonstrated less overall bleeding risk when compared to warfarin except increased gastrointestinal bleeding in the high-dose form. No direct comparison studies of the direct factor Xa inhibitors have been performed. Out of pocket costs of the direct factor Xa inhibitors is high, however, direct factor Xa inhibitors provided an overall cost savings with reduced number of stroke and/or systemic embolism occurrence.

The direct factor Xa inhibitors lack a reversal agent, however, the direct factor Xa inhibitors are associated with lower death rates compared to warfarin.

Table 2:

- Table examining stroke prevention efficacy of direct factor Xa inhibitors versus warfarin in nonvalvular atrial fibrillation.

Table 3:

- Table examining bleeding complications of direct factor Xa inhibitors versus warfarin in nonvalvular atrial fibrillation.

Table 4:

- Table examining cost of direct factor Xa inhibitors versus warfarin in nonvalvular atrial fibrillation.

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