Novel Oral Anticoagulants and the 73rd Anniversary of Historical Warfarin


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Abstract

The last 70 years of Warfarin use has been associated with extreme problems. The Novel Oral Anticoagulants (NOACs) are not well utilized in patients with Atrial Fibrillation (AF). We thought to excavate the clinical utility of NOACs and provide some insights into their usefulness as suitable alternatives to Warfarin.

Methods: The main objective is to raise awareness of clinicians regarding the underutilized NOACs and shed light on concerns surrounding their use as suitable alternatives to Warfarin. We searched the literature for recent meta-analysis about NOACs.

Results: The choice between the four NOACs depends largely on the cost and patient’s preferences rather than their safety profile. They were better when compared with Warfarin, nevertheless; no head-to-head comparison was performed between NOACs members. The selection of one NOAC over the others rely on patients characteristics (age), cost, insurance coverage, dosing interval (once versus twice) and renal status. One more obstacle to utilization of NOACs is the reversal of bleeding.

Discussion: There are three integrated grey areas for suitability to NOAC required to be discussed and argued in light of all of the trials, meta-analysis and pharmaceutical-race. The first is relevant to patient in term of demographics (e.g. age), co-morbidities (e.g. chronic kidney disease), degree of renal impairment (creatinine clearance > 30 mL/min), adherence to daily dosing and risk of bleeding. Most patients with AF are having comorbidities with problematic poly-pharmacy issues. The second is implications of cost and insurance coverage on NOAC selection which is considered highly significant for clinicians. The third is relevant to each NOAC pharmacokinetic and pharmacodynamics profile as dosing interval.

Conclusion: The messages taken from this overview is to encourage utility of NOACs in daily clinical practice, evaluate the patient preferences, consider cost and insurance coverage and select a NOAC over Warfarin when the overall clinical judgment is optimal.

Keywords: Novel oral anticoagulants (NOACs); Atrial fibrillation; Warfarin

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Historical Background

"The can of un-coagulated blood lying on the floor of Link’s laboratory was to change the course of history, and little did Link know what the long-term implications would be", [1]. The Wisconsin Alumni Research Fund (WARF), the scientist Karl Paul Link and his senior student Wilhelm Schoeffel would have never thought that their research would live longer to nearly 73 years (1941). Karl has named the researched substance after the organization that supported his research. The last 70 years of Warfarin use has been associated with extreme problems. The Novel Oral Anticoagulants (NOACs) are not well utilized in patients with Atrial Fibrillation (AF). We thought to excavate the clinical utility of NOACs and provide some insights into their usefulness as suitable alternatives to Warfarin.

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In the last few years, emerging novel or new oral anticoagulants refer to as NOACs [Apixaban (Eliquis*)], Edoxaban (Lixiana) and
Rivaroxaban (Xarelto®)-factor Xa inhibitors; Dabigatran (Pradaxa®)-direct thrombin inhibitor), have been used in patients for prophylaxis and treatment of atrial fibrillation (AF) and venous thromboembolism (VTE) as suitable alternatives to the perpetual Warfarin (vitamin K antagonists-VKAs) to prevent stroke in patients with non-valvular AF. The major trials of NOACs in AF were: Aristotle, Engage-AF, Rocket-AF and Re-ly; respectively [2-5]. It is prudent to discuss the issues of concerns to physicians and patients in order to gain knowledge of how to use these drugs effectively and safely in specific clinical situations. With respect to physicians, the clinical scenarios should emphasize the practical start-up and follow-up scheme for patients on NOACs. The process of how to measure the anticoagulant effect of NOACs should be clearly informed. The procedure for switching between anticoagulant regimens is of critical importance. The issue of management of bleeding and steps to do if there is a (suspected) overdose without bleeding, or a clotting test is indicating a risk of bleeding. The management of bleeding complications; patients undergoing a planned surgical intervention or ablation and patients undergoing an urgent surgical intervention deserve special attention for NOAC therapy.

The special populations as patients with chronic kidney disease; patients with AF and coronary artery disease, cardioversion in a NOAC-treated patient, patients presenting with acute stroke while on NOACs; NOACs vs. VKAs in AF patients with a malignancy should be addressed clearly in guidelines and management plan. With respect to patients drug–drug interactions and pharmacokinetics of NOACs and issues of adherence to NOAC intake and how to deal with dosing errors are of critical concerns.

The problem

The last 70 years and more of Warfarin use has been associated with extreme problems for patients, patients’ family, healthcare providers and healthcare systems (bleeding, visits to emergency, hospitalizations/costs. length of stay, multiple INR tests, commercial variability on generics and others).

The rational

In day-to-day clinical practice Warfarin use poses many limitations. NOACs represent an archetype shift in the management of non-valvular atrial fibrillation. The NOACs are more specific, possess rapid onset of action with predictable pharmacokinetics profile (fixed dosing and no coagulation monitoring). The use of NOACs has been addressed in spot points as drug interactions, switch-therapy, patient selection, renal impairment, risk of myocardial infarction, use in patients with ACS requiring antplatelet (e.g. cardio version and percutaneous coronary intervention-PCI) and the most annoying bleeding.

The NOACs are not well utilized in patients with AF despite their approved indications by Food and Drug Agency (FDA) and an array of published literature supporting their utility, safety and efficacy. However, other aspects of NOACs as patient’s satisfaction and quality of life deserve further emphasis and respective research.

Aims and objectives

We thought to excavate the clinical utility of NOACs and provide some insights into their usefulness. This report main objective was to raise awareness of clinicians regarding the underutilized oral anticoagulants and encourage the use of NOACs in daily clinical practice as suitable alternatives to Warfarin.

Methods

NOACs perspective

The choice between the four NOACs depends largely on the cost and patient’s preferences rather on their safety profile. They were more or less similar, were better when compared with Warfarin, nevertheless; no head-to-head comparison was performed between NOACs members. The selection of one NOAC over the others, rely on patients characteristics (e.g. age), dosing interval (once versus twice) and renal dosing [6]. One more obstacle to utilization of NOACs is the reversal of bleeding, with possible solution on horizons of new anti-dote for Dabigatran, which is on its way to clinicians for routine monitoring.

NOAC’s evidence

The first randomized trial of the anticoagulants (Nicoumalone and Heparin) was performed in 1960, [7]. From that time a plethora of studies has been performed with Acenocoumorol, Dicoumorol and later Warfarin. The fairy-tale carry on with the promising NOAC’s. The literature is immense with evidence from randomized trials to observational studies regarding the use of NOACs.

A recent network meta-analysis (indirect comparison), published in the May 2014 issue of “Thrombosis and Haemostasis” compared the efficacy and safety of Edoxaban with other NOACs. The study found some differences among NOACs, allowing treatment selections according to the clinical profile of each patient. Indirect comparisons of efficacy endpoints demonstrated that high-dose Edoxaban was comparable to Dabigatran 110 mg bid, yet inferior to Dabigatran 150 mg. Moreover, high-dose Edoxaban was comparable in efficacy to Apixaban, but Apixaban had less bleeding endpoints.

Efficacy of low-dose Edoxaban was either similar or less effective than its competitors. When safety endpoints were compared, low-dose Edoxaban emerged as the best, with the least bleeding. The differences among the drugs also suggested that patient-related factors such as expected compliance, individual focus on efficacy and side-effects as well as renal function, shall be taken into account when selecting a drug. The limitation of this study that their findings, similarly to previous indirect comparisons of NOACs, are not based on direct head-to-head comparisons (which remain the gold standard), thus be considered with some caveats [8].

In 2012 a systematic review and meta-analysis of randomized controlled trials (3 trials) compared the efficacy and safety of NOACs to those of Warfarin in patients with AF. The NOACs were found to be more efficacious than Warfarin for the prevention of stroke and systemic embolism in patients with AF. The authors concluded decreased risk for intracranial bleeding and favorable safety profile in favor of NOACs [9].

A systematic review from 2001 through July 2012, compared the benefits and harms of NOACs versus Warfarin for AF and VTE. The authors concluded that, NOACs are a viable option for patients receiving long-term anticoagulation. Treatment benefits compared with Warfarin are small and vary depending on the control achieved by Warfarin treatment. There were no head-to-head comparisons of NOACs and limited data on harms [10].

Advantages of oral anticoagulation therapy over Warfarin

The use of NOAC as compared with Warfarin is associated with both cons and pros. The limitations of warfarin were well established. However, warfarin is highly effective when used optimally, is well
established and accepted, and is inexpensive (although the monitoring and adverse reactions are an enormous burden to the healthcare system and to many patients). The NOAC to be as first choice for most patients, must not only be more convenient (a key advantage that may also increase adherence and persistence) but also need to result in better clinical outcomes, at an acceptable cost, with consistency in all major subgroups of patients.

Table 1 shows the effect of the new agents versus warfarin on major clinical outcomes.

Table 2 shows result of the randomized clinical trials of NOACs as compared to Warfarin.

**Dabigatran**

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, a non-inferiority randomized trial with open-label Warfarin that included 18 113 patients with AF and at least 1 risk factor for stroke, demonstrated that Dabigatran is safe and effective compared with Warfarin. Dabigatran 150 mg was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) and systemic embolism by 34% (P<0.001) with no significant difference in major bleeding. Dabigatran 110 mg was non-inferior to Warfarin in preventing stroke and systemic embolism and was associated with a 20% relative risk reduction in major bleeding compared with Warfarin (P=0.003). Gastrointestinal bleeding was more common with higher-dose Dabigatran than Warfarin, and dyspepsia was more common with Dabigatran (11.8% of patients with 110 mg and 11.3% of patients with 150 mg compared with 5.8% with Warfarin; P<0.001 for both) [11].

**Rivaroxaban**

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a double-blind, randomized comparison of rivaroxaban 20 mg once daily (with dose adjustment for renal function) versus dose-adjusted warfarin (INR target between 2.0 and 3.0, which was achieved a median of 58% of the time). The trial targeted high-risk patients with a CHADS2 score of ≥ 2, and approximately half had history of prior stroke. There was a 12% relative risk reduction in the occurrence of stroke and systemic embolism in AF patients treated with rivaroxaban that did not reach statistical significance but was clearly noninferior to warfarin. Similar to dabigatran, there were significant reductions in intracranial hemorrhage, as well as in bleeding causing death [12].

**Apixaban**

The ARISTOTLE trial compared Apixaban with Warfarin for the prevention of stroke and systemic embolism in patients with AF and at least 1 additional risk factor for stroke. Compared with Warfarin, Apixaban reduced stroke and systemic embolism by 21% (P=0.01), resulted in 31% less bleeding (P<0.001), and resulted in 11% lower mortality (P=0.047). Apixaban was better tolerated than Warfarin, with fewer drug discontinuations [13].

**Edoxaban**

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF-TIMI 48) trial has randomized >2 0 000 patients who have AF and a CHADS2 score of ≥2. Patients were randomized in a double-blind fashion to warfarin (target INR, 2.0 - 3.0) or 1 of 2 doses of edoxaban given once daily, with dose adjustments both at baseline and subsequently for factors associated with higher drug exposure, including renal insufficiency [14].

Warfarin has been highly effective treatment to reduce stroke in AF and its limitations are well studied. NOACs have been shown to be convenient, have important advantages in improving clinical outcomes, including fewer strokes, less intracranial hemorrhage, and lower mortality. These benefits are consistent in Warfarin naive or Warfarinized patients. Furthermore, the cost is somewhat acceptable, particularly in light of the major advantage with regard to convenience (Tables 1 and 2).

**New emerging indication for NOAC**

More recently in last 4 years, NOACs in addition to antiplatelet treatment after an acute coronary syndrome (ACS) has been studied for reducing ischaemic events but increase bleeding risk. A recent meta-analysis was performed to evaluate the efficacy and safety of adding NOACs to single (Aspirin) or dual (Aspirin and Clopidogrel) antiplatelet therapy.

The following were the included trials: Esteem, Appraise-1, Atlas ACS-TIMI46, Redeem, and Ruby-1. Appraise-2 and Atlas ACS2-TIMI51 [15-21]. The meta-analysis concluded that in patients with a recent ACS, the addition of a NOAC to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase in bleeding, most pronounced when NOACs are combined with dual antiplatelet therapy. It is commendable to mention that these randomized trials were under-powered for the evaluation of efficacy [22].

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
<td>Twice a day</td>
<td>Once a day</td>
</tr>
<tr>
<td>Target</td>
<td>Vitamin K–dependent factors</td>
<td>Factor II</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>3–5 d</td>
<td>1 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Dose</td>
<td>Variable</td>
<td>150 mg twice a day and 110 mg twice a day</td>
<td>20 mg every day (15 mg every day for renal impairment)</td>
<td>5 mg twice a day (2.5 mg twice a day for high risk)</td>
<td>30 mg every day and 60 mg every day (with adjustment for high exposure)</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>12-14 h</td>
<td>7-11 h</td>
<td>12 h</td>
<td>9-11 h</td>
</tr>
<tr>
<td>Interactions</td>
<td>Multiple</td>
<td>Inhibitors of P-glycoprotein transporter†</td>
<td>Inhibitors of CYP 3A4 And P-glycoprotein transporter†</td>
<td>Inhibitors of CYP 3A4 and P-glycoprotein transporter†</td>
<td>Inhibitors of CYP 3A4 and P-glycoprotein transporter†</td>
</tr>
<tr>
<td>Renal clearance %</td>
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<td>80</td>
<td>35</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Anticoagulation monitoring</td>
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<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vitamin K</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

†Inhibitors of P-glycoprotein transporter include amiodarone (cautions with interaction) and verapamil.

Table 1: Comparison of Pharmacological Characteristics of Warfarin and the New Oral Anticoagulants for Atrial Fibrillation

NOACs have the everlasting success in the area of organ transplantation as prophylactic or therapeutic option. Vascular occlusion after organ transplantation is not uncommon clinical situation, with special concern to the pediatric heart and liver transplant situation. Interventional treatment for vascular occlusion after organ transplantation, showed a high success rate and good long-term results. Comprehensive interventional treatment should be used for extensive vascular occlusion. The percutaneous thrombolysis therapy was determined, NOACs still saving many patients post-transplant.

Discussion
The main objective of this short report is to raise the awareness of clinicians regarding the underutilized NOACs and shed light on the main concerns surrounding their utility as suitable alternatives to Warfarin.

The convenience of NOAC
The NOACs are far more convenient than Warfarin because they have predictable pharmacodynamic effects and at doses tested in the large trials, have good efficacy and safety profiles without anticoagulation monitoring. They avoid the need for frequent dose adjustment that may contribute to dosing errors. Dabigatran and Apixaban are administered twice a day. Rivaroxaban and Edoxaban are given once a day. All of the NOACs have the advantage of rapid onset of action and relatively short half-life periods, making their use around the world.
The study showed that patients favor a favorable risk-benefit ratio compared with warfarin and positive results and bleeding has shown some favorable results. NOACs provide more balance between efficacies and bleeding risk (safety). The choice characteristics and the best choice of agent may be dependent on individual patient (not Rivaroxaban). The NOACs have slightly different properties of GI bleeding with Dabigatran and Rivaroxaban compared to warfarin. There are fewer drug-drug interactions, food-drug interactions and intracranial warfarin), short half-life, requirement for anticoagulant monitoring, NOACs: more stable anticoagulation (in patients poorly controlled on control appears to be the case for Rivaroxaban and Apixaban as well control ranges. The pattern of a consistent benefit regardless of INR intracranial hemorrhage appeared to be nearly identical across INR warfarin), stroke risk (CHADS, -VASC score) and risk of bleeding. Renal impairment is crucial for selection of NOAC, for instance Dabigatran should not be used in patients with creatinine clearance < 30 mL/minute. While, Rivaroxaban, Apixaban and Dabigatran are contraindicated in patients with creatinine clearance < 15 mL/min. NOACs are not approved for use in dialysis patients. Patients with a history of stroke or bleeding complications are more likely to be switched from VKA to NOAC.

The efficacy outcomes

NOACs are at least as good as Warfarin at preventing stroke and the benefit compared with no therapy is of major outcome. Dabigatran 150 mg twice daily and Apixaban 5 mg twice daily are more effective than Warfarin in terms of preventing stroke. All of the three drugs result in a ~10% reduction in mortality, although this reached statistical significance only for Apixaban [23].

The safety outcome

With more remarkable than the superior efficacy, the rate of hemorrhagic stroke was reduced by 40% to 70% and that of intracranial hemorrhage by ~50% with all 3 of the agents, suggesting a liability to Warfarin in regard to intracranial hemorrhage. Both lower-dose Dabigatran and Apixaban resulted in important reductions in major bleeding. These important benefits in clinical outcomes provide the most compelling rationale for their use as first-line agents [23].

The effect on mortality

Apixaban, Dabigatran and Rivaroxabans result in a ~10% reduction in mortality, although this reached statistical significance only for Apixaban. The fact that mortality tends to be lower suggests that, overall, the clinical benefits clearly outweigh the risks [23].

Switching from Warfarin to NOACS

Some have suggested that although the new agents provide important benefits for patients not previously on Warfarin, there is little advantage to switching if patients are tolerating warfarin with good INR control (not evident). The benefits of the new anticoagulants were similar regardless of prior use of Warfarin [11].

With dabigatran, there was no statistically significant evidence of less benefit of stroke prevention in centers with better INR control. Importantly, the benefit of Dabigatran over warfarin in reducing intracranial hemorrhage appeared to be nearly identical across INR control ranges. The pattern of a consistent benefit regardless of INR control appears to be the case for Rivaroxaban and Apixaban as well [23].

The following are considered pros of switching from Warfarin to NOACs: more stable anticoagulation (in patients poorly controlled on warfarin), short half-life, requirement for anticoagulant monitoring, fewer drug-drug interactions, food-drug interactions and intracranial bleeding. The cons are: specific antidote so not reversible in bleeding patients or those requiring emergency surgery and increased frequency of GI bleeding with Dabigatran and Rivaroxaban compared to warfarin.

NOACs should be considered inpatients switching from Warfarin to NOACs: more stable anticoagulation (in patients poorly controlled on warfarin), due to poor INR control despite good compliance, patients with newly diagnosed non-valvular AF (Apixaban and Dabigatran, but not Rivaroxaban). The NOACs have slightly different properties and the best choice of agent may be dependent on individual patient characteristics.

The primary objective for the selection of NOACs is to maintain balance between efficacies and bleeding risk (safety). The choice between the four novel oral anticoagulants depends on their efficacy and safety profile. The effect of NOAC’s on risks of mortality, stroke and bleeding has shown some favorable results. NOACs provide more favorable risk-benefit ratio compared with warfarin and positive results in clinical trials. Therefore, NOACs should generally be used as first-line treatment for stroke prevention in AF.

The grey areas and mundane aspects of clinical practice

There are three integrated grey areas required to be discussed and argued in light of all of the randomized clinical trials, meta-analysis and pharmaceutical-race. We will discuss these grey areas and provide some glue to be easily thought by clinicians during their puzzles of whether to select Warfarin or NOAC’s in typical patient’s clinical scenarios.

The selection of patient suitability to NOACs

The most important determined factor for suitability to NOAC is relevant to patient suitability in term of demographics (e.g. age), comorbidities (e.g. chronic kidney disease), degree of renal impairment (creatinine clearance > 30 mL/min), adherence to daily dosing, unstable INR, unwilling to take Warfarin, stroke risk (CHADS, -VASC score) and risk of bleeding. Renal impairment is crucial for selection of NOAC, for instance Dabigatran should not be used in patients with creatinine clearance < 30 mL/minute. While, Rivaroxaban, Apixaban and Dabigatran are contraindicated in patients with creatinine clearance < 15 mL/min. NOACs are not approved for use in dialysis patients. Patients with a history of stroke or bleeding complications are more likely to be switched from VKA to NOAC.

A recent study with unique experimental results in an assessment of the relative value and weight of clinical events associated with anticoagulant therapy concluded that not all outcomes are created equally in the minds of patients [24]. The study showed that patients highly valued taking drugs that carried a lower risk of fatal bleeding, reporting they were willing to accept a 2.8% risk of nonfatal stroke, a 2.2% risk of nonfatal MI, and a 3.4% risk of cardiovascular death to avoid a 1% risk of fatal bleeding. The NOACs are characterized by their efficacy outcomes (reduction in major cardiovascular events) and the likelihood of side effects (risk of minor, major, or fatal bleeding). The decision on choice of drug to take, implicit in that decision is the relative weight the authors relate to clinical outcomes. This weight was assumed to be different from patient to patient or from physician to patient [24].

The finding that patients would prefer a NOAC to warfarin rely solely on basis of its “newness” and not necessarily because of any conferred benefit “suggests that labels can influence patients’ medication choices” and “should be used with caution in the shared decision-making process.” Overall, patients are not particularly concerned about need for monitoring with warfarin. The preference for “avoiding the inconvenience of international normalized ratio [INR] monitoring is trivial when compared with a preference for avoiding clinical outcomes” [24].

The economic burden

There are growing concerns that patients do not take the costly medications nor continue availing them as cost of medications surge beyond their budgets. Most patients with AF are having co-morbidities with problematic poly-pharmacy issues. The multi-drug pill can go beyond their budgets. Most patients with AF are having co-morbid illnesses nor continue availing them as cost of medications surge beyond their budgets. Most patients with AF are having co-morbidities with problematic poly-pharmacy issues. The multi-drug pill can go beyond their budgets.
mostly a retired person. The implications of cost on NOAC selection is considered highly significant for clinicians.

The selection of NOACs

There are dosing reasons to choose a certain NOAC from the four available patent compounds. Dabigatran and Apixaban are taken in twice dosing interval, while Edoxaban and Rivaroxaban are once daily dosing schedule. The short half-life of the Apixaban may be of particular benefit where abrupt withdrawal can be achieved without worrying about sudden withdrawal effects of bleeding.

The NOACs are not well utilized in patients with AF. There is a report which showed that contrary to current guidelines, 30% of patients with AF are not prescribed any NOACs. This may be attributed to the stable clinical status of some patients, low risk of CHADSVAS scores, clinical judgment of clinician, patient refusal, family issues and other factors

NOACs limitations

NOACs have some limitations, such as no reversal agent in the event of bleeding. However, currently antidote for each specific NOAC reversal is on the run (Phase 11 and III trials) such as Idaricuzumab for Dabigatran (REVERSE-AD trial), Andexanet for Abixapan-Alfa (ANNEXA-TM trial).

In order to be implicated in clinical practice, the following are to be considered:
1. The clinical use according to patient need: life-threatening hemorrhage, trauma, procedure with anticipated risk for major bleeding.
2. Careful risk assessment will be needed.
3. The risk for bleeding outweighs the benefit of thrombo-prophylaxis.
4. Attention to fundamentals of hemostasis and supportive measures.
5. Will the availability of NOACs antidotes drive the uptake of NOACs?

The future of NOACs

There is some gaps need to be addressed for a clinician to select a NOAC and/or convert and switch from Warfarin to NOAC. These gaps have to be highlighted by expert opinions from the gained meta-analysis and summarized for clinicians without any bias or conflict of interest.

The research by clinicians working on day-to-day clinical practice will be of extreme value as their views and that of their patients will delve-deeper the authentic clinical utility of NOACs. Researchers are encouraged to focus on patient satisfaction and quality of life aspects of these NOACs.

Conclusion

The messages taken from this overview can be summarized as follows, encourage the use of NOACs in daily clinical practice, evaluate the patient preferences, consider cost and insurance coverage and select a NOAC over Warfarin when the overall clinical judgment is optimal.

The last to say, are we going to conjecture whether Warfarin will still be used after its 73rd anniversary. The future is for no doubt goes to NOACs, we are very thankful for Warfarin and Karl and his senior student but it is high time to say a warm good-by. We wish Warfarin a retirement plan (downward count) and with respect request the way forth to the new generation of NOACs.

Recommendations

1. Limit the use of Warfarin to certain populations with pre-defined criteria such as (renal impaired patient e.g. creatinine < 30 mL/minute, cost issues, insurance barriers).
2. In cases where NOAC’s can be a suitable alternative, initiate NOAC’s as per guidelines.
3. Consider NOAC in patients intolerant to Warfarin with repeated bleeding episodes, multiple hospitalization, unpredictable INR and variable responses to Warfarin dosing.
4. The concerns about risk of bleeding tendencies due NOACs need to be estimated in diverse populations and in varied groups of patients with low, medium, high risk and associated comorbidities.
5. Special maneuvers (such as prophylactic proton pump inhibitors) for preventing and protecting patients against NOACs-induced risk of bleeding (or gastritis) deserve more clinical input from physicians (awareness and enforced in guidelines).
6. Special considerations for switching patients from Warfarin to any NOACs, with strictly following guidelines and recommended INR threshold (< 2 for initiating Dabigatran/Apixaban, ≤ 3.0 (European Medical Agency-EMA) or < 3.0 (FDA) for initiating Rivaroxaban) [24-28].

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References


