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Deciding the Gold Standard for Oral Anticoagulation Therapy

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Abstract

Healthcare practitioners have many anticoagulant options for treating various disease states pertaining to blood clots and blood clot formation. Each anticoagulant has pros and cons and the decision of which pharmacological agent to use can be confusing and difficult. In years past, Vitamin K antagonists have been the standard of care when treating specific disease states such as atrial fibrillation and venous thromboembolism based on habit and cost of care. The emergence of newer anticoagulants should be considered the new standard of care based on the evidence presented over the last several years.

Keywords

Oral Anticoagulation, NOAC, VKA, Gold Standard, Rivaroxaban, AC Therapy

1. Introduction

1.1. Significance of the Study

Vitamin K Antagonists (VKAs), like warfarin, have been the standard of care in the treatment of patients with atrial fibrillation (AF) and venous thromboembolism (VTE) for over 50 years despite the introduction of new treatment therapies. Due to the narrow therapeutic index, VKA treatment requires constant blood monitoring through routine International Normalized Ratio (INR) testing to ensure the patient is within the Time in Therapeutic Range (TTR). Many foods and drugs interact with VKA therapy which can cause a patient to be over- or under-exposed, leading the patient to be at risk of either a thrombotic event or bleeding event. AF is expected to increase by an estimated 12.1 million individuals by 2030 with an estimated annual cost of $26 billion [1]. Non-vitamin K antagonist (or Novel) oral anticoagulants (NOACs, also known as DOACs) have

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entered the pharmacological marketplace within the last several years.

1.2. Research Problems, Studies That Have Addressed Them, and Their Deficiencies

Hundreds of studies have been performed assessing the safety and efficacy of NOACs versus warfarin but failed to provide information based on cost and patient satisfaction. Some trials have found NOACs perform better depending on risk stratification, secondary prevention, or serious adverse events such as intracranial hemorrhaging [2] [3] [4]. Real-world evidence (RWE) has helped determine the effectiveness of NOACs outside of the clinical trial setting. There have been many studies showing the proven efficacy and safety of NOACs among many different patient populations and disease states, including those patients with cancer-related VTEs [5]. Other RWE trials have shown a benefit toward NOACs versus warfarin regarding cardiovascular death in the elderly patient population [6]. All of the trials and studies listed in this section failed to analyze the cost of NOAC therapy versus vitamin K antagonists or patient satisfaction.

Other trials have looked at issues dealing with patient satisfaction, but not safety and efficacy. While warfarin dosing adjustments can be confusing to patients, three of the four NOACs have once a day dosing which could be considered more convenient for patients and help with patient compliance [7] [8].

Cost is a considerable aspect to the healthcare setting in determining the use of specific therapies. Dr Amin studied cost as it relates to a warfarin patient's TTR [9]. Amanda Harrington quantified the quality-adjusted life expectancy, risk of adverse events and net costs over a 30-year time frame [10]. All of these trials relating to cost were limited in analyzing efficacy, safety, and/or patient satisfaction. One trial attempted to include efficacy and safety into the cost analysis but failed to address patient satisfaction [11].

1.3. Purpose Statement

The objective of this meta-analysis study is to explore the possibility of direct oral anticoagulants (DOACs) becoming the gold standard for clot prevention versus vitamin K antagonists, like warfarin, in adult men and women who have been diagnosed in the hospital setting, or a physician's office, as having nonvalvular atrial fibrillation (AFIB) or venous thromboembolism (VTE). For the purposes of this study, a tentative definition for gold standard will be the best available option when considering efficacy, safety, and cost.

2. Literature Review

Anticoagulation is a therapeutic option to help prevent clot formation due to stasis of blood flow, endothelial injury, or hypercoagulability (also known as Virchow's triad). Clot formation can lead to serious injury, including death. Specific disease states are caused by clots including deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic strokes, peripheral artery disease (PAD),

and coronary artery disease (CAD) to name a few. While there have been several injectable options available for decades (heparin, low molecular weight heparin, fondaparinux, etc.) there have been few oral pharmacologic therapies until the last 10 years. Warfarin, also known by the brand name Coumadin, has been available since 1954. Warfarin was a groundbreaking pharmacologic therapy designed to help prevent disease states caused by clot formations. For 50+ years this oral agent was the gold standard of anticoagulation therapy. However, in 2012 newer therapies began being released. These oral options named non-vitamin K antagonists, or NOACs, have several advantages versus warfarin. Many favorable aspects arose with NOACs compared to warfarin including fewer drug and food interactions, no required routine blood monitoring, and the quick onset of patients becoming fully anticoagulated. Non-vitamin K antagonist patients become fully anticoagulated in 2 - 4 hours versus warfarin in which patients become fully anticoagulated in 5 - 7 days.

The Components Involved for the Gold Standard and Addressing the Needs

NOACs should be considered as the new gold standard to anticoagulation therapy within the healthcare industry if they prove to benefit patients more so than warfarin. There are several considerations to analyze regarding the impact NOACs will have on the healthcare industry. The broadest topic being NOACs have positive efficacy and safety results when being compared to the standard of care, warfarin. A pharmacological treatment should be considered the standard of care if that therapy is at least as efficacious, if not more, than the previous standard of therapy. Efficacy data can be analyzed not only in the phase 1 - 3 settings but considering the NOACs have been utilized for several years in medical offices and hospital systems, real-world data and experiences should be considered when analyzing the impact of NOACs as the new gold standard. Patient cost should be included when considering the patient's quality of life and satisfaction. The next item to consider would be patient satisfaction and their quality of life.

Patients have a variety of ailments and comorbidities, hence practitioners can have difficult decisions in deciding the best pharmacological therapy for their patients. To aid providers in their decisions, specific risk stratification tools have become prevalent. In assessing stroke risk, CHADS2 became the gold standard followed by CHADS-VASc which is more detailed. While all the NOACs have shown to be either non-inferior or superior to warfarin in individual studies, Dr. Hernandez was able to find a pronounced difference in favor of NOACs versus warfarin in patients with lower CHADS-VASc score pertaining to efficacy and safety. Patients with higher CHADS-VASc scores did find benefit in both safety and efficacy versus warfarin, but more studies should be performed in this subgroup population [2]. Secondary events need to be assessed, too. If a stroke patient survives, the risk of that patient having another event is increased as well as

the severity of the stroke. Investigators have found patients on warfarin who have had a secondary event to be higher than that of a NOAC, 32.3% versus 18.5% respectively [3]. One of the biggest safety concerns for warfarin is intracranial hemorrhages (ICHs). AF patients on warfarin should have an INR level between 2.0 - 3.0 [6]. Though many drugs and foods can cause a warfarin patient to fall outside the therapeutic range, 65% of ICHs occur when a patient has a normal INR reading [4]. All NOACs have provided evidence of lower risks for hemorrhagic strokes and intracranial bleeding in numerous published studies and journal articles. The proven efficacy and safety profiles of the NOACs have shown them to be a viable option compared to warfarin therapy.

In reviewing hospital systems, NOACs could be considered more appealing and the new standard of care because of the reduction of costs and the length of stay (LOS) for the patient which can be attributed to improved performance. Patient admits can be costly and drain resources that the hospital might not be able to afford. NOACs have been found to reduce the length of stay as well as costs versus warfarin. For example, a study reviewed deep vein thrombosis (DVT) patients on rivaroxaban versus LMWH/warfarin over a 2-year period and found a cost reduction of 22% in favor of rivaroxaban while previous studies have found similar results [12]. Multiple NVAF studies have been performed on individual NOACs and their related hospital costs and LOS. One study assessed apixaban versus warfarin in patients with NVAF after stating that approximately $26 billion dollars are spent annually with hospitalization accounting for 52% of the final costs. This study found apixaban had a statistically significant reduction in the mean LOS and cost analysis versus warfarin which align to what other NOAC trials have found [1]. From a hospital perspective, NOACs seem to be a more ideal therapeutic option versus warfarin based on not only the efficacy/safety evidence but the studies which have shown fewer costs and LOS in respect to prescribing NOACs versus warfarin. Saving costs from a patient perspective and saving time through preventing more events make NOACs an ideal choice. However, practitioners consider many items when choosing an anticoagulant in the hospital setting. Variations from patient risk factors to patient financial stability has determined what therapy a patient might receive, even with "robust evidence" being available, according to Dr. Patel [13].

Cost is a considerable aspect to the healthcare setting in determining the use of specific therapies and a potential gold standard option. Cost for the patient as well as the hospital institutions should be considered, as previously mentioned. There could be specific cases where NOAC therapy might not be financially sound. For instance, Dr. Amin found that as a warfarin patient's TTR increased, stroke risk and bleeding events decreased which in turn decreased medical costs. Those patients who are always in the therapeutic range will not find it financially feasible to switch to a NOAC, however previous real-world studies have shown warfarin patients average TTR was between 55% and 69.2% [9]. While strokes are expected to increase over the next several decades, the healthcare industry

should focus on the associated costs of strokes including ICHs, subarachnoid hemorrhages, and ischemic strokes. Amanda Harrington quantified the quality-adjusted life expectancy, risk of adverse events and net costs over a 30-year time frame using societal perspectives and found rivaroxaban, apixaban and dabigatran were more cost-effective than warfarin for stroke prevention in patients with nonvalvular AF [10]. Other studies were able to evaluate the cost-effectiveness of NOACs versus warfarin within shorter time frames. Using similar methods as Amanda Harrington, Dr. Reddy found NOACs to be more effective than warfarin at year 1 and achieved cost-effectiveness at year 16. Dr. Reddy ultimately found NOACs were more cost-effect than warfarin and stated NOACS could change the "treatment paradigm" for NVAF patients [14]. There have been many individual NOACs which have been studied versus warfarin to assess total cost effectiveness. One such studied analyzed rivaroxaban versus warfarin. Investigators studied various comorbidities including ischemic stroke, ICH, MI, extracranial hemorrhage, minor hemorrhage, and death. Dr. Lee found rivaroxaban to be economically dominant over warfarin [11].

Real-world evidence (RWE) has helped determine the effectiveness of NOACs outside of the clinical trial setting. There have been many studies showing the proven efficacy and safety of NOACs among many different patient populations and disease states. A recent real-world meta-analysis analyzed both prospective and retrospective studies in patients suffering from VTE. The investigators reviewed several large claims databases and payers and found that RWE support both the efficacy and safety of utilizing NOACs as a pharmacological treatment option for patients with VTE, including those patients with cancer-related VTEs [5]. Of course, when speaking to anticoagulation, the largest concern is safety or bleeding. Though all the individual NOAC trials were found to be non-inferior or superior regarding safety, the RWE has proven these finding to be consistent. Dr. Lip conducted an RWE study comparing the safety of rivaroxaban, dabigatran and apixaban to warfarin. Dr. Lip found consistency in that all three NOACs were found to have similar results as were in their own perspective clinical trials, ROCKET-AF, RE-LY, and ARISTOTLE [15].

Finally, patient experiences with warfarin and NOACs should be evaluated to help identify the potential impact of anticoagulants within the healthcare setting and the standard of care. Dosing with warfarin can be confusing and complicated. Patients must fall within the INR therapeutic range of 2.0 - 3.0. Patients outside the therapeutic range not only require dose adjustments but the effects can be life threatening. A warfarin patient with an INR > 3.0 are at risk of having a bleeding event while if the INR < 2.0 the AF patient is at risk of having a stroke. One study found non-adherence to warfarin therapy was 92% during a 32-week period [7]. While warfarin dosing adjustments can be confusing to patients, three of the four NOACs have once a day dosing which could be considered more convenient for patients and help with patient compliance. Besides dosing, there are several patient perceptions and comprehensions that should be

taken into consideration prescribing an anticoagulant. There are different levels of involvement patients experience when being prescribed warfarin or a NOAC. One such study analyzed patient themes between the two classes of anticoagulants. Patients prescribed warfarin were less likely to receive support or information regarding their diagnosis. Patients receiving warfarin were not told the importance of receiving oral anticoagulant therapy, were not told the differences between warfarin versus NOACs and were not given a risk assessment. Those same patients had a poor understanding of their treatment and had issues with adherence [8]. Based upon patient adherence, understanding of their disease state and therapeutic regimen NOAC therapy should be preferred over warfarin. These findings, along with the superior efficacy, safety, and overall costs of NOACs versus warfarin should support the suggestion that NOACs become the new gold standard for anticoagulation therapy among the appropriate patient types.

3. Methods

3.1. Design

This study incorporates a mixed method strategy utilizing both quantitative and qualitative data to design a theoretical assumption based on deciding the gold standard in anticoagulation therapy. Addressing a quantitative approach is necessary when considering the efficacy, safety, cost, and real-world evidence of non-vitamin K antagonists versus warfarin. The trials that will be analyzed for these metrics collected quantifiable, statistical information. However, a key component in deciding the gold standard is patient satisfaction and quality of life. Qualitative analyses relate to patient satisfaction by addressing patient's insights and experiences as it relates to anticoagulation therapy. The trials that will be analyzed for the purpose of this study spoke to the quality of specific therapeutic products via patient interpretation.

3.2. Data Collection

The analyzed trials consisted of using multiple databases, including claims data from CMS. Other data collection included surveys and utilizing data from previously performed trials. Data analysis and integration varied throughout the analyzed trials. The most common analysis consisted of 1:1 propensity score matching followed by the utilization of various Markov Models. There were multiple tests performed to account for covariables including Kruskal-Wallis, Chi-squared, and Wilcoxon signed-ranked tests [13] [15]. Other data analyses consisted of a probabilistic sensitivity analysis [10].

4. Data Analysis

4.1. Efficacy and Safety

Pharmacological therapies are FDA approved based on the product's efficacy and safety. Disease states usually have more than one product to help prevent or

manage symptoms. Furthermore, these products can differ in the benefits they provide for the patient including better risk prevention or safety outcomes. In referencing at-risk patients, the scientific community continuously develops risk stratification methods. For example, as previously mentioned for stroke patients, CHADS-VASc is the common method for determining a patient's risk of having a stroke. Dr. Hernandez studied patients regarding high and low CHADS-VASc scores and found NOACs to be more favorable versus warfarin, pertaining to efficacy and safety. While the benefits of NOAC usage proved beneficial according to Dr. Hernandez's study, more trials in this specific patient type would be beneficial [2]. The likelihood of a stroke patient suffering a second stroke is exponentially higher versus the risk of a patient having a stroke for the first time. This is a specific patient type that is often found in the medical community. These patient types have been studied extensively and investigators have found NOACs to be much more efficacious versus warfarin [3]. Unfortunately, a serious side effects of warfarin use are intracranial hemorrhages (ICHs). ICHs are dangerous because the bleed occurs in a closed cavity. The exposed blood puts pressure on the brain, which can cause debilitating effects or commonly, death. Regrettably, even though a patient may be in therapeutic range while taking warfarin, an ICH can occur [4]. A desired benefit for all NOACs is the medically based evidence of patients having lower risks for hemorrhagic strokes and intracranial bleeding which has been proven time and again. When considering the Gold Standard for anticoagulation, based on efficacy and safety as shown in **Figure 1**, NOACs are far more favorable than warfarin (**Table 1**).

Table 1. Trial findings based on authors' interpretation.

Efficacy/Safety		**warfarin**	**NOAC**
Hernandez, *et al.*, 2018	favors		✓
Kanai, *et al.*, 2018	favors		✓
Cost		**warfarin**	**NOAC**
Harrington, *et al.*, 2013	favors		✓
Reddy, *et al.*, 2015	favors		✓
Lee, *et al.*, 2012	favors		✓
Merli, *et al.*, 2016	favors		✓
Xie, *et al.*, 2016	favors		✓
Real-World Evidence		**warfarin**	**NOAC**
Beyer-Westendorf, 2018	favors		✓
Lip, *et al.*, 2016	favors		✓
Patient Satisfaction		**warfarin**	**NOAC**
Vrijens & Heidbuchel, 2015	favors		✓
Clarkesmith, *et al.*, 2017	favors		✓

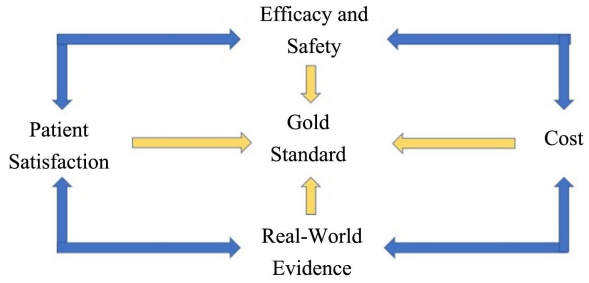

Figure 1. Components of gold standard therapy. Legend: Efficacy and Safety of oral anticoagulants. Cost relating to patients having an event, copays for anticoagulant products, and hospital stays. Real-World Evidence based on usage of products in patient populations after approval process. Patient Satisfaction relates to a patients' attitude toward receiving and adhering to oral anticoagulant therapy.

4.2. Cost

The cost of therapies tends to be a driving force among provider and patient use. There may be instances where a NOAC is not financially viable for a patient. When analyzing patients who suffer from disease states where anticoagulation would be used, these patients are typically older with several comorbidities. The older patient population is likely to be on Medicare. For those patients with Medicare Part D (prescription benefits), they are likely to hit the "Donut Hole". While a Medicare D patient is in the "Donut Hole" they are responsible for paying a higher percentage of the cash price for pharmacologic products. This translates to higher costs for brand name drugs versus generics. Hence, a patient's comorbidities could determine which pharmacologic agent they receive based on their financial status [13]. Yet, when considering the future of the medical industry, as previously mentioned, strokes are expected to increase over the next several decades which means there will be opportunities to cut costs. A primary focus on the associated costs of strokes should include both the safety aspect and efficacy. Investigators have found substantial cost benefits when considering NOAC use versus warfarin over a multiple decades [10]. In fact, studies have shown cost benefits associated with NOACs versus warfarin in as little as 16 years. When considering Gold Standard anticoagulation therapy authors have agreed that NOACS could become the new standard therapy [14]. While not all NOACs are the same, several individual NOACs have produced cost analysis studies versus warfarin and all have shown some level of benefit, including rivaroxaban [11]. Form a cost perspective, NOACs have proven to be more financially beneficial both short-term and long-term versus traditional warfarin therapy. These findings support the idea that NOACs should be considered the new standard of care (**Table 1**). Cost being an attribute toward defining the gold standard as depicted in **Figure 1**.

4.3. Cost in Hospital Setting

Medical institutions incur a lot of costs associated with patients suffering from clots. An opportunity for revenue among institutions includes reimbursements

from CMS (Centers for Medicaid and Medicare). Hospitals are given bonuses based on Quality Measures which include goals regarding the length of stay (LOS) for the patient along with patient readmits. In fact, hospitals may be penalized for poor performance based on these Quality Measures, too. Multiple NOAC studies have proven to have a reduced LOS and a reduction of patient readmits versus warfarin [1] [12]. When considering costs from an institutional viewpoint, NOACs are a more ideal therapeutic option versus warfarin from both an individual patient's perspective, as well as from an institutional perspective. These findings support the idea of NOACs becoming the new standard of care (**Table 1**).

4.4. Real-World Evidence (RWE)

Many times, providers are hesitant to use pharmacologic agents until they have been approved for over a year or more. The most common reason being how the product performs in a clinical setting versus a controlled clinical trial. The largest benefit for real-world evidence trials is to observe the performance of the product among providers who treat that specific patient type. Electronic health records and databases have proven useful in analyzing various products in a variety of patients with multiple comorbidities, such as cancer [5]. Considering the past evidence of safety issues among warfarin use, providers tend to be leery about prescribing anticoagulants. The fear being that a patient experiences a bleeding event. RWE evaluating safety with anticoagulant use can have a favorable effect on provider confidence. Dr. Lip's trial, which showed clear benefits for multiple NOACs versus warfarin is a prime example of why NOACs need to be the Gold Standard of anticoagulant therapy [15], as seen in **Figure 1** and **Table 1**.

4.5. Patient Satisfaction

Patient satisfaction needs to be addressed to ensure proper treatment. Patients who are not happy with their treatment regimen are likely to be noncompliant with their medicine. For example, some warfarin dosing plans can be confusing, or patients may struggle with following the diet that is require while on warfarin therapy. These issues can cause patients to be at risk of either a bleeding event, or a clotting event due to non-adherence or noncompliance [7]. Another benefit to NOAC therapy is the once-daily dosing which helps with compliance. Unfortunately, warfarin dosing has proven to be confusing to some patients. There could be many reasons as to why warfarin dosing could be confusing, but this issue could cause the patient to be at risk [8]. When considering the seriousness of the disease state, patient experiences are important to consider when addressing which product should be the standard of care (**Table 1**).

5. Conclusion

NOACs have had a dramatic impact on the healthcare industry. With the newer anticoagulation therapies come obvious benefits over the previous standard of

care, warfarin. These benefits, which have been stated earlier, have shown positive impacts for both patients and institutions. There have been many studies, both randomized clinical trials and RWE trials, which have proven NOACs to be just as beneficial, if not more so, than warfarin. Leading experts have stated that NOACs should be recommended over warfarin in most patients after a bleeding risk assessment has been performed, when considering cardiovascular death and in elderly patients [6]. Over the last several years NOACs have been utilized more often. Patient and hospital costs have decreased, and patient care has increased. Some guidelines have begun recommending NOAC therapy as a preferred option. The NOACs have brought about a positive change to patients' lives, hospital costs and admission rates, and the overall healthcare marketplace. Warfarin will eventually become redundant in patients with NVAF and VTE and NOACs are becoming the new standard of care in these disease states [16]. Based on the gathered data and upon analysis of the findings from this meta-analysis, it can be justified that NOACs should be the new gold standard when speaking to thrombotic prevention.

Validity

The convergent mixed method design will be used for the purposes of this study. The challenge with this approach pertains to the data being analyzed for this meta-analysis. The referenced trials consist of either a quantitative approach, or a qualitative approach. Data gathering from the analyzed trials could have certain limitations such as coding errors, human error when cataloging, and author bias depending on funding.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Xie, L., Vo, L., Keshishian, A., Price, K., Singh, P., Mardekian, J., Bruno, A., Baser, O., Kim, J., Tan, W. and Trocio, J. (2016) Comparison of Hospital Length of Stay and Hospitalization Costs among Patients with Non-Valvular Atrial Fibrillation Treated with Apixaban or Warfarin: An Early View. *Journal of Medical Economics*, **19**, 769-776. https://doi.org/10.3111/13696998.2016.1171774

[2] Hernandez, I., Zhang, Y. and Saba, S. (2018) Effectiveness and Safety of Direct Oral Anticoagulants and Warfarin, Stratified by Stroke Risk in Patients with Atrial Fibrillation. *The American Journal of Cardiology*, **122**, 69-75. https://doi.org/10.1016/j.amjcard.2018.03.012

[3] Kanai, Y., Oguro, H., Tahara, N., Matsuda, H., Takayoshi, H., Mitaki, S., Onoda, K. and Yamaguchi, S. (2018) Analysis of Recurrent Stroke Volume and Prognosis between Warfarin and Four Non-Vitamin K Antagonist Oral Anticoagulants' Administration for Secondary Prevention of Stroke. *Journal of Stroke and Cerebrovascular Diseases*, **27**, 338-345. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.007

[4] Verdecchia, P., Angeli, F., Aita, A., Bartolini, C. and Reboldi, G. (2016) Why Switch from Warfarin to NOACs? *Internal and Emergency Medicine*, **11**, 289-293. https://doi.org/10.1007/s11739-016-1411-0

[5] Beyer-Westendorf, J. (2018) What Have We Learned from Real-World NOAC Studies in Venous Thromboembolism Treatment? *Thrombosis Research*, **163**, 83-91. https://doi.org/10.1016/j.thromres.2018.01.034

[6] Cohen, A., Lip, G., De Caterina, R., Heidbuchel, H., Zamorano, J., Agnelli, G., Verheugt, F. and Camm, A. (2018) State of Play and Future Direction with NOACs: An Expert Consensus. *Vascular Pharmacology*, **106**, 9-21. https://doi.org/10.1016/j.vph.2018.04.001

[7] Vrijens, B. and Heidbuchel, H. (2015) Non-Vitamin K Antagonist Oral Anticoagulants: Considerations on Once- vs. Twice-Daily Regimens and Their Potential Impact on Medication Adherence. *European Society of Cardiology*, **17**, 514-523. https://doi.org/10.1093/europace/euu311

[8] Clarkesmith, D., Lip, G. and Lane, D. (2017) Patient's Experiences of Atrial Fibrillation and Non-Vitamin K Antagonist Oral Anticoagulants (NOACs), and Their Educational Needs: A Qualitative Study. *Thrombosis Research*, **153**, 19-27. https://doi.org/10.1016/j.thromres.2017.03.002

[9] Amin, A., Deitelzweig, S., Jing, Y., Makenbaeva, D., Wiederkehr, D., Lin, J. and Graham, J. (2014) Estimation of the Impact of Warfarin's Time-in-Therapeutic Range on Stroke and Major Bleeding Rates and Its Influence on the Medical Cost Avoidance Associated with Novel Oral Anticoagulant Use-Learnings from ARISTOTLE, ROCKET-AF, and RE-LY Trials. *Journal of Thrombosis and Thrombolysis*, **38**, 150-159. https://doi.org/10.1007/s11239-013-1048-z

[10] Harrington, A., Armstrong, E., Nolan Jr., P. and Malone, D. (2013) Cost-Effectiveness of Apixaban, Dabigatran, Rivaroxaban, and Warfarin for Stroke Prevention in Atrial Fibrillation. *Stroke*, **44**, 1676-1681. https://doi.org/10.1161/STROKEAHA.111.000402

[11] Lee, S., Anglade, M., Pham, D., Pisacane, R., Kluger, J. and Coleman, C. (2012) Cost-Effectiveness of Rivaroxaban Compared to Warfarin for Stroke Prevention in Atrial Fibrillation. *The American Journal of Cardiology*, **110**, 845-851. https://doi.org/10.1016/j.amjcard.2012.05.011

[12] Merli, G., Hollander, J., Lefebvre, P., Laliberte, F., Raut, M., Germain, G., Bookhart, B. and Pollack, C. (2016) Costs of Hospital Visits among Patients with Deep Vein Thrombosis Treated with Rivaroxaban and LMWH/Warfarin. *Journal of Medical Economics*, **19**, 84-90. https://doi.org/10.3111/13696998.2015.1096274

[13] Patel, P., Zhao, X., Fonarow, G., Lytle, B., Smith, E., Xian, Y., Bhatt, D., Peterson, E., Schwamm, L. and Hernandez, A. (2015) Novel Oral Anticoagulant Use among Patients with Atrial Fibrillation Hospitalized with Ischemic Stroke or Transient Ischemic Attack. *Circulation*: *Cardiovascular Quality Outcomes*, **8**, 383-392. https://doi.org/10.1161/CIRCOUTCOMES.114.000907

[14] Reddy, V., Akehurst, R., Armstrong, S., Amorosi, S., Beard, S. and Holmes, D. (2015) Time to Cost-Effectiveness Following Stroke Reduction Strategies in AF: Warfarin versus NOACs versus LAA Closure. *Journal of the American College of Cardiology*, **66**, 2728-2739. https://doi.org/10.1016/j.jacc.2015.09.084

[15] Lip, G., Keshishian, A., Kamble, S., Pan, X., Mardekian, J., Horblyuk, R. and Hamilton, M. (2016) Real-World Comparison of Major Bleeding Risk among Non-Valvular Atrial Fibrillation Patients Initiated on Apixaban, Dabigatran, Rivaroxaban, or Warfarin. *Thrombosis and Haemostasis*, **115**, 975-986. https://doi.org/10.1160/TH16-05-0403

[16] Oktay, E. (2015) Will NOACs become the New Standard of Care in Anticoagulation Therapy? *International Journal of the Cardiovascular Academy*, **1**, 1-4. https://doi.org/10.1016/j.ijcac.2015.06.007