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Review Article

DOACs vs Vitamin K Antagonists: a Comparison of Phase III Clinical Trials and a Prescriber Support Tool

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Abstract

AIM: The purpose of this article was to systematically review the literature assessing the efficacy and safety of phase III clinical trials for each direct oral anticoagulant versus vitamin K antagonists and to design a ''go-to'' table for the prescriber.

MATERIAL AND METHODS: A systematic review of specialist literature was conducted to identify RCTs which compared direct oral anticoagulants (DOACs) with standard warfarin treatment. Medline, Em-base, and the Cochrane databases were searched from January 2005- January 2019. The inclusion criteria were randomised controlled trials of oral anticoagulants in patients with non-valvular atrial fibrillation (NVAF). Four publications were phase III randomised control trials (RCTs) included in the final analysis.

RESULTS: Regarding the primary outcome in RELY the results were 1.69% per 100-year patients (p/y) for Warfarin compared to 1.11% p/y dabigatran etexilate 150mg BD (twice daily). In ROCKET AF the rates of the primary outcome were 2.2% p/y for warfarin compared to 1.7% p/y for rivaroxaban 20 mg OD (once daily). In ARISTOTLE trial the rates of the primary outcome were 1.60% p/y for warfarin compared to 1.27% p/y for apixaban 5 mg BD. In ENGAGE AF TIMI, the rates of the primary outcome were 1.50% p/y for warfarin compared to 1.18% p/y for edoxaban 60mg BD.

CONCLUSION: DOACs showed to be either noninferior or superior to warfarin with regards to the primary outcome with better safety patterns. Our ''go-to'' table provides a supportive tool for physicians in preventing medical errors when managing patients on oral anticoagulants.

Introduction

Atrial Fibrillation (AF) is one of the leading causes of cardiovascular morbidity and mortality worldwide [1]. The incidence and prevalence of AF have been increasing in recent years up to the point that one in four middle-aged adults in Europe and the US will develop this common cardiac arrhythmia [2], [3]. The above numbers reflect a growing number of patients requiring anticoagulants for stroke prevention.

The clinical management of patients with non-valvular AF (NVAF) has improved in recent years with the introduction of direct oral anticoagulant agents (DOACs) [4]. In the last decade, the four DOACs: dabigatran etexilate, rivaroxaban, apixaban and edoxaban have been used for the prevention of stroke and systemic embolism for people with NVAF with one or more risk factors: prior stroke or transient ischaemic attack; age 75 years or older; hypertension; diabetes mellitus; symptomatic heart failure [5].

Several characteristics distinguish DOACs from vitamin K antagonists (VKAs): rapid onset of action (1-3 h), do not require bridging with parenteral anticoagulants and there is no need for routine monitoring of anticoagulation. Additionally, DOACs have similar (7-15 h) half-lives and are partially eliminated by the kidney: 85% of dabigatran etexilate, 50% of edoxaban, 33% of rivaroxaban, and 27% of apixaban [5]. Patients who are taking Warfarin should be aware of the potential risks and benefits of

switching to DOACs and their level of international normalised ratio (INR) control taken into consideration when switching between anticoagulants [5], [6].

The availability of several drugs with similar efficacy and safety for stroke prevention in NVAF patients offers a selection for prescribers and users. Consequently, prescribers should have a good knowledge of these agents' characteristics and the trials in which their use was established to counsel and care for the growing number of patients on oral anticoagulants.

The decision to take lifelong drugs such as oral anticoagulants should be made in collaboration between a patient and their doctor after an informed discussion about the risks and benefits of all the different drugs [7]. Medical professionals, particularly busy general practitioners/family doctors can find difficulties in keeping up to date with all the current guidelines and the new emerging drugs used in medical practice. If prescribers are better informed, then they can proficiently counsel their patients and collaborate with them when initiating an oral anticoagulant.

The purpose of this article was to systematically review the literature assessing the efficacy and safety of phase III clinical trials for each DOAC versus VKAs used in stroke prevention in patients with NVAF. Also, it aimed to design a ''go-to'' table for the prescriber to make an informed decision when comparing the oral anticoagulant drugs.

Material and Methods

A systematic review of specialist literature was conducted to identify phase III randomised control trials (RCTs) in patients receiving DOACs compared with standard warfarin treatment. Medline, Embase, and the Cochrane databases were searched from January 2005- January 2019 with no language restrictions using medical keywords to identify RCTs including ''Dabigatran'', ''Rivaroxaban'', ''Apixaban'', ''Edoxaban'', ''Atrial Fibrillation'', ''Humans'', ''Randomized Controlled Trial''. After combining the results and removing duplicates, the titles and abstracts were screened in 50 studies (Figure 1).

The full text of eight publications was retrieved and evaluated for eligibility, and four articles were phase III RCTs included in the final analysis. Studies had to meet the following inclusion criteria: randomised controlled trials of VKAs and DOACs in patients with NVAF. The research was excluded if patients were not followed up, if these were not randomised trials, and if papers were guidelines or any expert opinions.

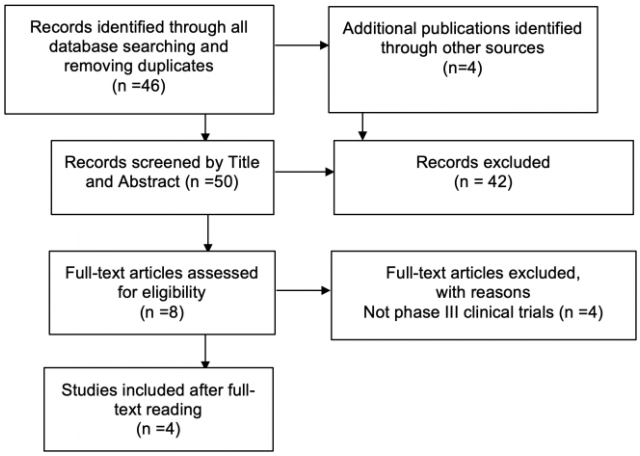

Figure 1: Prisma flow diagram illustrating the study selection process

Results

Four phases III clinical trials were evaluated, and in Table 1 and Table 2 we have compared the characteristics of phase III clinical trials for each DOAC that was on the market at the time of this study. Due to the heterogeneity of the key parameters, analysis of the statistical data was not attempted.

Table 1: Phase III clinical trials NOACs purpose and specific data characteristics

Study Name	RELY 2009	ROCKET AF 2011	ARISTOTLE 2012	ENGAGE AF TIMI 48 2013
Purpose	Dabigatran etexilate 150 mg BD or 110 mg BD to open-label dose adjusted Warfarin	Rivaroxaban 20 mg OD to dose-adjusted Warfarin	Apixaban 5 mg BD to dose-adjusted Warfarin	Edoxaban 30 mg OD and 60 mg OD to dose-adjusted Warfarin
Method-all were Prospective randomised pivotal phase III clinical trial	unblinded	double-blind, double-dummy	double-blind, double-dummy	double-blind, double-dummy
Number of patients	18113	14246	18201	21105
Follow up (years)	2	1.9	1.8	2.8
CHADS2	2.1	3.5	2.1	2.8
TTR (%)	64%	55%	62%	68%
Females (%)	37%	39%	35%	37%
Age mean (years)	71	73	70	72
Jadad score	3	5	5	5

RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy); ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF); ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF); ENGAGE AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in AF- Thrombolysis in Myocardial Infarction 48).

ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban) and ENGAGE AF TIMI (edoxaban) were double-blind double-dummy trials. RELY (dabigatran etexilate) and ARISTOTLE trials had a similar number of patients of approximately 18100. The follow-up period in all trials ranged from 1.8-2.8 years. RELY and ARISTOTLE participants had an equal CHADS2

score of 2.1. ENGAGE AF TIMI and ROCKET AF participants had a CHADS2 score of 2.8 and 3.5, respectively. Time in the therapeutic range INR (TTR) varied from 64%, 55%, 62% and 68% respectively.

Table 2: Phase III clinical trials DOACs efficacy and bleeding rates

Study name and purpose	Primary Outcome	Bleeding/Mortality of 100 patients per year
RE-LY 2009	Rates of the primary outcome (stroke or systemic embolism): 1.69% p/y warfarin 1.53% p/y dabigatran etexilate 110 mg BD-noninferiority 1.11% p/y dabigatran etexilate 150 mg BD-superiority	The rate of major bleeding: 3.36% p/y warfarin 2.71% p/y dabigatran etexilate 110 mg BD 3.11% p/y dabigatran etexilate 150 mg BD The rate of hemorrhagic stroke: 0.38% p/y warfarin 0.12% p/y dabigatran etexilate 110 mg BD 0.10% p/y dabigatran etexilate 150 mg BD The mortality rate: 4.13%p/y warfarin 3.75% p/y dabigatran etexilate 110 mg BD 3.64% p/y dabigatran etexilate 150 mg BD
ROCKET AF 2011	Rates of the primary outcome (stroke or systemic embolism): 2.2 %p/y warfarin 1.7% p/y rivaroxaban 20 mg OD noninferiority	The rate of nonmajor bleeding: 14.5% p/y warfarin 14.9% p/y rivaroxaban 20 mg OD The rate of major bleeding: 3.4% p/y warfarin 3.6% p/y rivaroxaban 20 mg OD The rate of gastrointestinal bleeding: 2.2% p/y warfarin 3.2% p/y rivaroxaban 20 mg OD The rate of hemorrhagic stroke: 0.7% p/y warfarin 0.5% p/y rivaroxaban 20 mg OD The mortality rate: 2.2% p/y warfarin 1.9% p/y rivaroxaban 20 mg OD
ARISTOTLE 2012	Rates of the primary outcome (stroke or systemic embolism): 1.60% p/y Warfarin 1.27% p/y Apixaban 5 mg BD superiority	The rate of major bleeding: 3.09% p/y warfarin 2.13% p/y apixaban 5 mg BD The rate of hemorrhagic stroke: 0.47% p/y warfarin 0.24% p/y apixaban 5 mg BD The mortality rate: 3.94% p/y warfarin 3.52% p/y apixaban 5 mg BD
ENGAGE AF TIMI 48 2013	Rates of the primary outcome (stroke or systemic embolism): 1.50% p/y Warfarin 1.18% p/y Edoxaban 60 mg OD 1.61% p/y Edoxaban 30 mg OD noninferiority	The rate of major bleeding: 3.43% p/y warfarin 2.75% p/y edoxaban 60 mg OD 1.61% p/y edoxaban 30 mg OD The rate of gastrointestinal bleeding: 1.23% p/y warfarin 1.51% p/y edoxaban 60 mg OD 0.82% p/y edoxaban 30 mg OD The rate of hemorrhagic stroke: 0.47% p/y warfarin 0.26% p/y edoxaban 60 mg OD 0.16% p/y edoxaban 30 mg OD The mortality rate: 3.17% p/y warfarin 2.74% p/y edoxaban 60 mg OD 2.71% p/y edoxaban 30 mg OD

Regarding the primary outcome in RELY the results were 1.69% per 100-year patients (p/y) for warfarin compared to 1.53% p/y dabigatran etexilate 110 mg BD and 1.11% p/y dabigatran etexilate 150 mg BD. In ROCKET AF the rates of the primary outcome were 2.2% p/y for warfarin compared to 1.7% p/y for rivaroxaban 20 mg OD. In ARISTOTLE trial the rates of the primary outcome were 1.60% p/y for warfarin compared to 1.27% p/y for apixaban 5 mg BD. In ENGAGE AF TIMI the rates of the primary outcome were 1.50% p/y for warfarin compared to 1.18% p/y for edoxaban 60 mg BD and 1.61% p/y for edoxaban 30 mg BD. Taking into consideration all the important literature in oral anticoagulation for NVAF we designed a comprehensive but simple to follow ''go-to'' table (Table 3) [8], [9], [10], [11], [12], [13], [14], [15] to aid the prescribers worldwide.

Table 3: Oral Anticoagulants Specific Information A Prescriber Support Tool

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Dose/Frequency	INR Dependent OD	150 mg BD	20 mg OD	5 mg BD	60 mg OD
Peak/Half-life	3-5 days Half-life 40 hours	2 days Half-life 12-14 hours	2-3 days Half-life 5-13 hours	1-2 days Half-life 8-15 hours	1-2 days Half-life 9-11 hours
Reduced dose	N/A	110 mg BD	15 mg OD	2.5 mg BD	30 mg OD
Age	N/A	Age > 80 years Also consider in > 75years	No dose adjustment	Age > 80 years	No dose adjustment
Weight	Extreme weight > 120 kg BMI > 40 kg/m2	< 50 kg	No dose adjustment	< 60 kg	< 60 kg
Renal	Not affected	CrCl < 5 0mL/min Cl CrCl < 30 mL/min 85%	CrCl < 15-49 mL/min Cl CrCl < 15 mL/min 33%	Creatinine > 133 micromoles/L or > 1.5 mg/dl Cl CrCl < 15mL/min 27%	CrCl < 15-49 mL/min Cl CrCl < 15 mL/min 50%
Interactions CAUTION IF	Abciximab Alteplase Amiodarone Amoxicillin Aprepitant Antiplatelets Azathioprine Azoles (fluco,mico, itra,vori) Barbiturates Bosentan Carbamazepine Chloramphenicol Ciprofloxacin Clarithromycin Coamoxiclav Capecitabine Danazol Disulfiram Doxycycline Erythromycin Fibrinolytics Fibrates Flucloxacillin Fluorouracil	Amiodarone Quinidine Clarithromycin Erythromycin Dose reduction: Verapamil (take at the same time)	Clarithromycin Erythromycin Fluconazole Amiodarone Quinidine	Diltiazem Naproxen	Ciclosporin Tacrolimus Ketoconazole Itraconazole Voriconazole Posaconazole Amiodarone Quinidine Dose reduction: Clarithromycin Erythromycin Dronedarone Ciclosporin Tacrolimus
Interactions AVOID IF	Fluvastatin Fluvoxamine Fenofibrate Glucagon HIV protease inhibitors Ivermectin Levofloxacin Leflunomide Lymecycline Metronidazole Mercaptopurine Mesalamine NSAIDs Ofloxacin Quinidine Quinine Paclitaxel Prostacyclin Paracetamol Phenytoin Propofol	Ketoconazole Itraconazole Voriconazole Posaconazole Dronedarone Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital Ritonavir Anticoagulants Tacrolimus Cyclosporin	Ketoconazole Itraconazole Voriconazole Posaconazole Dronedarone Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital Ritonavir Anticoagulants	Ketoconazole Itraconazole Voriconazole Posaconazole Dronedarone Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital Ritonavir Anticoagulants	Ritonavir Rifampicin St John's Wort Carbamazepine Phenytoin Phenobarbital Anticoagulants
Dose reduction for DOACs if > 2 factors	Rifampicin Ribavirin SSRI SNRI Steroids St John's Wort Sulfasalazine Tamoxifen Terbinafine Vandetanib		Antiplatelets NSAIDs Systemic steroids Thrombocytopenia HASBLED > 3	History of GI bleeding Recent surgery on critical organ (brain, eye)	
Liver AVOID IF	Caution	Elevated liver enzymes > 2 upper limits of normal Hepatic impairment or liver disease expected to have any impact on survival	Hepatic disease associated with coagulopathy Cirrhotic patients with Child-Pugh B and C	Hepatic disease associated with coagulopathy Severe hepatic impairment	Hepatic disease associated with coagulopathy Elevated liver enzymes > 2 upper limits of normal total bilirubin ≥ 1.5 x upper limit of normal
Side effects	Hair loss Rare vascular calcification and skin necrosis	Oesophagitis Gastritis Duodenitis HASBLED > 3 Anaemia	Anaemia, Dizziness, Headache, Serious skin reactions (rare) Galactose intolerance	Contains lactose Anaemia	Anaemia, Dizziness, Headache High bilirubin High gamma glutamyltransferaseskin rash
Food interaction	Brocolli/Green leafs vegetables, Garlic, Ginger, Grapefruit, Cranberry, Mango, Green tea, Alcohol	X	X must be taken with food	X	X
Switching between anticoagulants	Overlap until INR > 2.0 May take 5-10 days	INR < 2.0	INR < 3.0	INR < 2.0	INR < 2.5
Compliance aid	Risk assessment	No	Yes	Yes	Yes
Swallow whole	Most brands of Warfarin tablets will disperse in water	Yes (tartaric acid)	No, can be crushed	No, can be crushed	Yes
Missed Dose	next dose as normal	up to 6h before the next dose	up to 12h before the next dose	up to 6h before the next dose	up to 12h before the next dose
Bleeding	All DOACs showed less Intracranial bleeding compared to Warfarin Antidote Vitamin K Prothrombin complex concentrate	Major bleeding D150 mg BD = W D110 mg BD < W GI bleeding D150 mg BD > W D110 mg BD = W Antidote Idarucizumab Haemodialysis	Major bleeding R = W GI bleeding R > W No antidote Prothrombin complex concentrate	Major bleeding A < W GI bleeding A = W No antidote Prothrombin complex concentrate	Major bleeding E < W GI bleeding E60mg OD > W No antidote Prothrombin complex concentrate
Specific Populations	Obese >120kg Renal/Hepatic Impairment (caution) 2nd-trimester pregnancy	110mg BD if previous GI haemorrhage High bleeding risk HASBLED>3; 150mg BD if recurrent stroke despite well managed VKA	For Asian patients use another DOAC Preference for once daily preparations	Previous GI haemorrhage High bleeding risk HASBLED>3 Elderly patients Renal impairment	Preference for once daily preparations High bleeding risk HASBLED>3 Elderly patients

Discussion

General characteristics of the four RCTs

ROCKET AF, ARISTOTLE and ENGAGE AF TIMI were double-blind, double-dummy trials, whereas RELY was an open-label trial which suggested a possible bias for this trial. The RELY trial authors state the risk of bias was reduced by the implementation of several validated procedures, including blinded evaluation of outcome events [16]. RELY and ARISTOTLE trials had a similar number of patients of more than 18100, ROCKET AF had the smallest number of participants of 14246, whereas ENGAGE AF TIMI had the largest population of 21105 which showed that all trials were large trials of high importance. The follow-up period was similar in RELY, ROCKET AF and ARISTOTLE but considerably longer in ENGAGE AF TIMI at 2.8 years. RELY and ARISTOTLE participants had an equal CHADS2 score of 2.1. However, ENGAGE AF TIMI and ROCKET AF participants had a higher CHADS2 score of 2.8 and 3.5, respectively. This was a significant finding and should be taken into account when choosing a particular DOAC for a patient.

The mean percentage of TTR was lower in ROCKET-AF (55%) compared to TTR in ARISTOTLE (62%), RE-LY (64%) and ENGAGE AF TIMI (68%). This is also an important finding and should be taken into account particularly for patients who are switching from a VKA to a DOAC. In ROCKET AF the low TTR was interpreted as poor control of the patients anticoagulant status. Age and sex of the studied population were similar in all studies ranging from 70-73 years and female percentage between 35-39%. These numbers show similarities with the general epidemiological data in AF (2). Finally, all the RCTs obtained a good Jadad score.

RE-LY

For the primary outcomes, dabigatran etexilate 150 mg twice daily was superior to warfarin, and dabigatran etexilate 110 mg twice daily was noninferior to warfarin. Major bleeding was significantly decreased with the 110 mg twice daily dose of dabigatran etexilate. However, the group on the 150 mg twice daily dose of dabigatran etexilate showed increased major bleeding events compared to warfarin. The risk of hemorrhagic stroke was also significantly lower with both the 110 mg and 150 mg doses [16]. These findings show that dabigatran etexilate was noninferior or superior (150 mg BD) when compared to warfarin, but the bleeding risk should be considered in both anticoagulants.

Interestingly, the rate of myocardial infarction was higher with both doses of dabigatran etexilate compared with warfarin but not statistically significant. A reason for this was explained by Connolly et al., (RELY) that warfarin provides better protection against coronary ischaemic events compared to dabigatran [16] (Table 2).

Dabigatran etexilate capsules contain coating with tartaric acid to enhance the gastric absorption which requires a more acidic environment. This acidity may explain the increased incidence of dyspeptic symptoms with both dabigatran etexilate doses [16]. This should be taken into consideration when prescribing dabigatran etexilate in patients with known gastro-oesophagal pathology.

ROCKET AF

For the primary outcomes, the trial demonstrated noninferiority for rivaroxaban compared with warfarin in patients with NVAF who were at moderate to high risk for stroke. Major bleeding was similarly reported for rivaroxaban and warfarin groups. However, less fatal bleeding and less intracranial haemorrhage were found in the rivaroxaban group. In contrast, gastrointestinal (GI) bleeding was more frequently reported in the rivaroxaban group [17]. Consequently, extra caution should be taken when prescribing rivaroxaban in patients with previous GI bleeding (Table 2).

At the end of the trial, patients transitioning to open-label therapy had more strokes with rivaroxaban compared with warfarin [18]. Patel et al. explained that the difficulty in transitioning from blinded trial therapy to the open-label use of a VKA could have been the cause for this [17]. Presumably many patients who had previously been assigned to the warfarin group would have already had a therapeutic INR compared to the patients in the rivaroxaban group [17]. This should be taken into account when switching between anticoagulants.

ARISTOTLE

Granger at al described it was the only study of a DOAC that showed significantly lower rates of all-cause mortality reported at 3.52% in the apixaban group compared to 3.94% in the warfarin group [19]. Apixaban has shown to be significantly more effective than warfarin, with fewer overall strokes and systemic emboli by 21%, major bleeding events by 31% and decreased mortality by 11% [19]. Consequently, further studies showed positive findings for apixaban in comparing DOACs indirectly. A meta-analysis of the above trials indicated that there were no statistically significant differences between dabigatran etexilate, rivaroxaban or apixaban in the incidence of stroke, systemic embolism and all-cause mortality [6], [18]. Additionally, apixaban was associated with a significantly lower incidence of all bleeding outcomes compared with rivaroxaban and a lower incidence with clinically relevant non-major bleeding compared to dabigatran etexilate 150 mg twice daily [18].

ENGAGE AF TIMI

This was the largest DOAC trial, and it showed that both once-daily regimens of edoxaban were noninferior when compared with warfarin regarding the primary outcome. Of note, the follow-up period in this trial was long, and the TTR was higher compared to the previous three DOAC trials. This illustrated good management of patients on oral anticoagulants within the trial. Edoxaban regimens were associated with significantly lower rates of bleeding and mortality from cardiovascular causes compared to warfarin [18]. The rates of life-threatening bleeding, intracranial bleeding, and major bleeding plus clinically relevant non-major bleeding were significantly lower in the edoxaban group. However, the annualised rate of major gastrointestinal bleeding was higher with high dose edoxaban than with warfarin (1.51% vs 1.23%), but the gastrointestinal bleeding rate was lowest with low dose edoxaban (0.82%). Giugliano et al. stated that the rate of myocardial infarction was not altered with edoxaban, and there was no increase in the risk of stroke or bleeding when patients in the edoxaban groups made the transition to open-label anticoagulant therapy at the end of the study [20].

DOACs and specific patient characteristics

DOACs appeared to be equally or more effective and safer than Warfarin in preventing systemic embolism irrespective of the patients' comorbidities [6], [16], [17], [18], [20]. Subsequently, ''real world'' studies showed that the risks of mortality, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran etexilate compared with warfarin [18], [21]. We are in agreement with Shields et al. that direct comparison of the results from large, international, multicenter randomized control trials of DOACs versus warfarin for NVAF should be interpreted with caution due to differences in the mean CHADS2 score, TTR and rates of stroke and systemic embolism and hemorrhage in the warfarin group of the trials [15], [22].

In patients with NVAF with a significant risk of stroke, DOACs were reported as highly effective at preventing strokes compared to VKAs, and these provide a major improvement in the management of NVAF patients [23]. DOACs showed to have a more favourable safety profile and side effects, particularly for intracranial bleeding. Since the introduction of DOACs, there has been reported an increase in newly diagnosed patients with NVAF at risk of stroke who are receiving guideline-recommended therapy [4], [21].

Furthermore, due to the relatively recent introduction of these drugs, prescribers need to be aware of their characteristics, cautions and contraindications. Audits on prescribing oral anticoagulants reported frequent medical errors [23]. We agree with Heidbuchel et al., that the choice of the most appropriate DOAC for a patient should be based on the pharmacokinetics, pharmacodynamics and the integration of the clinical data concerning the patient's characteristics [14]. Recommendations from EHRA (European Heart Rhythm Association) suggested that patients with a history or high risk of gastrointestinal bleeding may have a lower risk of bleeding complications with apixaban and low dose edoxaban compared with dabigatran etexilate, rivaroxaban or high dose edoxaban [14]. Moreover, there was reported some evidence that patients with a high risk for ischemic stroke may benefit from dabigatran etexilate 150 mg twice daily [24].

Regarding patient-centeredness, evidence was reported that patients adhere better to once daily medications compared with those medications taken twice daily. [25] Patient's compliance was an important factor in the management of NVAF and data suggested in GARFIELD AF that patient refusal (11.2% for high-risk patients) has been the main patient factor affecting the rates of anticoagulation [4]. In patients without a contraindication to DOAC therapy, the selection among the agents was left primarily to physician and patient decision.

Wilke et al. reviewed the preferences of AF patients towards anticoagulation and showed that stroke risk reduction and limited bleeding risk were the most important attributes for an NVAF patient when deciding about oral anticoagulation [26]. NVAF patients were willing to accept higher bleeding risks if a certain threshold in reduced stroke risk could be reached [7], [26]. Steinberg et al. considered that involving the patient in the decision making when selecting a DOAC was vital for optimal management in NVAF [27]. Therefore this article encourages physicians to counsel patients about the risks and benefits of treatment and work out which is the best oral anticoagulant agent based on their characteristics (Table 3).

Conclusion

Based on the results in phase III randomised control trials discussed in this article, DOACs have shown similar efficacy but better safety patterns when compared with warfarin for NVAF management. To safely use anticoagulants, physicians should take into account patient-specific factors and shared decision making when prescribing an oral anticoagulant.

Our ''go-to'' table provides a supportive tool for physicians in preventing medical errors when managing patients on oral anticoagulants. Finally, research should be continued in clinical trials particularly for the specific populations.

Implications for Research

In this systematic review was summarised the important facts from the RCTs on oral anticoagulants. Also, a prescription tool was designed to aid family doctors/ prescribers in choosing the right agent for the right patient.

Limitations

Although we comprehensively reviewed and summarised the literature, our search was not exhaustive, and new data are emerging rapidly.

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