XXII Giornate Cardiologiche Torinesi

# Great Innovations in Cardiology

## 6th Joint Meeting with Mayo Clinic

### Torino, Italy - October 14-15, 2010

### Session III: Featured Lectures – Sala G. Agnelli

**October 14, 2010 – 16:30-18:10**

# New perspectives in Antithrombotic Therapy

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"G. d'Annunzio" University – Chieti and
"G. Monasterio" Foundation – Pisa, Italy

*October 14 2010, 16:50-17:10 - 20 min + disc.*

# Disclosures

Fees and honoraria from:

- Boehringer Ingelheim
- BristolMyers-Squibb
- Sanofi Aventis
- Pfizer
- Bayer
- Daiichi-Sankyo
- Lilly
- Astra Zeneca

For topics related to antithrombotic therapy in AF
Co-author of the recent ESC AF Guidelines

European Heart Journal
doi:10.1093/eurheartj/ehq278



# Guidelines for the management of atrial fibrillation

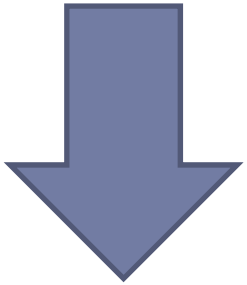
The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)†

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

# Focus on two main intertwined issues

- Stratification of thromboembolic risk



- Therapeutic decisions

# Stratification of thromboembolic risk – well established facts

Stroke risk factors in AF

- Prior stroke/TIA/thrombo-embolism
- Age
- Hypertension
- Diabetes
- Structural heart disease (the presence of moderate to severe LV systolic dysfunction on 2-D is the only independent echocardiographic risk factor for stroke on multivariable analysis).

Hughes M & Lip GY. Thromb Haemost 2008;99:295–304.
Stroke in AF working group. Neurology 2007;69:546–554

# Stratification of thromboembolic risk – more recent evidence (ii)

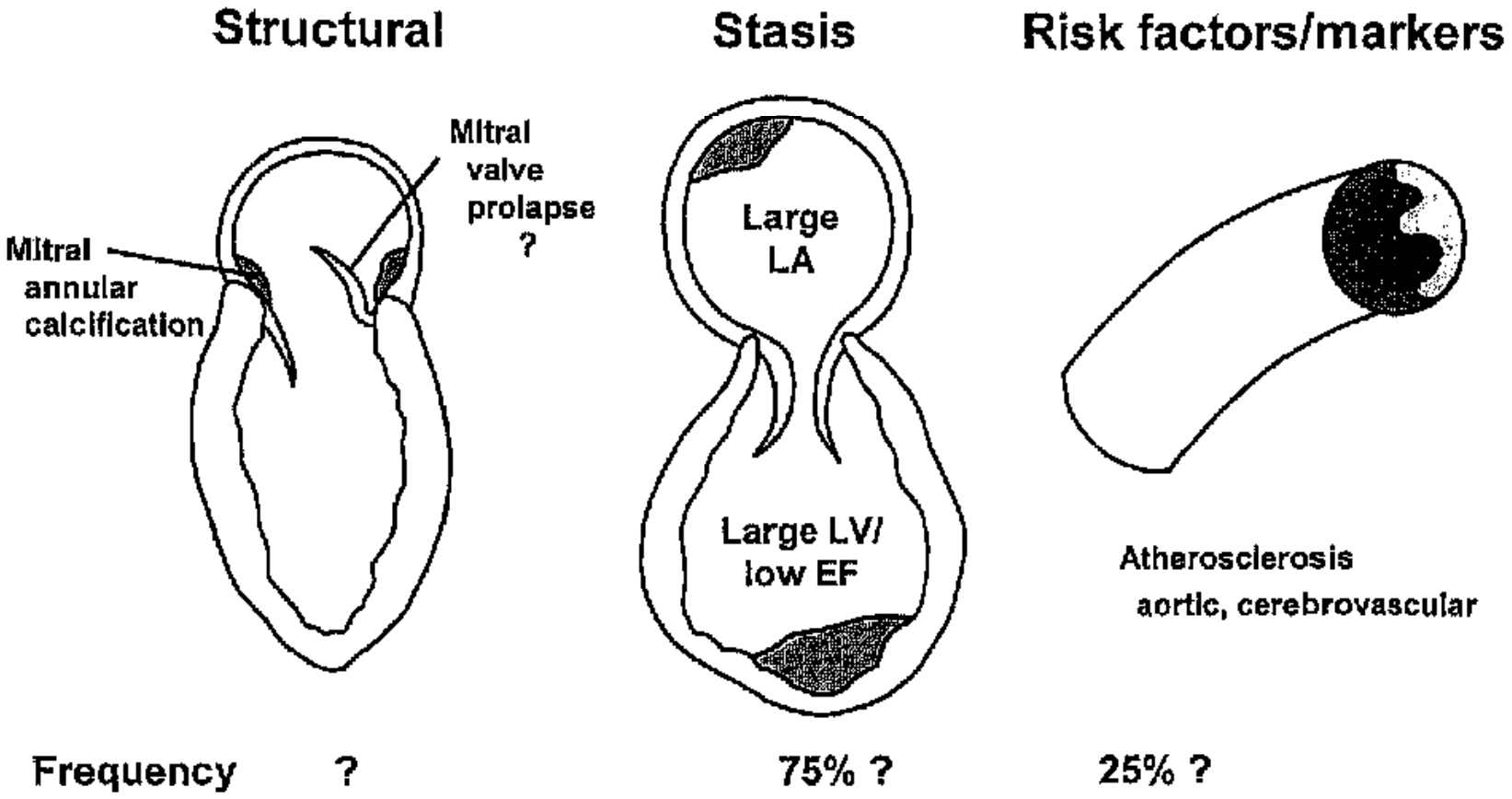
- Paroxysmal AF should be regarded as having a stroke risk similar to persistent or permanent AF
- Patients aged <60 years, with 'lone AF', i.e. no clinical history or echocardiographic evidence of cardiovascular disease, carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years
- The probability of stroke in young patients with lone AF appears to increase with advancing age or development of hypertension, emphasizing the importance of re-assessment of risk factors for stroke over time

Hughes M & Lip GY. Thromb Haemost 2008;99:295–304.
Stroke in AF working group. Neurology 2007;69:546–554

# Caveats, inconsistencies, and areas for further research now clearly outlined

- Age is not a dichotomic risk factor, but a continuous one
- Hypertension has been variably defined in various trials, with various threshold and/or the use of anti-hypertensive drugs - It may be that well-controlled hypertension is no longer a risk factor
- While altered LV function is certainly a risk factor, a purely clinical diagnosis of heart failure is not
- The prognostic implications of heart failure with preserved LV ejection fraction is less defined
- Atherosclerotic vascular disease may contribute to thromboembolic risk (e.g. previous MI, complex aortic plaques on TOE…), but is the increased risk of stroke due to thromboembolism or to atherothrombosis?

# AF and stroke




*Gersh et al, 1995*

# From the assessment of thromboembolic risk factors to risk stratification

**Table 7** $CHADS_2$ score and stroke rate

| $CHADS_2$ score | Patients ($n$ = 1733) | Adjusted stroke rate (%/year)[a] (95% confidence interval) |
|---|---|---|
| 0 | 120 | 1.9 (1.2–3.0) |
| 1 | 463 | 2.8 (2.0–3.8) |
| 2 | 523 | 4.0 (3.1–5.1) |
| 3 | 337 | 5.9 (4.6–7.3) |
| 4 | 220 | 8.5 (6.3–11.1) |
| 5 | 65 | 12.5 (8.2–17.5) |
| 6 | 5 | 18.2 (10.5–27.4) |

[a]The adjusted stroke rate was derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalized AF patients, published in 2001, with low numbers in those with a CHADS2 score of 5 and 6 to allow an accurate judgement of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalized cohorts may also vary from these estimates. Adapted from Gage BF *et al.*[50]

AF = atrial fibrillation; CHADS2 = Cardiac failure, hypertension, age, diabetes, stroke (doubled).

Adapted from Gage BF et al. JAMA 2001; 285:2864–2870.

# Problems with the $CHADS_2$ score

- Moderate c-statistics (0.58) in the whole cohort to predict stroke (…but no worse than 11 other risk stratification schemes compared by the Stroke in AF Working Group)
- Most subjects categorized as “moderate” risk (score=1)
- These subjects overall still appear to derive benefit from oral anticoagulants vs aspirin

# Risks and Benefits of Oral Anticoagulation Compared With Clopidogrel Plus Aspirin in Patients With Atrial Fibrillation According to Stroke Risk

## The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W)

Jeff S. Healey, MD, MSc; Robert G. Hart, MD; Janice Pogue, MSc; Marc A. Pfeffer, MD, PhD; Stefan H. Hohnloser, MD; Raffaele De Caterina, MD; Greg Flaker, MD; Salim Yusuf, MD, DPhil; Stuart J. Connolly, MD

**Table 2. $CHADS_2$-Specific Stroke Rates for Patients Treated With Clopidogrel Plus Aspirin vs Oral Anticoagulation (OAC)**

| CHADS Score | Stroke Rate With ASA (/100 pt-yrs)*[4] | No. of Patients in ACTIVE-W | Stroke Rate C+A (/100 pt-yrs) | Stroke Rate OAC (/100 pt-yrs) | Relative Risk (C+A vs OAC)† |
|---|---|---|---|---|---|
| 0 | 0.8 | 178 (3%) | 1.90 | 0.80 | 3.02 |
| 1 | 2.2 | 2436 (36%) | 1.21 | 0.40 | 3.11 |
| 2 | 4.5 | 2286 (34%) | 1.93 | 1.86 | 1.04 |
| 3 | 8.6 | 1107 (17%) | 2.79 | 1.72 | 1.62 |
| 4 | 10.9 | 490 (7%) | 6.73 | 3.25 | 2.07 |
| 5 | 12.3 | 183 (3%) | 11.65 | 2.69 | 7.01 |
| 6 | 13.7 | 26 (0.4%) | 0 | 0 | NA |

*Annual rate of stroke among 2580 aspirin-treated patients with atrial fibrillation.[4]
†Influence of baseline $CHADS_2$ score on RR ($P$ trend=0.29).
¶Patients had to have evidence of peripheral vascular disease or coronary artery disease and be older than 55 years.

***Stroke. 2008;39:000-000***

# Problems with the $CHADS_2$ score

- Moderate c-statistics (0.58) in the whole cohort to predict stroke (…but no worse than 11 other risk stratification schemes compared by the Stroke in AF Working Group)
- Most subjects categorized as “moderate” risk (score=1)
- These subjects overall still appear to derive benefit from oral anticoagulants vs aspirin
- Also, the CHADS2 score does not include many stroke risk factors, and other ‘stroke risk modifiers’ need to be considered in a comprehensive stroke risk assessment

## Table 8

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

[a]Prior myocardial infarction, peripheral artery disease, aortic plaque.

| (b) Risk factor-based approach expressed as a point based scoring system, with the acronym $CHA_2DS_2$-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points) | |
|---|---|
| **Risk factor** | **Score** |
| Congestive heart failure/LV dysfunction | 1 |
| Hypertension | 1 |
| Age ≥75 | 2 |
| Diabetes mellitus | 1 |
| Stroke/TIA/thrombo-embolism | 2 |
| Vascular disease[a] | 1 |
| Age 65–74 | 1 |
| Sex category (i.e. female sex) | 1 |
| **Maximum score** | **9** |

| (c) Adjusted stroke rate according to $CHA_2DS_2$-VASc score | | |
|---|---|---|
| $CHA_2DS_2$-VASc score | Patients ($n$=7329) | Adjusted stroke rate (%/year)[b] |
| 0 | 1 | 0% |
| 1 | 422 | 1.3% |
| 2 | 1230 | 2.2% |
| 3 | 1730 | 3.2% |
| 4 | 1718 | 4.0% |
| 5 | 1159 | 6.7% |
| 6 | 679 | 9.8% |
| 7 | 294 | 9.6% |
| 8 | 82 | 6.7% |
| 9 | 14 | 15.2% |

Lip GY. et al, Stroke 2010

# Therefore (Recommendations)

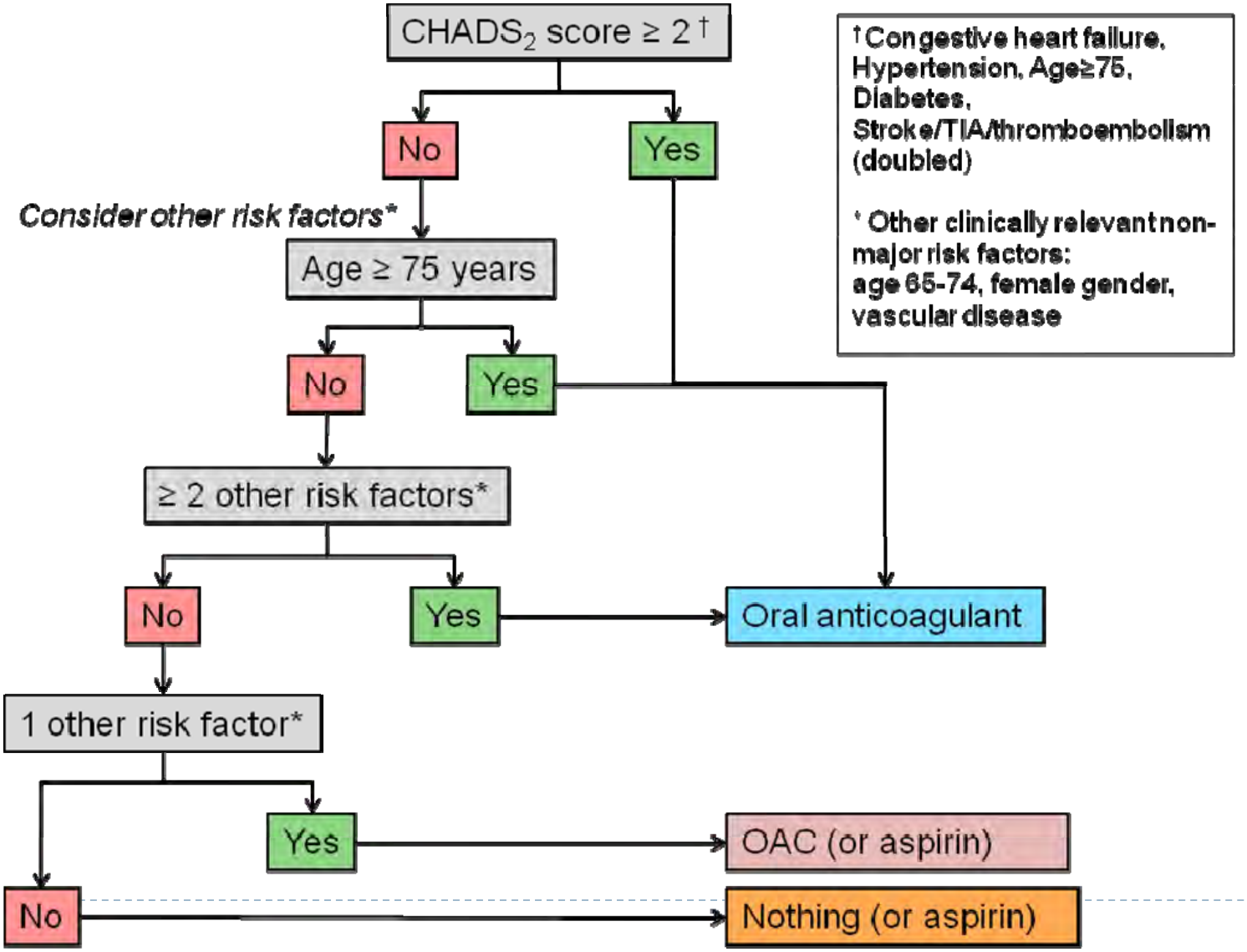
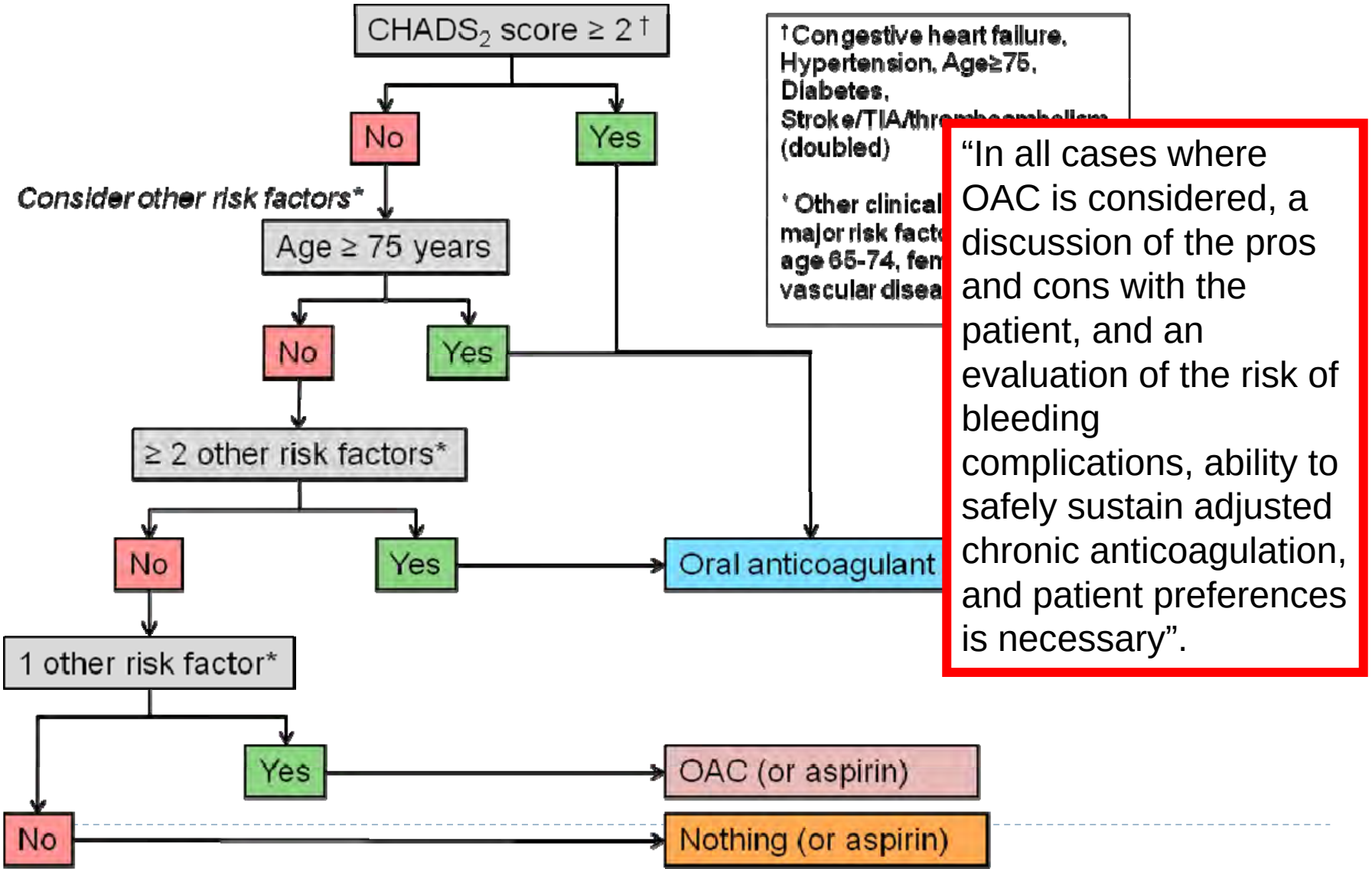


**Table 9** Approach to thromboprophylaxis in patients with AF

| Risk category | $CHA_2DS_2$-VASc score | Recommended antithrombotic therapy |
|---|---|---|
| One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors | ≥ 2 | OAC[a] |
| One 'clinically relevant non-major' risk factor | 1 | Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin. |
| No risk factors | 0 | Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin. |

# Therefore (Recommendations)




"In all cases where OAC is considered, a discussion of the pros and cons with the patient, and an evaluation of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences is necessary".

# Bleeding Risk - considerations

- Despite anticoagulation of more elderly patients with AF, rates of intracerebral haemorrhage are considerably lower than in the past, typically between 0.1 and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension.
- Intracranial bleeding increases with INR values >3.5–4.0, and there is no increment in bleeding risk with INR values between 2.0 and 3.0 compared with lower INR levels.

# Bleeding Risk – considerations (ii)

- It is reasonable to assume that the major bleeding risk with aspirin is similar to that with VKA, especially in elderly individuals*
- The fear of falls may be overstated, as a patient may need to fall 300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of OAC in stroke prevention

Mant J, et al. (BAFTA Study). Lancet 2007;370:493–503.

**Table 10** Clinical characteristics comprising the HAS-BLED bleeding risk score

| Letter | Clinical characteristic[a] | Points awarded |
|---|---|---|
| H | Hypertension | 1 |
| A | Abnormal renal and liver function (1 point each) | 1 or 2 |
| S | Stroke | 1 |
| B | Bleeding | 1 |
| L | Labile INRs | 1 |
| E | Elderly (e.g. age >65 years) | 1 |
| D | Drugs or alcohol (1 point each) | 1 or 2 |
| | | Maximum 9 points |

[a]Hypertension' is defined as systolic blood pressure>160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.
INR = international normalized ratio.

Pisters R, et al.
Chest 2010; March 18
[Epub ahead of print].

**"a score of ≥3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy…"**

# Therefore

- Strong emphasis on preferring OAC over aspirin whenever possible
- Other antithrombotic agents?
- …and which OAC?

# Other antithrombotic therapies

- Based on ACTIVE A, “aspirin plus clopidogrel therapy could perhaps be considered as an interim measure where VKA therapy is unsuitable, but not as an alternative to VKA in patients at high bleeding risk”
- …indobufen, triflusal: “more data are required”
- Combinations of VKA (INR 2.0–3.0) with antiplatelet therapy has been studied, but no beneficial effect on ischaemic stroke or vascular events was seen, while more bleeding was evident. Thus, in patients with AF who sustain an ischaemic stroke despite adjusted dose VKA (INR 2.0–3.0), raising the intensity of anticoagulation to a higher INR range of 3.0–3.5 may be considered, rather than adding an antiplatelet agent, given that an appreciable risk in major bleeding only starts at INRs >3.5

# The good old Vitamin K antagonists (VKAs) – until now the gold standard for antithrombotic therapy in AF

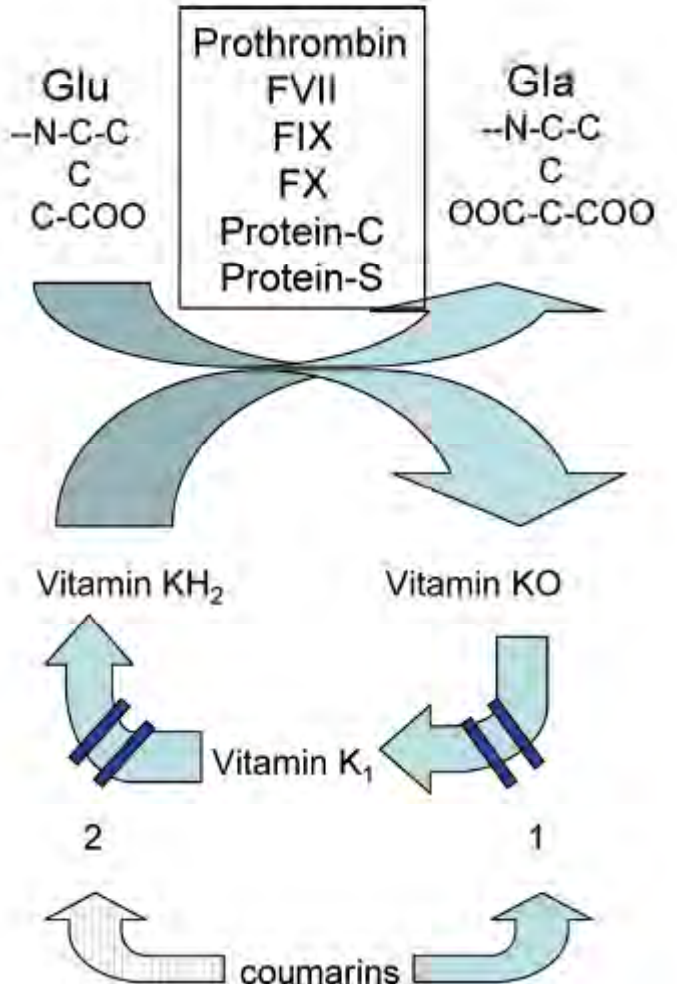
European Heart Journal Advance Access published April 10, 2007

European Heart Journal
doi:10.1093/eurheartj/ehl492

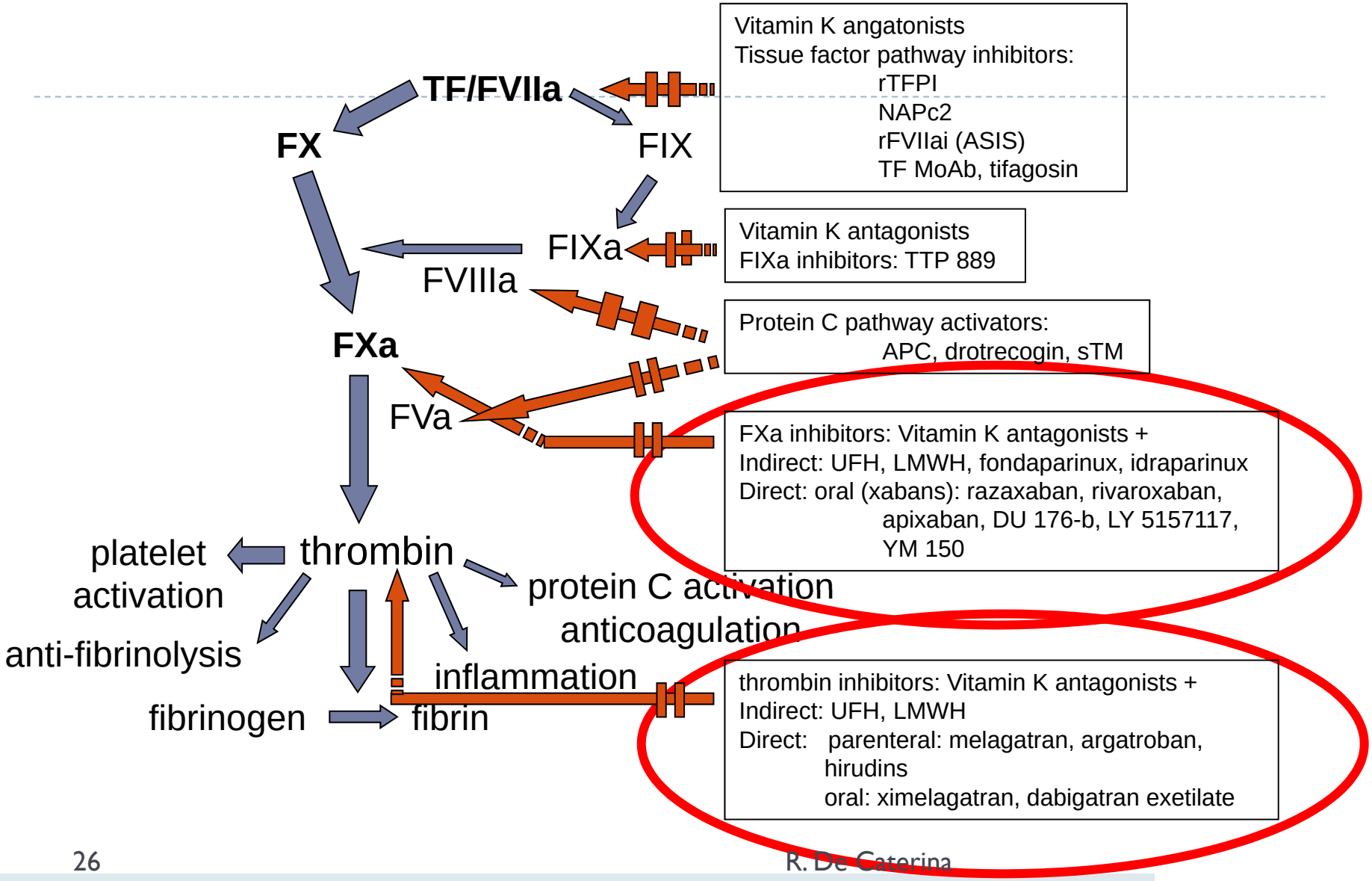
ESC position paper

**Anticoagulants in heart disease: current status and perspectives‡**

Raffaele De Caterina*† (Italy), Steen Husted† (Denmark), Lars Wallentin† (Sweden), Giancarlo Agnelli (Italy), Fedor Bachmann (Switzerland), Colin Baigent (United Kingdom), Jørgen Jespersen (Denmark), Steen Dalby Kristensen (Denmark), Gilles Montalescot (France), Agneta Siegbahn (Sweden), Freek W.A. Verheugt (The Netherlands), Jeffrey Weitz (Canada)




- De Caterina R. et al., EHJ 2007






De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913

# Stroke or systemic embolism (SSE)

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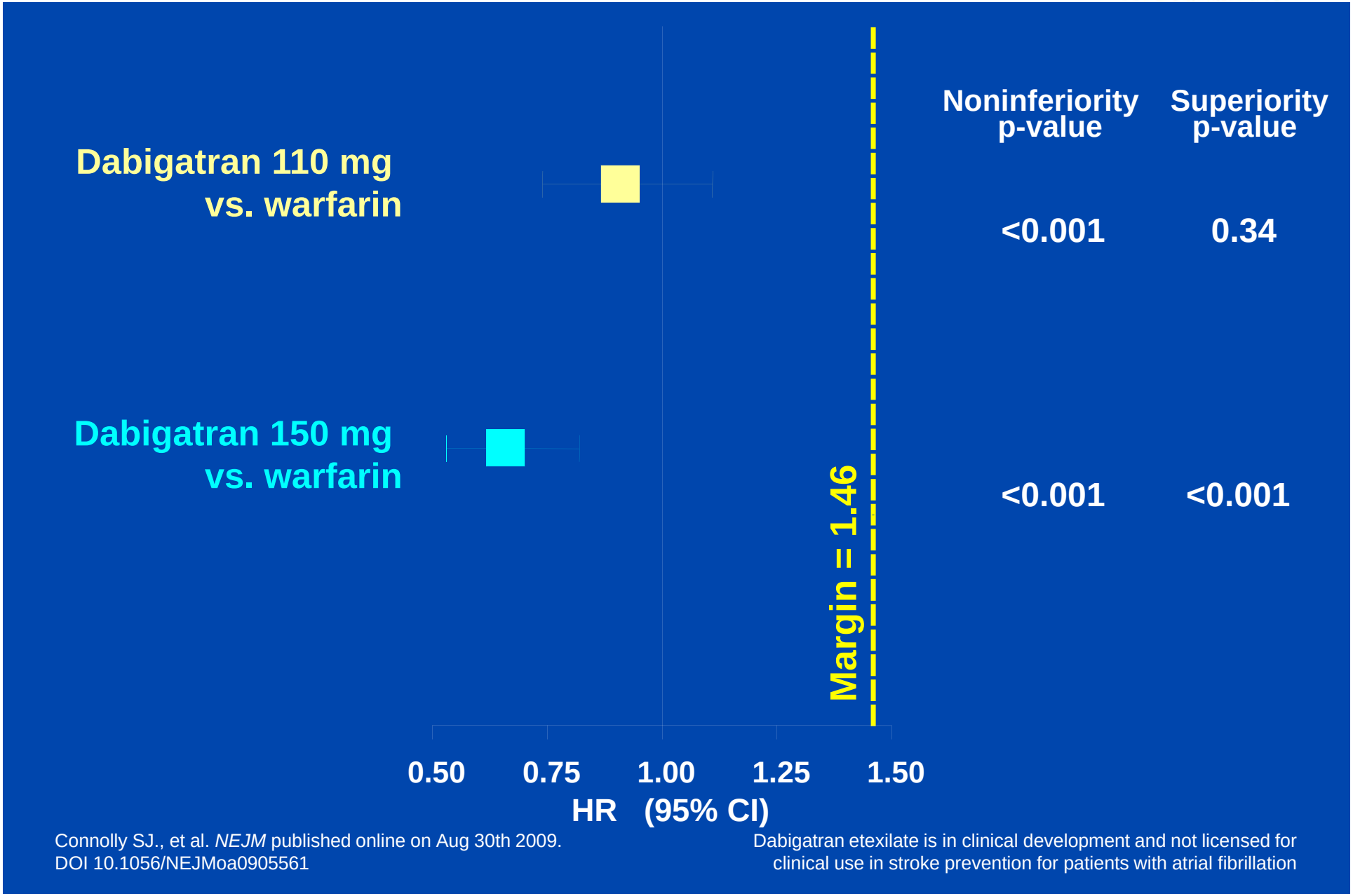
Study of stroke prevention in atrial fibrillation




Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

# Time to first stroke / SSE

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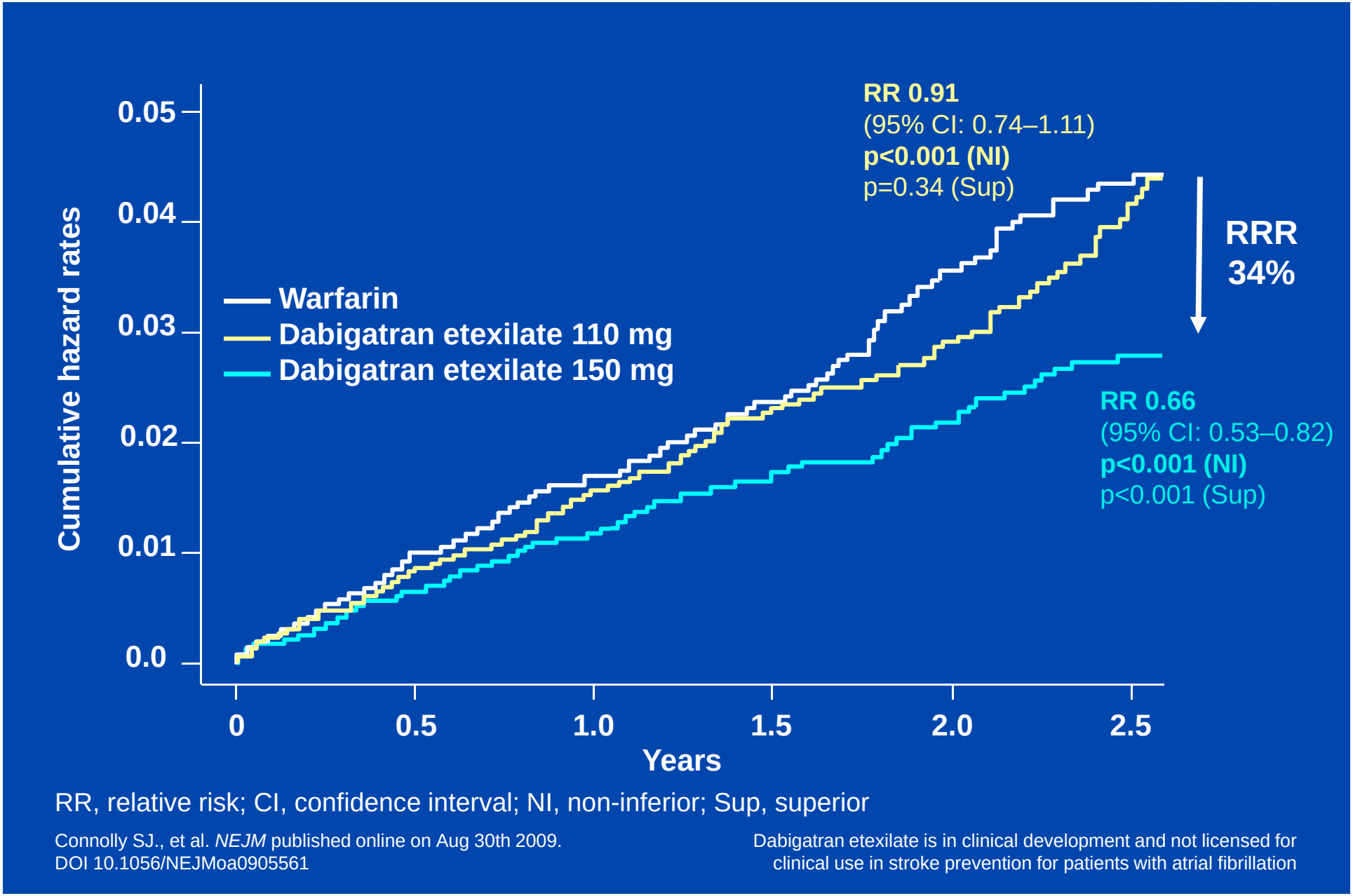
Study of stroke prevention in atrial fibrillation




RR, relative risk; CI, confidence interval; NI, non-inferior; Sup, superior

Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

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# Hemorrhagic stroke

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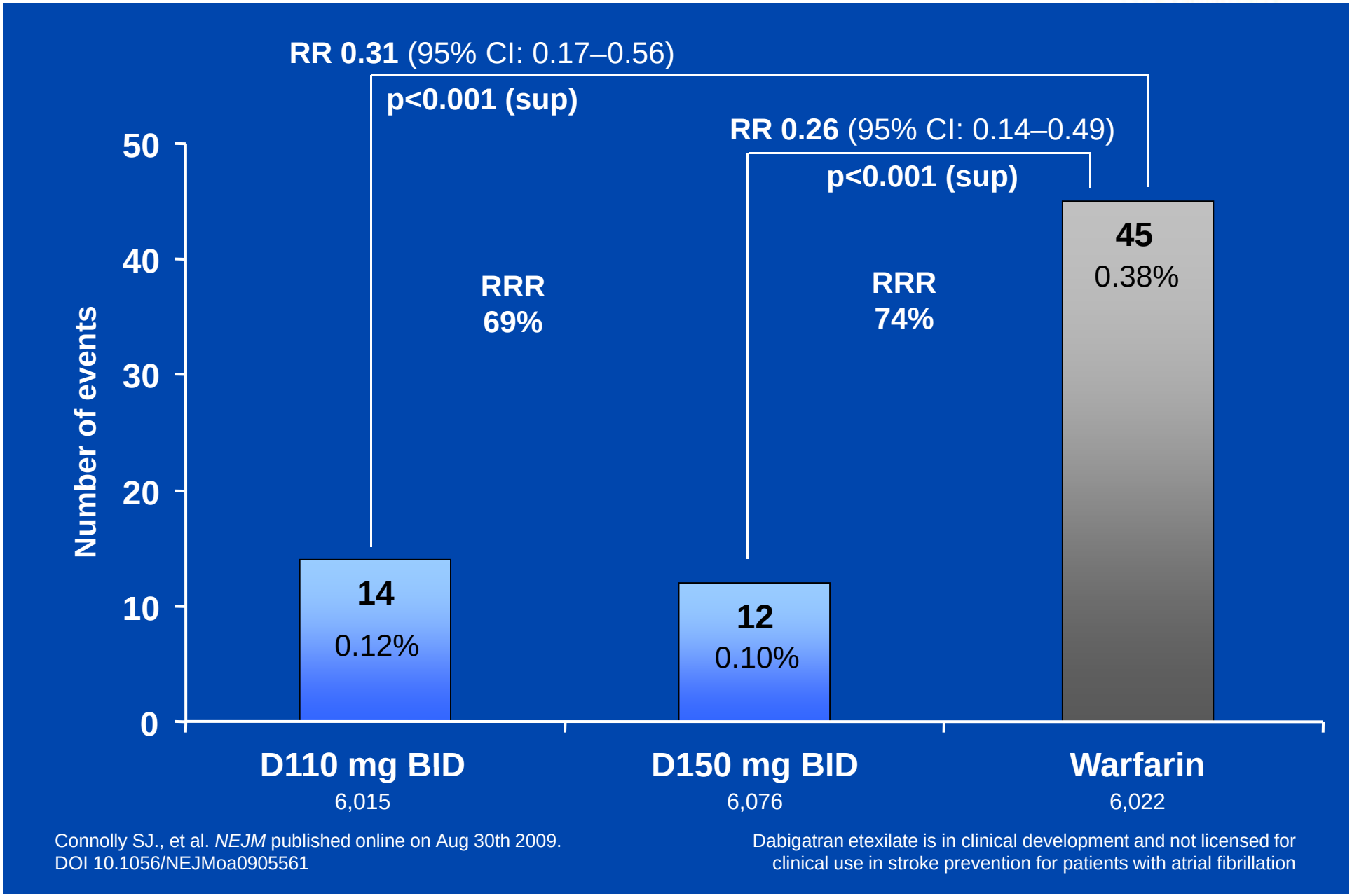


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
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# Vascular mortality

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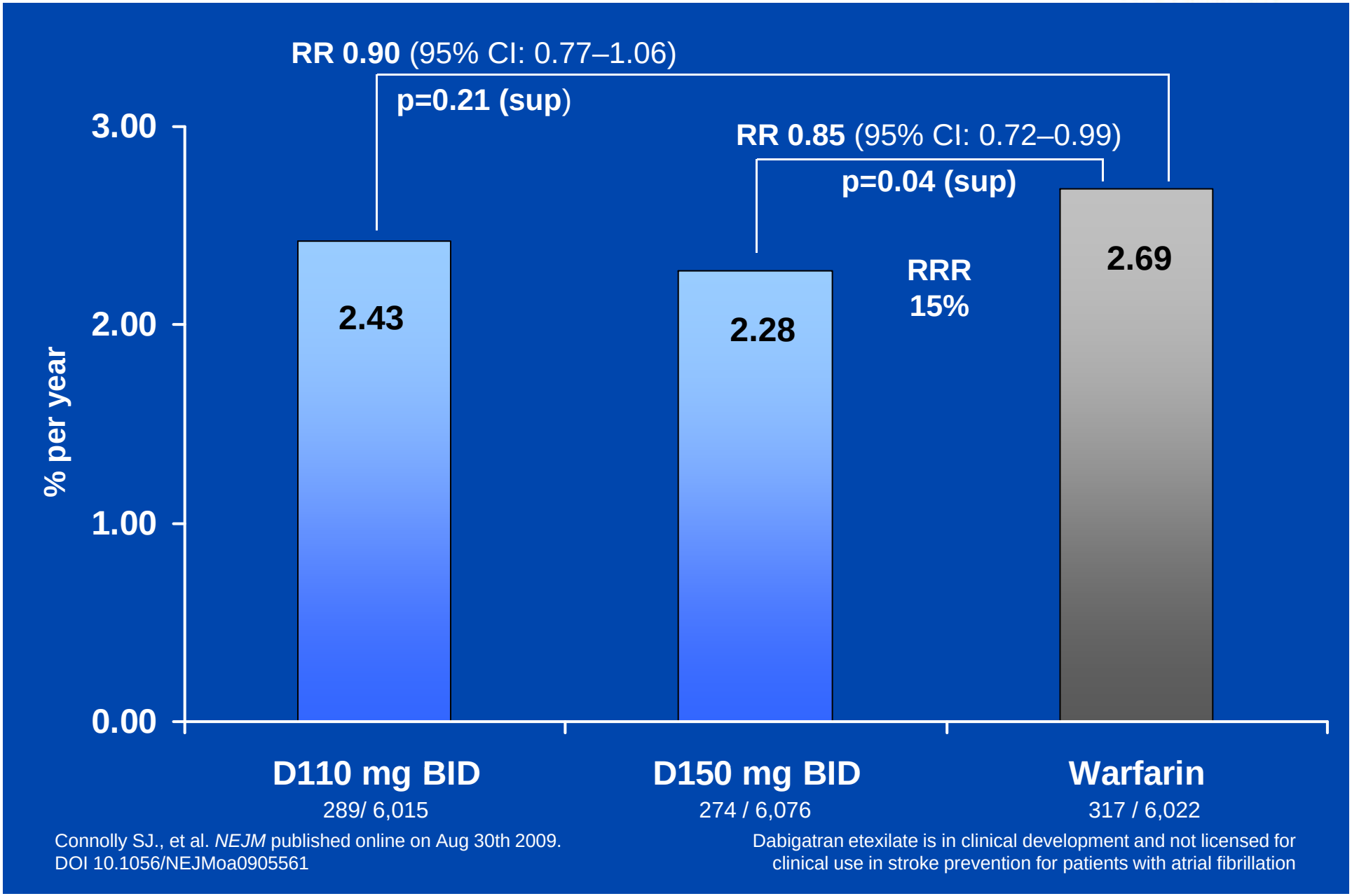


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

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# RE-LY® in perspective

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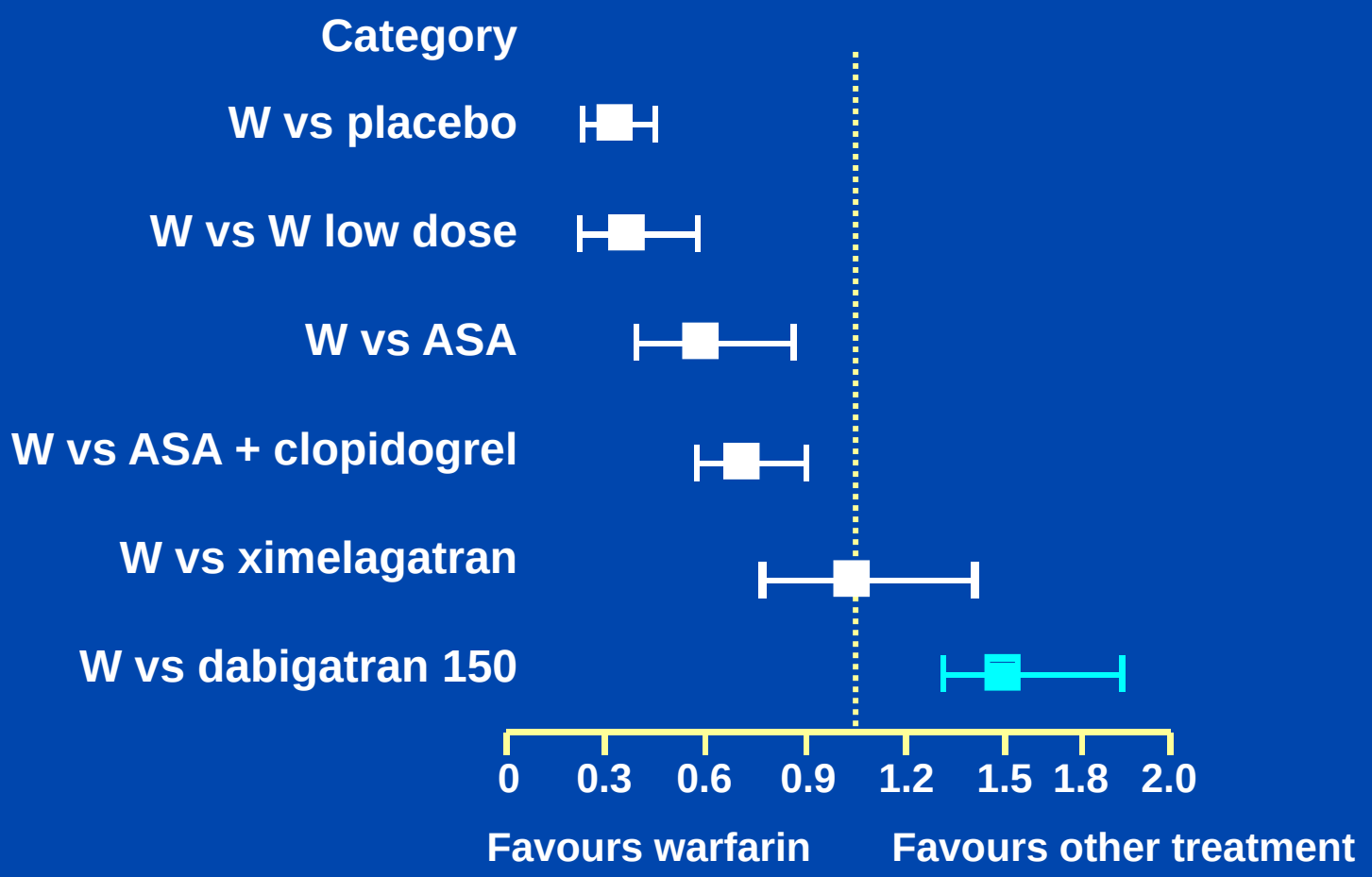
## Meta-analysis of ischaemic stroke or systemic embolism




Camm J.: Oral presentation at ESC on Aug 30th 2009.

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# Major bleeding rates

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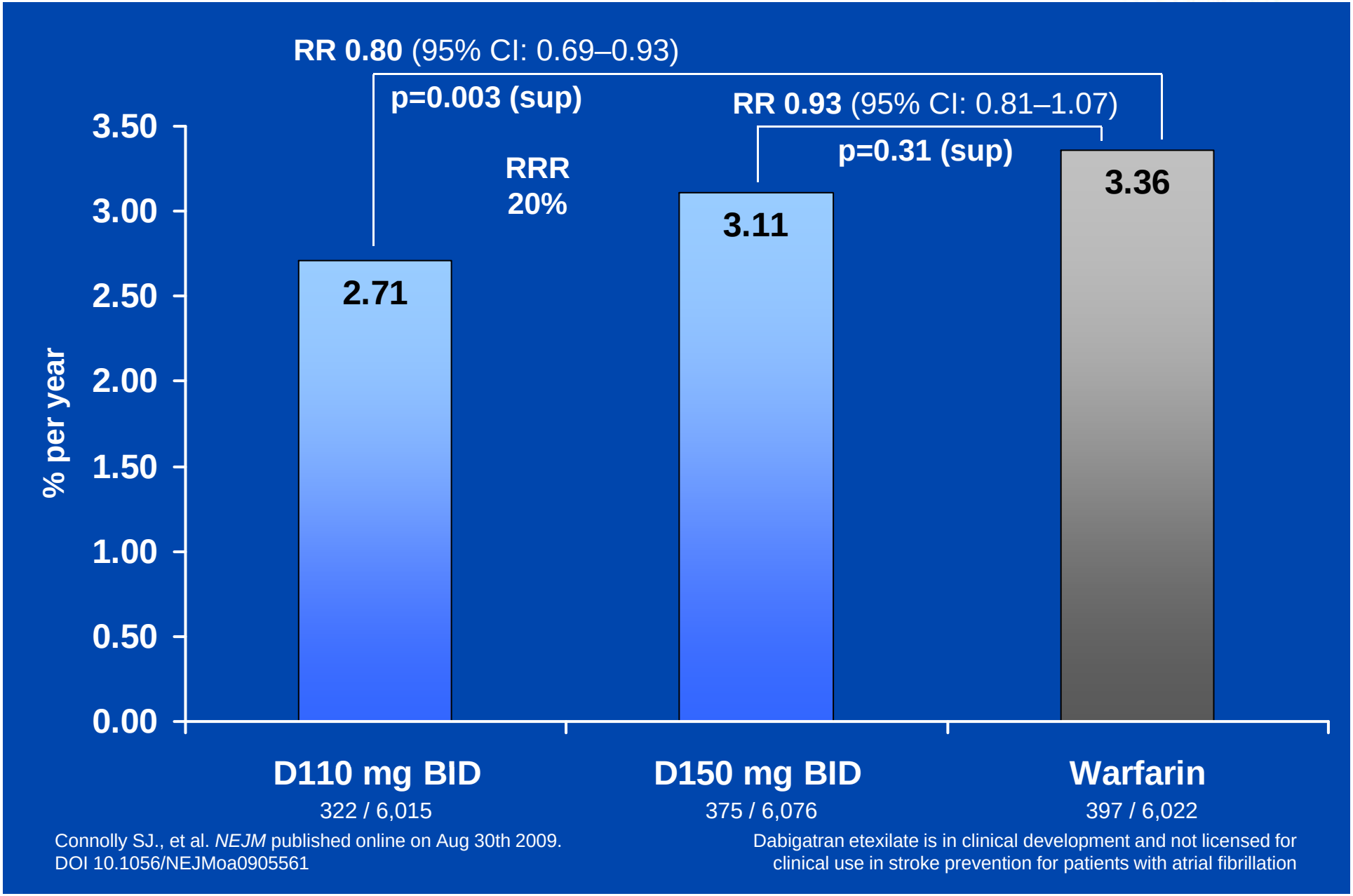


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
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# Total bleeding rates

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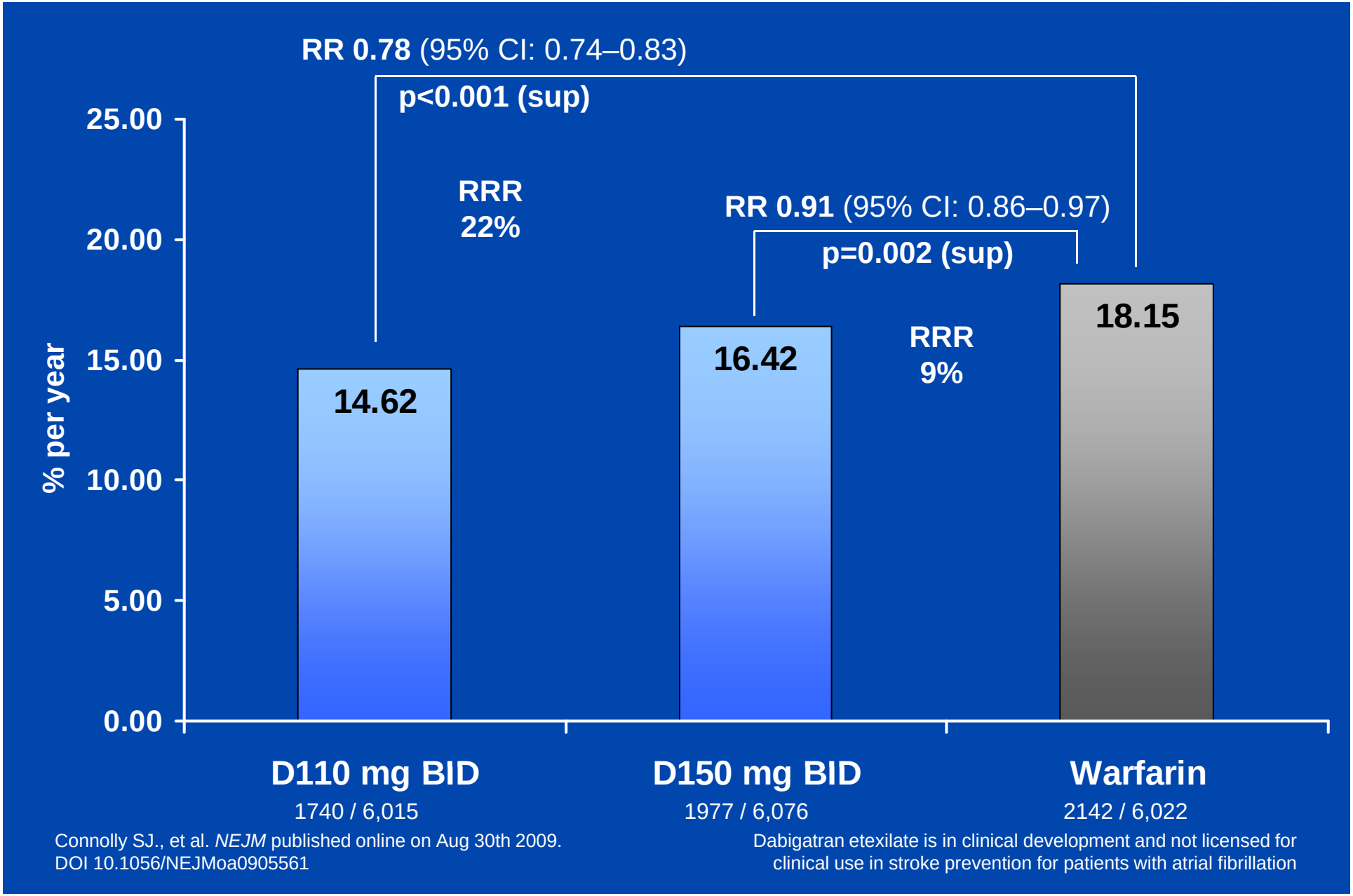


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

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# Life threatening bleeding

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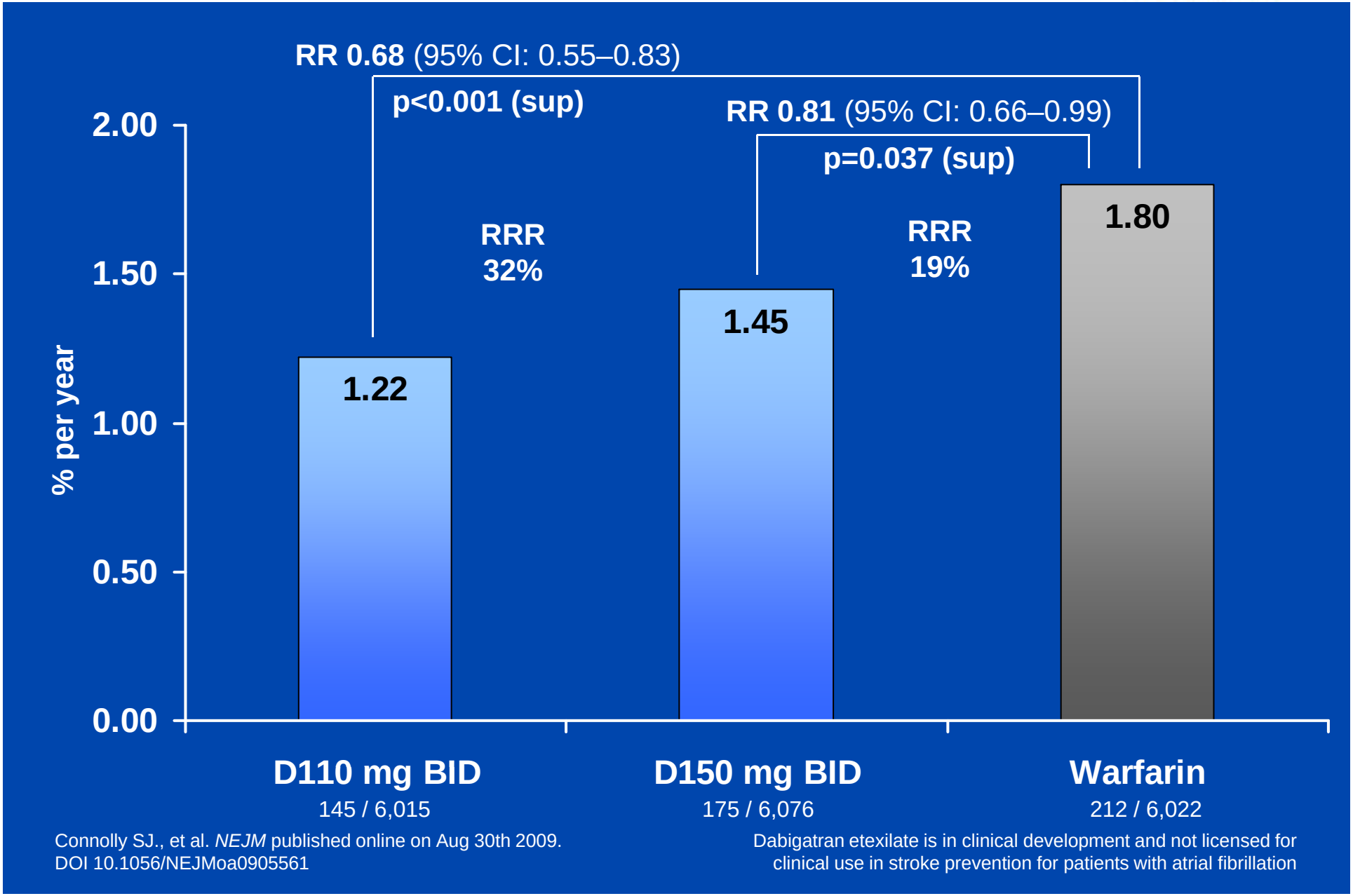


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

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# Intra-cranial bleeding rates

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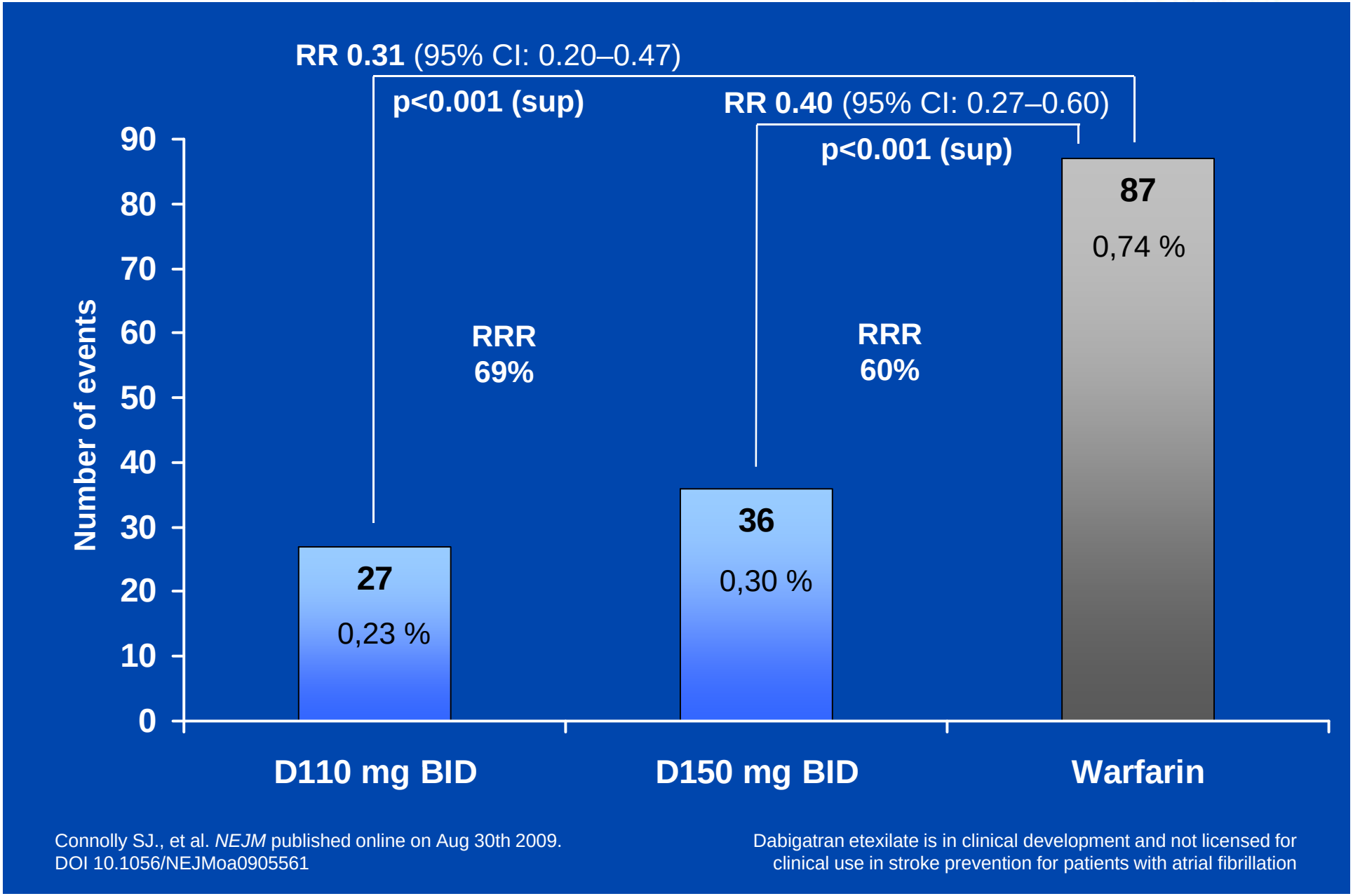


Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

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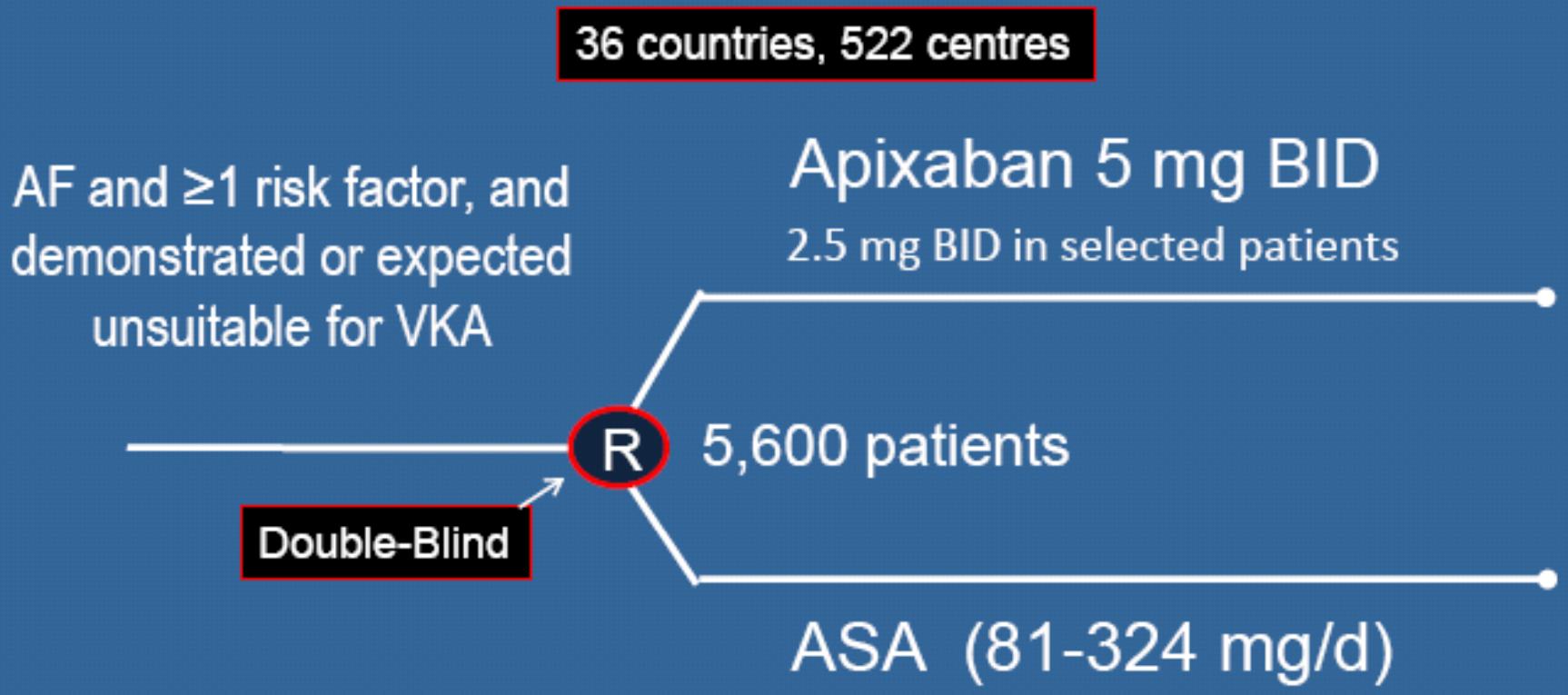
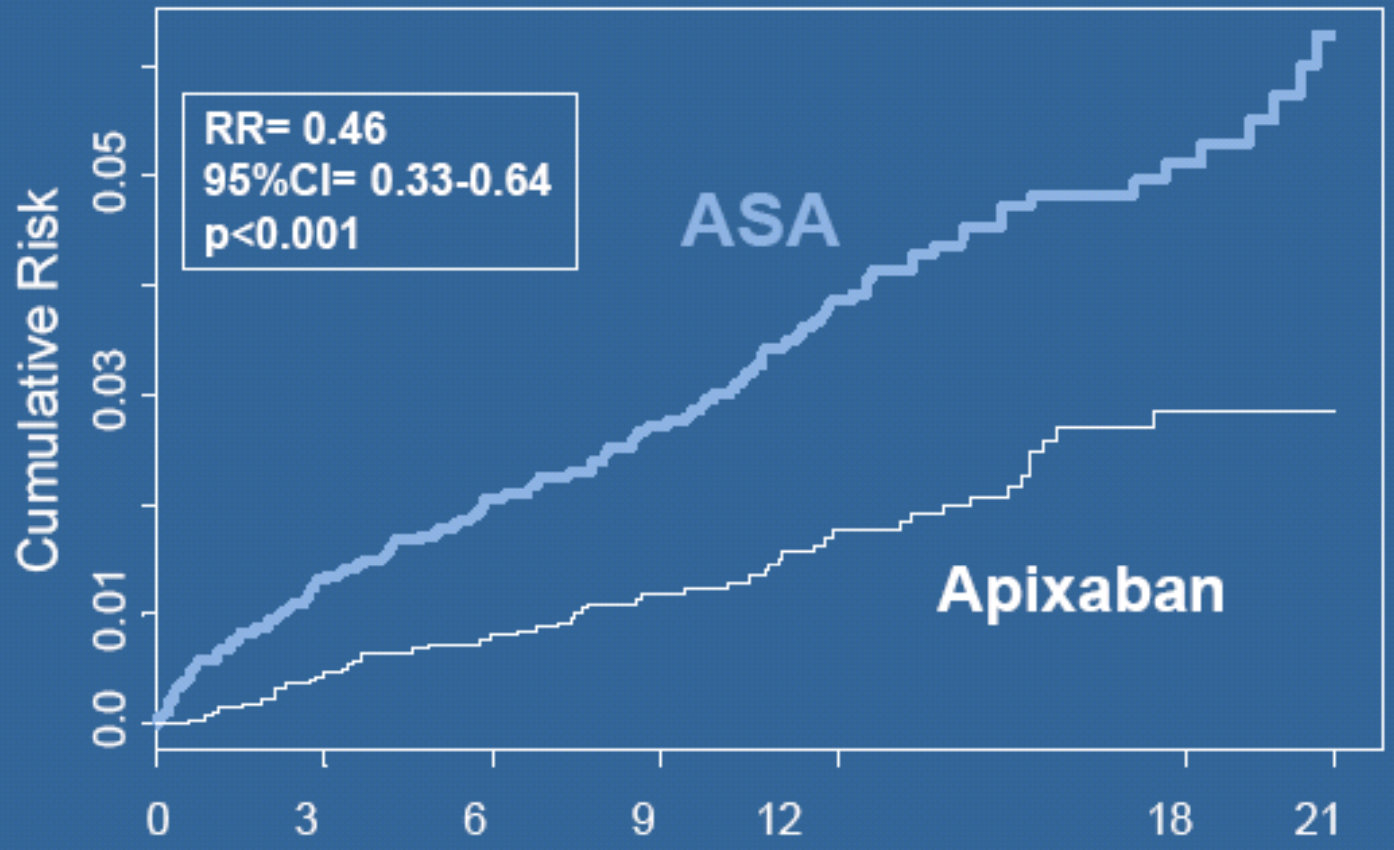
# AVERROES Design




Primary Outcome: Stroke or Systemic Embolic Event (SEE)

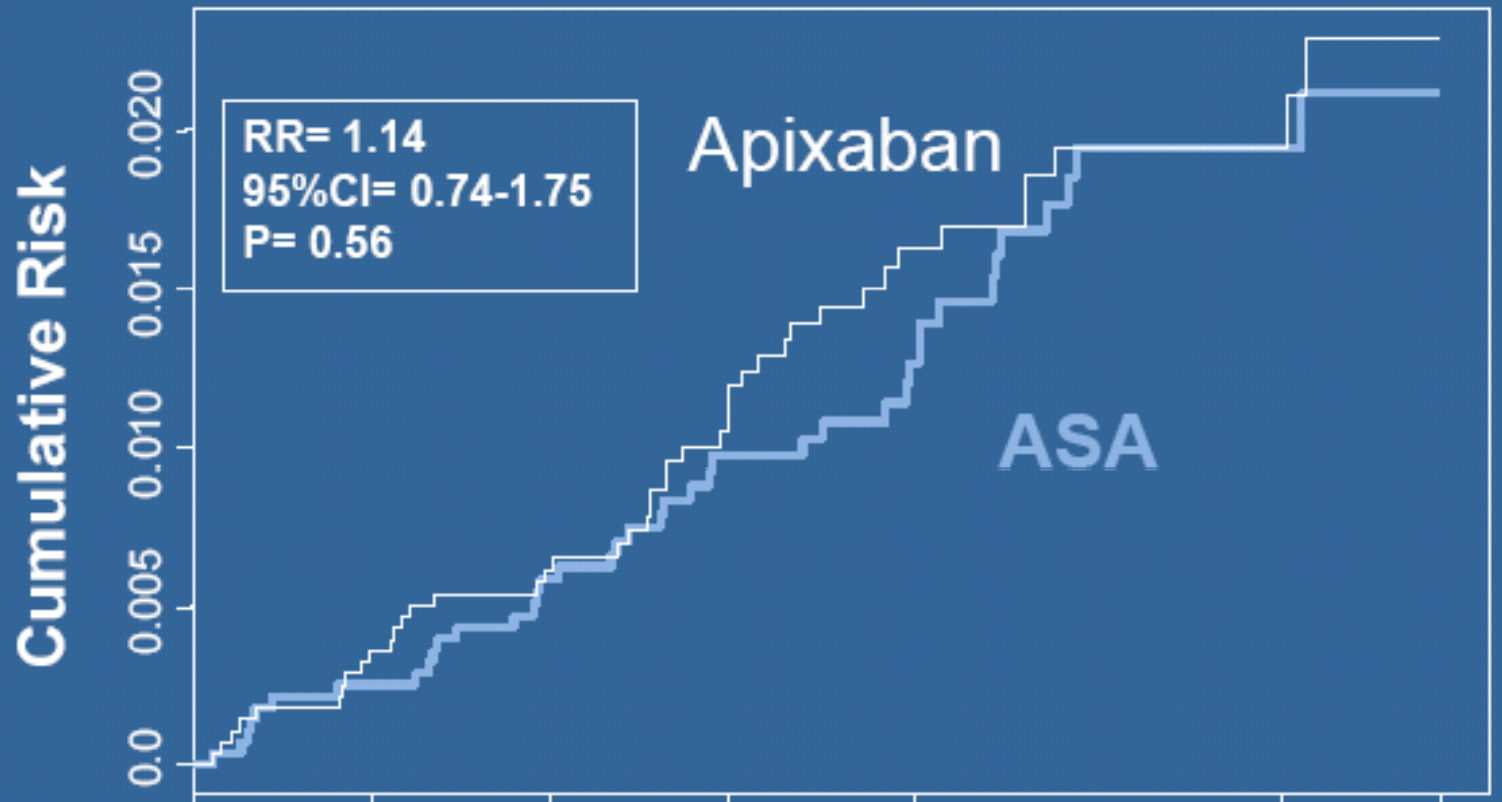
# Stroke or Systemic Embolic Event




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| ASA | 2791 | 2720 | 2541 | 2124 | 1541 | 626 | 329 |
| Apix | 2809 | 2761 | 2567 | 2127 | 1523 | 617 | 353 |

preliminary Results

# Major Bleeding




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| ASA | 2791 | 2744 | 2572 | 2152 | 1570 | 642 | 340 |
| Apix | 2809 | 2763 | 2567 | 2123 | 1521 | 622 | 357 |

preliminary Results

A focused update of these Guidelines is planned as soon as important new therapeutic options will be made available to patients by European regulatory agencies

# Thank you!

**Table 11** Recommended antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

| Haemorrhagic risk | Clinical setting | Stent implanted | Recommendations |
|---|---|---|---|
| Low or intermediate (e.g. **HAS-BLED** score 0–2) | Elective | Bare metal | 1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin ?100 mg/day + clopidogrel 75 mg/day<br>Lifelong: VKA (INR 2.0–3.0) alone |
| | Elective | Drug eluting | 3 (-olimus[a] group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin ?100 mg/day + clopidogrel 75 mg/day<br>Up to 12th months: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b]<br>(or aspirin 100 mg/day)<br>Lifelong: VKA (INR 2.0–3.0) alone |
| | ACS | Bare-metal/ drug-eluting | 6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ?100 mg/day + clopidogrel 75 mg/day<br>Up to 12th months: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b]<br>(or aspirin 100 mg/day)<br>Lifelong: VKA (INR 2.0–3.0) alone |
| High (e.g. **HAS-BLED** score ?3) | Elective | Bare metal[c] | 2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ?100 mg/day + clopidogrel 75 mg/day<br>Lifelong: VKA (INR 2.0–3.0) alone |
| | ACS | Bare metal[c] | 4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ?100 mg/day + clopidogrel 75 mg/day<br>Up to 12th months: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b]<br>(or aspirin 100 mg/day)<br>Lifelong: VKA (INR 2.0–3.0) alone |

ACS = acute coronary syndrome; AF = atrial fibrillation; INR = international normalized ratio; VKA = vitamin K antagonist.
Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary.
[a]Sirolimus, everolimus, and tacrolimus.
[b]Combination of VKA (INR 2.0–3.0) + aspirin ≤100 mg/day (with PPI, if indicated) may be considered as an alternative.
[c]Drug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.