Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet Dec 2013

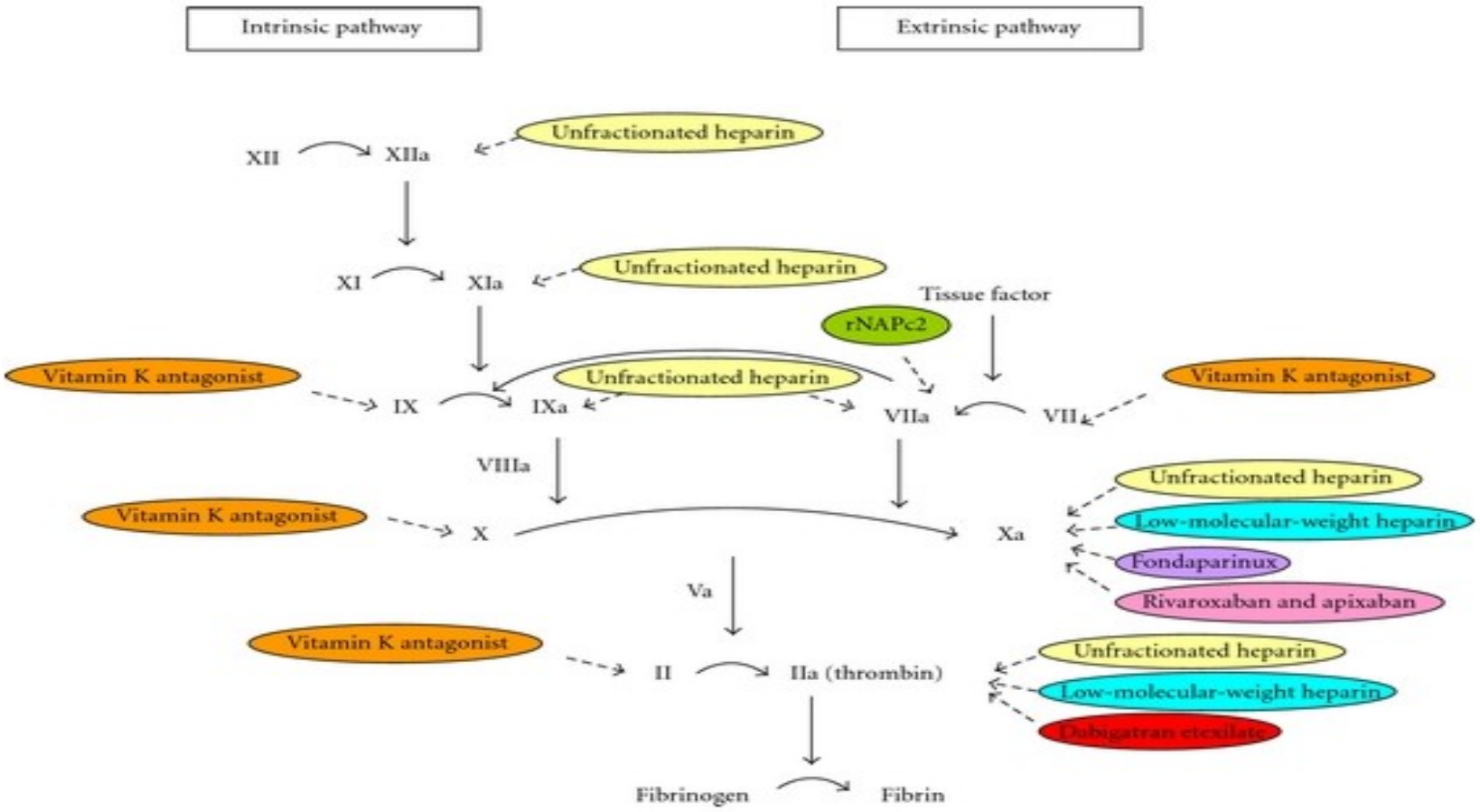
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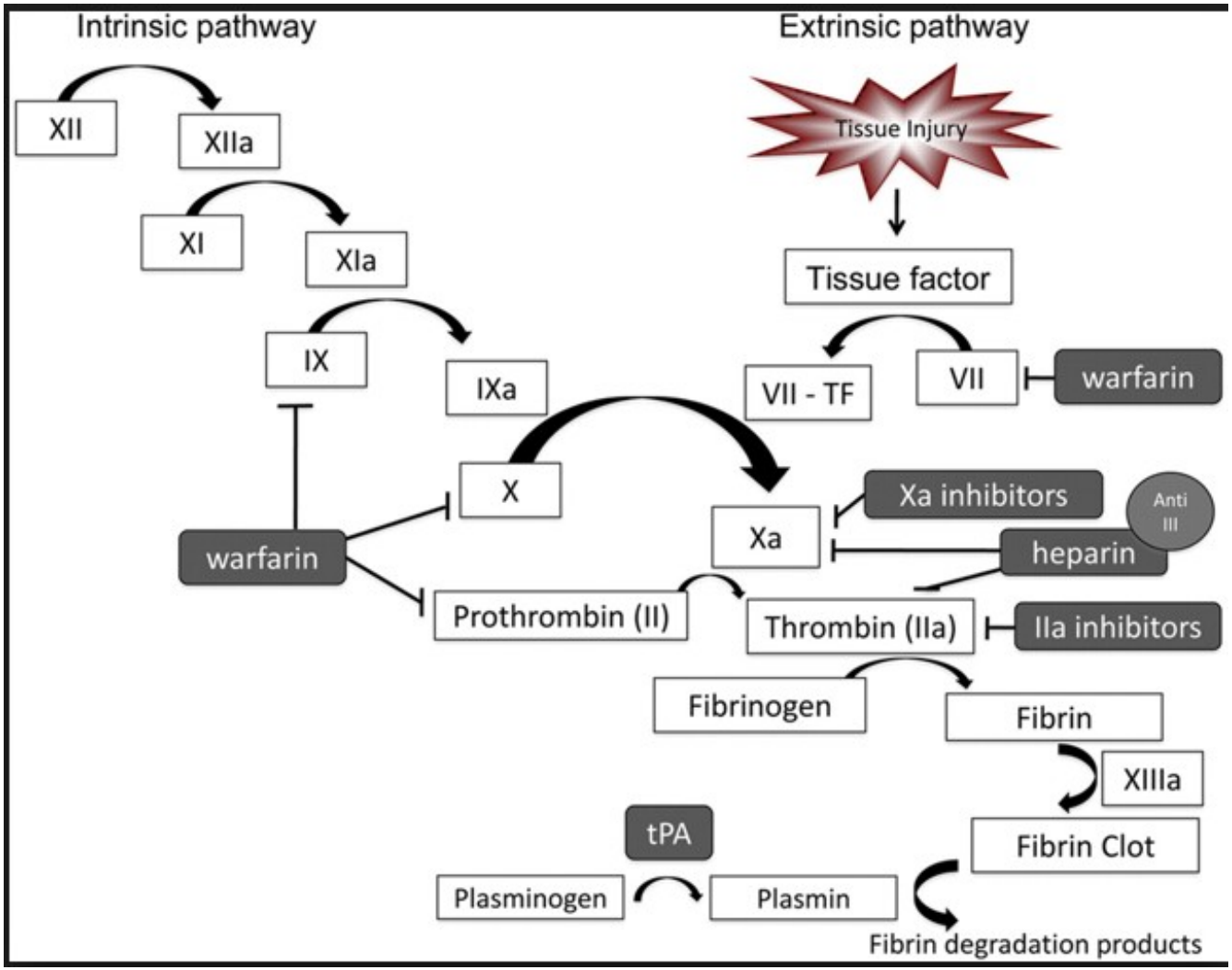
Epidemiology

- Atrial fibrillation affects more than 2.2 million persons in the United States.
- Incidence: (Strongly age-dependent), affects 4% > 60 years and 8% > 80 years.
- Approximately 25% of individuals aged 40 years and older will develop AF during their lifetime.
- Prevalence of AF: 0.1% <55, 3.8% >60, 10% >80.
- Rate of ischaemic stroke for AF 5%/year (2-7 times higher than without AF).

Coagulation cascade



Anticoagulants



Warfarin

- Introduced in 1948 as a pesticide. (1920s haemorragic cattle disease).
- Name: Acronym Wisconsin Alumni Research Foundation + arin.
- Approved for medical use 1954 (1951 US armee inductee incident).
- Mechanism of action 1970s. (Inhibits epoxide reductase, interferes vit K metabolism).

Disadvantages

- Difficulty of establishing and maintaining an adequate level of the INR.
  - intercurrent illnesses,
  - a myriad of interacting drugs,
  - dietary changes, alcohol.
- Monitor INR, adjust dose.
- Long half-life, delayed onset of action.

Dabigatran

- 1980s Discovered from a panel of chemicals with similar structure to benzamidine-based thrombin inhibitor α-NAPAP (N-alpha-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide), which had been known since the 1980s as a powerful inhibitor of thrombin and trypsin.
- 2008 – 2010 approved by European Medicines Agency, NHS, FDA. For non valvular AF, hip and knee surgery.

RE-LY

- (RE-LY), demonstrated in an unblinded design that patients randomly assigned to 150 mg BID of the new drug in comparison with warfarin had a significantly lower rate of ischemic stroke, and no higher risk of major bleeding.7
- Several other prespecified outcomes added additional nuances of the sort that make clinical decision making in this realm so multifaceted and challenging: in comparison with warfarin, dabigatran caused significantly fewer intracerebral hemorrhages and deaths from vascular causes, although the risk of major bleeding was similar overall.
- It had a nearly significant (P0.051) advantage for all-cause mortality as well.
- Yet, the new drug also led to significantly more symptomatic dyspepsia.
- A statistically significant 38% increase in the risk of myocardial infarction with dabigatran was initially reported; when 30 new myocardial infarctions were found on closer inspection of trial data, that incidence remained elevated at a 27% increase, but fell below the conventional level of statistical significance.8
- Overall, however, the findings indicated that the net clinical risk-benefit balance for the 2 drugs favored dabigatran, at least as far as the data from RE-LY went.

thebmj

BMJ 2014;349:g4670 doi: 10.1136/bmj.g4670 (Published 23 July 2014)

FEATURE

ANTICOAGULANTS

Dabigatran: how the drug company withheld important analyses

In an investigation by *The BMJ* **Deborah Cohen** finds that recommendations for use of new generation oral anticoagulants may be flawed because regulators did not see evidence showing that monitoring drug plasma levels could improve safety

Deborah Cohen *investigations editor, The BMJ*

Mechanical valves

BACKGROUND

Dabigatran is an oral direct thrombin inhibitor that has been shown to be an effective alternative to warfarin in patients with atrial fibrillation. We evaluated the use of dabigatran in patients with mechanical heart valves.

METHODS

In this phase 2 dose-validation study, we studied two populations of patients: those who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier. Patients were randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. The selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

RESULTS

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in 7 patients (4%) and 2 patients (2%), respectively. All patients with major bleeding had pericardial bleeding.

CONCLUSIONS

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. (Funded by Boehringer Ingelheim; ClinicalTrials.gov numbers, NCT01452347 and NCT01505881.)

Rivaroxaban

- Highly selective direct Factor Xa inhibitor with oral bioavailability and rapid onset of action.
- No effect on thrombin or platelets.
- Predictable pharmacokinetics.
- Allows predictable anticoagulation with no need for dose adjustments and monitoring.
- Trials excluded patients with liver disease therefore safety is unknown.

Disadvantages of NOAC

Short half-life
Potential for increased risk of stroke or systemic embolism with poor drug adherence
No routine coagulation monitoring required
Potential for increased risk of stroke or systemic embolism with poor drug adherence
No coagulation assay easily available to precisely measure anticoagulation effect
Cannot titrate dose
Cannot assess cause for failure of therapy (poor adherence vs failure)
Cannot easily assess degree of coagulation inhibition in emergent situations such as need for urgent surgery or in the setting of life-threatening bleeding
No antidote or well-established procedure for reversing anticoagulation in emergent situations
Cost

CHADS2

Table 1. $CHADS_2$ Score: Stroke Risk Assessment in Atrial Fibrillation (Open Table in a new window)

Score	$CHADS_2$ Risk Criteria
1 point	Congestive heart failure
1 point	Hypertension
1 point	Age >75 years
1 point	Diabetes mellitus
2 points	Stroke/transient ischemic attack

Table 2. Treatment Recommendations Based on $CHADS_2$ Score (Open Table in a new window)

CHADS2 Score	Risk	Recommendation
0	Low	Aspirin (81-325 mg) daily
1	Intermediate	Aspirin (81-325 mg) daily or warfarin (INR 2.0–3.0), based on patient preference
2 or more	High (CHADS2 revised) or intermediate (CHADS2 classic)	Warfarin (INR 2.0-3.0), unless there are reasons to avoid it

Table 3. $CHADS_2$ Score and Corresponding Annual Stroke Risk (Open Table in a new window)

$CHADS_2$ Score	Annual Stroke Risk, %
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

Relevant risk scores

Table 1: Stroke and bleeding risk stratification with the CHA_2DS_2-VASc and HAS-BLED schemas

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

Baseline characteristics

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

ata are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. $CHADS_2$=stroke risk factor scoring system in which one point is given for history of congestive heart ilure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeuti nge. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left entricular ejection fraction<40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used KAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

able: Baseline characteristics of the intention-to-treat populations of the included trials

Results

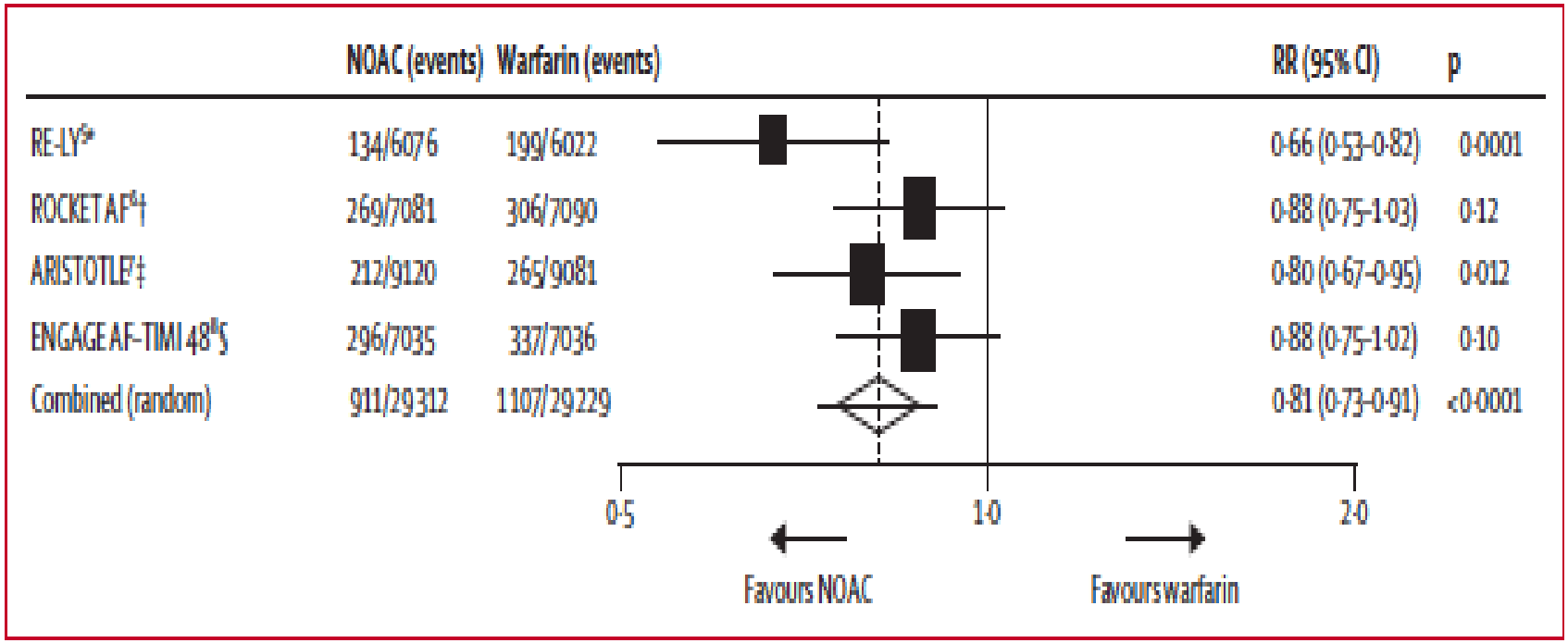


Figure 1: Stroke or systemic embolic events

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Results

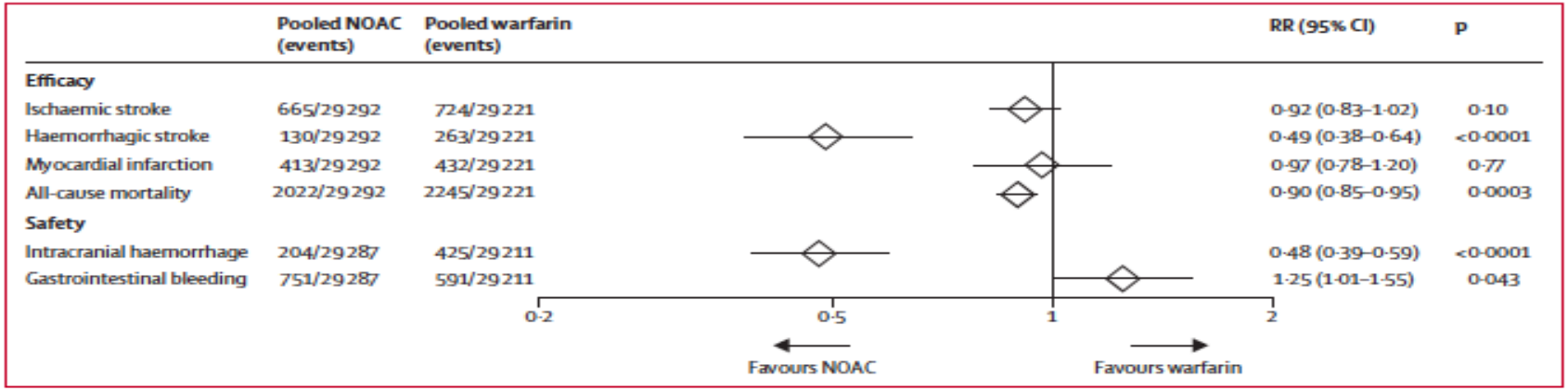


***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

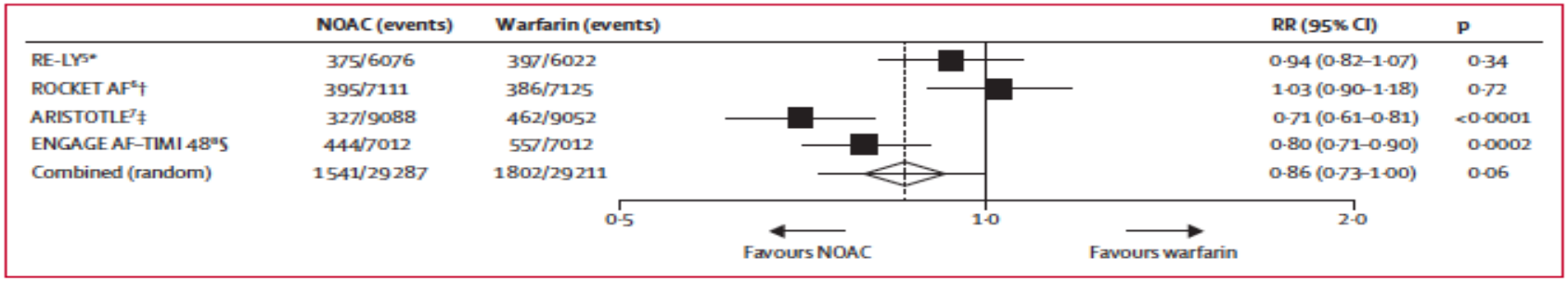


***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Discussion

- Our results show that stroke and systemic embolic events were signifi cantly reduced in patients receiving new oral anticoagulants. This benefi t was mainly driven by substantial protection against haemorrhagic stroke, which was reduced by half.
- For the prevention of ischaemic stroke, the new oral anticoagulants had similar effi cacy to warfarin, which itself is very eff ective in this regard and reduces ischaemic stroke by two-thirds compared with placebo.27
- In general, the new oral anticoagulants had a favourable safety profi le compared with warfarin; however, they were associated with an increase in gastrointestinal bleeding.
- They were also associated with a signifi cant reduction in all cause-mortality compared with warfarin.
- the two low-dose new oral anticoagulant regimens showed that although they have a similar effi cacy to warfarin for protection against all stroke or systemic embolic events, they are not as eff ective for protection against ischaemic stroke in particular. However, they do have a safer profi le than warfarin and preserve the mortality benefi t noted with the high-dose regimens. Consequently, low-dose regimens might be an appealing option for frail patients or for those who have a high risk for bleeding with full-dose anticoagulation.

Conflict of interest

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

CTR has served as a consultant and has received honoraria from Daiichi Sankyo, Boehringer Ingelheim, and Bristol-Myers Squibb. RPG has served as a consultant and has received honoraria from Bristol-Myers Squibb, Janssen, Daiichi Sankyo, Merck, Sanofi, and is a member of the TIMI Study Group, which has received research grant support from Daiichi Sankyo, Johnson & Johnson, and Merck. EB has recieved grants and personal fees for lectures from Daiichi Sankyo; grants from Duke University, AstraZeneca, Johnson & Johnson, Merck & Co, Sanofi-Aventis, GlaxoSmith Kline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, and Pfizer; uncompensated personal fees for consultancy from Merck & Co; personal fees for consultancies from Genyzme, Amorcyte, Medicines Co, CardioRentis, and Sanofi-Aventis; uncompensated personal fees for lectures from Merck and CVRx; and personal fees for lectures from Eli Lilly, Menarini International, Medscape, and Bayer outside the submitted work. MDE has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Johnson & Johnson, Janssen, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Sanofi, Portola, Medtronics, Aegerion, Merck, Gilead, and Pozen. AJC has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. JIW has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Janssen, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. BSL has served as a consultant to Bayer, Bristol-Myers Squibb, and Pfizer and received research grants in these trials from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. AP has received a research grant from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb. TY has received honoraria from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. EMA has received a research grant from Daiichi Sankyo. All other authors declare that they have no conflicts of interest.

Literature review

Annals of Internal Medicine | REVIEW

Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous Thromboembolism

A Systematic Review

Soheir S. Adam, MD; Jennifer R. McDuffie, PhD; Thomas L. Ortel, MD, PhD; and John W. Williams Jr., MD

Background: New oral anticoagulants (NOACs), including direct thrombin inhibitors (DTIs) and factor Xa (FXa) inhibitors, are emerging alternatives for prophylaxis and treatment of atrial fibrillation (AF) and venous thromboembolism (VTE).

Purpose: To compare the benefits and harms of NOACs versus warfarin for AF and VTE.

Data Sources: MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from January 2001 through July 2012; U.S. Food and Drug Administration (FDA) database for adverse event reports.

Study Selection: English-language, randomized, controlled trials (RCTs) comparing NOACs with warfarin for management of AF or VTE and observational studies and FDA reports on adverse effects.

Data Extraction: Two independent reviewers abstracted data and rated study quality and strength of evidence.

Data Synthesis: Six good-quality RCTs compared NOACs (2 DTI studies, 4 FXa inhibitor studies) with warfarin. In AF, NOACs decreased all-cause mortality (risk ratio [RR], 0.88 [95% CI, 0.82 to 0.96]); in VTE, NOACs did not differ for mortality or VTE outcomes. Across indications, adverse effects of NOACs compared with warfarin were fatal bleeding (RR, 0.60 [CI, 0.46 to 0.77]), major bleeding (RR, 0.80 [CI, 0.63 to 1.01]), gastrointestinal bleeding (RR, 1.30 [CI, 0.97 to 1.73]), and discontinuation due to adverse events (RR, 1.23 [CI, 1.05 to 1.44]). Subgroup analyses suggest a higher risk for myocardial infarction with DTIs than with FXa inhibitors. Bleeding risk for NOACs may be increased in persons older than 75 years or those receiving warfarin who have good control.

Limitation: There were no head-to-head comparisons of NOACs and limited data on harms.

Conclusion: New oral anticoagulants 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.

Primary Funding Source: Department of Veterans Affairs.

Ann Intern Med. www.annals.org

For author affiliations, see end of text.

This article was published at www.annals.org on 28 August 2012.

Stroke

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Shimoli V. Shah, MD; Brian F. Gage, MD, MSc

Background—Recent studies have investigated alternatives to warfarin for stroke prophylaxis in patients with atrial fibrillation (AF), but whether these alternatives are cost-effective is unknown.

Methods and Results—On the basis of the results from Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. We ran our Markov model in a hypothetical cohort of 70-year-old patients with AF using a cost-effectiveness threshold of $50 000/quality-adjusted life-year. We estimated the cost of dabigatran as US $9 a day. For a patient with an average risk of major hemorrhage (≈3%/y), the most cost-effective therapy depended on stroke risk. For patients with the lowest stroke rate ($CHADS_2$ stroke score of 0), only aspirin was cost-effective. For patients with a moderate stroke rate ($CHADS_2$ score of 1 or 2), warfarin was cost-effective unless the risk of hemorrhage was high or quality of international normalized ratio control was poor (time in the therapeutic range <57.1%). For patients with a high stroke risk ($CHADS_2$ stroke score ≥3), dabigatran 150 mg (twice daily) was cost-effective unless international normalized ratio control was excellent (time in the therapeutic range >72.6%). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective.

Conclusions—Dabigatran 150 mg (twice daily) was cost-effective in AF populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk AF populations unless international normalized ratio control was poor. (***Circulation***. **2011;123:2562-2570.**)

Key Words: anticoagulants ■ aspirin ■ atrial fibrillation ■ cost-benefit analysis ■ stroke ■ warfarin

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DOI 10.1007/s40256-014-0092-1

ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of New Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation in Two Different European Healthcare Settings

Talitha I. Verhoef · William K. Redekop · Fazila Hasrat · Anthonius de Boer · Anke Hilse Maitland-van der Zee

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Abstract

Objectives Our objectives were to investigate the cost effectiveness of apixaban, rivaroxaban, and dabigatran compared with coumarin derivatives for stroke prevention in patients with atrial fibrillation in a country with specialized anticoagulation clinics (the Netherlands) and in a country without these clinics (the UK).

Methods A decision-analytic Markov model was used to analyse the cost effectiveness of apixaban, rivaroxaban, and dabigatran compared with coumarin derivatives in the Netherlands and the UK over a lifetime horizon.

Results In the Netherlands, the use of rivaroxaban, apixaban, or dabigatran increased health by 0.166, 0.365, and 0.374 quality-adjusted life-years (QALYs) compared with coumarin derivatives, but also increased costs by €5,681, €4,754, and €5,465, respectively. The incremental cost-effectiveness ratios (ICERs) were €34,248, €13,024, and €14,626 per QALY gained. In the UK, health was increased by 0.302, 0.455, and 0.461 QALYs, and the incremental costs were similar for all three new oral anticoagulants (€5,118–5,217). The ICERs varied from €11,172 to 16,949 per QALY gained. In the Netherlands, apixaban had the highest chance (37 %) of being cost effective at a threshold of €20,000; in the UK, this chance was 41 % for dabigatran. The quality of care, reflected in time in therapeutic range, had an important influence on the ICER.

Conclusions Apixaban, rivaroxaban, and dabigatran are cost-effective alternatives to coumarin derivatives in the UK, while in the Netherlands, only apixaban and dabigatran could be considered cost effective. The cost effectiveness of the new oral anticoagulants is largely dependent on the setting and quality of local anticoagulant care facilities.

Key Points

New oral anticoagulants such as apixaban, rivaroxaban, and dabigatran likely result in higher quality-adjusted life-years (QALY) if compared with coumarin anticoagulants in the Netherlands and the UK, but at increased treatment costs.

Compared with coumarin derivatives, all new oral anticoagulants could be considered cost effective in both the Netherlands and the UK, except rivaroxaban in the Netherlands.

Electronic supplementary material The online version of this article (doi:10.1007/s40256-014-0092-1) contains supplementary material, which is available to authorized users.

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PharmacoEconomics (2014) 32:601–612
DOI 10.1007/s40273-014-0152-z

ORIGINAL RESEARCH ARTICLE

Economic Evaluation of Warfarin, Dabigatran, Rivaroxaban, and Apixaban for Stroke Prevention in Atrial Fibrillation

Torbjørn Wisløff · Gunhild Hagen · Marianne Klemp

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Abstract

Background Atrial fibrillation is a major risk factor for stroke, which causes thousands of deaths and sequelae. It is recommended that atrial fibrillation patients at medium or high risk of stroke use an oral anticoagulant to reduce the risk of stroke. In the past few years, three new oral anticoagulants (NOACs), dabigatran, rivaroxaban, and apixaban, have been introduced in competition to the older oral anticoagulant warfarin.

Objective The objective of this study was to evaluate the relative cost effectiveness of warfarin, dabigatran, rivaroxaban, and apixaban in a Norwegian setting.

Methods We created a probabilistic decision–analytic Markov model to simulate the life of patients with atrial fibrillation. We performed several scenario analyses, including changing the switching age for dabigatran from 80 to 75 years old.

Results Assuming the European Society of Cardiology guidance, sequential dabigatran (2 × 150 mg daily until 80 years old, 2 × 110 mg thereafter) seems to be the most cost-effective alternative for high-risk AF patients. For medium-risk patients, apixaban (2 × 5 mg daily) seems to be somewhat more effective than dabigatran, but dabigatran is still marginally the most cost-effective alternative. In scenario analyses reducing dabigatran from 2 × 150 mg to 2 × 110 mg at the age of 75 years (instead of at age 80), apixaban (2 × 5 mg daily) becomes the most cost-effective alternative for both risk groups.

Conclusion We have found apixaban or sequential dabigatran to be the alternatives most likely to be considered cost effective, depending on the switching age for dabigatran. These conclusions are highly sensitive to assumptions made in the analysis.

Electronic supplementary material The online version of this article (doi:10.1007/s40273-014-0152-z) contains supplementary material, which is available to authorized users.

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ovel Anticoagulants for Stroke Prevention in Atrial ibrillation: A Systematic Review of Cost-Effectiveness lodels

endan L. Limone[1,2], William L. Baker[1], Jeffrey Kluger[3], Craig I. Coleman[1,2]*

partment of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Connecticut, United States of America, 2 Department of Pharmacy, Ha pital, Hartford, Connecticut, United States of America, 3 Department of Cardiology, Hartford Hospital, Hartford, Connecticut, United States of America

Abstract

Objective: To conduct a systematic review of economic models of newer anticoagulants for stroke prevention in atrial fibrillation (SPAF).

Patients and Methods: We searched Medline, Embase, NHSEED and HTA databases and the Tuft's Registry from January 1, 2008 through October 10, 2012 to identify economic (Markov or discrete event simulation) models of newer agents for SPAF.

Results: Eighteen models were identified. Each was based on a lone randomized trial/new agent, and these trials were clinically and methodologically heterogeneous. Dabigatran 150 mg, 110 mg and sequentially-dosed were assessed in 9, 8 and 9 models, rivaroxaban in 4 and apixaban in 4. Warfarin was a first-line comparator in 94% of models. Models were conducted from United States (44%), European (39%) and Canadian (17%) perspectives. Models typically assumed patients between 65–73 years old at moderate-risk of stroke initiated anticoagulation for/near a lifetime. All models reported cost quality-adjusted life-year, 22% reported using a societal perspective, but none included indirect costs. Four models reported an incremental cost-effectiveness ratio (ICER) for a newer anticoagulant (dabigatran 110 mg (n = 4)/150 mg (n = 2) rivaroxaban (n = 1)) vs. warfarin above commonly reported willingness-to-pay thresholds. ICERs vs. warfarin ranged from $3,547–$86,000 for dabigatran 150 mg, $20,713–$150,000 for dabigatran 110 mg, $4,084–$21,466 for sequentially-dosed dabigatran and $23,065–$57,470 for rivaroxaban. Apixaban was found economically-dominant to aspirin, and dominant o cost-effective ($11,400–$25,059) vs. warfarin. Indirect comparisons from 3 models suggested conflicting comparative cost effectiveness results.

Conclusions: Cost-effectiveness models frequently found newer anticoagulants cost-effective, but the lack of head-to-head trials and the heterogeneous characteristics of underlying trials and modeling methods make it difficult to determine the most cost-effective agent.

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er Oral Anticoagulants Should Not Be Used as
gents to Prevent Thromboembolism
With Atrial Fibrillation and Risk
Stroke or Thromboembolism

oagulants Should Not Be Used as First-Line
nt Thromboembolism in Patients With
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1939, isolated the substance
eet clover that was the caus-
ease of cattle,[1] it is unlikely
hat the vitamin K antagonists
rs later and would be used to
mboembolism in 1% to 2% of
ed countries. The longevity of
any perceived drawbacks as
K antagonist, says something
rugs can be listed as consis-
he incidence of a devastating
cardiac rhythm? Yet, great
uction of the new oral antico-
warfarin. Entire pages of *The*
direct-to-consumer advertise-
osia are conducted at profes-
reviews appear in medical
But just how good are these
as first-line therapy for stroke
(AF)? Let us briefly examine

Response by Granger and Armaganijan

Dabigatran etexilate, an oral direct thrombin inhibitor,
when dosed at 150 mg twice daily in the Randomized
Evaluation of Long-Term Anticoagulant Therapy (RE-LY)
trial, produced a significant reduction in stroke and systemic
embolism compared with warfarin in selected patients with
nonvalvular AF (1.11% versus 1.69%; relative risk, 0.66;
95% confidence interval [illegible]; P<0.001 for noninferiority and P=0.005 for superiority) with a similar incidence of major bleeding (3.11%
versus 3.36%; relative risk, 0.93; 95% CI, 0.81–1.07;
P=0.31).[2] The efficacy of [illegible]
late (110 mg twice daily) [illegible]
(1.53% versus 1.69%; relative risk, 0.91; 95% CI, 0.74–1.11;
P<0.001 for noninferiority), whereas the rate of major
bleeding was significantly [illegible]
relative risk, 0.80; 95% CI, 0.69–0.93; P=0.003 for superiority). Rivaroxaban, an oral direct factor Xa inhibitor, was
shown to be noninferior [illegible]
stroke or systemic embolism in patients with nonvalvular AF
in the Rivaroxaban Once Daily Oral Direct Factor Xa

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In summary, it cannot be denied that the new oral direct factor inhibitor anticoagulants offer pharmacokinetic characteristics of interest to patients and clinicians. However, there are enough unknowns at the present time to caution healthcare providers against the use of these agents as first-line therapy for patients with AF. Until we understand the impacts that various levels of drug nonadherence have on outcome, the appropriate assays to measure anticoagulant effect when needed, the means to manage major bleeding or drug overdose or drug reversal, and the characteristics of the appropriate patient candidate, these new agents should not automatically replace warfarin in patients with AF and should not be used as first-line therapy in patients with AF.

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Review Article

Common flaws exist in published cost-effectiveness models of pharmacologic stroke prevention in atrial fibrillation

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Objectives

Decision makers use models to assist in evaluating the cost-effectiveness of pharmacologic stroke prevention in atrial fibrillation (SPAF).

Study Design and Setting

We performed a search of databases through October 3, 2012 to identify pharmacologic SPAF cost-effectiveness models.

Results

Of 30 identified models, 28 included warfarin, but only 60% assessed the impact of warfarin control on conclusions. Aspirin, dual antiplatelet, and newer anticoagulants were included in 41%, 10%, and 63% of models, respectively. Models used similar structures but included varying health states and made varying assumptions. They rarely reported performing a literature search to identify anticoagulant-specific inputs and used similar and older sources. Sixteen models used a lone randomized trial to reflect the efficacy and safety of main comparisons. One-third of models claimed a societal perspective; however, none included indirect costs. Patients typically initiated anticoagulation in the sixth or seventh decade of life and are followed for their lifetimes. Almost 70% of incremental cost-effectiveness ratios were below reported willingness-to-pay thresholds. All used deterministic sensitivity analyses and 77% conducted Monte Carlo simulation. Less than half of the models were rated "high quality," yet were frequently published in high-impact journals.

Conclusion

Pharmacologic SPAF cost-effectiveness models have been extensively reported, but many may have flaws giving reason for decision makers to use caution. We provide 10 recommendations to avoid common flaws in SPAF cost-effectiveness models.

Ahmed Oliemy

- **Pros**
- -High impact factor journal.
- -High level of evidence.
- **Cons**
- -Putting 4 drugs with different mechanisms of action in the same basket is not quiet reasonable as this makes it a heterogeneous group which adversely affect the accuracy of the results,
- -the 4 new anti-coagulants still need to be compared against each other to figure out which is the best regarding stroke prevention and bleeding complications.

Pros

1. Meta-analysis
2. Lancet
3. Reputable authors
4. Comprehensive analysis using TTR 65% (new NICE 2014)
5. Acknowledgement of under-representation of vulnerable population –adults more than 75, prev stroke, renal impairment
6. Shows effectiveness of NOAC even in Warfarin experienced patients
7. Separate analysis of high dose + low dose regiments
8. Conflicts declared

Cons

1. Assumption that all NOACs are equal in efficacy- trials considered different NOACs
2. The overall beneficial effect was mainly driven by a large reduction in haemorrhagic stroke (RR on combined data: 0.49)
3. Reduction in all cause mortality done using RCTs which were not powered to consider all cause mortality as a secondary outcome.
4. Higher rate of GI bleeding – no further discussion
5. No mention of reversal, which would be of benefit should there be a ?GI bleed??
6. Biggest reduction was seen with TTR<65% - should they have been on warfarin in the first place?
7. CHADS2 score 0-1 ? Should they be warfarinised? Previously aspirin!
8. Cost benefit analysis not done

In summary – minimal benefit if TTR>65% for VKA (better ICH profile) but may increase GI Bleeds. Benefit in Ischaemic stroke similar to warfarin at high dose, inferior at low dose. MI increased at low dose

Sanjeet Singh

Article

Pros

- Meta-analysis with large overall patient numbers
- Patient factors such as age and gender were well matched among trials.
- Apart from strokes and systemic embolism, other secondary end points were included

Cons

- Patient's risk for stroke differed significantly across the trials.
- Drugs compared to warfarin were two different class of drugs.

Rodger

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with AF.

Positives:

- Population sampling was good.
- High risk and vulnerable groups of patients were included.
- The trials selected were subjected to a thorough meta-analysis.

Negatives:

- The study centred on the benefits of high dose new anti-coagulants compared with warfarin, which may not be suitable for all patients.
- The article claims not be funded however there are considerable conflicts of interests stated by the contributors.

Key results	Study weakness
42 411 NOAC vs 29 272 warfarin – quite even populations	Four studies from stage 3, drug company funded
Favours NOAC with 19% reduction of **Stroke or systemic embolic events**	ROCKET (rivaroxaban) p=0.12 and ENGAGE (edoxaban) p=0.10 non-significant NOAC significantly better only in haemorrhagic - not ischaemic stroke
Low dose studies show increase in ischaemic stroke vs warfarin	Low dose regimens looked at only at dabigatran and edoxaban
	CHAD 0-1 ?Anticoagulants in RE-LY and Aristotle