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Comparison of Rivaroxaban and Warfarin in the Prevention of Recurrent Venous Thromboembolism

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Abstract

The purpose of this systematic literature review is to determine the efficacy and safety of rivaroxaban (Xarelto) compared to warfarin (Coumadin), for the long term prophylaxis of recurrent venous thromboembolism (VTE). Rivaroxaban was chosen as the primary representative of factor Xa inhibitors because of its simplistic once a day dosing regimen. The PubMed database was extensively searched, using a variety of key terms, from September 10 to November 30, 2018. Works chosen include propensity-matched cohorts, retrospective studies, systematic reviews, and meta-analyses. All of which were published within the last 10 years; sources dated prior to 10 years were excluded. Studies with poor design or dual antiplatelet therapies were also grounds for exclusion. For this review, 11 resources were selected for analysis; 7 additional resources were included for contextual information. Much of the research revealed that rivaroxaban is an adequate alternative for VTE prophylaxis, but the purpose of this research was to determine if its efficacy and safety is superior to that of warfarin. Despite statistically superior results for several aspects of rivaroxaban, an absence of distinct recommendations remain. The following results are intended to make the difficult decision of choosing an anticoagulant clearer for medical professionals and patients.

Introduction

- Venous thromboembolism (VTE) refers to the formation of a blood clot in a vein. The term VTE encompasses two types, deep vein thrombosis (DVT) and pulmonary embolism (PE). (American Heart Association, 2017)
- Virchow's triad is a theory that helps describe the pathogenesis of VTE. The triad consists of alterations in blood flow (i.e. stasis), vascular endothelial injury, and hypercoagulable state. One or more of these risk factors can be identified in 80% of patients with VTE. (Bauer & Lip, 2018)
- Nearly 900,000 individuals in the United States are impacted by VTE each year. The estimated total annual healthcare cost for VTE can range from $7,594 to $16,644. (Beckman, Hooper, Critchley, & Ortel, 2010)
- It is thought that 60,000-100,000 will die from a VTE each year. About 33% of people who have had a VTE will have a recurrence within 10 years. (Beckman et al., 2010)
- Warfarin has been the mainstay for VTE prophylaxis for many years, which can burden the patients with many drug and dietary interactions, as well as requires routine international normalized ratio (INR) therapeutic monitoring (Kreutz, 2014).
- On the other hand, NOACs do not require regular therapeutic monitoring and have far fewer drug and dietary interactions (Kreutz, 2014).
- For the purpose of this review, rivaroxaban will be the NOAC that is compared to warfarin because of the simplistic dosing regimen, requiring just once daily oral administration; other NOACs require twice daily oral administration. Warfarin also follows once daily oral administration.

Statement of the Problem

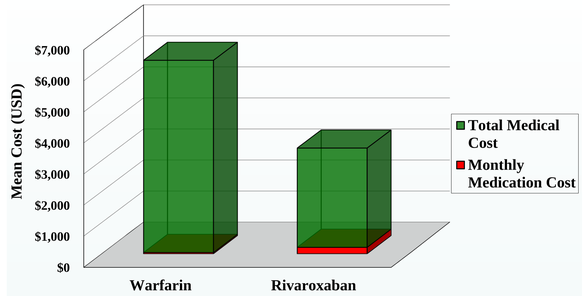
The choice of agent for VTE prophylaxis, warfarin or NOACs, is a collective decision between the patient and provider. In the end, the choice of agent is often in the hands of the patient, and the decision is commonly based on cost and number of required clinic visits. Most prescribing providers have a general knowledge about the efficacy and safety of the two types of medications, but it often remains difficult to give a recommendation for one versus the other. Therefore, providers need to be informed on the latest studies to help differentiate which treatment is the best fit for a specific patient.

Research Questions

- When treating patients with anticoagulants for prophylaxis of recurrent VTE, is there a statistical difference in efficacy and safety with rivaroxaban versus warfarin?
- When treating patients with anticoagulants for prophylaxis of recurrent VTE, is there a statistical difference in cost and adherence of therapy with rivaroxaban versus warfarin?
- When treating patients with anticoagulants, is there a statistical difference in potential drug and dietary interactions with rivaroxaban versus warfarin?

Literature Review

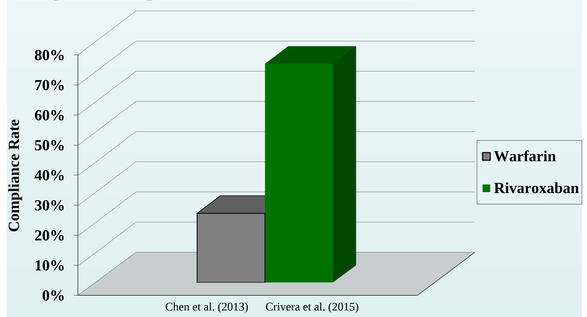
Comparison of costs



Seaman et al. (2013)

- The mean medical cost reduction for those treated with rivaroxaban was -$2979 US (Amin et al., 2015) and -$2993 US (Seaman et al., 2013), when compared to warfarin.
- Monthly medication costs were estimated at $39 per month for warfarin and $205 per month for rivaroxaban (Seaman et al., 2013).

Comparison of patient adherence to treatment



- Noncompliant patients on warfarin therapy were at a 2.6 times greater risk for recurrent VTE than compliant patients. A 43% higher risk of recurrent VTE was observed in patients who discontinued warfarin. (Chen et al., 2013)

Comparison of food and drug interactions

- There are over 120 known dietary and drug interactions with warfarin, and that list is expected to continuously grow. Rivaroxaban is associated with considerably reduced numbers of drug interactions and no known dietary interactions. (Nutescu et al., 2011)

Literature Review Cont'd

Comparison of efficacy and safety

- At 6 months, rivaroxaban was associated with reduced rates of GIB (HR 0.81, 95% CI 0.63–1.05) and markedly lower incidence of ICH (HR 0.21, 95% CI 0.09–0.62), when compared to warfarin. Similar results were seen at 3 months. (Coleman et al., 2018)
- In contrast, Raschi et al. (2016) found rivaroxaban to have no statistically significant protective effect for ICH, when compared to warfarin. Results also provided no statistically significant differences in risk of GIB, major bleeding, fatal bleeding, and clinically relevant bleeding, due to lack of consistency amongst included studies.
- Rivaroxaban therapy resulted in 65 ICH events, causing 34 deaths, and VKA therapy resulted in 108 ICH events, causing 61 deaths. Also, rivaroxaban users had 36 extracranial bleeding events, resulting in 1 death; 60 of such cases were reported with VKA therapy, resulting in 5 deaths. (Skaistis & Tagami, 2015)
- Prins et al. (2013) concluded that rivaroxaban is noninferior ($p < 0.001$) compared to standard anticoagulation therapy, for the treatment of acute symptomatic DVT and/or PE.

Comparison of Recurrent VTE Rates in Rivaroxaban and Warfarin Users

Study	HR	95% CI
Larsen et al. (2017)		
3 months	0.75	0.56 – 1.01
6 months	0.74	0.56 – 0.96
Coleman et al. (2018)		
3 months	0.61	0.54 – 0.68
6 months	0.60	0.54 – 0.67
12 months	0.53	0.47 – 0.61
Prins et al. (2013)	0.89	0.66 – 1.19
Raschi et al. (2016)		
Upper Limit	0.33	0.21 – 0.53
Lower Limit	0.91	0.54 – 1.54

Note. HR = hazard ratio, CI = confidence interval

Comparison of Bleeding Rates in Rivaroxaban and Warfarin Users

Study	HR	95% CI
Larsen et al. (2017)		
3 months	0.99	0.47 – 2.07
6 months	1.19	0.66 – 2.13
Coleman et al. (2018), major bleeding		
3 months	0.77	0.60 – 0.98
6 months	0.80	0.66 – 0.98
12 months	0.71	0.56 – 0.89
Prins et al. (2013)		
Major bleeding	0.54	0.37 – 0.79
Nonmajor clinically relevant and major bleeding	0.93	0.81 – 1.06

Note. HR = hazard ratio, CI = confidence interval

Discussion

- Increased medication costs of warfarin are offset by the increased risk of complications associated with warfarin, rendering rivaroxaban a more cost-effective alternative to warfarin.
- All reviewed studies found rivaroxaban to have a reduced risk of recurrent VTE compared to warfarin; all but one had strong quality of evidence.
- Analysis of bleeding risk resulted in mixed results. Rivaroxaban was associated with reduced risk of bleeding, intracranial and extracranial, in about half of the studies. The others displayed no statistical difference in bleeding risk between rivaroxaban and warfarin. Due to mixed results, no definite conclusion can be made about bleeding risk.
- NOACs have always been limited by the lack of practical reversal agents. That aspect has recently changed with the release of an FDA approved agent, andexanet alpha. However, limited data is available on its efficacy and risks.
- Rivaroxaban is associated with no known dietary interactions and considerably reduced numbers of drug interactions, compared to warfarin.
- Rivaroxaban was associated with significantly higher rates of treatment compliance, when compared to warfarin.

Applicability to Clinical Practice

- The initial cost of rivaroxaban will be more, but it will be offset by additional costs that are associated with warfarin therapy; such as regular INR checks, increased risk of recurrent VTE, and decreased safety.
- Due to the mixed results, bleeding risks were inconclusive, but current data suggests that rivaroxaban is associated with a reduced or at least equal risk.
- NOACs have a potential drawback, which is the lack of a proven and affordable reversal agent. The recent release of andexanet alpha, a reversal agent for NOACs, appears promising. However, more information is needed to prove its efficacy and safety.
- Rivaroxaban is associated with far fewer drug interactions and has no known dietary interactions; unlike warfarin, which has many drug and dietary interactions. These qualities may be significant for patients with multiple comorbidities and/or those who do not maintain regular dietary habits, which may put them at risk recurrent VTE or bleeding events.
- Rivaroxaban was shown to have a significantly higher rate of adherence compared to warfarin, although a missed dose renders them completely unprotected because of a shorter half-life.
- Rivaroxaban surfaced as a viable option for prevention of recurrent VTE.
- Despite the evidence presented, the choice of agent is often the patients' decision, but it is up to the medical professional to properly educate the patient. Offering this information will provide the patient an opportunity to make a well educated decision. However, it is undeniably easier to take the same dose every day, with no regular therapeutic monitoring.

References

- American Heart Association. (2017). What is venous thromboembolism (VTE)? Retrieved from http://www.heart.org/en/health-topics/venous-thromboembolism/what-is-venous-thromboembolism-vte
- Amin, A., Bruno, A., Trocio, J., Lin, J., & Lingohr-Smith, M. (2015). Real-world medical cost avoidance when new oral anticoagulants are used versus warfarin for venous thromboembolism in the United States. Clinical and Applied Thrombosis/Hemostasis, 22(1), 5-11. http://doi.org/10.1177/1076029615585991
- Bauer, K. A., & Lip, G. Y.H. (2018). Overview of the causes of venous thrombosis. In G. Finlay (Ed.), UpToDate. Retrieved from https://www.uptodate.com/contents/overview-of-the-causes-of-venous-thrombosis?search=vte&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H61
- Beckman, M. G., Hooper, W. C., Critchley, S. E., & Ortel, T. L. (2010). Venous thromboembolism: A public health concern. American Journal of Preventive Medicine, 38(4), S495-S501. http://doi.org/10.1016/j.amepre.2009.12.017
- Chen, S., Wu, N., Gulseth, M., Lamori, J., Bookhart, B. K., Boulanger, L., . . . Schein, J. (2013). One-year adherence to warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events. Journal of Managed Care Pharmacy, 19(4), 291-301. http://doi.org/10.18553/jmcp.2013.19.4.291
- Coleman, C. I., Peacock, W. F., Bunz, T. J., & Beyer-Westendorf, J. (2018). Effectiveness and safety of rivaroxaban versus warfarin in patients with unprovoked venous thromboembolism: A propensity-score weighted administrative claims cohort study. Thrombosis Research, 168, 31-36. http://doi.org/10.1016/j.thromres.2018.05.031
- Crivera, C., Laliberté, F., Nelson, W. W., Germain, G., Bookhart, B., . . . Deitelzweig, S. (2015). Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the pharmacy quality alliance measure. Current Medical Research and Opinion, 31(12), 2167-2173. http://doi.org/10.1185/03007995.2015.1096242
- Kreutz, R. (2014). Pharmacokinetics and pharmacodynamics of rivaroxaban – An oral, direct factor Xa inhibitor. Current Clinical Pharmacology, 9(1), 75-83. http://doi.org/10.2174/15748847086661311112046 58
- Larsen, T. B., Skjøth, F., Kjældgaard, J. N., Lip, G. Y., Nielsen, P. B., & Søgaard, M. (2017). Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: A propensity-matched nationwide cohort study. The Lancet Haematology, 4(5). http://doi.org/10.1016/s2352-3026(17)30054-6
- Nutescu, E., Chuatrisorn, I., & Hellenbart, E. (2011). Drug and dietary interactions of warfarin and novel oral anticoagulants: An update. Journal of Thrombosis and Thrombolysis, 31(3), 326-343. http://doi.org/10.1007/s11239-011-0561-1
- Prins, M. H., Lensing, A. W., Bauersachs, R., van Bellen, B., Bounameaux, H., Brighton, T. A., … Wells, P. S. (2013). Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: A pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thrombosis Journal, 11, 21. http://doi.org/10.1186/1477-9560-11-21
- Raschi, E., Bianchin, M., Ageno, W., Ponti, R. D., & Ponti, F. D. (2016). Risk–benefit profile of direct-acting oral anticoagulants in established therapeutic indications: An overview of systematic reviews and observational studies. Drug Safety, 39(12), 1175-1187. http://doi.org/10.1007/s40264-016-0464-3
- Seaman, C. D., Smith, K. J., & Ragni, M. V. (2013). Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: A U.S. perspective. Thrombosis Research, 132(6), 647-651. http://doi.org/10.1016/j.thromres.2013.09.015
- Skaistis, J., & Tagami, T. (2015). Risk of fatal bleeding in episodes of major bleeding with new oral anticoagulants and vitamin k antagonists: A systematic review and meta-analysis. Plos One, 10(9). http://doi.org/10.1371/journal.pone.0137444

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