Current state of the art and new horizons for stroke prevention in AF

How to Improve Practical Decision-making in Everyday Clinical Practice

GREGORY Y H LIP  MD-FRCP (Lon Edin Glas) 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, University of Leeds, UK
Visiting Professor of Cardiology, University of Belgrade, Serbia

Institute of Cardiovascular Sciences
City Hospital
Birmingham B18 7QH
England UK

Declaration of Interests


- **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, Europace; 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
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 CHA$_2$DS$_2$-VASc score
(‘Birmingham schema’)

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

- Low risk [CHA2DS2-VASc 0 in males, 1 in females]
- 1 risk factor [CHA2DS2-VASc 1 in males; 2 in females]

Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with low risk of stroke (CHA2DS2-VASc score 0 in males, or 1 in females)

Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with 1 additional risk factor (CHA2DS2-VASc score 1 in males, 2 in females)

OAC and the risk of stroke or death in patients with AF and 0-1 stroke risk factors: the Loire Valley AF Project

Fauchier... Lip. Chest 2015 doi 10.1016/j.chest.2015.09.009
Net Clinical Benefit analysis of stroke prevention strategy for AF patients with 1 NGR stroke risk factor (CHA$_2$DS$_2$VASc 1 in males, 2 in females)

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

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

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 differencesΔR = Rate not treated – Rate treated; w1 * ΔRischemic stroke + w2 * ΔRICH + w3 * ΔRmajor bleeding + w4 * ΔRMI

ICH= intracerebral hemorrhage, major bleeding = major extracranial bleeding, MI= myocardial infarction, VKA= vitamin K antagonist weights w1=1, w2=3.08, w3=0.67, w4=0.95.

Risk stratification and thromboprophylaxis made easy

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

Patient with atrial fibrillation

STEP 1 Is the patient ‘low risk’?

‘Low risk’ defined as CHA$_2$DS$_2$VASc score = 0 (male) or 1 (female)

If yes ...

No antithrombotic therapy

STEP 2 Offer OAC if ≥1 additional stroke risk factors*

VKA (eg. warfarin) with Time in Therapeutic Range (TTR) >70%

NOAC

NOAC, non-Vitamin K antagonist oral anticoagulant

* 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.
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).

How to best identify those patients who would do well on VKA with high TTR?

Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin:
The SAMe-TT2R2 score
Apostolakis ... Lip. Chest 2013;144(5):1555-63

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definitions</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Sex (female)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age (less than 60 years)</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>Medical history*</td>
<td>1</td>
</tr>
<tr>
<td>e</td>
<td>Treatment (interacting Rx eg. amiodarone for rhythm control)</td>
<td>1</td>
</tr>
<tr>
<td>T</td>
<td>Tobacco use (within 2 years)</td>
<td>2</td>
</tr>
<tr>
<td>R</td>
<td>Race (non Caucasian)</td>
<td>2</td>
</tr>
</tbody>
</table>

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-TT$_2$R$_2$ 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.

<table>
<thead>
<tr>
<th>SAMe-TT$_2$R$_2$ score</th>
<th>0−1 (n=613)</th>
<th>≥2 (n=443)</th>
<th>p-value</th>
<th>0−2 (n=929)</th>
<th>≥3 (n=127)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR</td>
<td>65.6%±26.2%</td>
<td>61.3%±25.3%</td>
<td>&lt;0.005</td>
<td>64.3%±26%</td>
<td>60%±24.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Proportion of INR in range</td>
<td>61.6%±24.9%</td>
<td>57.2%±24.6%</td>
<td>&lt;0.01</td>
<td>66.7%±25.1%</td>
<td>56.3%±24.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>INR variability</td>
<td>0.20±0.26</td>
<td>0.22±0.24</td>
<td>&lt;0.001</td>
<td>0.21±0.25</td>
<td>0.23±0.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time above range</td>
<td>15.7%±20.1%</td>
<td>18.7%±22.1%</td>
<td>&lt;0.05</td>
<td>15.9%±19.8%</td>
<td>19.8%±22.4%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with any INR &gt;3 (n=725)</td>
<td>61.9%</td>
<td>77.9%</td>
<td>&lt;0.001</td>
<td>66.2%</td>
<td>86.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time above INR &gt;4</td>
<td>1.9%±66.3%</td>
<td>2.8%±7.4%</td>
<td>&lt;0.05</td>
<td>2.9%±6.8%</td>
<td>3.2%±7.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with any INR &gt;4 (n=368)</td>
<td>26.9%</td>
<td>45.1%</td>
<td>&lt;0.001</td>
<td>31.12%</td>
<td>62.9%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- Discriminated good anticoagulation control (TTR ≥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)

Efficacy and safety of 4 high dose NOACs vs warfarin: meta-analysis of phase III trials

<table>
<thead>
<tr>
<th>Stroke/SE</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ENGAGE AF</th>
<th>Combined (random)</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
<th>Combined (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0.94 (0.82–1.07)</td>
<td>1.03 (0.90–1.18)</td>
<td>0.71 (0.61–0.81)</td>
<td>0.80 (0.71–0.90)</td>
<td>0.86 (0.73–1.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There have been no head-to-head studies between NOACs. Conclusions about the relative efficacy or safety of any the NOACs cannot be drawn from these data.

<table>
<thead>
<tr>
<th>Secondary efficacy and safety outcomes</th>
<th>Favour NOAC</th>
<th>Favour warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.92 (0.83–1.02)</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.49 (0.38–0.64)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.97 (0.76–1.20)</td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.90 (0.85–0.95)</td>
<td></td>
</tr>
<tr>
<td>GI bleeding</td>
<td>0.41 (0.30–0.53)</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction NOAC, non-VKA oral anticoagulant; SE, systemic embolism

GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction NOAC, non-VKA oral anticoagulant; SE, systemic embolism
Randomized controlled trial
Does it work under IDEAL circumstances?
aka ‘Unreal world’

Practice-based ‘real world’ observational data
Does it work under USUAL circumstances?

Invited Editorial Focus

**“Unreal world” or “real world” data in oral anticoagulant treatment of atrial fibrillation**

Ron Friedman**, Gregory Y. H. Lip**

**North Sydney Institute, Charles Perkins Centre, and Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia; Department of Cardiology and Atherosclerosis Research Institute, Concord Hospital, Concord, from South Wales, Australia; University of Birmingham Institute of Cardiovascular Science, City Hospital, Birmingham, UK, Aalborg Pensions Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark**

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

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

12,701 dabigatran 150 mg BID, 7,192 rivaroxaban 20 mg OD, 6,349 apixaban 5 mg BID, 35,436 warfarin

<table>
<thead>
<tr>
<th></th>
<th>Any bleeding</th>
<th>Major bleeding</th>
<th>Ischaemic stroke, SE or death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>0.61 (0.51–0.74)</td>
<td>0.58 (0.47–0.71)</td>
<td>0.78 (0.64–0.94)</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>0.63 (0.53–0.76)</td>
<td>0.61 (0.49–0.75)</td>
<td>0.79 (0.70–0.88)</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg OD</td>
<td>0.99 (0.86–1.14)</td>
<td>1.06 (0.91–1.23)</td>
<td>0.87 (0.79–0.96)</td>
</tr>
</tbody>
</table>

Risk of any bleeding, major bleeding, or death significantly lower for dabigatran and apixaban vs warfarin
**Fit your drug to your patient profile …**

Things to consider when starting/choosing a NOAC … think ABCDE


**A** Abnormally low weight (dose reduction may be needed with some agents)

**B** Bleeding risk, esp. gastrointestinal

**C** Creatinine clearance (as a measure of renal function)

**D** Drug interactions (eg. reduce dose of verapamil with dabigatran)

**E** Elderly age (dose reduction may be needed)
Patient with Atrial Fibrillation; Eligible for Oral Anticoagulation

Bleeding risk assessment

Identifies ‘at risk’ patients for more regular review and follow-up

Review and address potentially reversible bleeding risk factors
- Uncontrolled hypertension
- Labile INRs (if on VKA)
- Concomitant use of aspirin and NSAIDs in anticoagulated patient
- Alcohol excess

For patients with an increased risk of bleeding the benefit of OAC usually, but not always, outweighs the bleeding risk; thus, regular review and careful monitoring of bleeding risk is important
Do not withhold OAC solely because the patient is at risk of falls

A ‘high risk’ bleeding risk score is not a reason or excuse to withhold OAC

EHR and ‘electronic alerts’
Low risk=No action
High risk=Patient ‘flagged up’ for review

Bleeding Risk Assessment in AF: Observations on the Use and Misuse of Bleeding Risk Scores

Lip and Lane.
J Thromb Haemostat 2016
DOI: 10.1111/jth.13386

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

Modifiable bleeding risk factors:
- Hypertension (especially when systolic blood pressure is >160 mmHg)
- Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
- Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
- Excess alcohol (≥8 drinks/week)

Potentially modifiable bleeding risk factors:
- Anaemia
- Impaired renal function
- Impaired liver function
- Reduced platelet count or function

Non-modifiable bleeding risk factors:
- Age (>65 years) (≥75 years)
- History of major bleeding
- Previous stroke
- Dialysis-dependent kidney disease or renal transplant
- Cirrhotic liver disease
- Malignancy
- Genetic factors

Biomarker-based bleeding risk factors:
- High-sensitivity troponin
- Growth differentiation factor-15
- Serum creatinine/estimated CrCl

www.escardio.org/guidelines
European Heart Journal - doi:10.1093/eurheartj/ehw210
A Novel User-friendly Score To Assess One-year Risk Of Major Bleeding In AF Patients
Pisters et al ... Lip. Chest 2010; 138(5):1093-100

The Birmingham Atrial Fibrillation Bleeding Schema

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic*</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension ie. uncontrolled BP</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding tendency or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs (only applies if taking warfarin)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (eg. age &gt;65, frail condition)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs (concomitant aspirin, NSAIDs etc) or alcohol abuse (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points

<table>
<thead>
<tr>
<th>HAS-BLED</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Any score</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>798</td>
<td>1286</td>
<td>744</td>
<td>187</td>
<td>46</td>
<td>8</td>
<td>3071</td>
</tr>
<tr>
<td>No. of bleeds</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>Bleeds per 100 patient#</td>
<td>1.13</td>
<td>1.02</td>
<td>1.88</td>
<td><strong>3.74</strong></td>
<td><strong>8.70</strong></td>
<td><strong>12.50</strong></td>
<td>1.56</td>
</tr>
</tbody>
</table>

A Novel User-friendly Score To Assess One-year Risk Of Major Bleeding In AF Patients
Pisters et al ... Lip. Chest 2010; 138(5):1093-100

The Birmingham Atrial Fibrillation Bleeding Schema

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic*</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension ie. uncontrolled BP</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding tendency or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs (only applies if taking warfarin)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (eg. age &gt;65, frail condition)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs (concomitant aspirin, NSAIDs etc) or alcohol abuse (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points

<table>
<thead>
<tr>
<th>HAS-BLED</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Any score</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>798</td>
<td>1286</td>
<td>744</td>
<td>187</td>
<td>46</td>
<td>8</td>
<td>3071</td>
</tr>
<tr>
<td>No. of bleeds</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>Bleeds per 100 patient#</td>
<td>1.13</td>
<td>1.02</td>
<td>1.88</td>
<td><strong>3.74</strong></td>
<td><strong>8.70</strong></td>
<td><strong>12.50</strong></td>
<td>1.56</td>
</tr>
</tbody>
</table>
The Birmingham ‘3-step’ ....
Lip. Ear Heart J 2017

**Step 1**
Identify low-risk patients

Low stroke risk
CHA₂DS₂-VASc score:
0 in males
1 in females

No antithrombotic treatment

**Step 2**
Consider stroke prevention (ie. oral anticoagulant) in all AF patients with ≥1 additional stroke risk factors*

*Also calculate the HAS-BLED score. If HAS-BLED ≥3, address the modifiable bleeding risk factors and plan a closer clinical follow-up.

**Step 3**
Decide on NOAC or VKA with high time in therapeutic range

No antithrombotic treatment

Current state of the art and new horizons for stroke prevention in AF
How to Improve Practical Decision-making in Everyday Clinical Practice

The ‘BIRMINGHAM 3-STEP’ management pathway .... to streamline decision-making for stroke prevention in patients with atrial fibrillation

**STEP 1**
CHA₂DS₂-VASc is simple and best at initial identification of “truly low risk” patients who do not need any antithrombotic therapy

**STEP 2**
All others with ≥1 stroke risk factors can be offered stroke prevention, ie. OAC

- HAS-BLED to ‘flag up’ patients potentially at risk, and to address potentially correctable risk factors for bleeding.

**STEP 3**
The SAME-TTR₂ score helps decision making between NOAC and VKA with good TTR

- Think ABCDE when considering NOAC type/dose

**SIMPLICITY IS BEST !**