

Innovating, Optimizing, and Advancing Antithrombotic Treatment in AF

Real-word evidence for oral anticoagulation

GREGORY Y H LIP MD FRCP (Lond Edin Glasg) FACC FESC

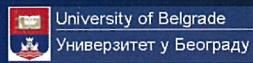
Professor of Cardiovascular Medicine, University of Birmingham, UK

Adjunct Professor of Cardiovascular Sciences, Thrombosis Research Unit, Aalborg University, Denmark

Visiting Professor of Haemostasis Thrombosis & Vascular Sciences, Aston University, Birmingham, UK

Visiting Professor of Cardiology, University of Belgrade, Serbia

**Centre for Cardiovascular Sciences
City Hospital
Birmingham B18 7QH
England UK**



Declaration of Interests

- **Guideline membership/reviewing:** ESC Guidelines on Atrial Fibrillation, 2010 and Focused Update. 2012; ESC Guidelines on Heart Failure, 2012; American College of Chest Physicians Antithrombotic Therapy Guidelines for Atrial Fibrillation, 2012; NICE Guidelines on Atrial Fibrillation, 2006 and 2014; NICE Quality Standards on Atrial Fibrillation 2015; ESC Cardio-oncology Task Force, 2015; ESC Working Group on Thrombosis position documents (2011-). Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Reviewer for various guidelines/position statements from ESC, EHRA, NICE etc.
- **Steering Committees/trials:** Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc.
- **Editorial Roles:** Editor-in-Chief (clinical), Thrombosis & Haemostasis; Associate Editor, Europe; Guest Editor, Circulation, American Heart Journal.
- **Consultant/Advisor/Speaker:**
 - Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo.
 - Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo

THE LANCET

Series

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 **Atrial fibrillation 1**

Stroke prevention in atrial fibrillation

Ben Freedman, Tatjana S Potpara, Gregory Y H Lip

Lancet 2016; 388: 806–17
See Editorial page 731
This is the first in a Series of three papers about atrial fibrillation
Heart Research Institute, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia
(Prof B Freedman MBBS, Department of Cardiology and Anzac Research Institute,

Atrial fibrillation is estimated to affect 33 million people worldwide...There are no excuses to ignore this common cardiac disorder."

.... reduce stroke burden by better recognising stroke risk, which is a continuum, and to make oral anticoagulant treatment the default unless low risk is truly shown.

Once patients are deemed at low risk, they need to be regularly reviewed since their risk profile might change over time *The Lancet*

Lancet 2016; 388: 806–17

The CHA₂DS₂-VASc score
(‘Birmingham schema’)

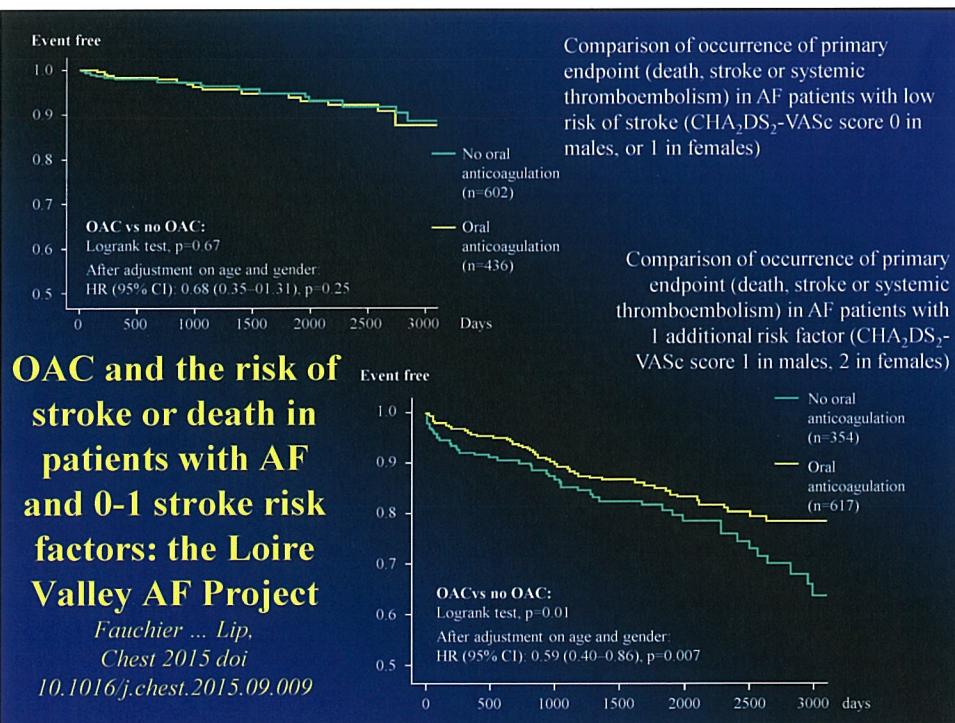
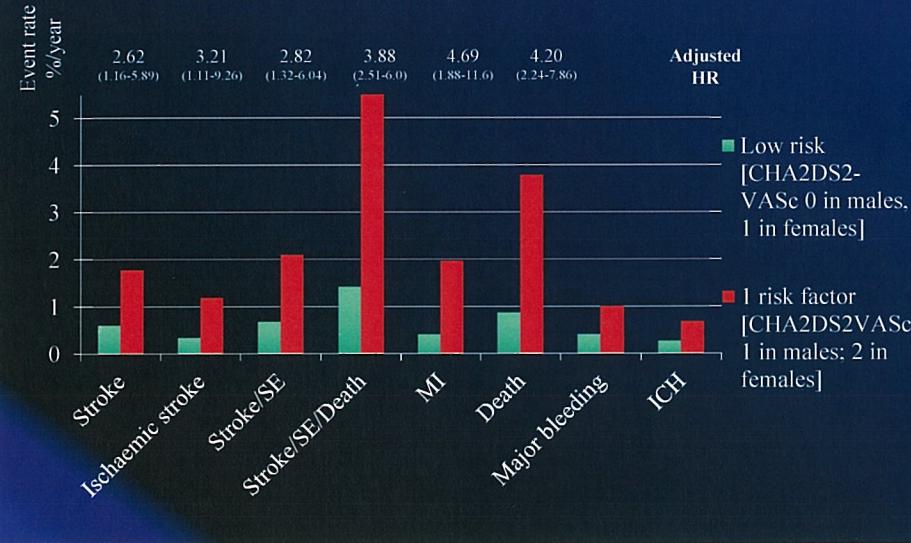
Lip et al Chest. 2010;137:263-72

a) Risk factors for stroke and thromboembolism in non-valvular AF	
'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke, TIA or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%] Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease*

Stroke risk factors	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior MI, PAD, or aortic plaque]	1
Aged 65–74 years	1
Sex category [i.e. female gender]	1

Event rates for different outcomes for non-anticoagulated AF patients with less than 2 Non-Gender Related stroke risk factors

Fauchier ... Lip. Stroke 2016 DOI: 10.1161/STROKEAHA.116.013253



**Net Clinical Benefit analysis of stroke prevention strategy for AF patients with 1 NGR stroke risk factor
(CHA₂DS₂VASc 1 in males, 2 in females)**

Fauchier ... Lip. Stroke 2016 DOI: 10.1161/STROKEAHA.116.013253

Stroke prevention strategy	Net Clinical Benefit, %/year (95%CI) according to Singer et al.	Net Clinical Benefit, %/year (95%CI) according to Connolly et al.
<i>Compared to no antithrombotic therapy</i>		
Anti-platelet drugs (and no VKA)	-0.13 (-1.06 to -0.02)	-0.72 (-1.50 to -0.34)
VKA	0.30 (0.15-0.61)	1.42 (1.01-1.99)
<i>Compared to anti-platelet drugs (and no VKA)</i>		
VKA	0.43 (0.24-0.78)	2.14 (1.62-2.82)

NCB according to Singer et al = (ischemic stroke rate on no treatment minus ischemic stroke rate on anti-thrombotic therapies) – 1.5x (ICH rate on anti-thrombotic therapies minus ICH rate on no treatment).

NCB according to Connolly et al = weighted sum of rate differences ΔR = Rate not treated – Rate treated: $w_1 * \Delta R_{\text{ischemic stroke}} + w_2 * \Delta R_{\text{ICH}} + w_3 * \Delta R_{\text{major bleeding}} + w_4 * \Delta R_{\text{MI}}$.

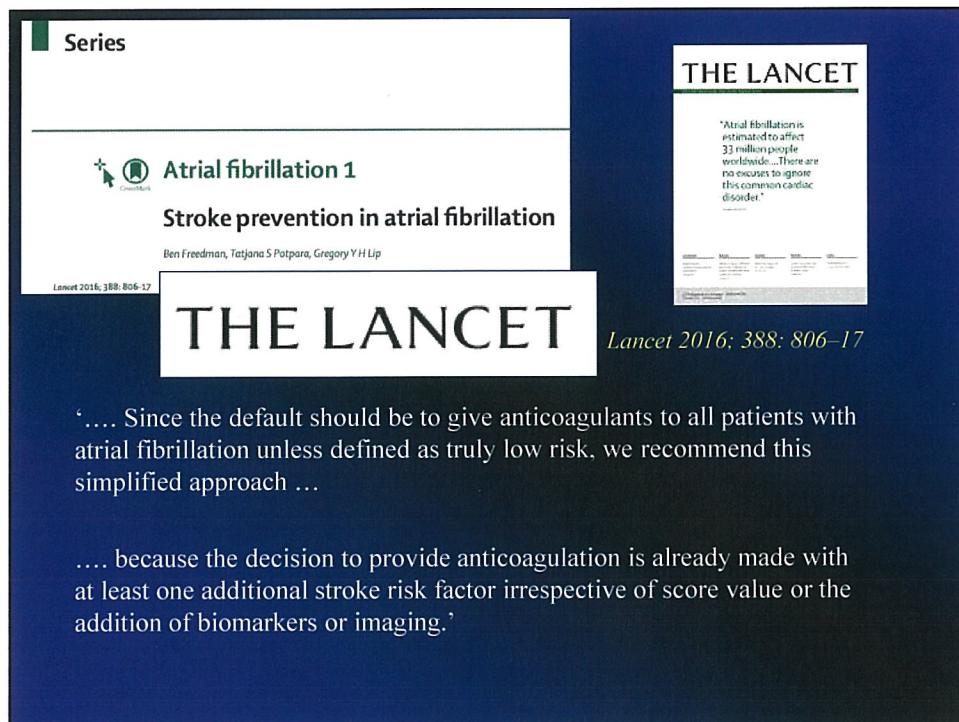
ΔR =ischemic stroke + $w_2 * \Delta R_{\text{ICH}}$ + $w_3 * \Delta R_{\text{major bleeding}}$ + $w_4 * \Delta R_{\text{MI}}$.
ICH=intracerebral hemorrhage, major bleeding =major extracranial bleeding, MI= myocardial infarction, VKA= vitamin K antagonist weights $w_1=1$, $w_2=3.08$, $w_3=0.67$, $w_4=0.95$.

Risk stratification and thromboprophylaxis made easy

Lip and Lane Circ J 2014 June; Griffiths and Lip Circulation 2014;130(21):1837-9

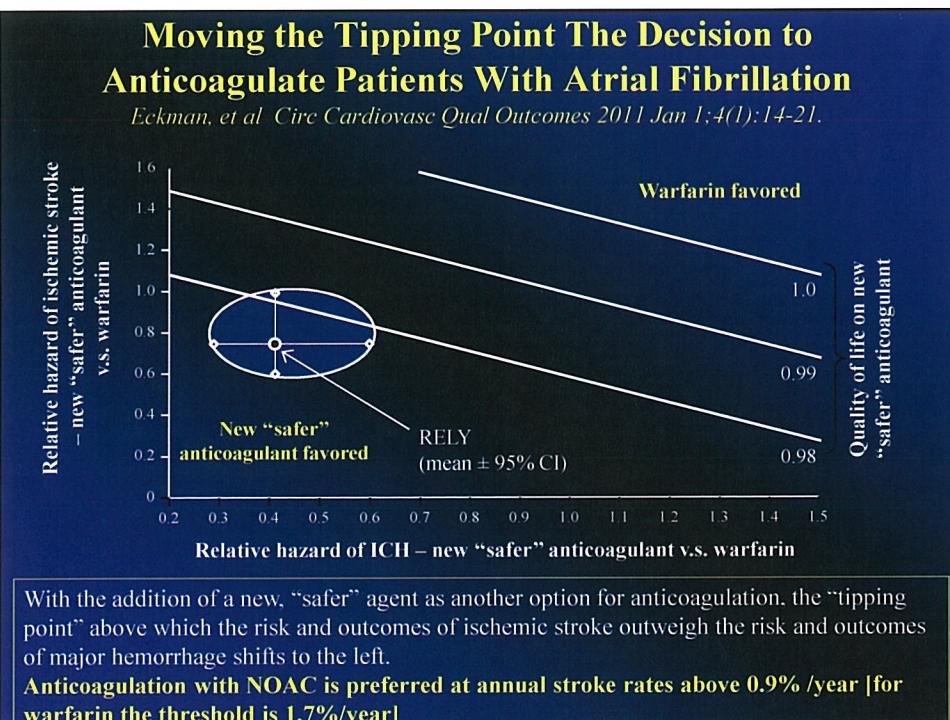


* Use the HAS-BLED score to identify patients at 'high risk' of bleeding for more careful review and followup, and to address reversible risk factors for bleeding. A high HAS-BLED score (≥ 3) does not preclude use of OAC, and may help with NOAC dose selection



.... Since the default should be to give anticoagulants to all patients with atrial fibrillation unless defined as truly low risk, we recommend this simplified approach ...

.... because the decision to provide anticoagulation is already made with at least one additional stroke risk factor irrespective of score value or the addition of biomarkers or imaging.'



Major outcomes in atrial fibrillation patients with one risk factor: impact of time in therapeutic range [SPORTIF]

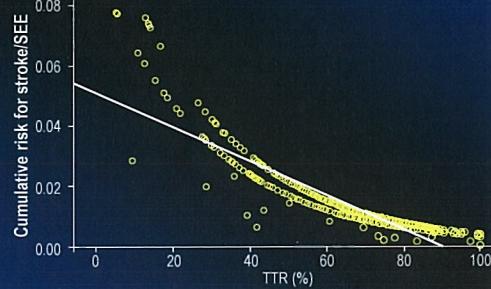
Proietti and Lip Am J Med 2015; DOI 10.1016/j.amjmed.2016.03.024

	Per 100 pt/yr	Stroke/ SE	All- cause death	Composite
Hypertension	0.9	1.4	2.1	
Diabetes	1.4	0	1.4	
Vascular disease	0.5	1.6	2.0	
CHF	1.1	3.7	4.4	

Warfarin patients (n=1097)
from SPORTIF trial

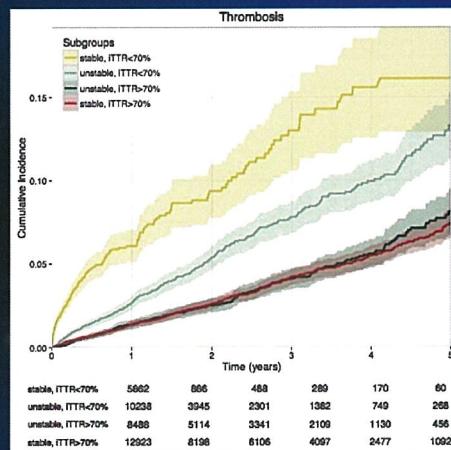
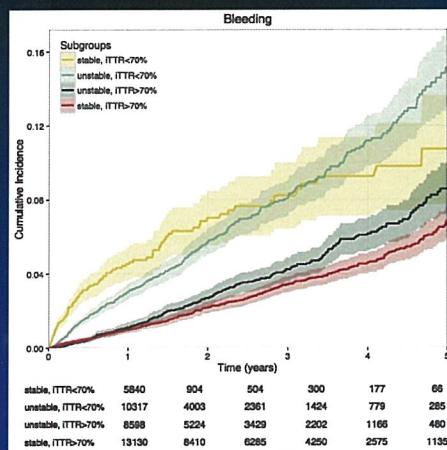
Scatterplot and regression line
between TTR and cumulative risk
for stroke/SE

Cox regression analysis in patients treated with warfarin only found TTR to be inversely associated with stroke/SE ($P=0.034$) and all-cause death ($P=0.015$)



Outcomes in a Contemporary Warfarin-Treated Population With Atrial Fibrillation

Björck ... Lip et al JAMA Cardiology 2016 doi:10.1001/jamacardio.2016.0199



N=29146

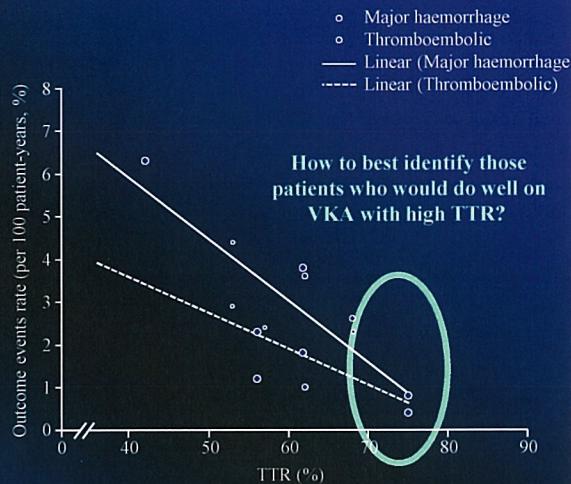
Stable equals low INR variability (light blue box mean INR variability); unstable, high INR variability (<mean INR variability).

Well-managed warfarin therapy is associated with a low risk of complications

Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation

Wan et al
Circ Cardiovasc Qual Outcomes. 2008;1:84-91

For retrospective studies, a 6.9% improvement in the TTR significantly reduced major hemorrhage by 1 event per 100 patient-years of treatment (95% CI, 0.29 to 1.71 events).



TTR negatively correlated with major hemorrhage ($r=-0.59$; $P=0.002$) and thromboembolic rates ($r=-0.59$; $P=0.01$).

Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin:

The SAMe-TT₂R₂ score

Apostolakis ... Lip. *Chest* 2013;144(5):1555-63

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (less than 60 years)	1
M	Medical history*	1
e		
T	Treatment (interacting Rx eg. amiodarone for rhythm control)	1
T	Tobacco use (within 2 years)	2
R	Race (non Caucasian)	2
Maximum points		8

*2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary disease, hepatic or renal disease.

'Using a mean TTR of approximately 0.65 as a cut off, the score could aid decision making by identifying those AF patients that would do well on VKA (SAMe-TT₂R₂ score=0-1), or conversely, those (ie. SAMe-TT₂R₂ score ≥ 2) who at risk of suboptimal anticoagulation control.'

Validation of the SAMe-TT₂R₂ score in a nationwide population of nonvalvular AF patients on VKAs

Ruiz-Ortiz et al Thromb Haemostat 2015; <http://dx.doi.org/10.1160/TH15-02-0169>

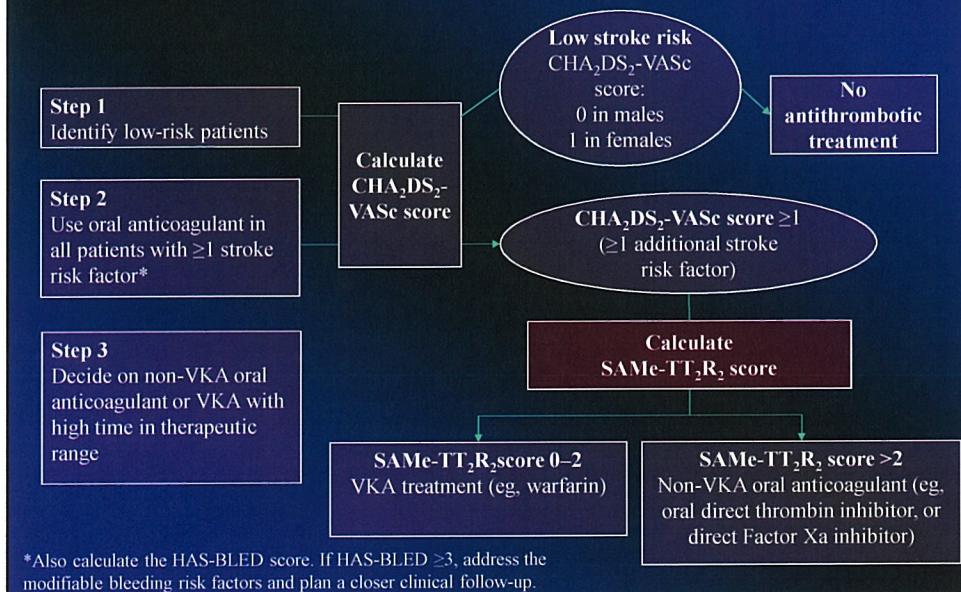
1,056 patients, mean age 73.6 ± 9.8 years, 42% female.

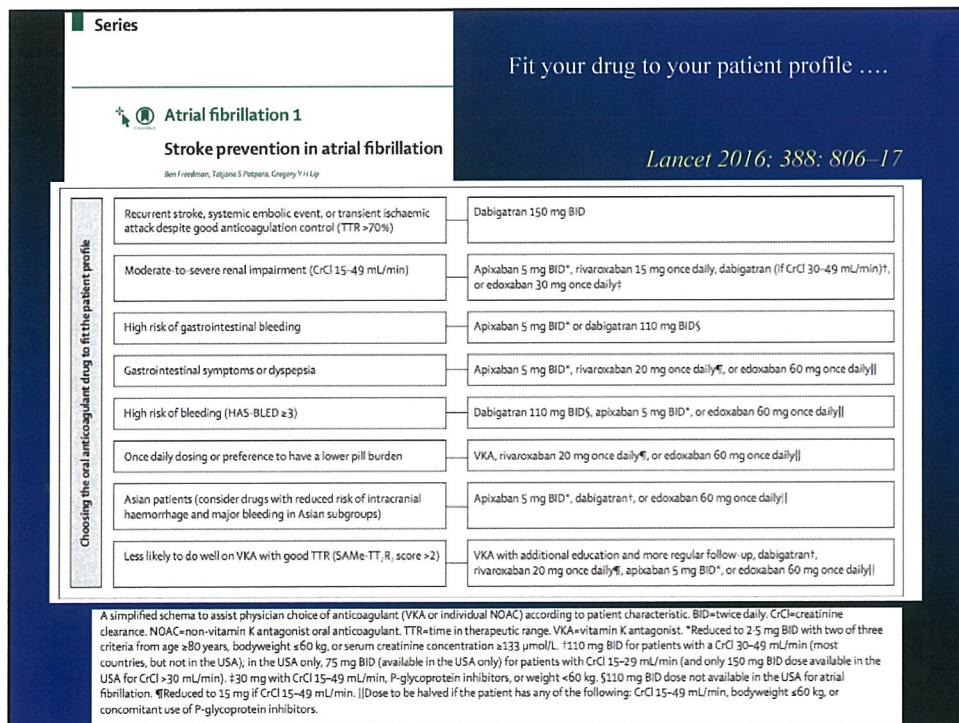
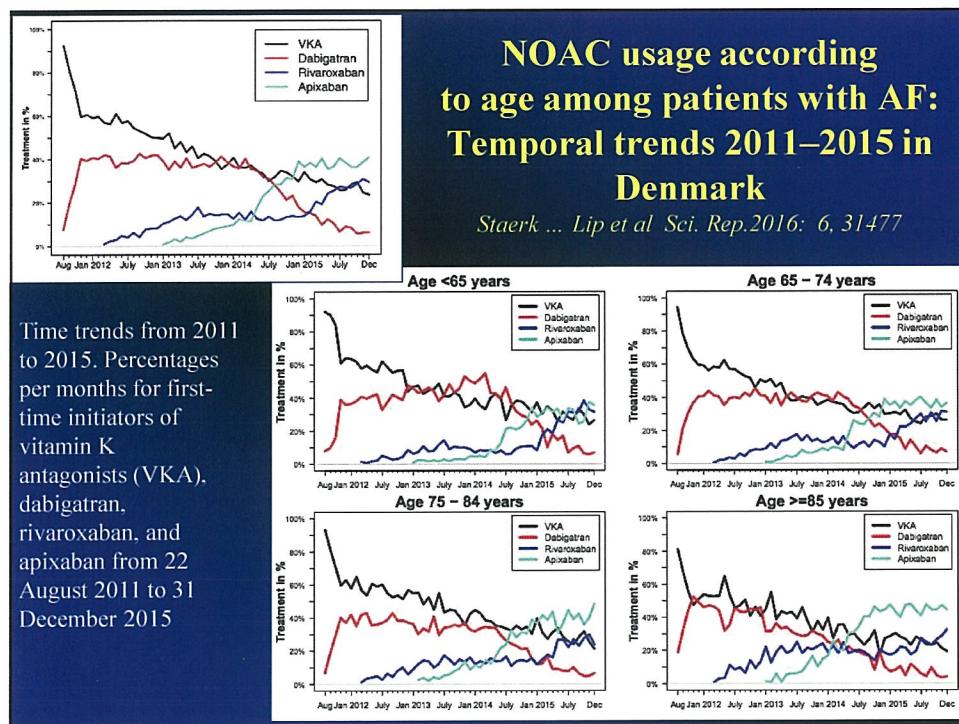
	SAMe-TT ₂ R ₂ score		p-value	0–2 (n=929)	≥ 3 (n=127)	p-value
	0–1 (n=613)	≥ 2 (n=443)				
TTR	65.6% \pm 26.2%	61.3% \pm 25.3%	<0.005	64.3% \pm 26%	60% \pm 24.5%	<0.05
Proportion of INR in range	61.6% \pm 24.9%	57.2% \pm 24.6%	<0.01	60.7% \pm 25.1%	56.3% \pm 24.5%	<0.05
INR variability	0.20 \pm 0.26	0.22 \pm 0.24	<0.001	0.21 \pm 0.25	0.23 \pm 0.26	<0.01
Time above range	15.7% \pm 20.1%	18.7% \pm 22.1%	<0.05	15.9% \pm 19.8%	19.8% \pm 22.4%	<0.05
Patients with any INR >3 (n=725)	61.9%	77.9%	<0.001	66.2%	86.6%	<0.01
Time above INR >4	1.9% \pm 6.3%	2.8% \pm 7.4%	<0.05	2.0% \pm 6.8%	3.2% \pm 7.2%	<0.05
Patients with any INR >4 (n=368)	26.9%	45.1%	<0.001	31.12%	62.9%	<0.01

- Discriminated good anticoagulation control (TTR $\geq 65\%$) with a C-statistic of 0.57 (95%CI 0.53–0.60, p<0.0005)
- Odds ratio of TTR< 65% if score was ≥ 2 was 1.64 (95 %CI 1.33–1.95, p<0.001)

Recommended decision pathway for treatment of newly diagnosed non-valvular atrial fibrillation

Freedman, Potpara & Lip. Lancet 2016;388:806–17





Testing and investigation of treatments should not end when a drug comes onto the market

RCTs: tightly controlled conditions for selected patients

Invited Editorial Focus

"Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation

Ben Freedman^{1,2}; Gregory Y. H. Lip^{3,4}

¹Heart Research Institute, Charles Perkins Centre, and Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia; ²Department of Cardiology and Anzac Research Institute, Concord Hospital, Concord, New South Wales, Australia; ³University of Birmingham, Birmingham, UK; ⁴Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Thromb Haemostat Oct 2016

Nallamothu et al. Circulation 2008

Real world data (RWD) clarifies whether the results observed under the tightly controlled conditions of an RCT are also observed in everyday clinical practice

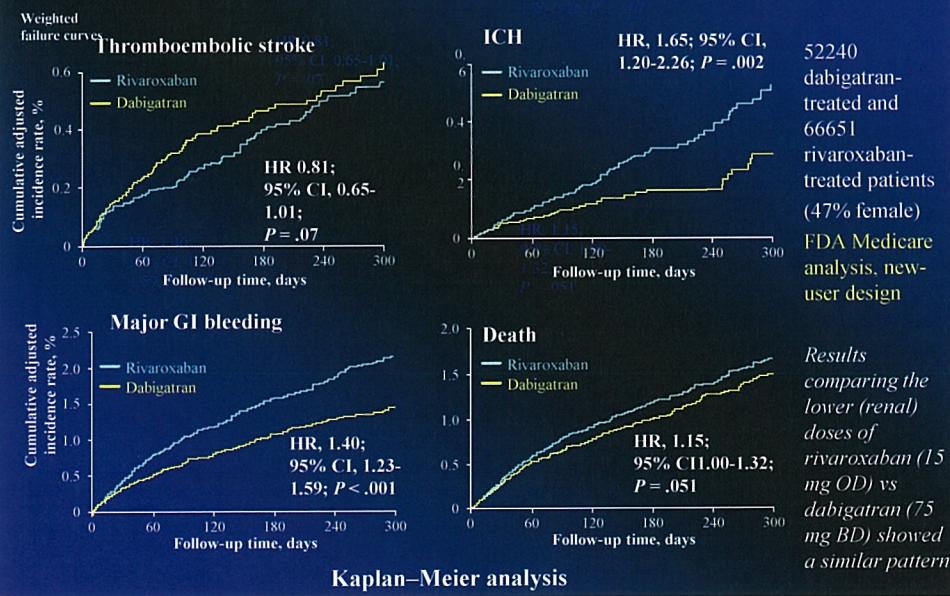
Differing:

- Age
- Race
- Co-morbidities
- Co-medications
- Adherence

Nallamothu et al. Circulation 2008

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for AF

Graham et al JAMA Intern Med. doi:10.1001/jamainternmed.2016.5954



US retrospective real-world database research (OptumLabs) to evaluate stroke/SE & bleeding outcomes for NOAC vs VKA

Yao X, et al. JAHA 2016;6:e003725

125 243 ELIGIBLE PATIENTS IDENTIFIED IN THE DATABASE THREE 1:1 PROPENSITY SCORE MATCHED COHORTS

Retrospective analysis of OptumLabs Data Warehouse administrative claims database in the US

- October 1, 2010 – June 30, 2015
- Cox proportional hazards regression to compare outcomes in each of the propensity score-matched cohorts
- Sensitivity and subgroup analyses performed

Apixaban vs warfarin
n=15 390

Rivaroxaban vs warfarin
n=32 350

Dabigatran vs warfarin
n=28 614

Study Population

- ≥18 years old
- ≥1 diagnosis of NVAF at baseline
- Prior warfarin exposure allowed
- No prior use of NOACs
- Excluded:
 - Valvular heart disease
 - End-stage kidney disease
 - Kidney transplant or dialysis
 - Hip or knee replaced <6 weeks prior to study
 - DVT or PE at baseline

Percentages of patients receiving reduced doses of NOACs were 18.1%, 21.5% and 8.8%, and patients were followed up for an average of 0.5±0.6, 0.6±0.7 and 0.7±0.8 years in the apixaban, rivaroxaban and dabigatran cohorts, respectively

US retrospective real-world database research (OptumLabs): Stroke/SE outcomes for NOAC vs VKA

Yao X, et al. JAHA 2016;6:e003725

PAIRWISE PROPENSITY-MATCHED MEDICATION COMPARISON

EVENT RATE PER 100 PERSON-YEAR APIXABAN VS WARFARIN			HR (95% CI)	P VALU	SUB GROUP ANALYSIS†
n=7695	n=7695	HR (95% CI)			
STROKE/SE*	1.33	1.66	0.67 (0.46-0.98)	0.04	Results consistent in all subgroup analyses
ISCHAEMIC	1.03	1.05	0.83 (0.53-1.29)	0.40	
HAEMORRHAGIC	0.19	0.46	0.35 (0.14-0.88)	0.03	

DABIGATRAN VS WARFARIN

DABIGATRAN VS WARFARIN			HR (95% CI)	P VALU	SUB GROUP ANALYSIS†
n=14 307	n=14 307	HR (95% CI)			
STROKE/SE*	1.18	1.22	0.98 (0.76-1.26)	0.88	Results consistent in all subgroup analyses
ISCHAEMIC	0.92	0.88	1.06 (0.79-1.42)	0.70	
HAEMORRHAGIC	0.16	0.29	0.56 (0.30-1.04)	0.07	

RIVAROXABAN VS WARFARIN

RIVAROXABAN VS WARFARIN			HR (95% CI)	P VALU	SUB GROUP ANALYSIS†
n=16 175	n=16 175	HR (95% CI)			
STROKE/SE*	1.26	1.29	0.93 (0.72-1.19)	0.56	Elevated risk of stroke/SE in warfarin-experienced patients ($p<0.01$)
ISCHAEMIC	0.95	0.88	1.01 (0.75-1.36)	0.95	
HAEMORRHAGIC	0.21	0.32	0.61 (0.35-1.07)	0.08	

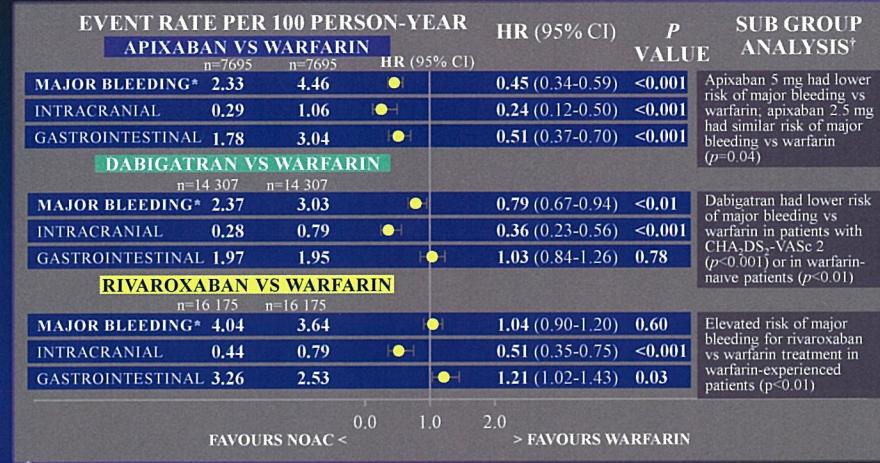
FAVOURS NOAC < > FAVOURS WARFARIN

*Included ischaemic stroke, haemorrhagic stroke, and SE; † Subgroup analyses were performed based on patients' baseline risk of stroke (CH_2DS_2-VASc score), baseline risk of bleeding (HAS-BLED score), previous warfarin exposure, and whether patients received reduced-dose NOAC (p-value for interaction)

US retrospective real-world database research (OptumLabs): Bleeding outcomes for NOAC vs VKA

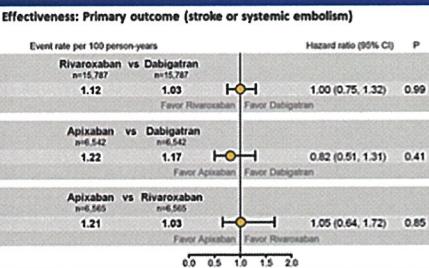
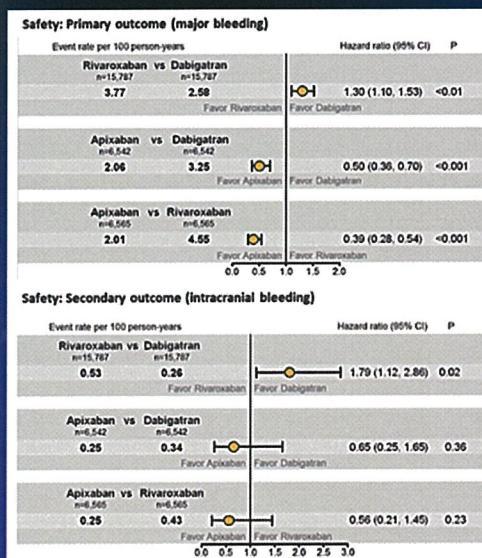
Yao X, et al. JAMA 2016;6:e003725

PAIRWISE PROPENSITY-MATCHED MEDICATION COMPARISON



*Included ischaemic stroke, haemorrhagic stroke, and SE; [†] Subgroup analyses were performed based on patients' baseline risk of stroke (CHA₂DS₂-VASc score), baseline risk of bleeding (HAS-BLED score), previous warfarin exposure, and whether patients received reduced-dose NOAC (p-value for interaction)

Optum Labs Data Warehouse (OLDW) claims database. Propensity-score matched cohorts (Rivaroxaban vs dabigatran [N=31,574]; apixaban vs dabigatran [N=13,084] and apixaban vs rivaroxaban [N=13,130]).

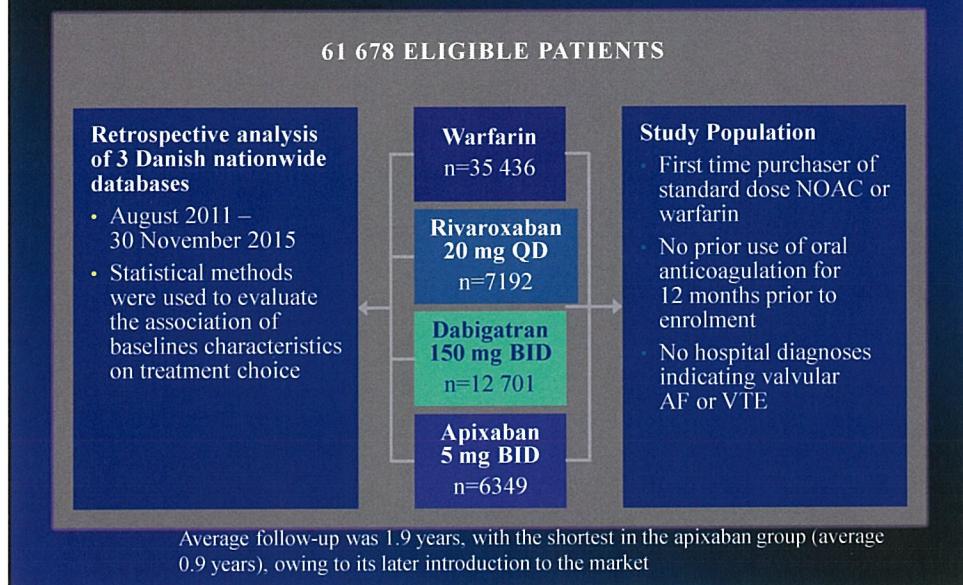


Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in non-valvular AF

Noseworthy et al
Chest 2016:
10.1016/j.chest.2016.07.013

Danish retrospective real-world registries NOACs vs VKA for stroke/SE and bleeding

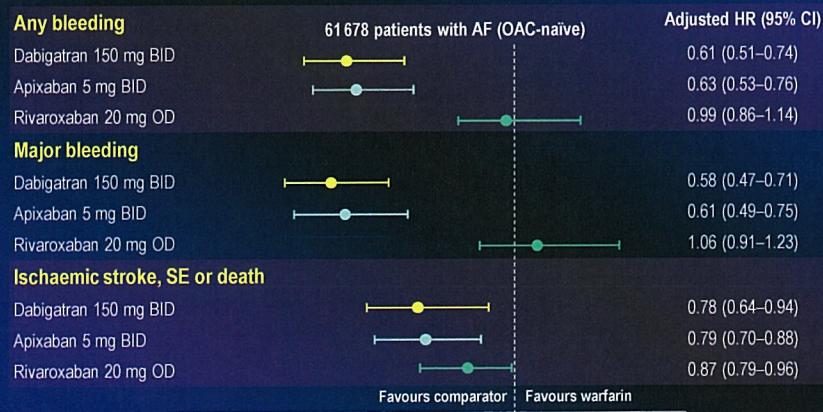
Larsen TB, et al. BMJ 2016;353:i3189



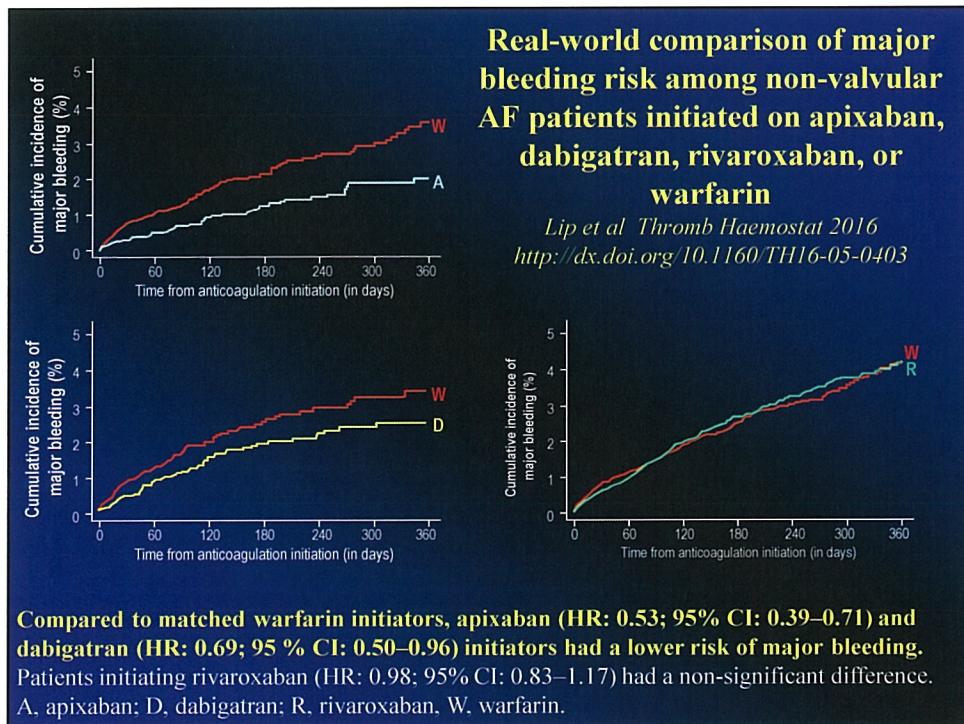
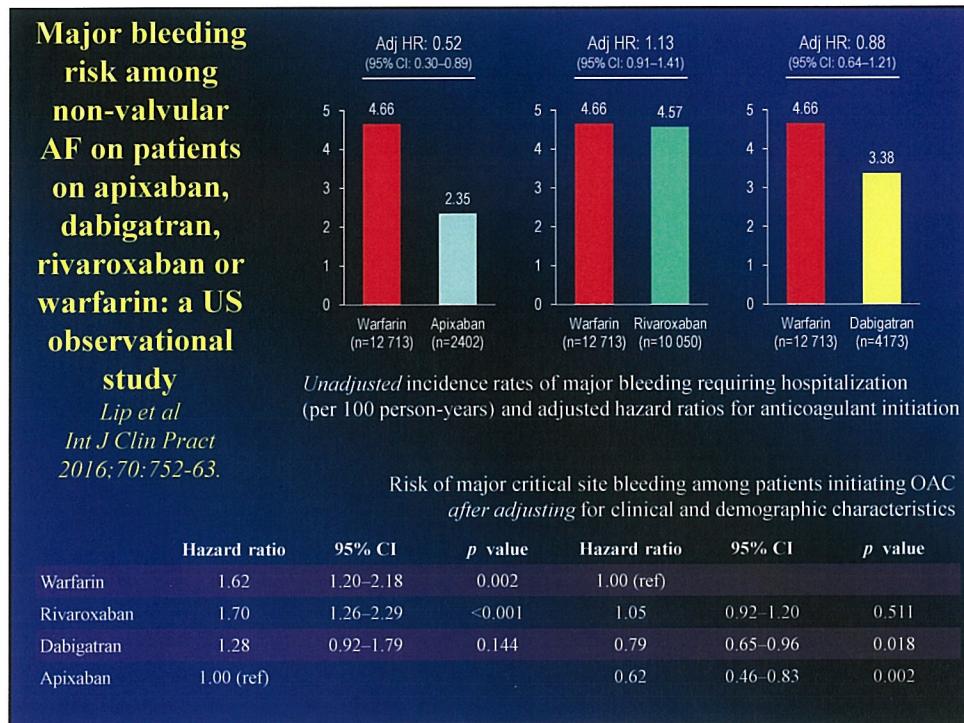
Comparative effectiveness & safety of NOACs vs warfarin in AF: propensity weighted nationwide cohort study

Larsen ... Lip. BMJ 2016;353:i3189

Analysis of prospective cohort from three nationwide Danish registries (Aug 2011–Oct 2015):
12 701 dabigatran 150 mg BID, 7192 rivaroxaban 20 mg OD, 6349 apixaban 5 mg BID,
35 436 warfarin

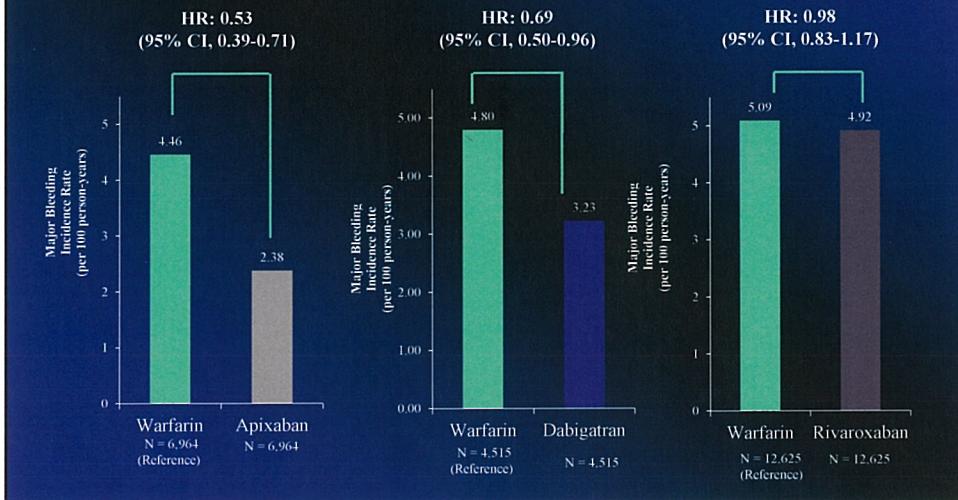


Risk of any bleeding, major bleeding, or death significantly lower for dabigatran and apixaban vs warfarin



Real-world comparison of major bleeding risk among non-valvular AF patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin

Lip et al. Thromb Haemostat 2016 <http://dx.doi.org/10.1160/TH16-05-0403>



Some final thoughts ...

The landscape of stroke prevention in AF is rapidly changing

- New guidelines, new approaches
- Not ‘do we treat’ ... but ‘how to treat’

Although methodologically different, real world research can complement and augment data from RCTs

- Results from RWD will depend upon the underlying population and the standard of care
- Marked consistency of results across these analyses despite the different geographical locations, types of data source, sample sizes, bleeding definitions and statistical methodology