KSC 2016, April 16, 2016

# Major Bleeding History During Anticoagulation

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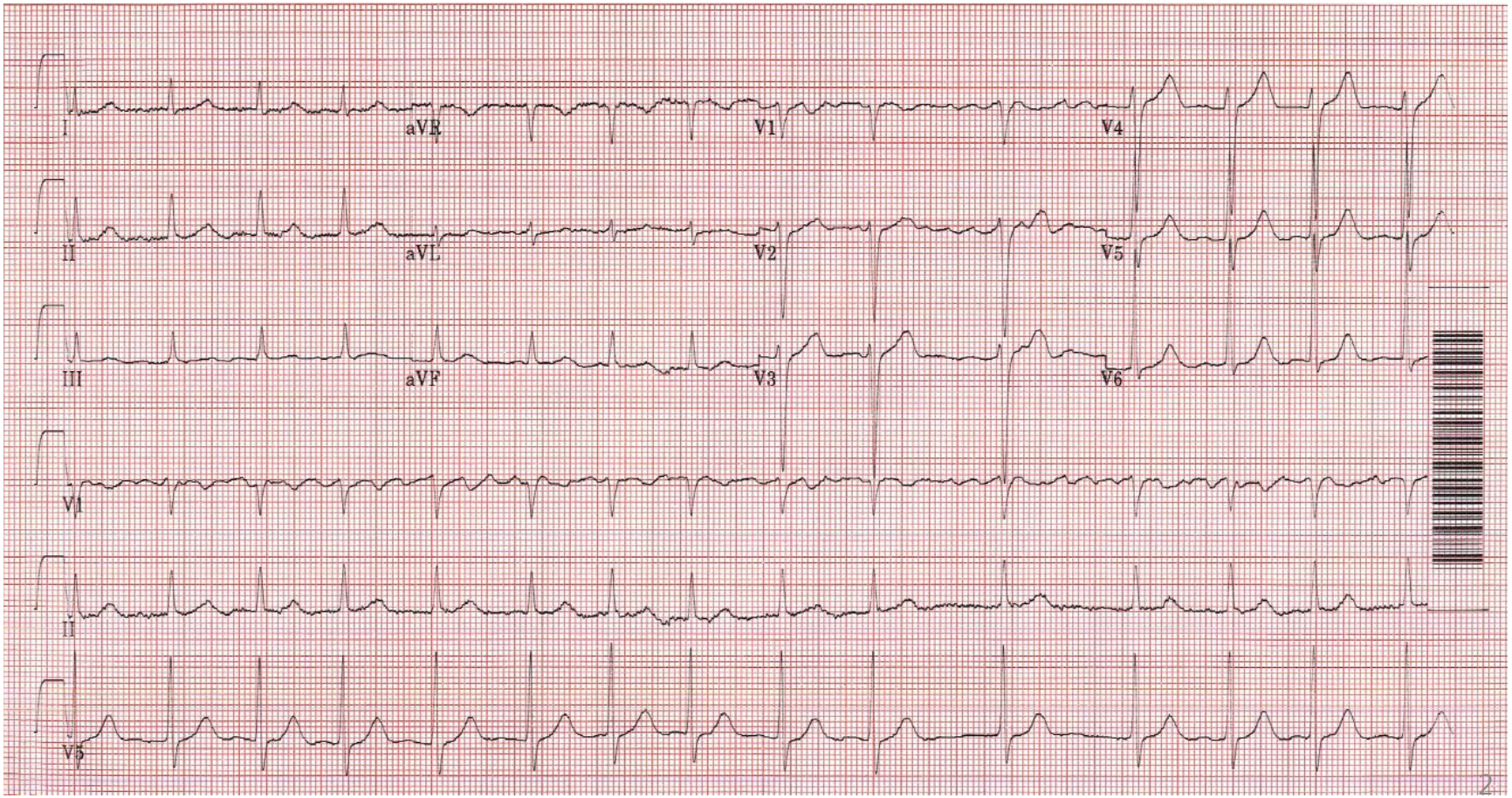
# Case 77/M

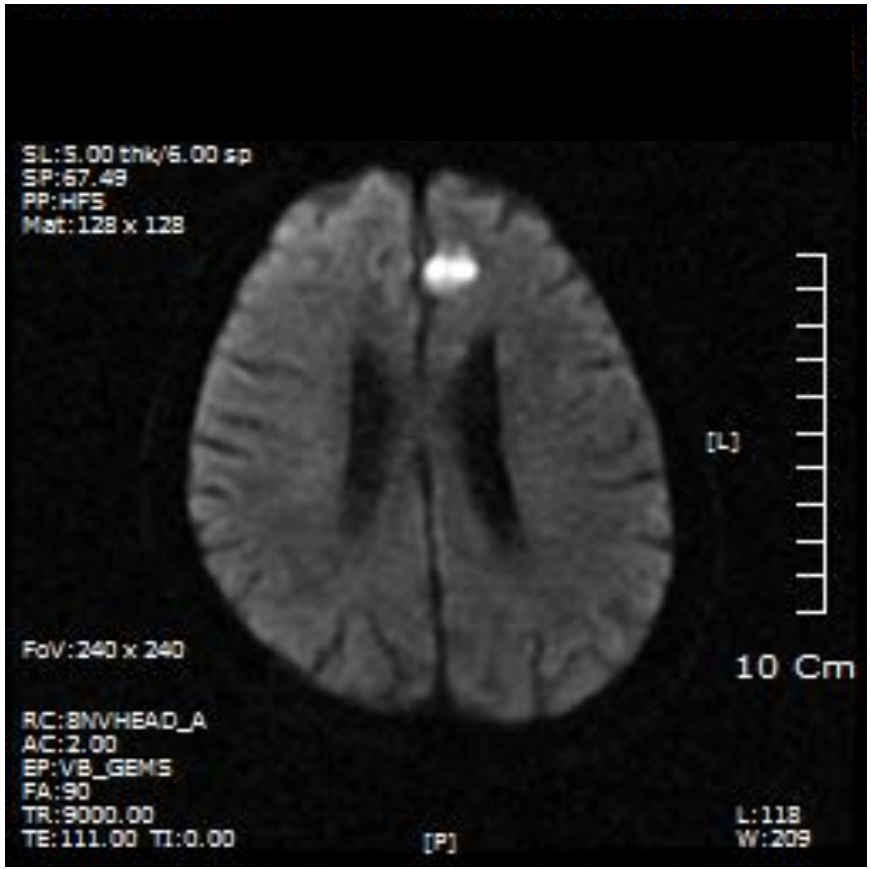
- C/C: Right hemiparesis (6 hrs), HTN(+) DM(+) HF(-)
- BP 150/80mmHg, PR 76 bpm, RR 18/min, BT 36.7℃



# Case 77/M

- C/C: Right hemiparesis (6 hrs), HTN(+) DM(+) HF(-)
- BP 150/80mmHg, PR 76 bpm, RR 18/min, BT 36.7℃
- BW: 53 Kg
- BUN/Cr 17.9/1.1 (GFR 42.16ml/min)
- AST/ALT 62/24 Bilirubin 0.9

# Case 77/M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TE:111.00 TI:0.00
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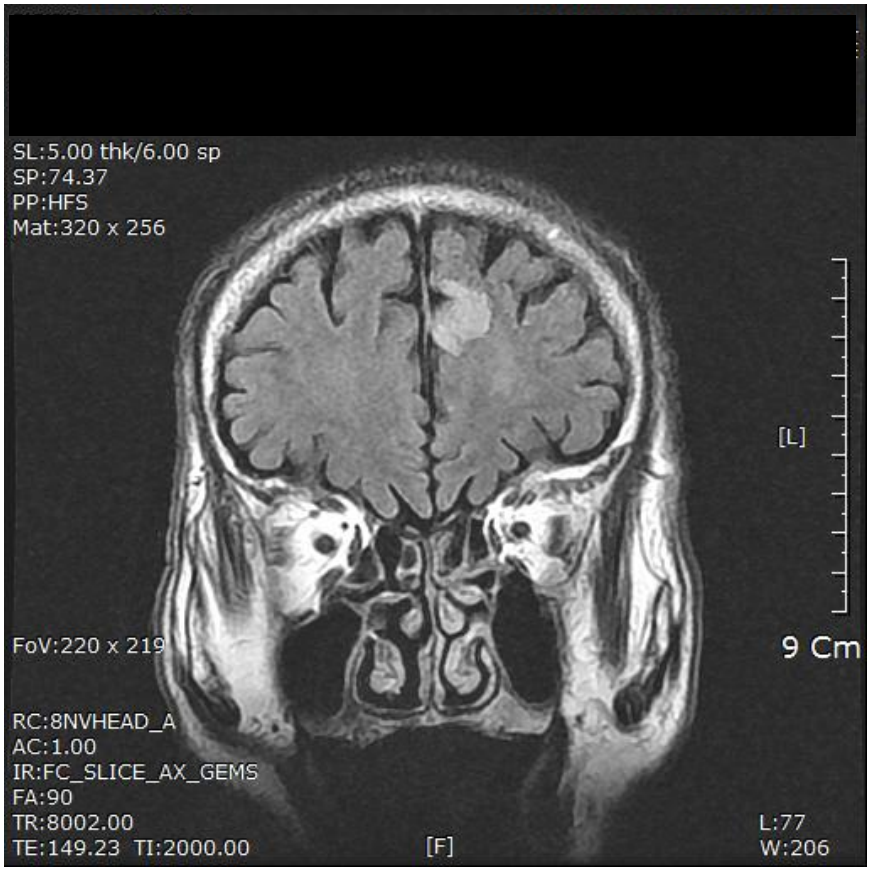
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[F]
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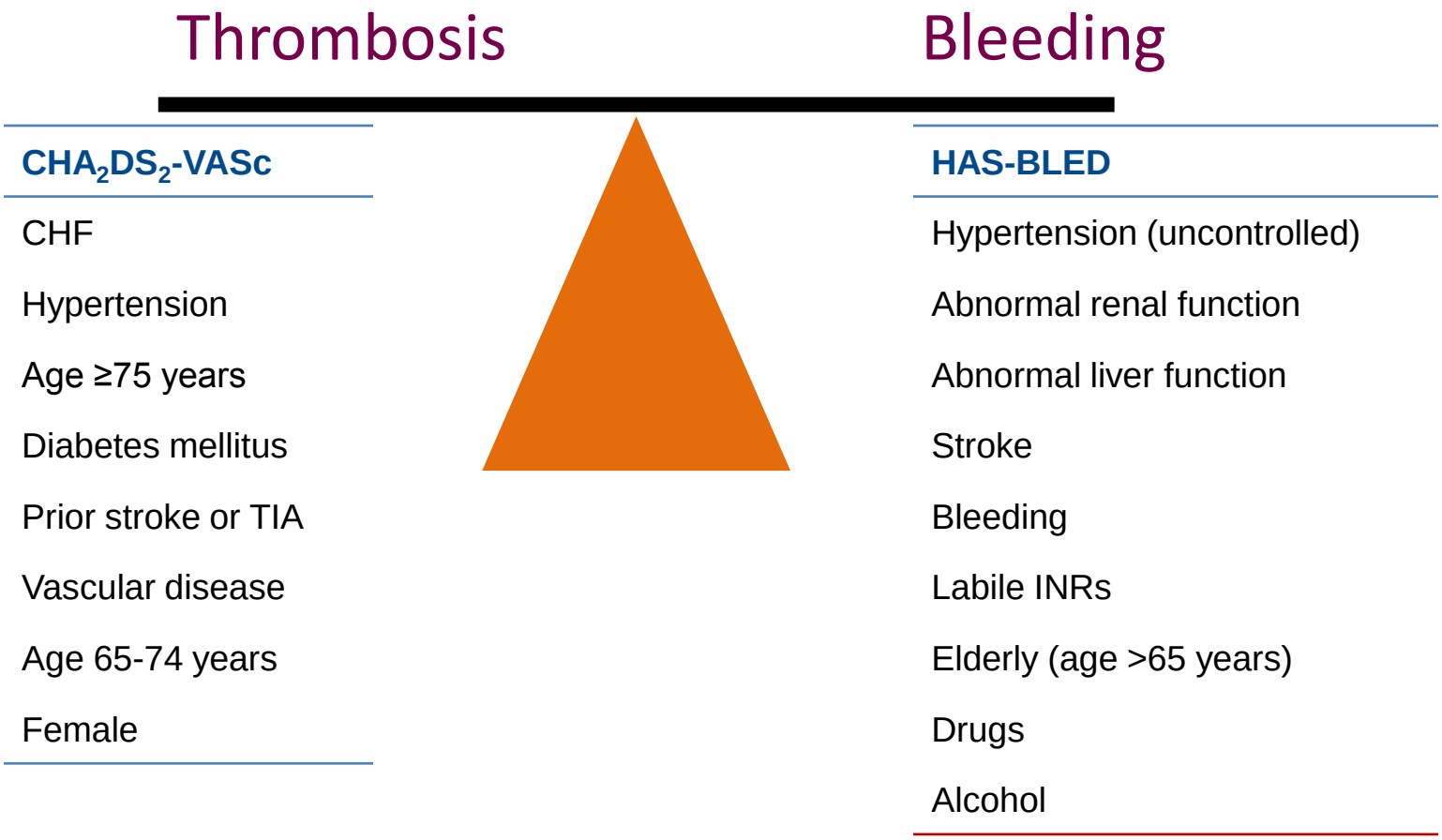
W:206

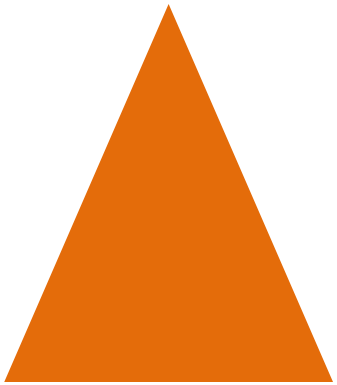
# Case 77/M, AF with embolic infarction

- **How much thrombosis risk?**
- **How much bleeding risk?**

# The therapeutic balance in anticoagulation



# The therapeutic balance in anticoagulation



## Thrombosis

**$CHA_2DS_2$-VASc**

- CHF
- **Hypertension**
- **Age ≥75 years**
- **Diabetes mellitus**
- **Prior stroke or TIA**
- Vascular disease
- Age 65-74 years
- Female

## Bleeding

**HAS-BLED**

- Hypertension (uncontrolled)
- Abnormal renal function
- Abnormal liver function
- **Stroke**
- Bleeding
- Labile INRs
- **Elderly (age >65 years)**
- Drugs
- Alcohol

# Case 77/M, AF with embolic infarction

- How much thrombosis risk?

  $CHA_2DS_2$-VASc = 6

- How much bleeding risk?

  HAS-BLED = 2

# The therapeutic balance in anticoagulation

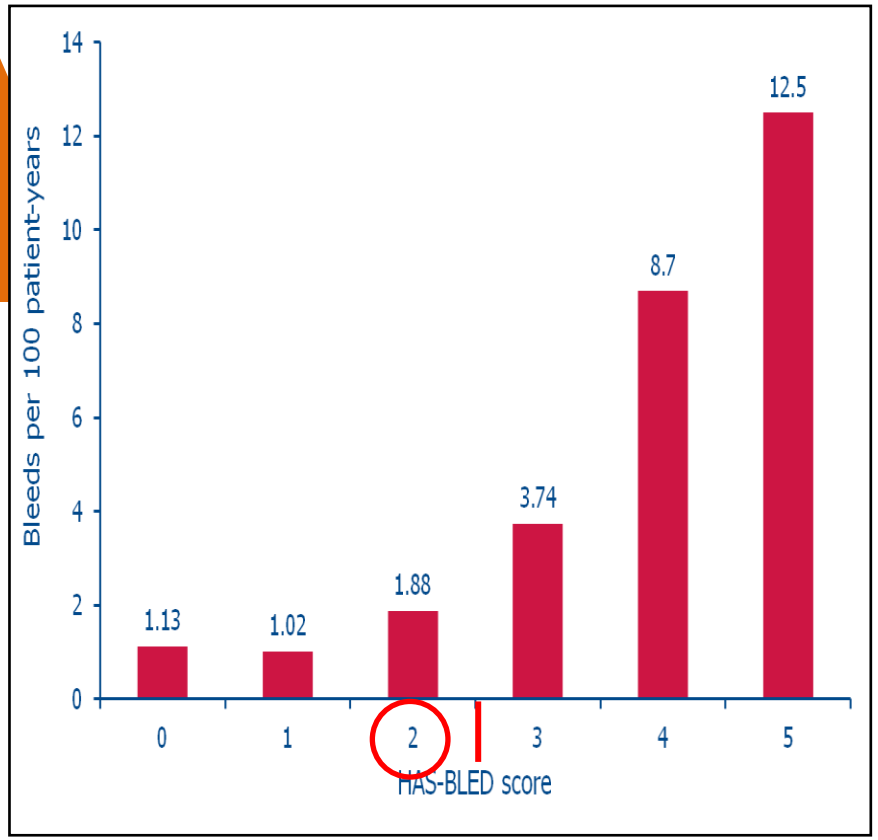
## Thrombosis

## Bleeding

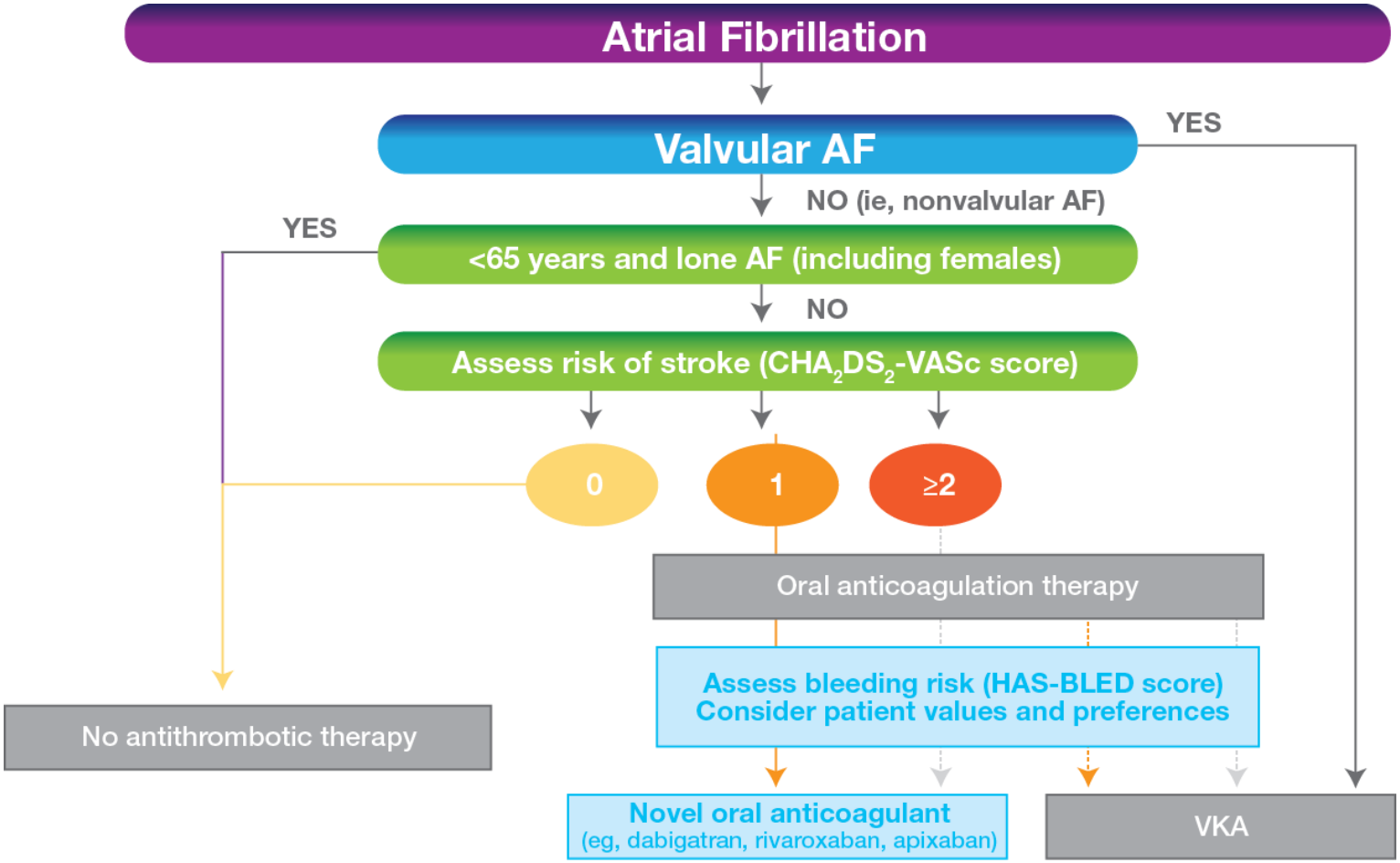
### $CHA_2DS_2$-VASc

| $CHA_2DS_2$-VASc | | $CHA_2DS_2$-VASc† | |
|---|---|---|---|
| Congestive HF | 1 | 0 | 0 |
| Hypertension | 1 | 1 | 1.3 |
| Age ≥75 y | 2 | 2 | 2.2 |
| Diabetes mellitus | 1 | 3 | 3.2 |
| Stroke/TIA/TE | 2 | 4 | 4.0 |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1 | 5 | 6.7 |
| Age 65-74 y | 1 | 6 | 9.8 |
| Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| Maximum score | 9 | 8 | 6.7 |
| | | 9 | 15.20 |

### HAS-BLED



# Prevention of Thromboembolism in NVAF




**1.** Camm AJ et al. *Eur Heart J.* 2012;33(21):2719-2747.

# Case 77/M, AF

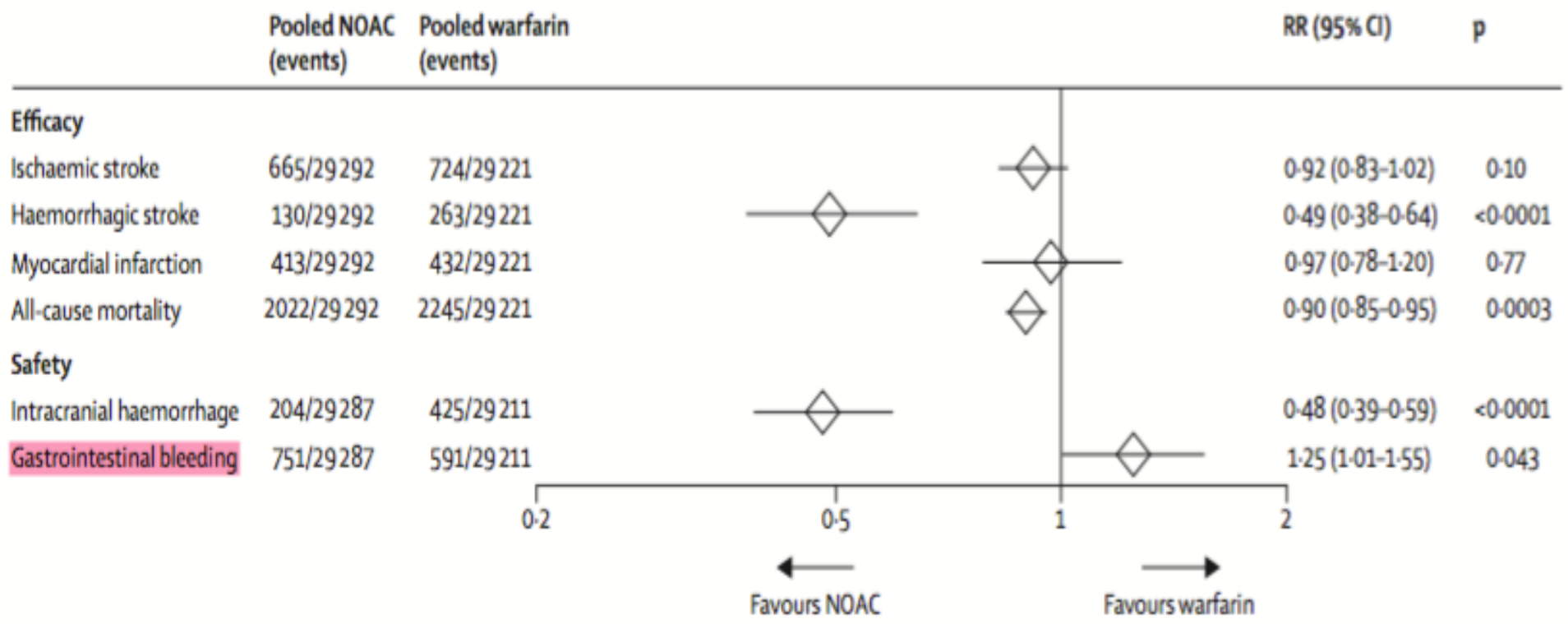
- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**

- **What anticoagulation?**

1. Warfarin

1. Dabigatran 110 mg bid
2. Dabigatran 150 mg bid
3. Rivaroxaban 20 mg qd
4. Apixaban 5 mg bid
5. Edoxaban 30 mg qd
6. Edoxaban 60 mg qd

# Secondary Efficacy and Safety Outcomes






*Lancet* 2014; 383: 955–62

# 2015 EHRA PRACTICAL GUIDE

## 1. Practical start-up and follow-up scheme for patients on non-vitamin K antagonist oral anticoagulants

### Choice of anticoagulant therapy and its initiation

**Indication for anticoagulation and choice between vitamin K antagonist and non-vitamin K antagonist oral anticoagulant**

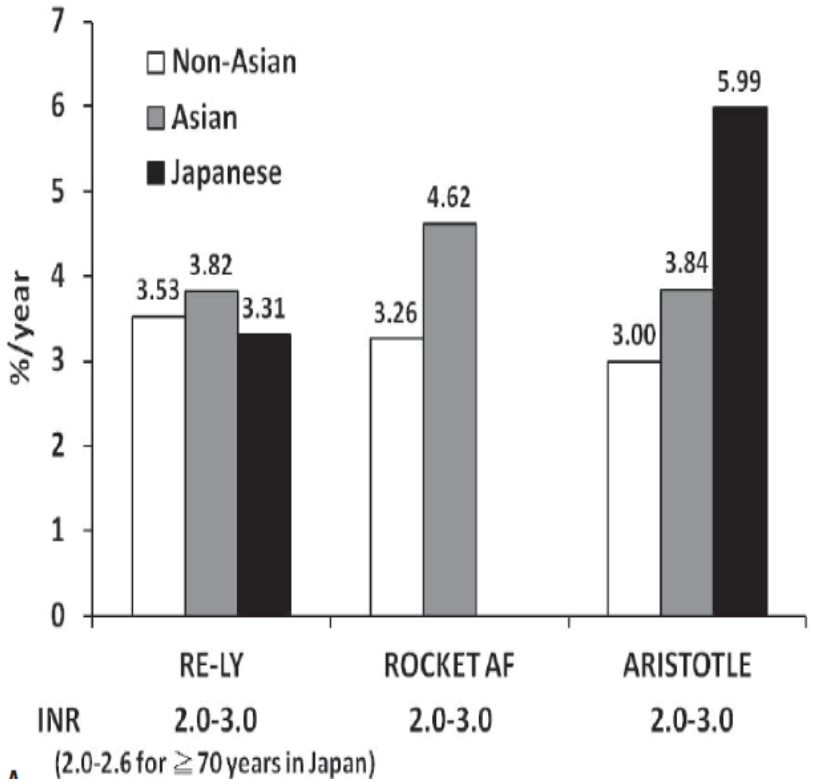
Before prescribing an NOAC to a patient with AF, it should have been decided that anticoagulation is merited based on a risk/benefit analysis

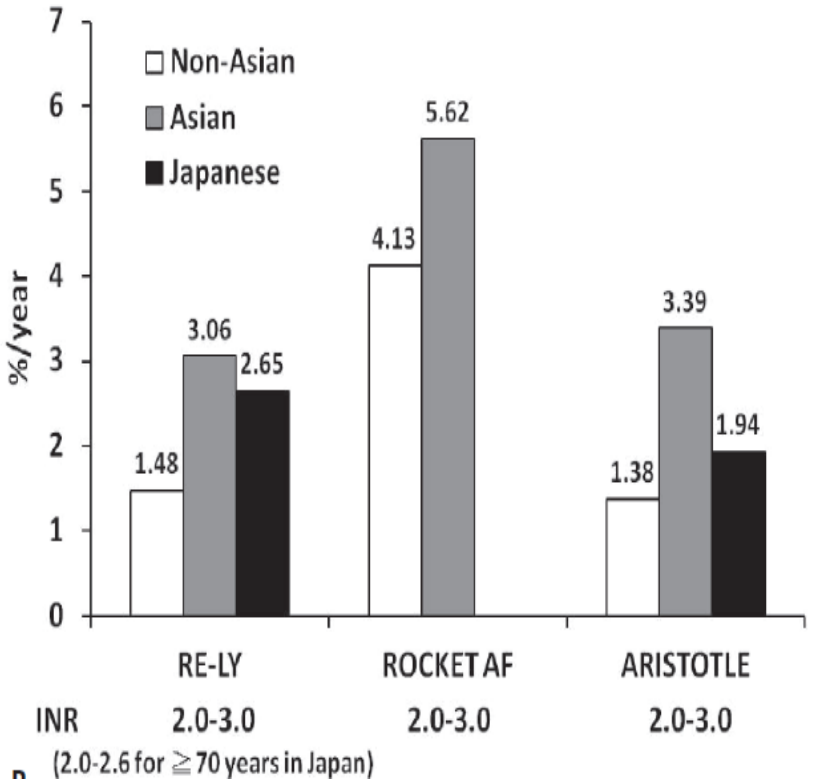
# 2015 EHRA PRACTICAL GUIDE

European guidelines have expressed a preference for NOACs over VKA in stroke prevention for AF patients, based on their overall clinical benefit.[5] Asians are especially vulnerable to VKA, with higher major bleeding and intracranial haemorrhage (ICH) rates than in non-Asians despite lower international normalized ratios (INRs). In contrast, NOACs are associated with a significantly higher relative risk reduction for bleeding and ICH in Asians, while maintaining their efficacy profile. Therefore, NOACs are considered to be preferentially indicated in Asians.[17]

5. Camm AJ et al. 2012 focused update of the ESC
17 Chiang CE et al Thromb Haemost 2014;111:789–97.

# SE and Bleeding in Asian

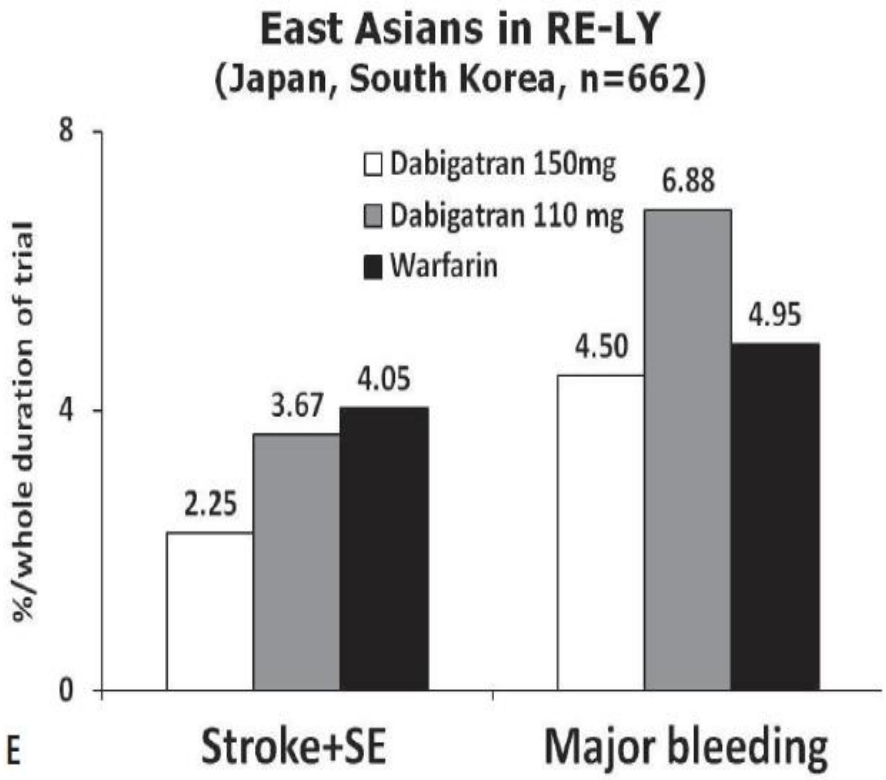


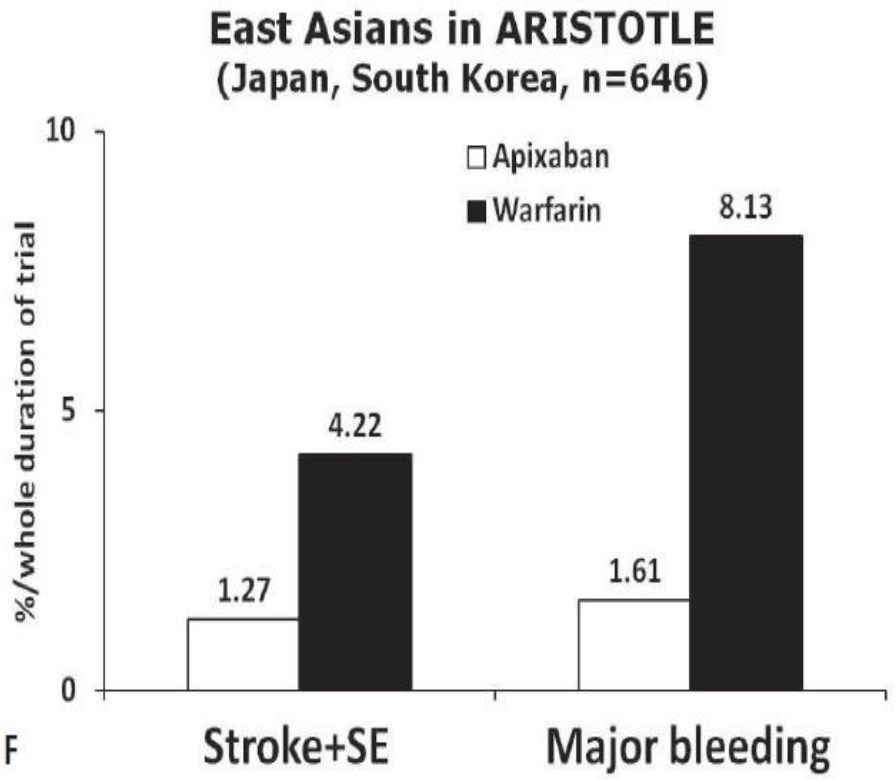




Chiang CE et al Thromb Haemost 2014;111:789–97.

# NOACs in Asian

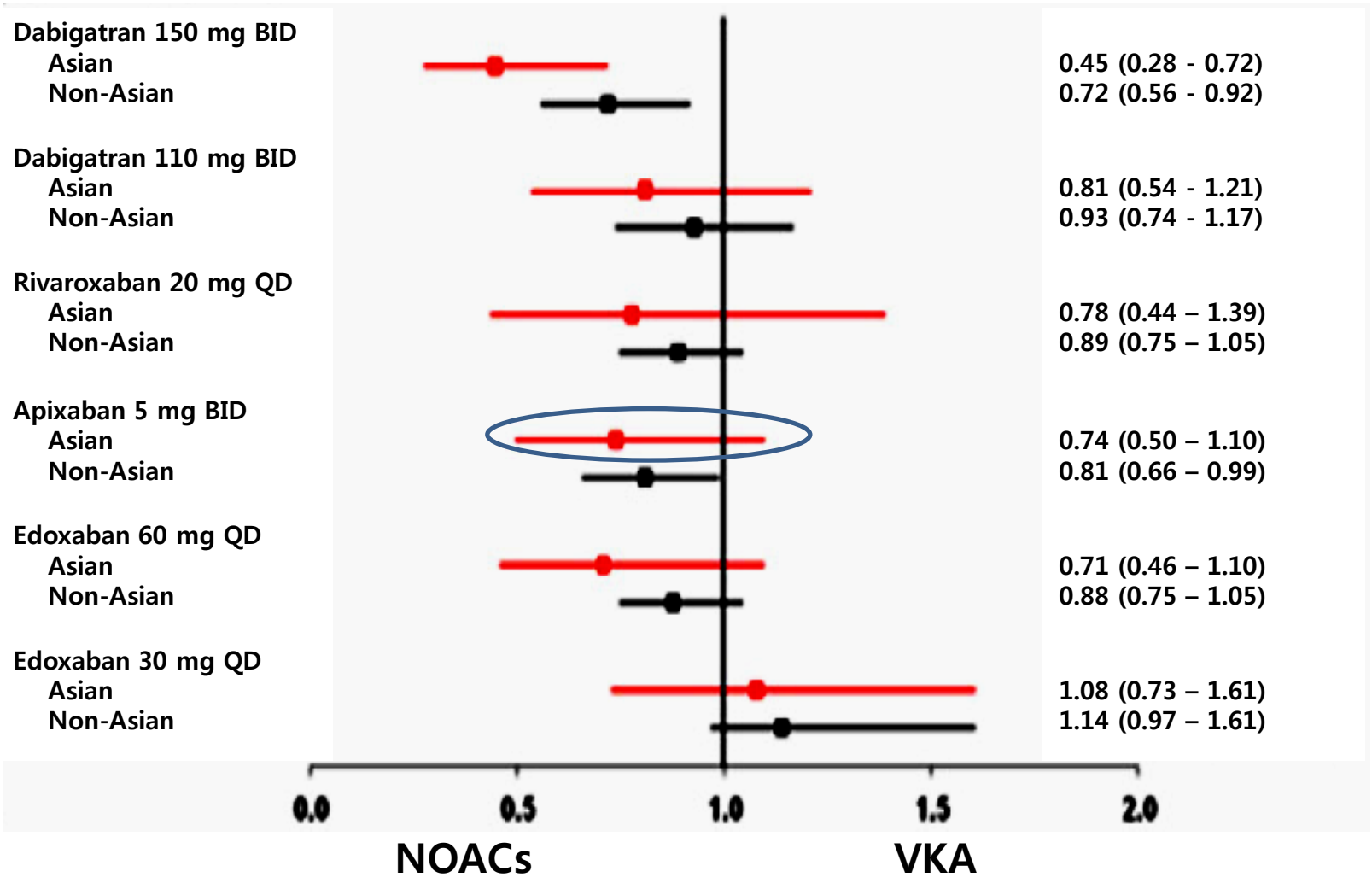
**( lower bleeding, similar efficacy )**




Chiang CE et al Thromb Haemost 2014;111:789–97.

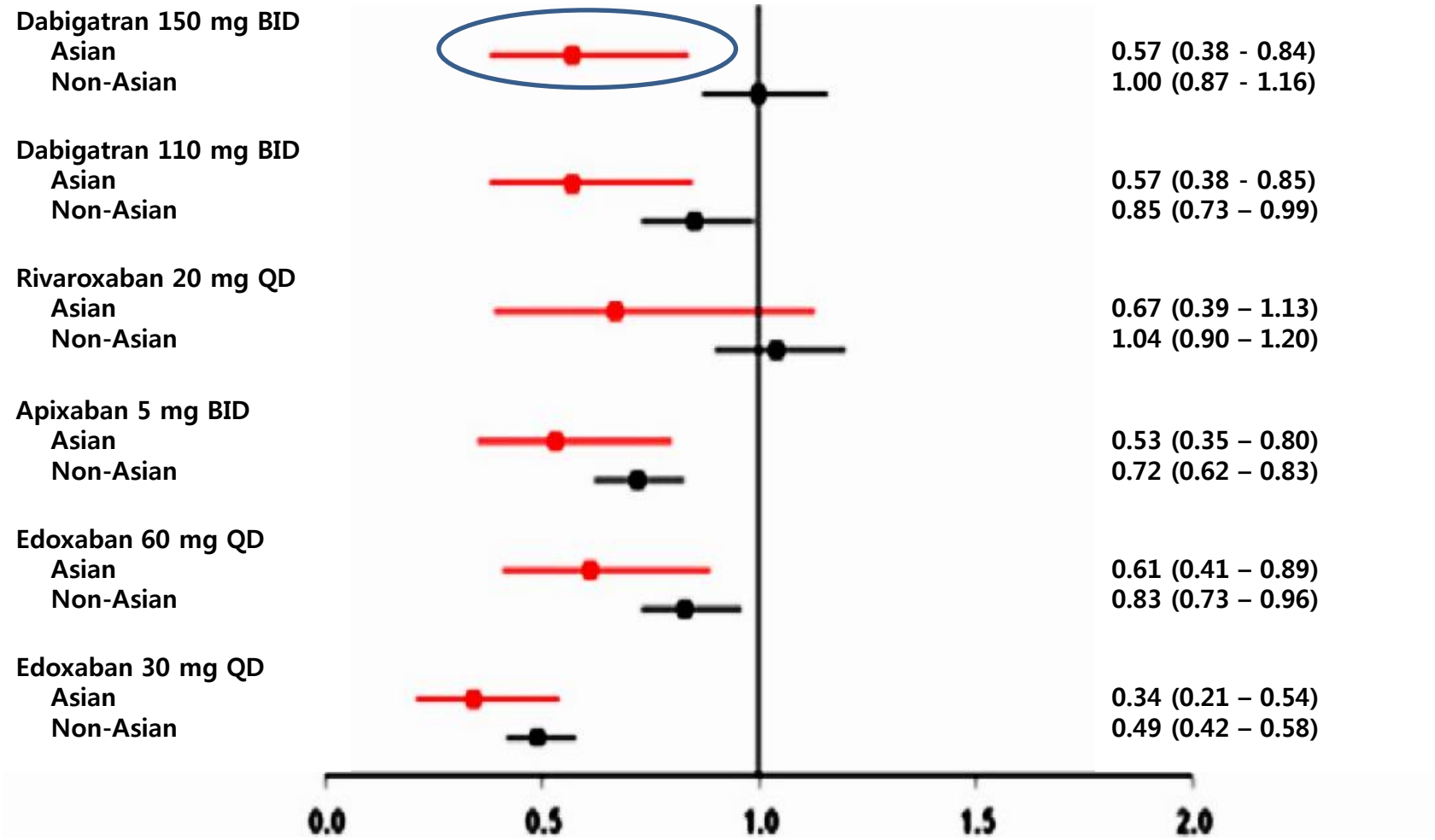
# NOACs in Asians: Stroke/SEEs






International Journal of Cardiology 180 (2015) 246–254

# NOACs in Asians: Major bleeding






International Journal of Cardiology 180 (2015) 246–254

# Case 77/M, AF

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**

- **What NOAC?**

1. Dabigatran 110 mg bid
2. Dabigatran 150 mg bid
3. Rivaroxaban 20 mg qd
4. Apixaban 5 mg bid
5. Edoxaban 30 mg qd
6. Edoxaban 60 mg qd

# 2015 EHRA PRACTICAL GUIDE

## Choosing the type and dose of non-vitamin K antagonist oral anticoagulant

- **NOAC availability**
  - (cost, formulary committee)
- **Co-medications**
  - (drug interactions, pharmacokinetics)
- **Age**
- **Weight**
- **Renal function**
- **Comorbidities**

# 2015 EHRA PRACTICAL GUIDE

## Choosing the type and dose of non-vitamin K antagonist oral anticoagulant

- **NOAC availability** → **Available**
  - (cost, formulary committee)
- **Co-medications** → **Diabetes med**
  - (drug interactions, pharmacokinetics)
- **Age** → **77 yo**
- **Weight** → **53 Kg**
- **Renal function** → **Cr 1.1, GFR 42.16 ml/min**
- **Comorbidities** → **recent stroke**

| | via | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| **Antiarrhythmic drugs:** | | | | | |
| Amiodarone | moderate P-gp competition | +12-60%[58] | No PK data[$] | +40%[63, 64, 244] | Minor effect[$] (use with caution if CrCl <50 ml/min) |
| Digoxin | P-gp competition | No effect[245] | No data yet | No effect | No effect[246, 247] |
| Diltiazem | P-gp competition and weak CYP3A4 inhibition | No effect[58] | +40%[60] | No data yet | Minor effect[#] (use with caution if CrCl 15-50 ml/min) |
| Dronedarone | P-gp competition and CYP3A4 inhibition | +70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min) | No PK or PD data: caution | +85% (Reduce NOAC dose by 50%) | Moderate effect[#] but no PK or PD data: caution and try to avoid |
| Quinidine | P-gp competition | +53%[248 & SMPC] | No data yet | +77%[240, 249, 250] (No dose reduction required by label) | Extent of increase unknown |
| Verapamil | P-gp competition (and weak CYP3A4 inhibition) | +12-180%[58] (reduce NOAC dose and take simultaneously) | No PK data | +53% (SR)[64, 249] (No dose reduction required by label) | Minor effect[##] (use with caution if CrCl 15-50 ml/min) |
| **Other cardiovascular drugs** | | | | | |
| Atorvastatin | P-gp competition and CYP3A4 inhibition | +18%[251] | No data yet | No effect | No effect[252] |
| **Antibiotics** | | | | | |
| Clarithromycin; Erythromycin | moderate P-gp competition and CYP3A4 inhibition | +15-20% | No data yet | +90%[64] (reduce NOAC dose by 50%) | +30-54%[42, 247] |
| Rifampicin*** | P-gp/ BCRP and CYP3A4/CYP2J 2 inducers | minus 66%[253] | minus 54%[238] | avoid if possible: minus 35%, but with compensatory increase of active metabolites[243] | Up to minus 50% |
| **Antiviral drugs** | | | | | |
| HIV protease inhibitors (e.g. ritonavir) | P-gp and BCRP competition or inducer; CYP3A4 inhibition | No data yet | Strong increase[SmPC] | No data yet | Up to +153%[247] |

| | via | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| **Fungostatics** | | | | | |
| Fluconazole | Moderate CYP3A4 inhibition | No data yet | No data yet | No data yet | +42% (if systemically administered)[247] |
| Itraconazole; Ketoconazole; Posaconazole; Voriconazole; | potent P-gp and BCRP competition; CYP3A4 inhibition | +140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min) | +100%[60] | +87-95%[64] (reduce NOAC dose by 50%) | Up to +160%[247] |
| **Immunosuppressive** | | | | | |
| Cyclosporin; Tacrolimus | P-gp competition | Not recommended | No data yet | +73% | Extent of increase unknown |
| **Antiphlogistics** | | | | | |
| Naproxen | P-gp competition | No data yet | +55%[254] | No effect (but pharmacodynamically increased bleeding time) | No data yet |
| **Antacids** | | | | | |
| H2B; PPI; Al-Mg-hydroxide | GI absorption | Minus 12-30%[45, 53, 58] | No effect[55] | No effect | No effect[241, 242] |
| **Others** | | | | | |
| Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort*** | P-gp/ BCRP and CYP3A4/CYP2J 2 inducers | minus 66%[253] | minus 54%[SmPC] | minus 35% | Up to minus 50% |
| **Other factors:** | | | | | |
| Age ≥ 80 years | Increased plasma level | | # | % | |
| Age ≥75 years | Increased plasma level | | | % | |
| Weight ≤ 60 kg | Increased plasma level | | # | | |
| Renal function | Increased plasma level | See Table 8 | | | |
| Other increased bleeding risk | | Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery (esp. GI or organ biopsy); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3 | | | |

# NOAC Dose Reduction in Studies: Age, Weight

| RE-LY[1] | ROCKET-AF[2] | ARISTOTLE[3] | ENGAGE-AF[4] |
|---|---|---|---|
| • None<br>• But<br>• 150 << 110 mg BID for:<br>– Creatinine clearance <30–49 mL/min<br>• 110 mg BID<br>– Age ≥80 years | • 20→15 mg QD for:<br>– Creatinine clearance <30–49 mL/min | • 5→2.5 mg BID for ANY TWO of:<br>– Age ≥80 years<br>– body weight ≤60 kg<br>– Serum creatinine ≥1.5 mg/dL | • 60→30 mg QD or 30→15 mg QD for:<br>– Creatinine clearance 30–50 mL/min<br>– body weight ≤60 kg<br>– Use of quinidine, verapamil or dronedarone |

1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907

# PK of NOACs

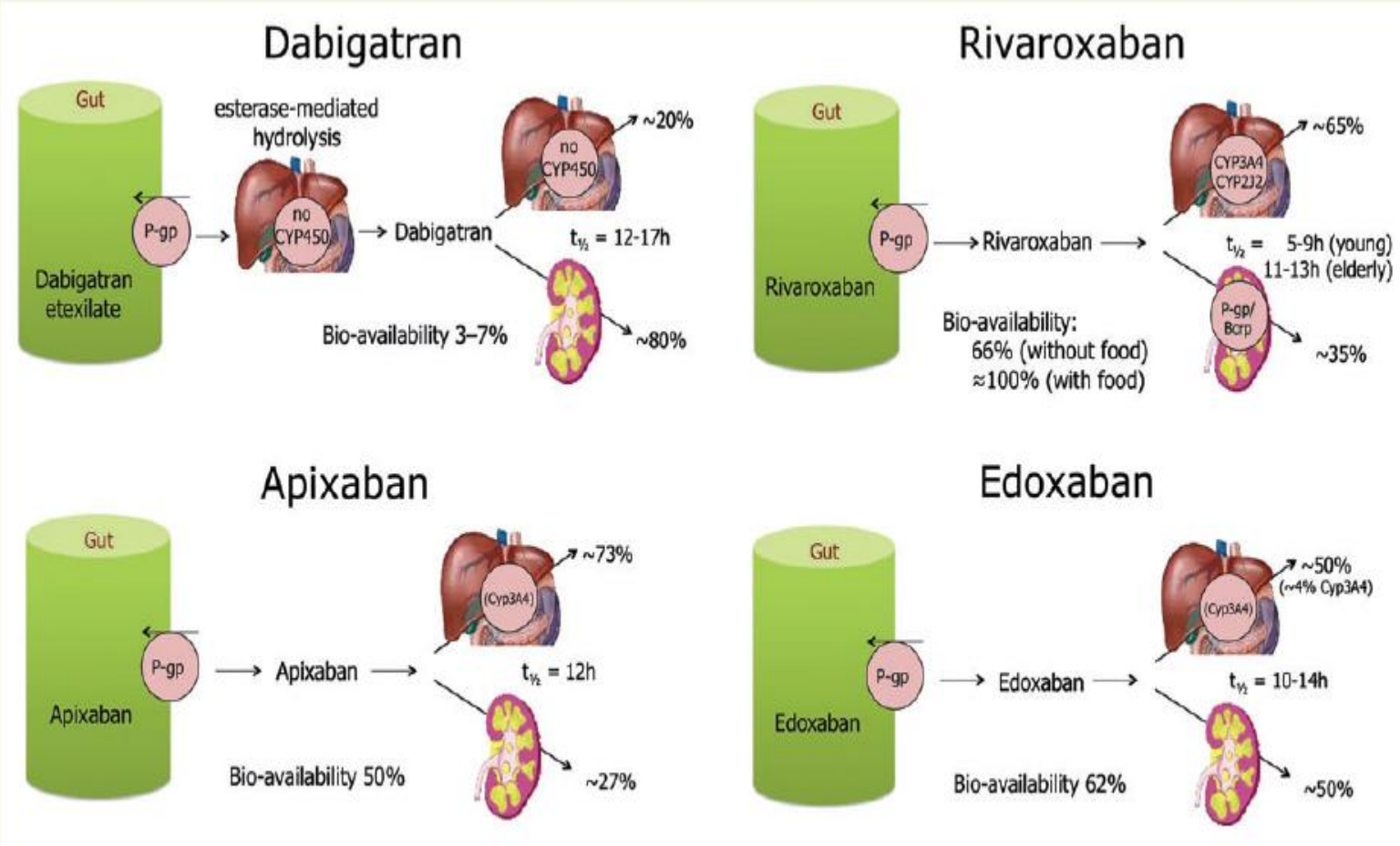



**Figure 3** Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

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# European labels for NOACs and dosing in CKD

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Fraction renally excreted of absorbed dose | 80% | 27%[52–55] | 50%[36] | 35% |
| Bioavailability | 3–7% | 50% | 62%[51] | 66% without food<br>Almost 100% with food |
| Fraction renally excreted of administered dose | 4% | 12–29%[52–55] | 37%[36] | 33% |
| Approved for CrCl ≥ … | ≥30 mL/min | ≥15 mL/min | ≥15 mL/min | ≥15 mL/min |
| Dosing recommendation | CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID) | Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a] | CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b] | CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD) |
| Dosing if CKD | When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5]<br>Note: 75 mg BID approved in US only[c]:<br>if CrCl 15–30 mL/min<br>if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil) | CrCl 15–29 mL/min: 2.5 mg BID<br>If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID | 30 mg OD when CrCl 15–49 mL/min | 15 mg OD when CrCl 15–49 mL/min |
| Not recommended if | CrCl < 30 mL/min | CrCl < 15 mL/min | CrCl < 15 mL/min | CrCl < 15 mL/min |

**Red:** contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

**EHRA PRACTICAL GUIDE 2015**

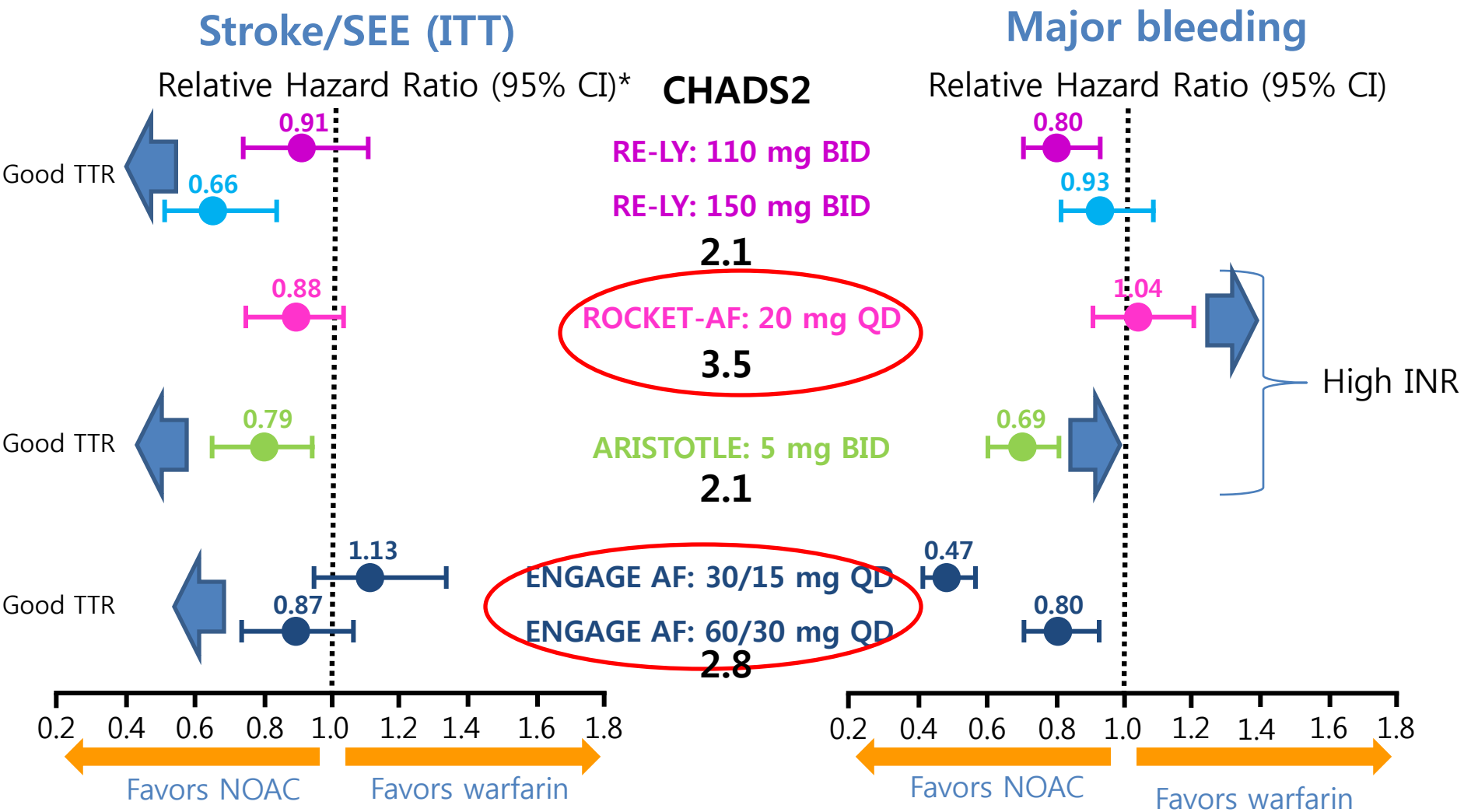
# Case 77/M, AF

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**

- **So, What ?**

1. Dabigatran 110 mg bid
2. Dabigatran 150 mg bid
3. Rivaroxaban 20 mg qd
4. Apixaban 5 mg bid
5. Edoxaban 30 mg qd
6. Edoxaban 60 mg qd

# Efficacy and Safety

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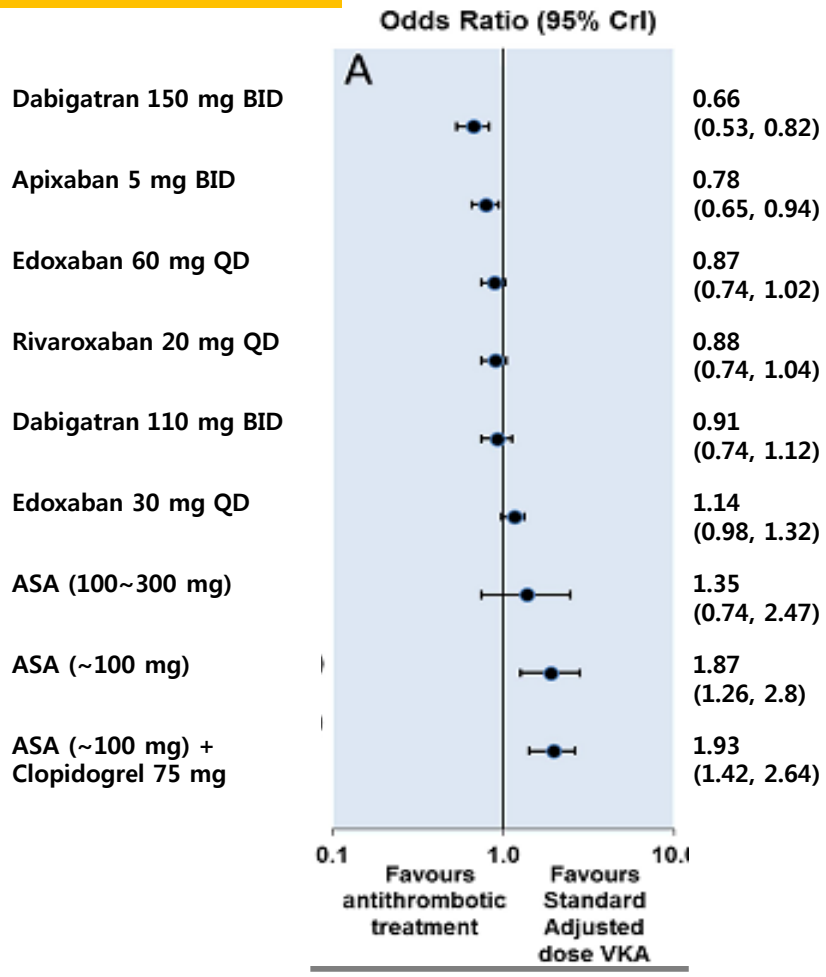
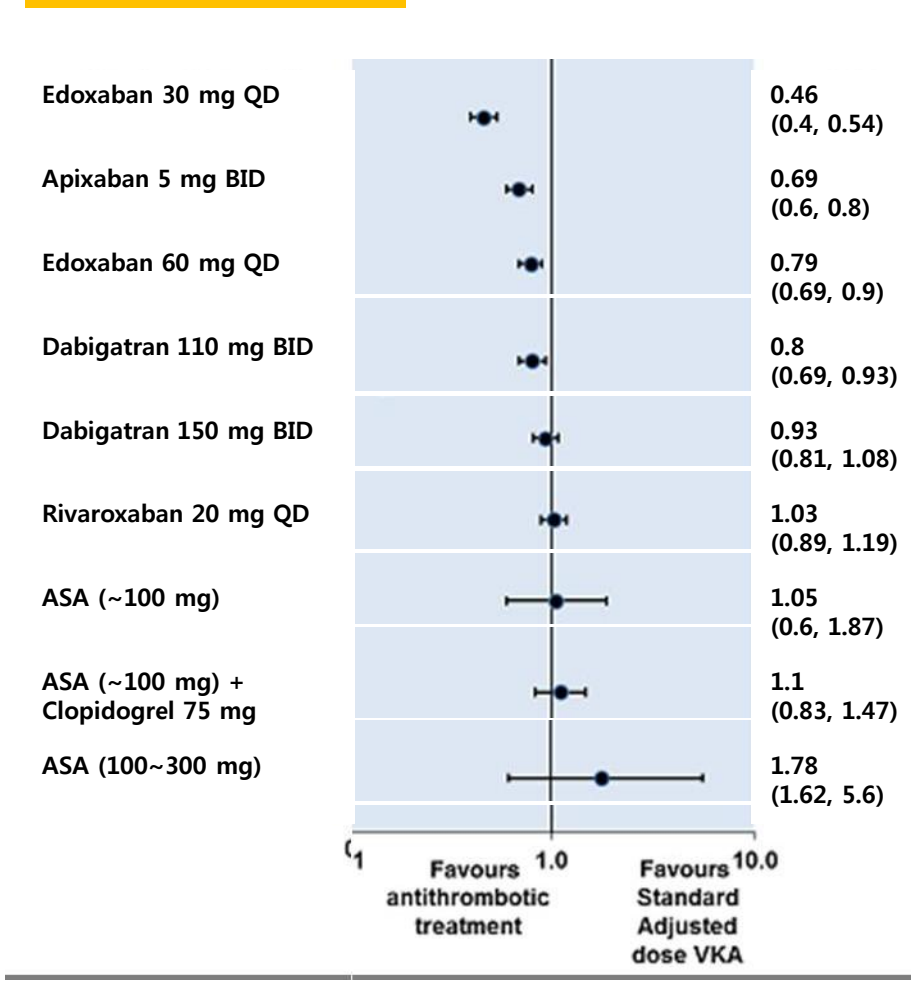
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907 5. Grip et al. Hot Topics Cardiol 2013;8:1–18

# NOACs in network meta-analysis

## Stroke or SEE




## Major bleeding






*Adapted from BMJ Open* 2014;**4**:e004301 doi:10.1136/bmjopen-2013-004301

# Comparisons in network meta-analysis

| Standard Adjusted-Dose VKA | 0.93 (0.81,1.08) | 0.69 (0.6,0.8) | 0.79 (0.69,0.9) | 1.03 (0.89,1.19) | 0.8 (0.69,0.93) | 0.46 (0.4,0.54) | 1.78 (0.62,5.6) | 1.05 (0.6,1.87) | 1.1 (0.83,1.47) |
|---|---|---|---|---|---|---|---|---|---|
| 0.66 (0.53,0.82) | Dabigatran 150 mg twice daily | **0.74 (0.6,0.91)** | 0.84 (0.69,1.03) | 1.1 (0.9,1.35) | 0.86 (0.74,1.003) | **0.5 (0.4,0.61)** | 1.91 (0.66,6.08) | 1.13 (0.63,2.04) | 1.18 (0.85,1.63) |
| 0.78 (0.65,0.94) | 1.19 (0.89,1.58) | Apixaban 5 mg twice daily | 1.14 (0.93,1.38) | **1.49 (1.21,1.82)** | 1.16 (0.94,1.43) | **0.67 (0.54,0.83)** | 2.57 (0.89,8.18) | 1.52 (0.85,2.75) | **1.59 (1.16,2.2)** |
| 0.87 (0.74,1.02) | **1.31 (1.002,1.73)** | 1.11 (0.87,1.41) | Edoxaban 60 mg daily | **1.31 (1.08,1.59)** | 1.02 (0.83,1.25) | **0.59 (0.5,0.69)** | 2.27 (0.78,7.17) | 1.34 (0.75,2.41) | **1.4 (1.02,1.92)** |
| 0.88 (0.74,1.04) | **1.33 (1.01,1.76)** | 1.12 (0.87,1.43) | 1.01 (0.8,1.28) | Rivaroxaban 20 mg daily | **0.78 (0.63,0.96)** | **0.45 (0.37,0.56)** | 1.74 (0.6,5.48) | 1.02 (0.57,1.85) | 1.07 (0.78,1.48) |
| 0.91 (0.74,1.12) | **1.38 (1.11,1.74)** | 1.17 (0.88,1.53) | 1.05 (0.81,1.37) | 1.04 (0.8,1.36) | Dabigatran 110 mg twice daily | **0.58 (0.47,0.72)** | 2.22 (0.77,7.03) | 1.31 (0.73,2.37) | 1.37 (0.99,1.9) |
| 1.14 (0.98,1.32) | **1.73 (1.32,2.26)** | **1.45 (1.15,1.84)** | **1.31 (1.13,1.54)** | **1.3 (1.04,1.63)** | 1.25 (0.97,1.61) | Edoxaban 30 mg daily | **3.85 (1.32,12.18)** | **2.27 (1.26,4.1)** | **2.38 (1.72,3.3)** |
| 1.35 (0.74,2.47) | **2.04 (1.08,3.9)** | 1.72 (0.92,3.24) | 1.56 (0.84,2.91) | 1.54 (0.83,2.88) | 1.48 (0.79,2.8) | 1.18 (0.64,2.21) | Medium Dose ASA (> 100 mg and ≤ 300 mg daily) | 0.59 (0.17,1.94) | 0.62 (0.19,1.84) |
| **1.87 (1.26,2.8)** | **2.84 (1.81,4.5)** | **2.39 (1.55,3.72)** | **2.16 (1.42,3.34)** | **2.14 (1.4,3.31)** | **2.05 (1.32,3.23)** | **1.64 (1.08,2.53)** | 1.39 (0.74,2.61) | Low Dose ASA (≤ 100 mg daily) | 1.05 (0.55,1.97) |
| **1.93 (1.42,2.64)** | **2.93 (2.01,4.3)** | **2.46 (1.73,3.54)** | **2.23 (1.58,3.17)** | **2.2 (1.55,3.14)** | **2.11 (1.46,3.07)** | **1.69 (1.21,2.4)** | 1.43 (0.73,2.81) | 1.03 (0.62,1.7) | Low dose ASA (≤ 100 mg daily) & Clopidogrel 75 mg daily |



*BMJ Open* 2014;**4**:e004301 doi:10.1136/bmjopen-2013-004301

( <1: Favor Rt, <1: Favor lower )

# Preferred NOACs

| Clinical situation | First choice | Second choice | Avoid |
|---|---|---|---|
| High thromboembolic and low bleeding risk | Dabigatran 150 mg | Apixaban, edoxaban 60 mg, rivaroxaban, dabigatran 110 mg | Edoxaban 30 mg |
| Low thromboembolic and high bleeding risk | Edoxaban 30 mg<br>Apixaban | Edoxaban 60 mg<br>Dabigatran 110 mg | Dabigatran 150 mg<br>Rivaroxaban |
| Moderate thromboembolic and bleeding risk | Apixaban<br>Edoxaban 60 mg<br>Dabigatran 110 mg | Rivaroxaban<br>Dabigatran 150 mg | Edoxaban 30 mg |
| High thromboembolic and bleeding risk | Apixaban | Rivaroxaban<br>Edoxaban 60 mg<br>Dabigatran 150 mg | Edoxaban 30 mg |
| Compliance concerns | Edoxaban 60 mg<br>Rivaroxaban[a] | Edoxaban 30 mg | Dabigatran or apixaban |
| Moderate renal dysfunction[b] | Apixaban | Rivaroxaban<br>Dabigatran 110 mg<br>Edoxaban 60 or 30 mg | Dabigatran 150 mg |



Ann Hematol (2016) 95:437–449

# Case 77/M, AF

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**

- **So, What ?**

1. **Dabigatran 110 mg bid**
2. **Dabigatran 150 mg bid**
3. Rivaroxaban 20 mg qd
4. Apixaban 5 mg bid
5. Edoxaban 30 mg qd
6. Edoxaban 60 mg qd

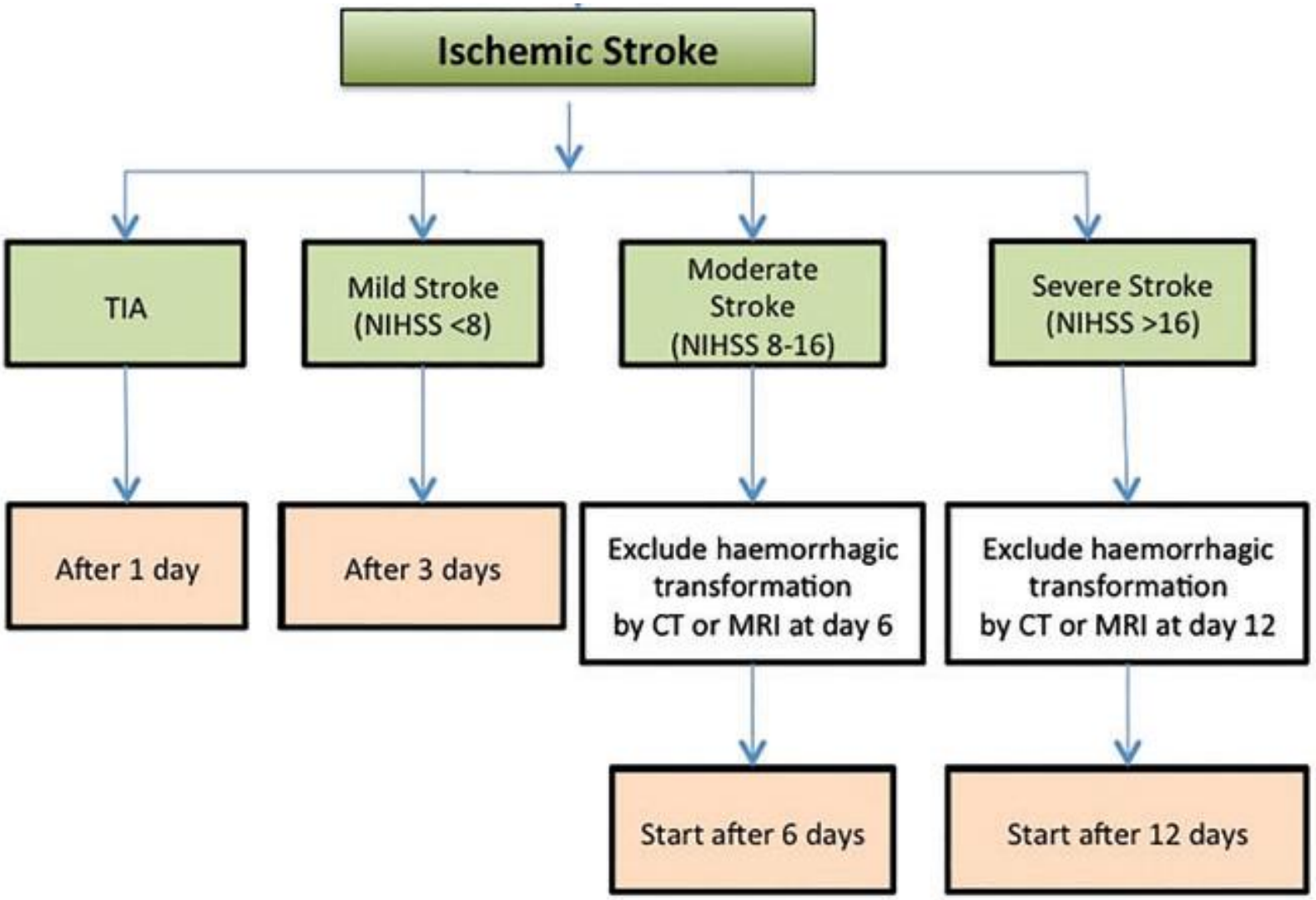
# Case 77/M, AF

- $CHA_2DS_2$-VASc = 6 (Embolic infarction)
- HAS-BLED = 2

- **When to start the NOAC?**

1. After 1 day
2. After 3 days
3. After 6 days
4. After 12 days
5. After 2 months

# When to start the NOAC in ischemic stroke




EHRA PRACTICAL GUIDE 2015

# Case 77/M, AF

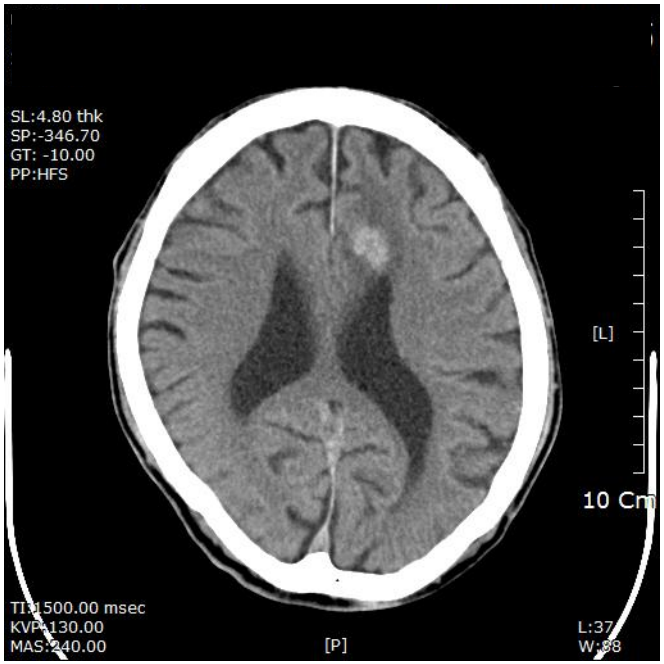
- $CHA_2DS_2$-VASc = 6 (Embolic infarction)
- HAS-BLED = 2

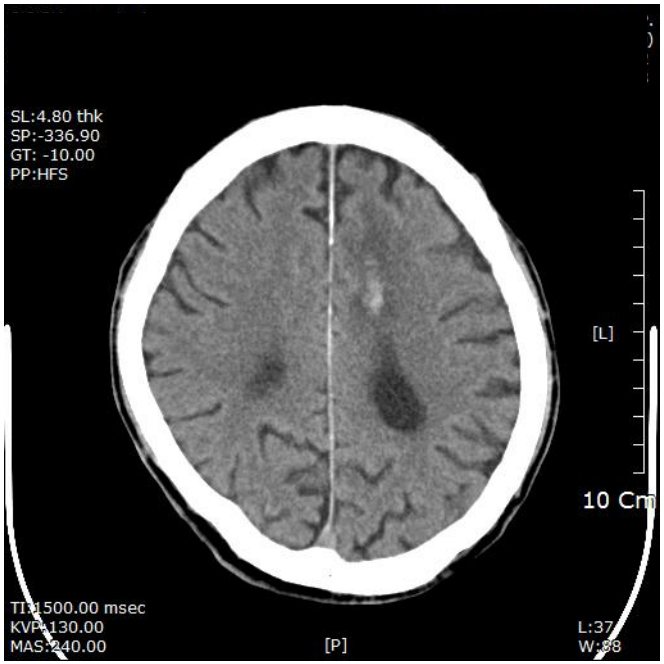
- When to start the NOAC?

1. After 1 day
2. After 3 days
3. After 6 days
4. After 12 days
5. After 2 months

# Case 77/M, AF, one month later

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**
- **Dabigatran 150 mg bid**
- **C/C Drowsy mental state**



# Case 77/M, AF, one month later

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 2**
- **Dabigatran 150 mg bid**
- **C/C Drowsy mental state,**

- **BP 160 / 75mmHg PR bpm, RR 20/min BT 36.9℃**
- **CBC 6100/12.5/235k**
- **PT INR 1.28, aPTT 53.2 (23-39)**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• Or Even Death
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SUBSTANTIAL COMPENSATION!
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Attorney
Bob Goldwater
1-800-781-6060
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# How to measure the effect of NOACs?

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Plasma peak level | 2 h after ingestion | 1–4 h after ingestion | 1–2 h after ingestion | 2–4 h after ingestion |
| Plasma trough level | 12 h after ingestion | 12 h after ingestion | 24 h after ingestion[36] | 24 h after ingestion |
| PT | Cannot be used | Can be prolonged but no known relation with bleeding risk[37] | Prolonged but variable and no known relation with bleeding risk[36,38]<br>Range at trough: NA | Prolonged but no known relation with bleeding risk<br>Range at trough: 12–26 s with Neoplastin Plus as reagent; local calibration required |
| INR | Cannot be used | Cannot be used | Cannot be used | Cannot be used |
| aPTT | Range (P10–P90) at trough D150: 40.3–76.4 s<br>Range (P10–P90) at trough D110: 37.5–60.9 s<br>At trough: >2× ULN may be associated with excess bleeding risk[39] | Cannot be used | Prolonged but no known relation with bleeding risk[36] | Cannot be used |
| dTT | No data from RE-LY trial on range of values<br>At trough: >200 ng/mL ≥65 s: may be associated with excess bleeding risk[39,40] | Cannot be used | Cannot be used[41] | Cannot be used |
| Anti-FXa chromogenic assays | Not applicable | Quantitative; no data on threshold values for bleeding or thrombosis<br>Range at trough: 1.4–4.8 IU/mL | Quantitative[41]; no data on threshold values for bleeding or thrombosis<br>Range at trough: 0.05–3.57 IU/mL[a] | Quantitative; no data on threshold values for bleeding or thrombosis<br>Range at trough: 6–239 μg/L |
| ECT | Range (P10–P90) at trough D150: 44.3–103<br>Range (P10–P90) at trough D110: 40.4–84.6<br>At trough: ≥3× ULN: excess bleeding risk[39] | Not affected[37] | Not affected | Not affected |
| ACT | Rather flat dose response. No investigation on its use.<br>Limited utility | No data.<br>Cannot be used | No data.<br>Cannot be used | Minor effect. Cannot be used |

Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.
PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; INR, international normalized ratio; ACT: activated clotting time; ULN, upper limit of normal.
[a](P2.5–P97.5) for edoxaban.

# Effects of NOACs on tests

**PT INR 1.28, aPTT 53.2 (23-39)**

| Anticoagulation | PT | aPTT | TT | ECT | Anti-Xa |
|---|---|---|---|---|---|
| Dabigatran | ↑ or ↔ | ↑ | ↑ | ↑ | NA |
| Rivaroxaban | ↑ or ↔ | ↑ or ↔ | NA | NA | ↑ |
| Apixaban | ↑ or ↔ | ↑ or ↔ | NA | NA | ↑ |
| Edoxaban | ↑ or ↔ | ↑ or ↔ | NA | NA | ↑ |

Adapted from Cuker A et al, J Thromb Thrombolysis 2015

# Thrombin Time

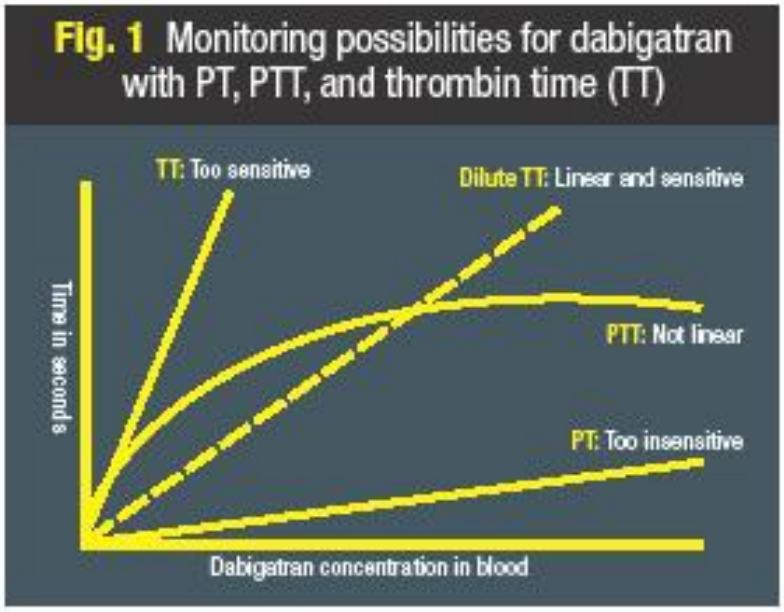
- Bypasses FII-XII
- Rate of fibrinogen conversion to fibrin
- Procedure

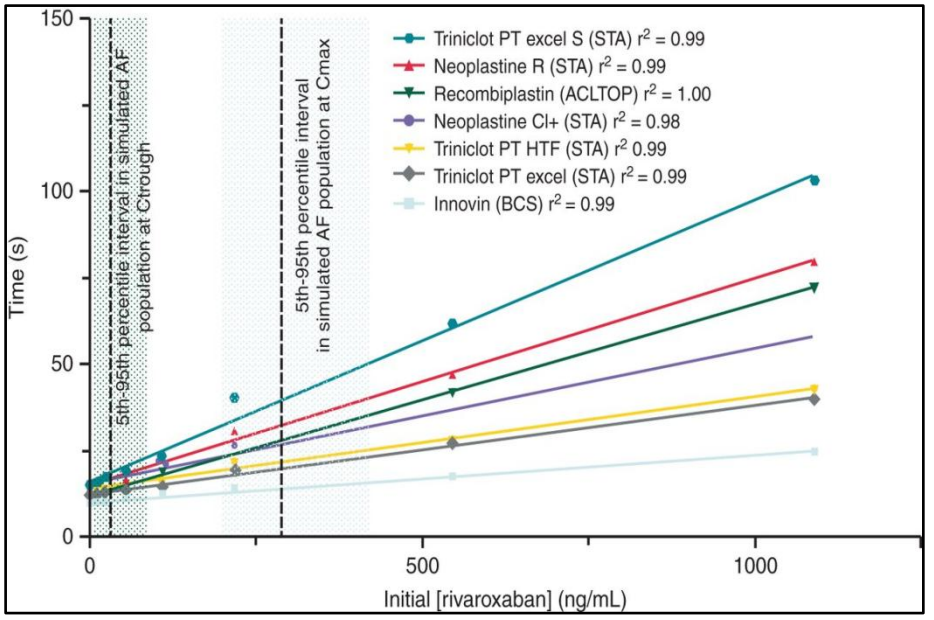
  thrombin + patient plasma

  Measure time to clot
- Variables

  sources and quantity of thrombin

# Effects of NOACs on tests




At trough: .200 ng/mL ≥65 s: may be associated with excess bleeding risk

EHRA PRACTICAL GUIDE 2015
*January 2013 issue of* CAP TODAY.

# Case 77/M, AF, one month later

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction), HAS-BLED = 2**
- **Dabigatran 150 mg bid**
- **Intracranial hemorrhage**
- **BP 160 / 75mmHg PR bpm, RR 20/min BT 36.9℃**
- **CBC 6100/12.5/235k, BUN/Cr 14.0/1.0 (GFR 46.38 ml/min)**

- **What to do first?**

1. **Discontinue medication**
2. **Estimate normalization of haemostasis**
3. **Charcoal hemoperfusion**
4. **Hemodialysis**
5. **Tranexamic acid**
6. **Idarucizumab 5 g IV**
7. **Fresh frozen plasma**
8. **Vitamin K IV**

# Estimation of normalized hemostasis

| Direct thrombin inhibitors (dabigatran) | FXa inhibitors (apixaban, edoxaban, and rivaroxaban) |
|---|---|
| Inquire last intake + dosing regimen.<br>Estimate normalization of haemostasis:<br>Normal renal function: 12–24 h<br>CrCl 50–80 mL/min: 24–36 h<br>CrCl 30–50 mL/min: 36–48 h<br>CrCl < 30 mL/min: ≥48 h | Inquire last intake + dosing regimen.<br>Normalisation of haemostasis: 12–24 h |

# Case 77/M, AF, one month later

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction), HAS-BLED = 2**
- **Dabigatran 150 mg bid**
- **Intracranial hemorrhage**
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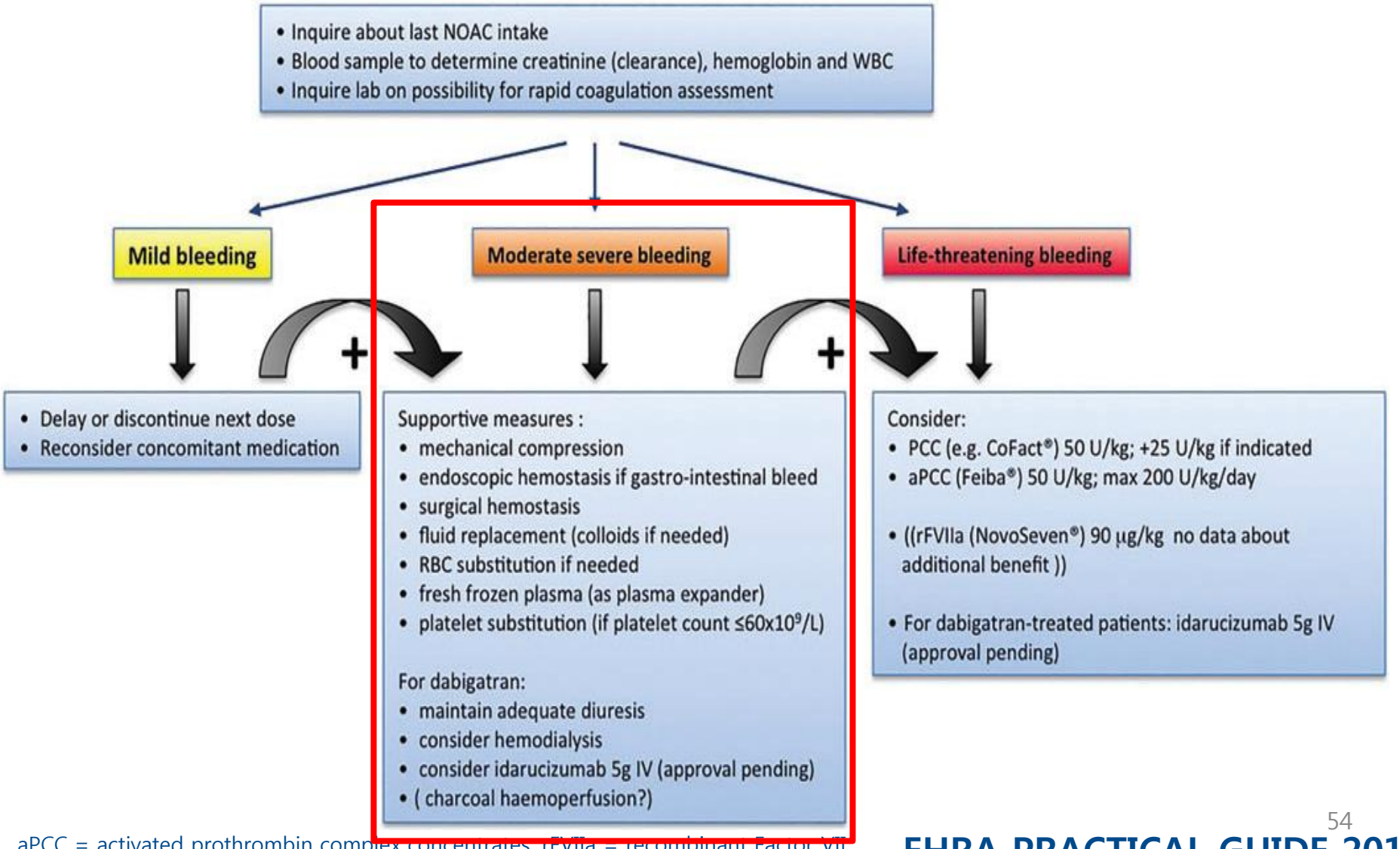
- **Dabigatran 150 mg bid**
- **Intracranial hemorrhage**
- **BP 160 / 75mmHg PR bpm, RR 20/min BT 36.9℃**
- **CBC 6100/12.5/235k**

- **What to do next?**

1. **Charcoal hemoperfusion**
2. **Hemodialysis**
3. **Tranexamic acid**
4. **Idarucizumab 5 g IV**
5. **Fresh frozen plasma**
6. **PCC (Prothrombin Complex Concentrate)**
7. **Activated PCC**
8. **Recombinant Factor VIIa (rVIIa)**

# Management of bleeding in NOACs




aPCC = activated prothrombin complex concentrates, rFVIIa = recombinant Factor VII a

# ISTH Definitions of Bleeding

**Major Bleeding in Non-Surgical Patients**[1]

1. Fatal bleeding.

2. Symptomatic bleeding in a critical area or organ, such as **intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial,** or intramuscular with **compartment syndrome**.

3. Bleeding causing a **fall in hemoglobin level of 2 g/dL** (1.24 mmol/L) or more, or leading to transfusion of **two or more units of whole blood or red cells**.

**Major Bleeding in Surgical Patients**

1. Fatal bleeding.

2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon.

3. Extrasurgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding.

4. **Surgical site bleeding that requires a second intervention** (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection.

5. Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause **hemodynamic instability**, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.

6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).

7. The population is those who have received at least one dose of the study drug.

**Table 9 Possible measures to take in case of bleeding**

| | Direct thrombin inhibitors (dabigatran) | FXa inhibitors (apixaban, edoxaban, and rivaroxaban) |
|---|---|---|
| None life-threatening bleeding | Inquire last intake + dosing regimen.<br>Estimate normalization of haemostasis:<br>Normal renal function: 12–24 h<br>CrCl 50–80 mL/min: 24–36 h<br>CrCl 30–50 mL/min: 36–48 h<br>CrCl < 30 mL/min: ≥48 h<br>Maintain diuresis. | Inquire last intake + dosing regimen.<br>Normalisation of haemostasis: 12–24 h |
| | Local haemostatic measures.<br>Fluid replacement (colloids if needed).<br>RBC substitution if necessary.<br>Platelet substitution (in case of thrombocytopenia ≤60 × $10^9$/L or thrombopathy).<br>Fresh frozen plasma as plasma expander (not as reversal agent)<br>Tranexamic acid can be considered as adjuvans.<br>Desmopressin can be considered in special cases (coagulopathy or thrombopathy) | Local haemostatic measures.<br>Fluid replacement (colloids if needed).<br>RBC substitution if necessary.<br>Platelet substitution (in case of thrombocytopenia ≤60 × $10^9$/L or thrombopathy).<br>Fresh frozen plasma as plasma expander (not as reversal agent)<br>Tranexamic acid can be considered as adjuvans.<br>Desmopressin can be considered in special cases (coagulopathy or thrombopathy) |
| | Consider dialysis (preliminary evidence: −65% after 4 h).[122]<br>Charcoal haemoperfusion can be considered (based on preclinical data) | |
| Life-threatening bleeding | All of the above.<br>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata).<br>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.<br>Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)<br>Idarucizumab 5 g IV (approval waiting) | All of the above.<br>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data)<br>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.<br>Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence) |

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.

# Nonspecific Reversal

- PCC(Prothrombin Complex Concentrate)
- Activated PCC
- Recombinant Factor VIIa (rVIIa)

# Prothrombin Concentrate Complex

- Developed for Vitamin K antagonist rapid revers al for bleeding or need for urgent surgery.
  - Ingredients:  II, VII, IX, X, Protein C&S, & Heparin
  - Dec. PT yet no effect on APPT or anti-Xa activity

- VTE Incidence 1.4%

Zahir H, Brown KS, Vandell A; 2015; Circulation.  131(1):82-90.
At highest dose 50U/kg, significant reduction of bleeding occurred after single 60 mg edoxaban dose.  Lesser dose of PCC had no meaningful effect.

# Activated PCC "Factor VIII Inhibitor"

- Designed for hemophiliacs w/hemorrhage
  - Ingredients: II, VII, IX, & X
  - Corrected abnormal thrombin generation indices

- VTE Incidence (4-8 events /10 infusions)

# Recombinant factor VIIa

- Designed for hemophiliacs w/hemorrhage
  - Ingredients: II, VII, IX, & X
  - Corrected abnormal thrombin generation indices

- VTE Incidence (4-8 events /10 infusions)

# When & How to Reverse

## Active Bleeding

- Minor/Moderate
  - Withdraw OAT
  - Consider mechanical/surgical (endovascular approach)
- Severe/Life Threatening
  - Admin nonspecific reversal agent(s)
    - PCC 50 U/kg
    - APCC 80 U/kg
  - Admin idarucizumab in dabigatran subjects

Siegal DM. J Thromb Thrombolysis 2015; 39: 395-402

## Overdose

- CRI, Overdose, Drug Interactions
  - Unclear if high levels increase bleeding risk, e.g. dose escalation trial showed no inc. bioavailability in doses above 40mg rivaroxaban or 25 mg apixaban

Kubitza D, Becka M, Roth A, et al. Curr Med Res Opin 2008; 24(10): 2757-2765.

# Management of Patient Bleeds on Dabigatran

| | Minor Bleeding | Moderate Bleeding | Major Bleeding |
|---|---|---|---|
| Testing | • CBC, INR/PTT<br>• Creatinine | • CBC, INR/PTT<br>• Creatinine<br>• Fibrinogen<br>• Type and Screen<br>• Thrombin Time | • CBC, INR/PTT<br>• Creatinine<br>• Fibrinogen<br>• Crossmatch<br>• Thrombin Time |
| Supportive Therapy | • Local therapy | • Local therapy / site control<br>• Transfusion<br>• Surgery / Intervention | • Local therapy<br>• Transfusion<br>• Surgery / Intervention<br>• Consider plt transfusion if antiplatelets agents in use |
| Drug Dosing | • Hold Dabigatran | • **Hold Dabigatran**<br>• Hold antiplatelet agents | |
| Reversal / Removal | None | • Consider **charcoal** < 2-4 hrs post dose**<br>• Consider **dialysis** | |
| Procoagulant Agents | None | • Tranexamic acid (10mg/kg IV or 25mg/kg PO)* | • Consider PCC 25-50u/kg or FIEBA 50 IU/kg<br>•If no PCC/FIEBA → tranexamic acid (10mg/kg IV)* |

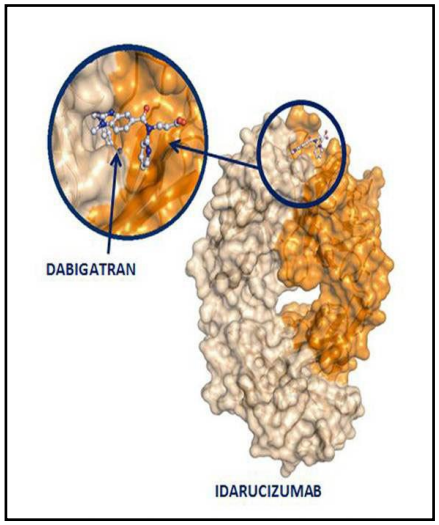
# Reversal agents

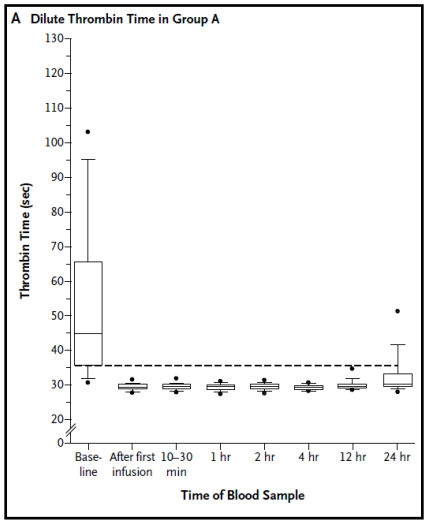
ORIGINAL ARTICLE

## Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

*N Engl J Med 2015; 373:511-520 August 6, 2015*



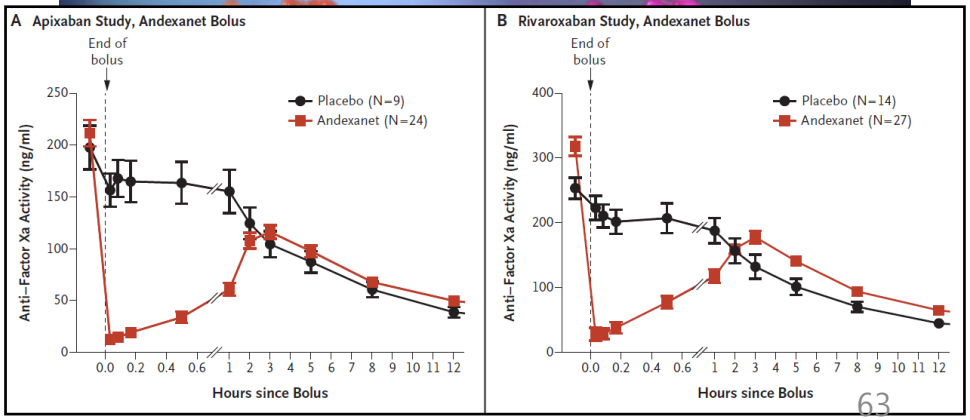




ORIGINAL ARTICLE

## Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

*November 11, 2015 DOI: 10.1056/NEJMoa1510991*

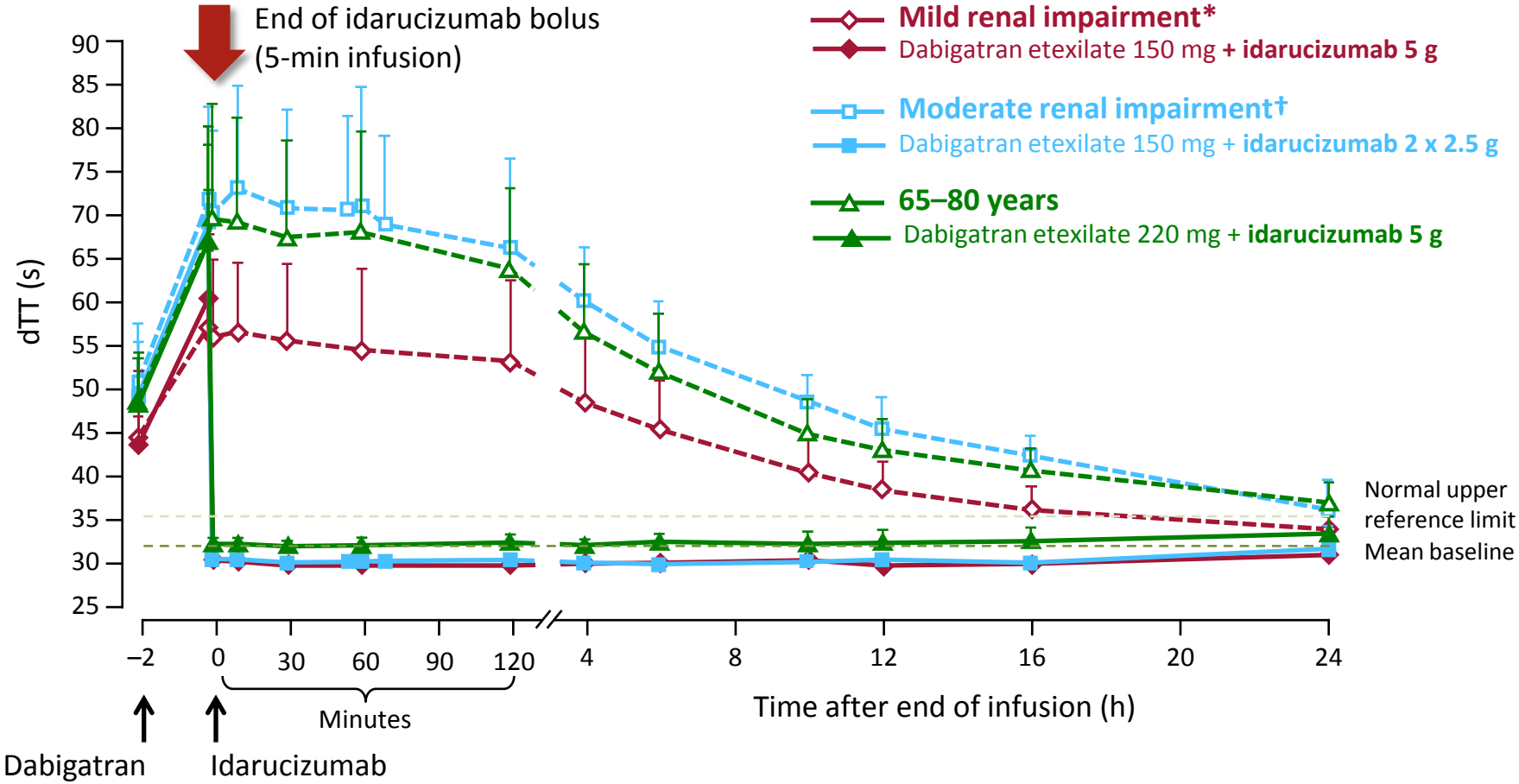



# Aripazine (PER977)

- Small synthetic water soluble molecule that **binds directly**: UFH, LMWH, lia & Xa inhibitors preventing OACs from binding to endogenous targets.
  - Single IV dose dec. bleeding rat tail to all drugs;
  - Single IV dose dec. bleeding in liver laceration model;
  - N180 healthy volunteers: 100-300 mg reversed 60 mg edoxaban dose & sustained effect for 24h

***Potential Universal Antidote***

# Idarucizumab in elderly and renal impairment



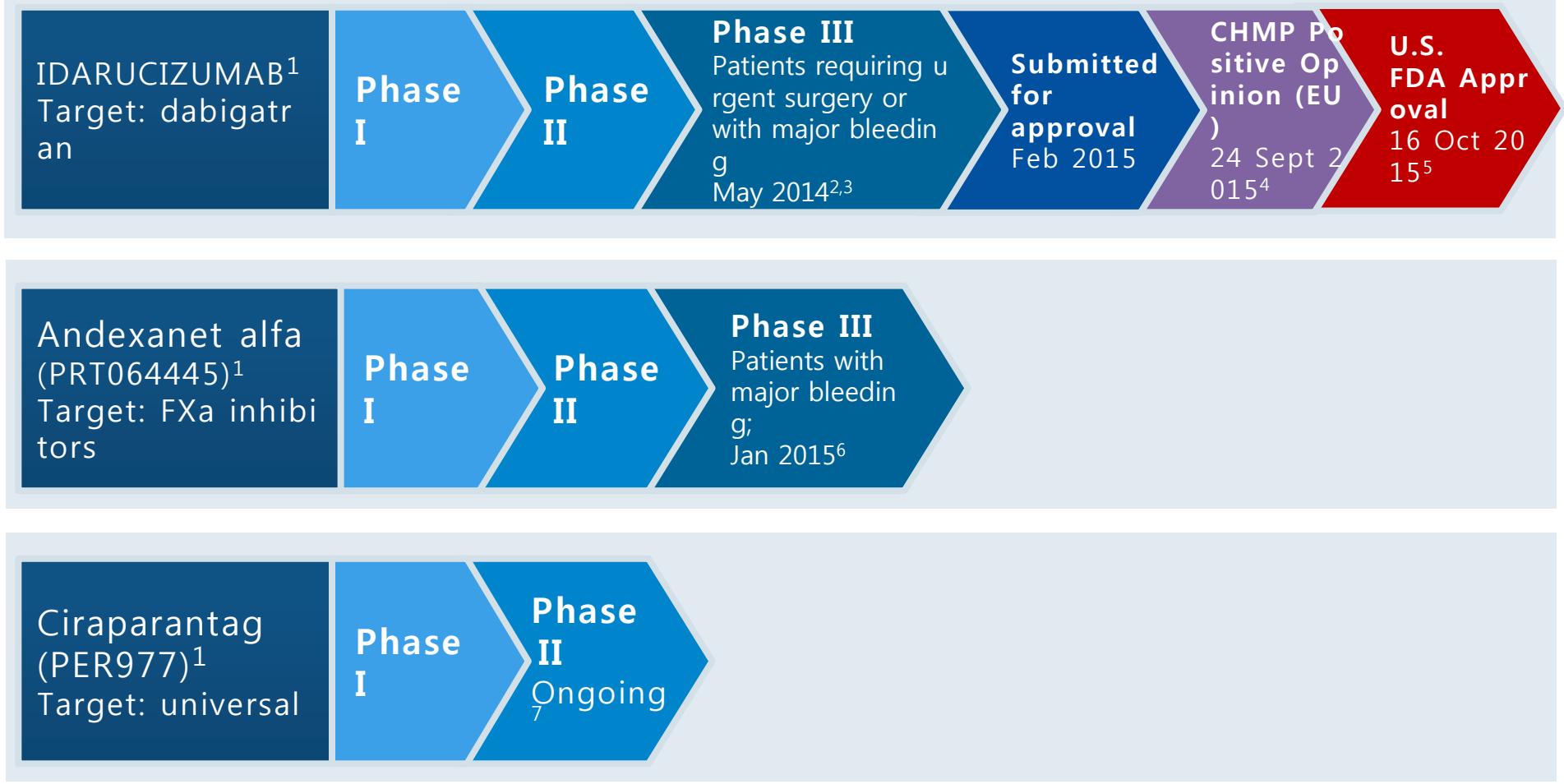

No serious drug-related AEs reported in total >200 volunteers

- **Idarucizumab is now approved in the U.S. only.**
  **The information presented here is intended for medical education purposes only.**

*CrCl ≥60–<90 mL/min; †CrCl ≥30–<60 mL/min; AE, adverse event; dTT, diluted thrombin time

1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015;113:943-51; 3. Glund S et a;/ abstr 344; presented at ASH 2014

# Studies of NOAC reversal agent




- **NOAC reversal agents are investigational compounds under development and have not been approved for use in Korea**

1. Adapted from Greinacher et al. Thromb Haemost 2015; 2. Clinicaltrials.gov: NCT02104947; 3. Pollack et al. Thromb Haemost. 2015
4. Committee for Medicinal Products for Human Use (CHMP). Minutes from 21–24 September 2015 meeting; 5. U.S. FDA press release 16 October 2015; 6. ClinicalTrials.gov Identifier: NCT02329327; 7. ClinicalTrials.gov Identifier: NCT02207257

# Case 77/M, AF, one month later

- $CHA_2DS_2$-VASc = 6 (Embolic infarction), HAS-BLED = 2
- Dabigatran 150 mg bid
- Intracranial hemorrhage
- BP 160 / 75mmHg PR bpm, RR 20/min BT 36.9℃
- CBC 6100/12.5/235k

- **What to do next?**

1. Charcoal hemoperfusion
2. Hemodialysis
3. Tranexamic acid
4. Idarucizumab 5 g IV
5. Fresh frozen plasma
6. PCC (Prothrombin Complex Concentrate)
7. Activated PCC
8. Recombinant Factor VIIa (rVIIa)

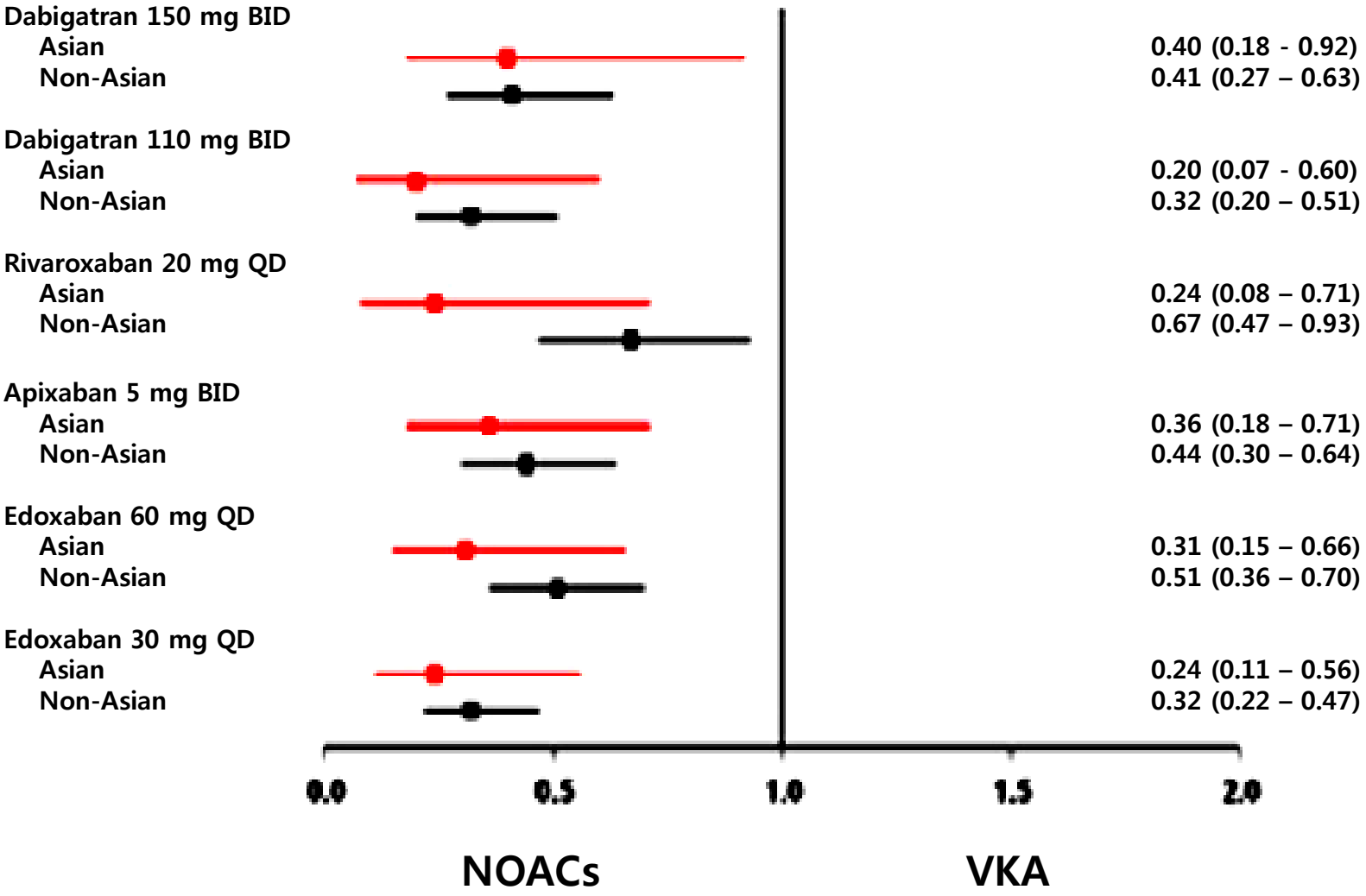
# Case 77/M, AF

- **$CHA_2DS_2$-VASc = 6 (Embolic infarction)**
- **HAS-BLED = 3 (Recent ICH)**

- **Now, What anticoagulant?**

1. Warfarin
2. ASA
3. Dabigatran 110 mg bid
4. Dabigatran 150 mg bid
5. Rivaroxaban 20 mg qd
6. Apixaban 2.5 mg bid
7. Apixaban 5 mg bid
8. Edoxaban 30 mg qd
9. Edoxaban 60 mg qd

# NOACs in Asians: ICH



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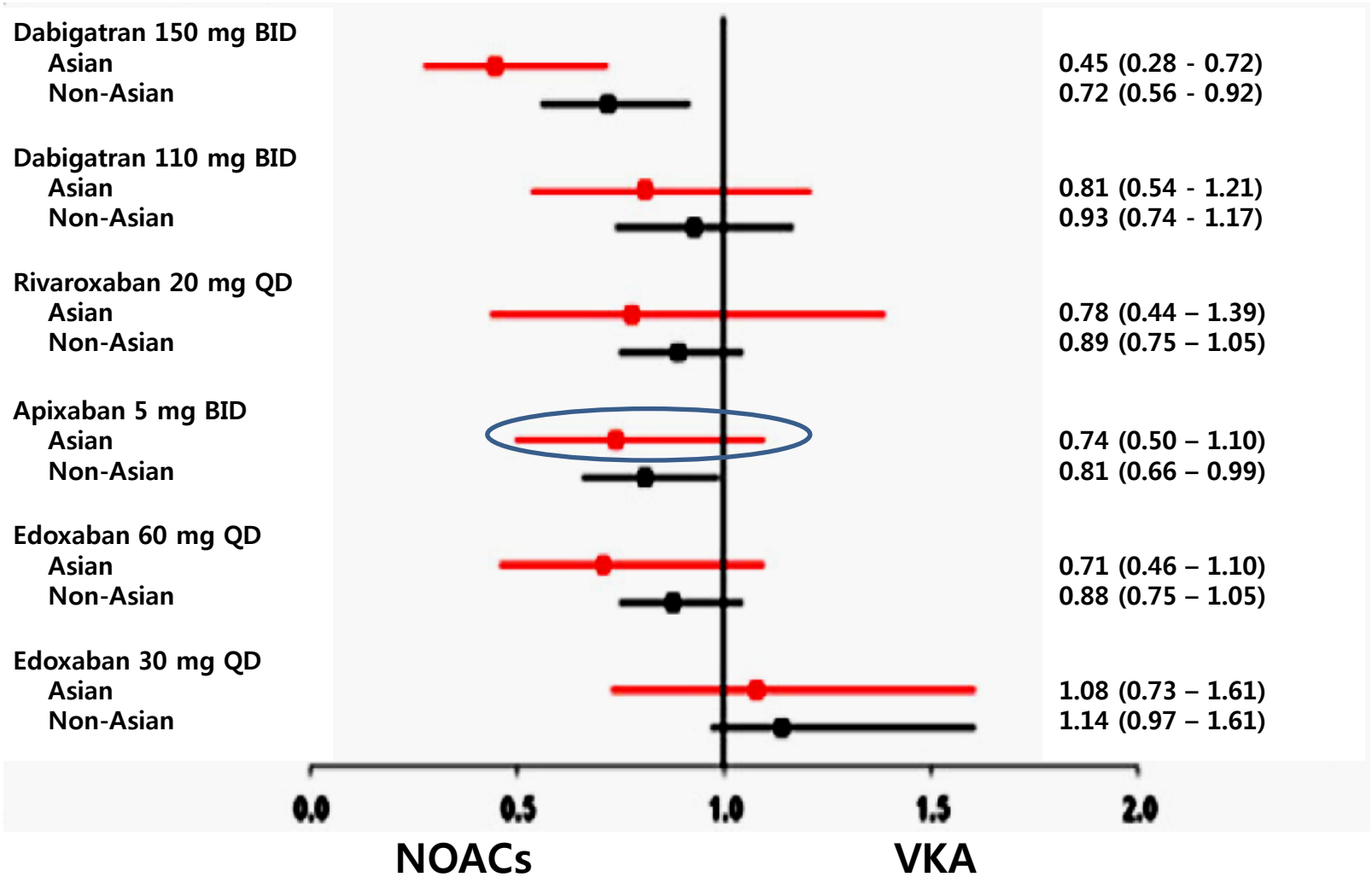
# NOACs in Asians: Stroke/SEEs



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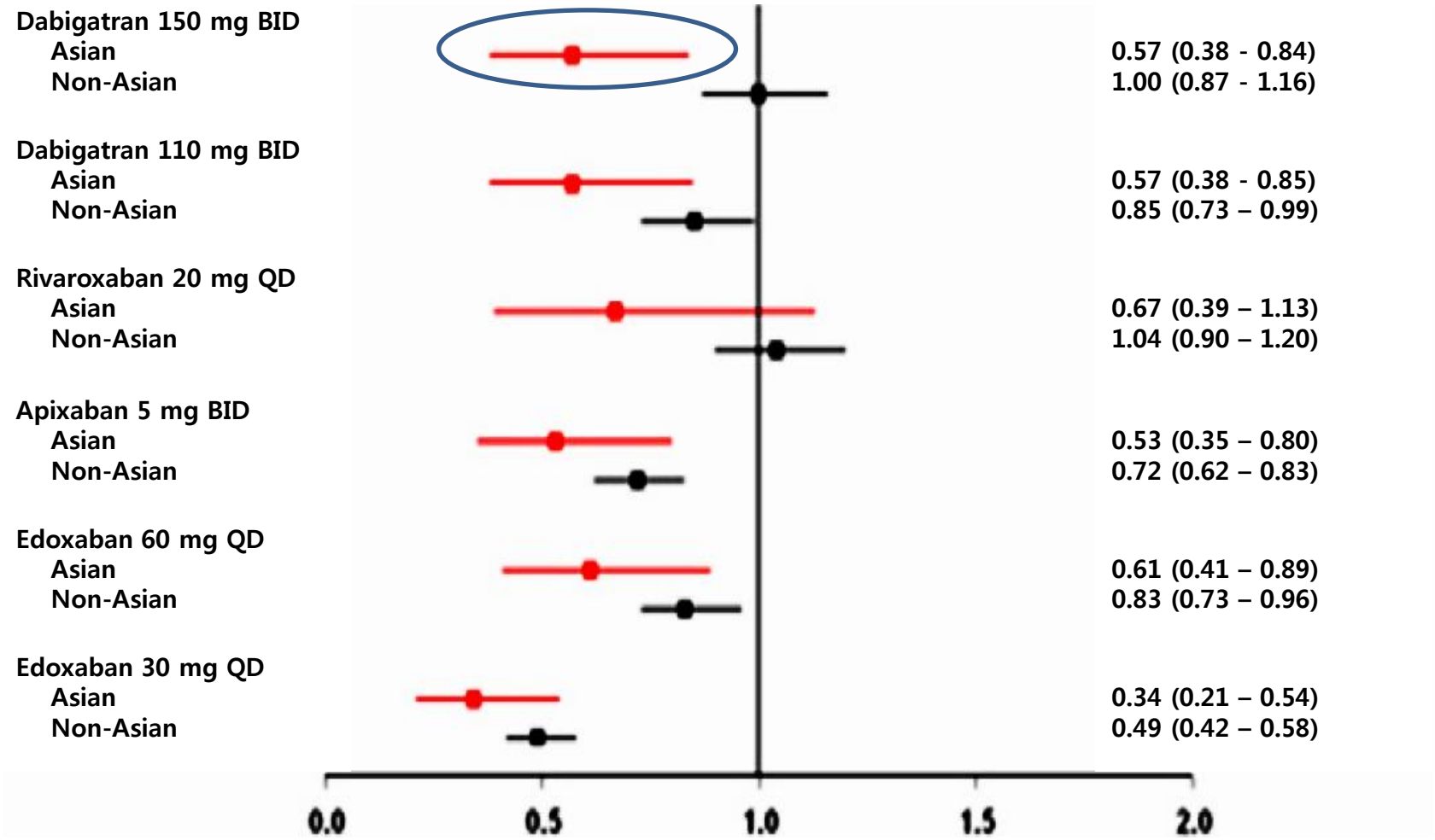
# NOACs in Asians: Major bleeding



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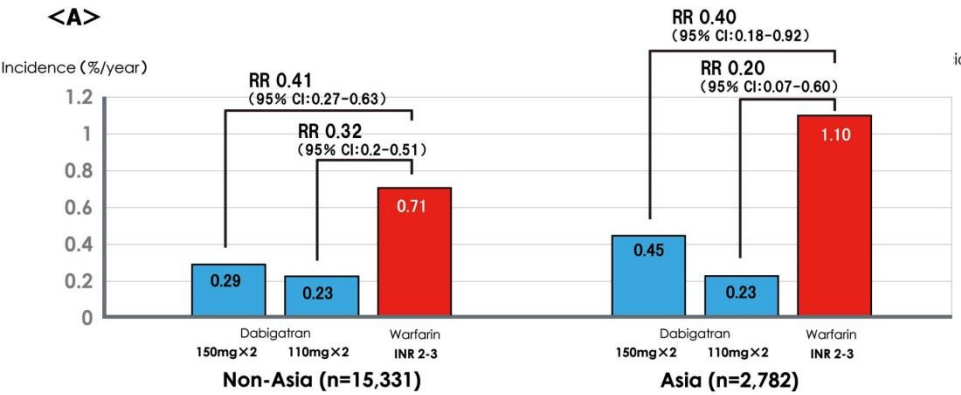
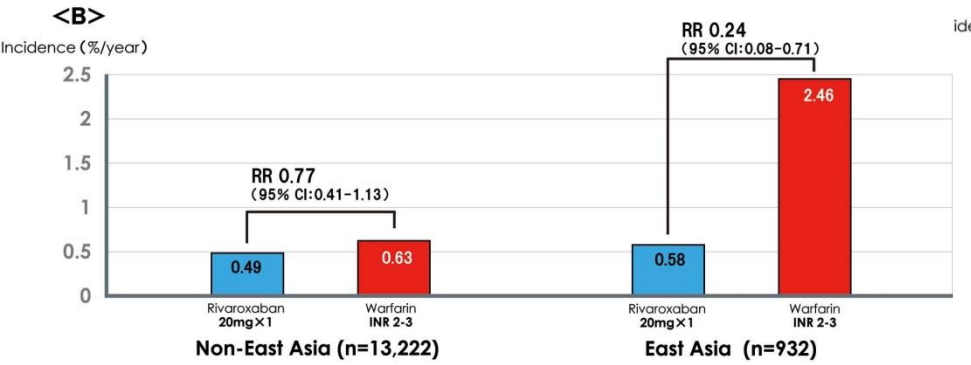
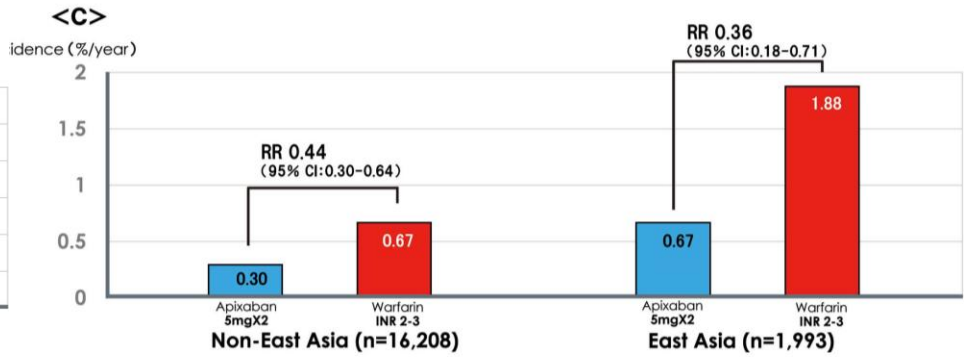
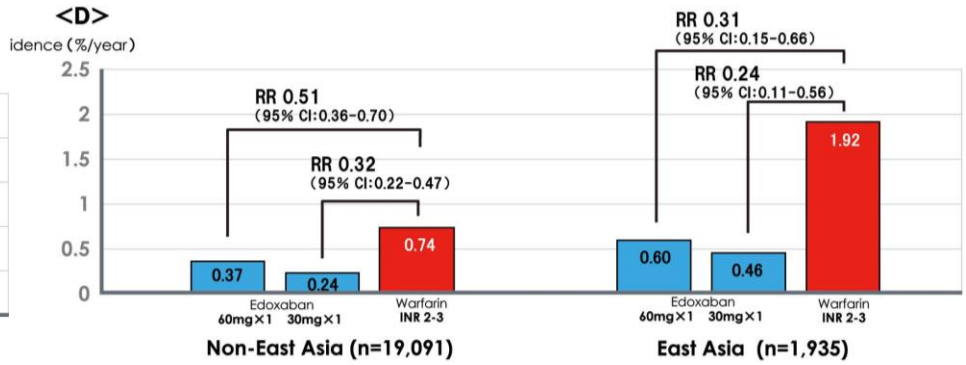
# NOACs in Asians: Major bleeding



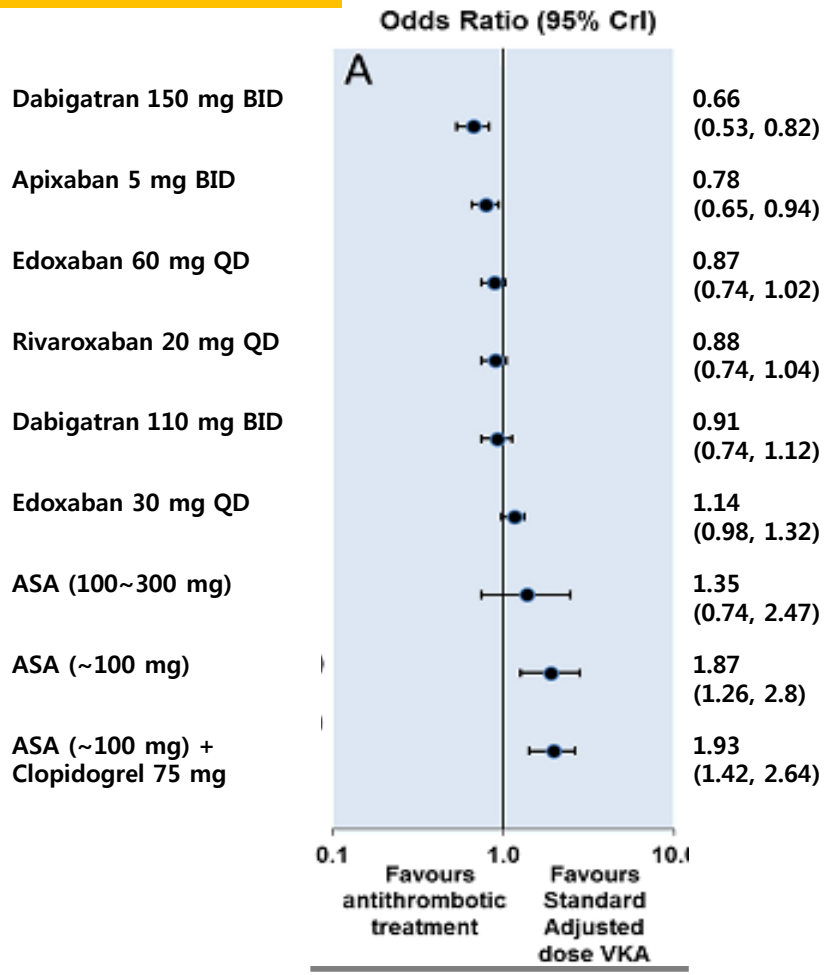



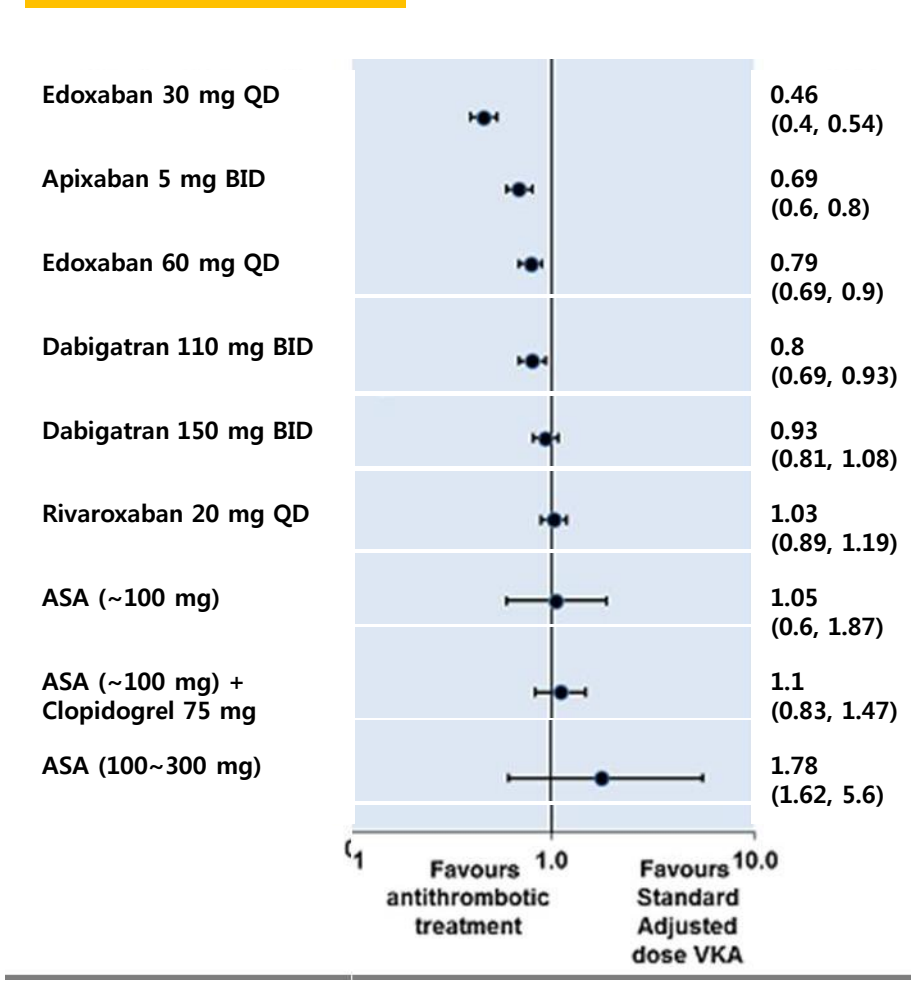



# NOACs in network meta-analysis

## Stroke or SEE




## Major bleeding






*Adapted from BMJ Open* 2014;**4**:e004301 doi:10.1136/bmjopen-2013-004301

# Preferred NOACs

| Clinical situation | First choice | Second choice | Avoid |
|---|---|---|---|
| High thromboembolic and low bleeding risk | Dabigatran 150 mg | Apixaban, edoxaban 60 mg, rivaroxaban, dabigatran 110 mg | Edoxaban 30 mg |
| Low thromboembolic and high bleeding risk | Edoxaban 30 mg<br>Apixaban | Edoxaban 60 mg<br>Dabigatran 110 mg | Dabigatran 150 mg<br>Rivaroxaban |
| Moderate thromboembolic and bleeding risk | Apixaban<br>Edoxaban 60 mg<br>Dabigatran 110 mg | Rivaroxaban<br>Dabigatran 150 mg | Edoxaban 30 mg |
| High thromboembolic and bleeding risk | Apixaban | Rivaroxaban<br>Edoxaban 60 mg<br>Dabigatran 150 mg | Edoxaban 30 mg |
| Compliance concerns | Edoxaban 60 mg<br>Rivaroxaban[a] | Edoxaban 30 mg | Dabigatran or apixaban |
| Moderate renal dysfunction[b] | Apixaban | Rivaroxaban<br>Dabigatran 110 mg<br>Edoxaban 60 or 30 mg | Dabigatran 150 mg |



Ann Hematol (2016) 95:437–449

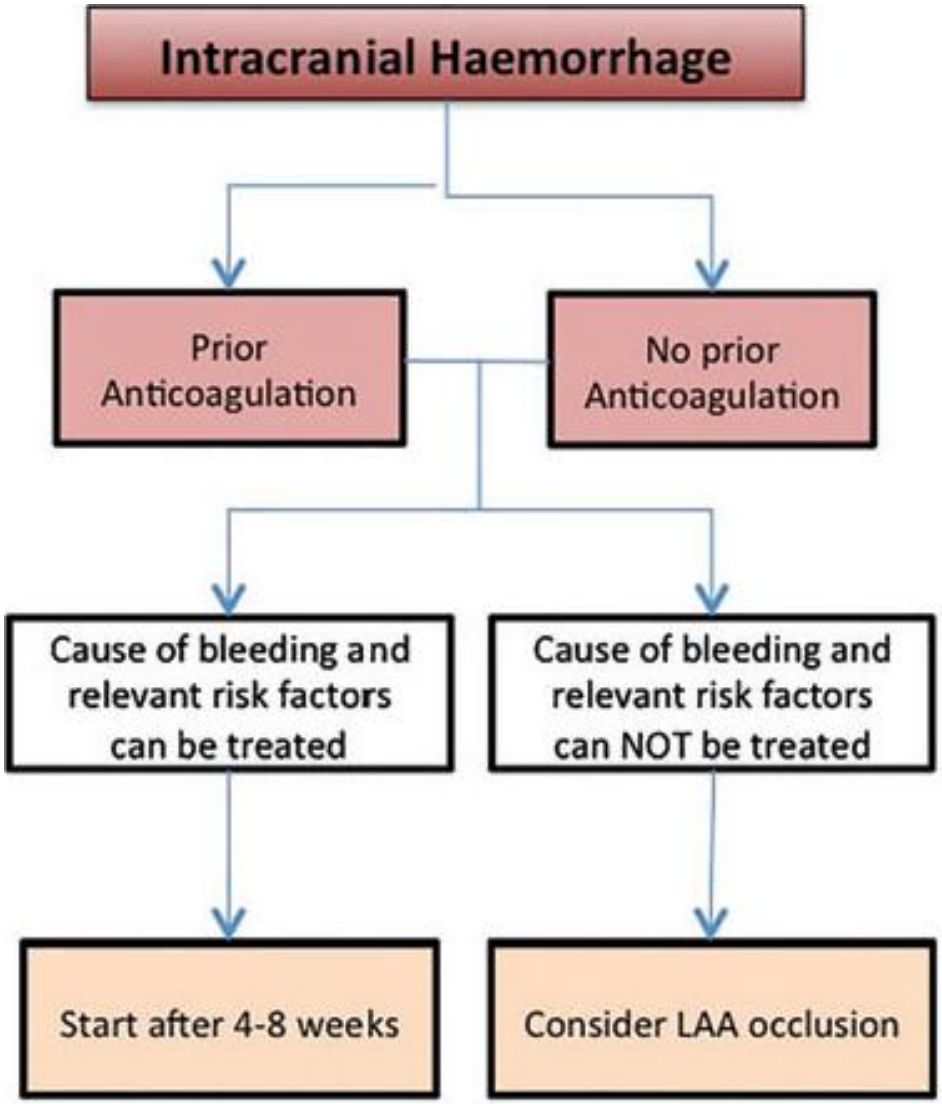
# Case 77/M, AF

- $CHA_2DS_2$-VASc = 6 (Embolic infarction)
- HAS-BLED = 3

- **When to start the NOAC?**

1. After 1 day
2. After 3 days
3. After 6 days
4. After 12 days
5. After 2 months

# When to start the NOAC after ICH




EHRA PRACTICAL GUIDE 2015

# Management of the post-ICH

To reintroduce or not to reintroduce

- High TE risk and low ICH risk: restart after 4–8 weeks
- Low TE risk and high ICH risk: ?
- High TE risk and high ICH risk: LAA?

# Management of the post-ICH

- Contraindication : spontaneous ICH, unless the cause of the bleeding has been reversed (uncontrolled hypertension, triple therapy, and INR .4–5 on VKAs)

- Arguments for no anticoagulation after ICH

  older age
  persistent uncontrolled hypertension,
  lobar bleeds,
  severe white matter lesions,
  multiple microbleeds on MRI (>30),
  chronic alcoholism
  DAPT after PCI.

- **What is the best for your individual patients?**

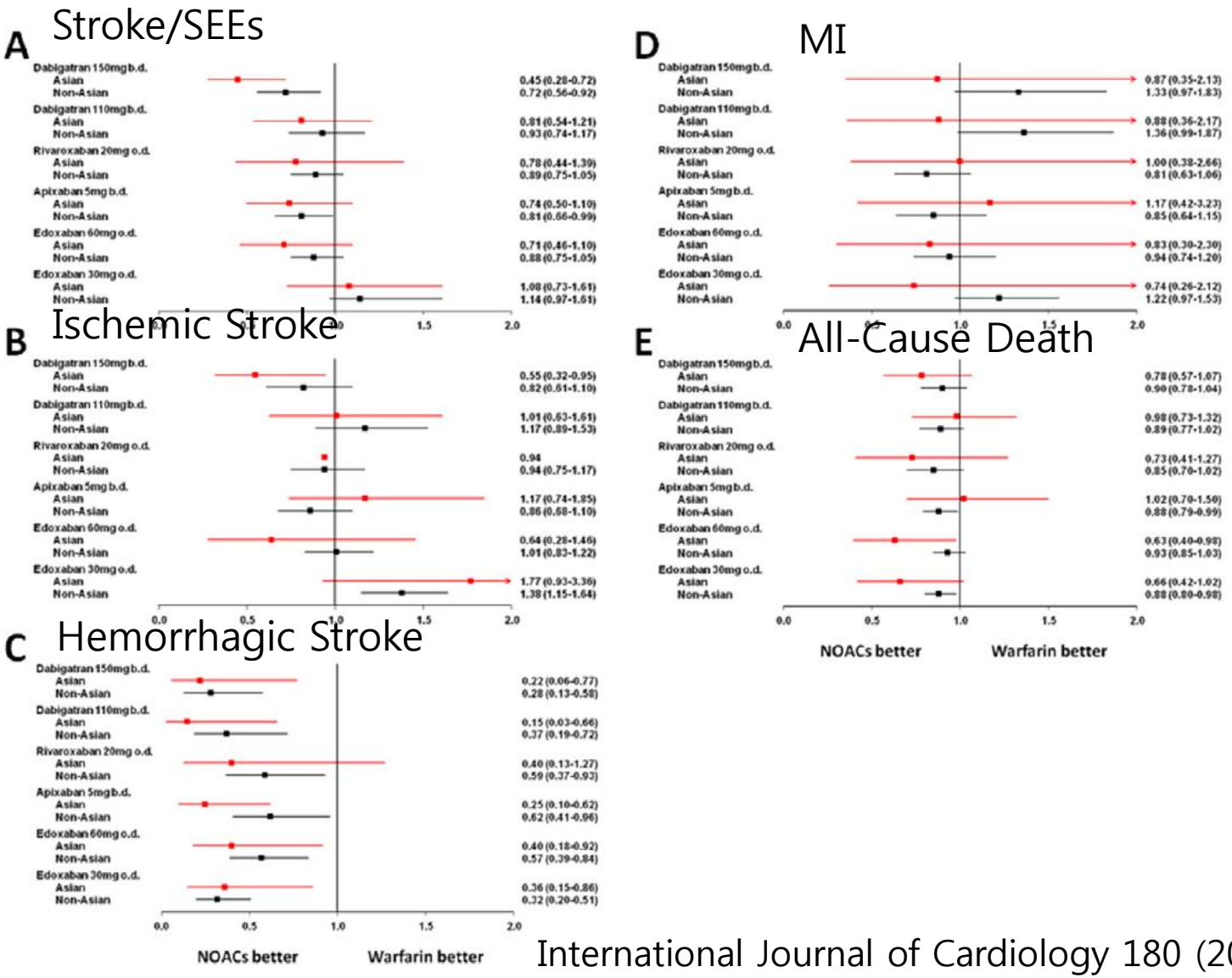
- **The answer is …..**

**Namsik Yoon**

**Chonnam National University Hospital, Korea**


NOACs
linked to:
• Bleeding on the Brain
• Intestinal Bleeding
• Kidney Bleeding
• Uncontrolled Bleeding
• Or Even Death
You may be entitled to
SUBSTANTIAL COMPENSATION!
Call Right Now!
Attorney
Bob Goldwater
1-800-781-6060
Call The Goldwater Law Firm Anytime, Day or Night

# NOACs in Asians: Efficacy Endpoints



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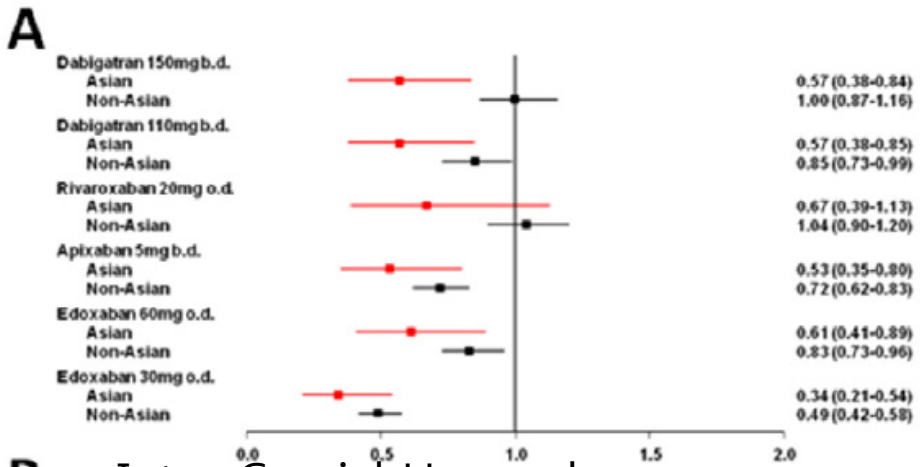
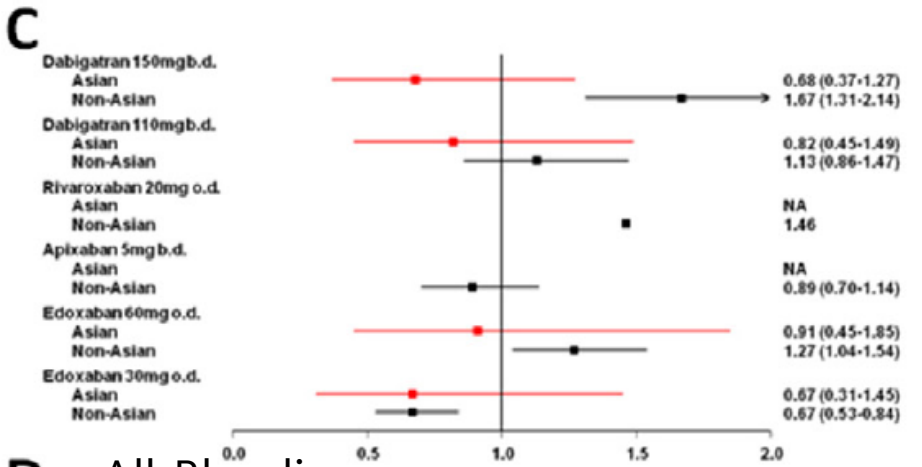
# NOACs in Asians: Safety Endpoints

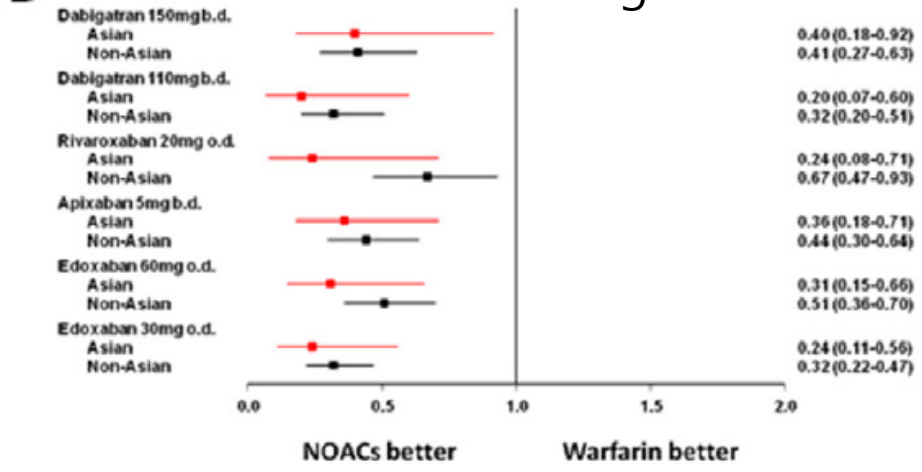
Major Bleeding



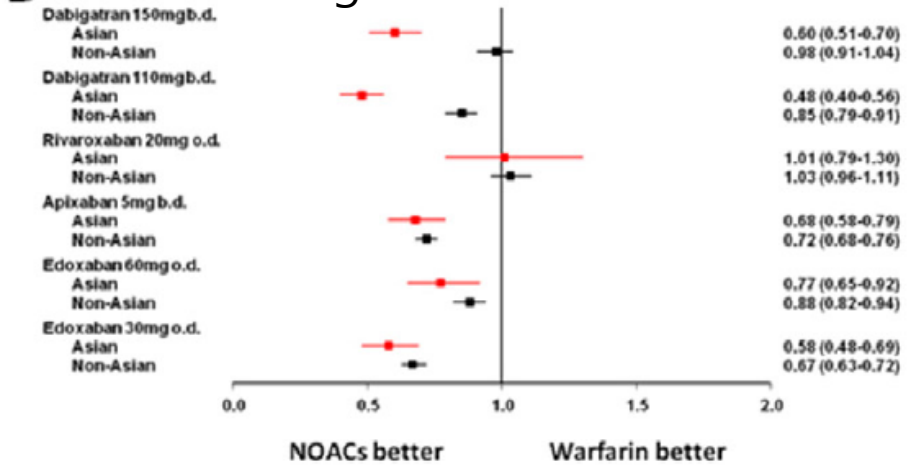

GI Bleeding




B Intra-Cranial Hemorrhage




D All Bleeding



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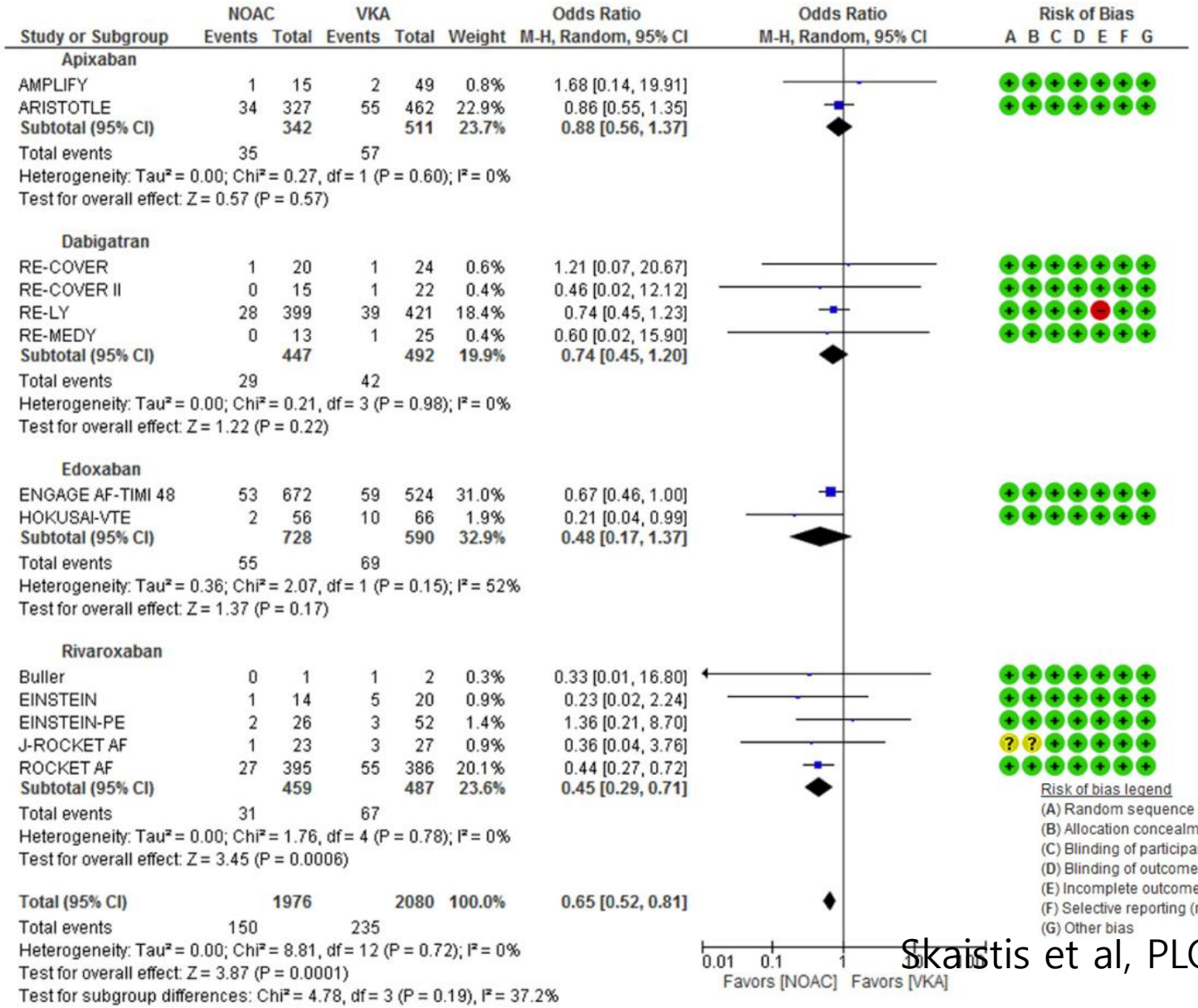
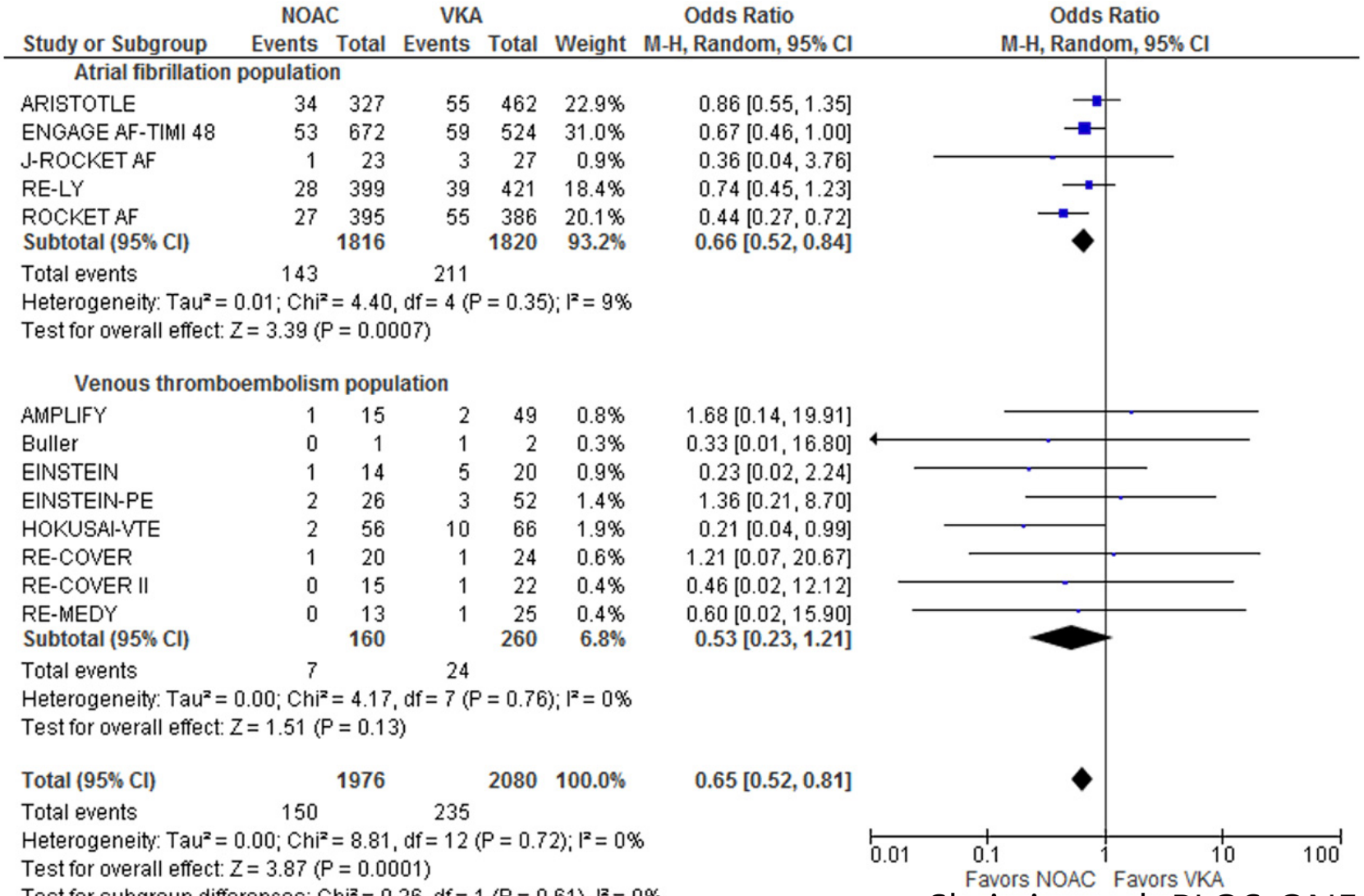
odds that **major bleeding** events will lead to fatal bleeding events.



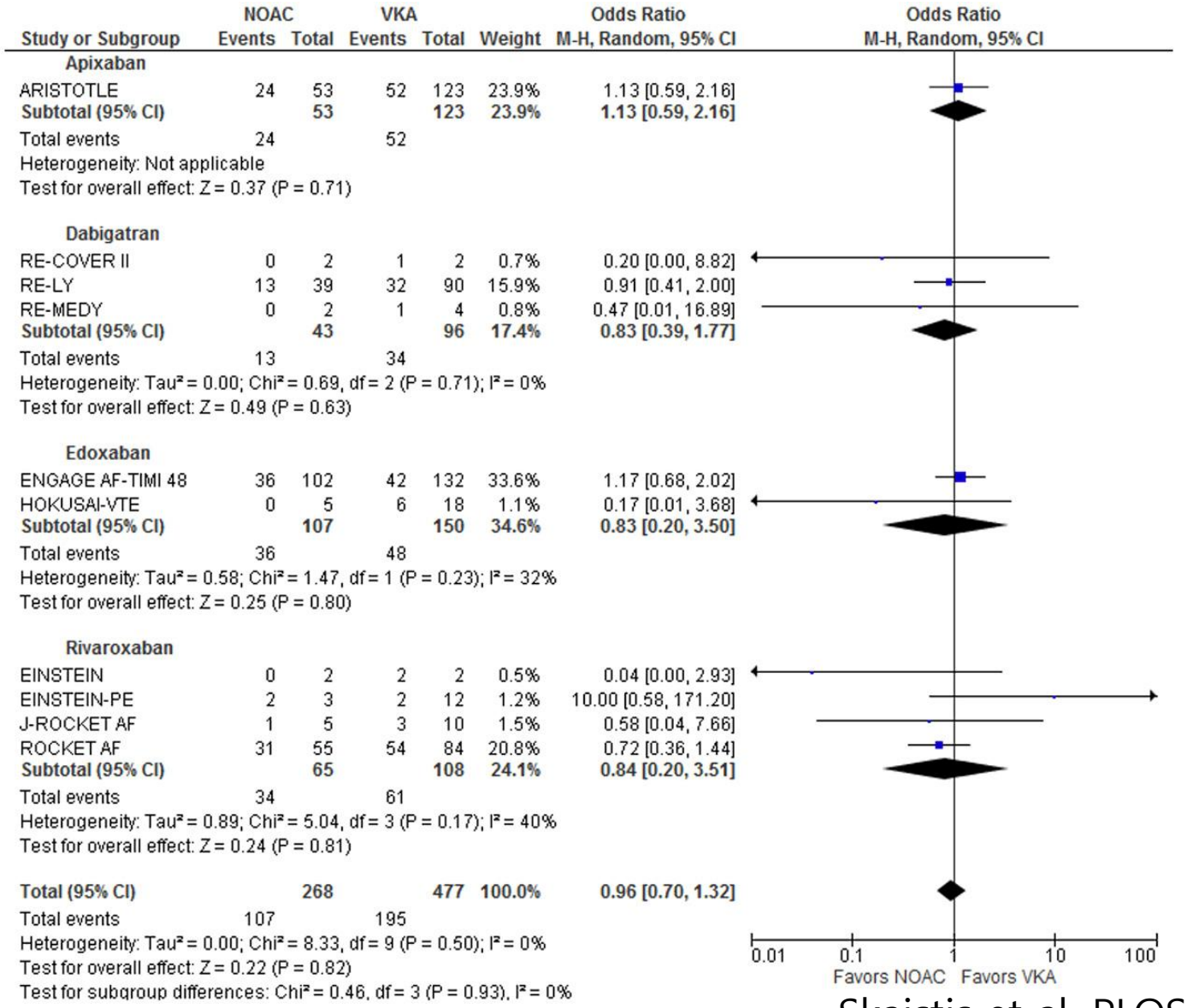

Skaistis et al, PLOS ONE 2015

Relative Odds **for fatal bleeding**




Skaistis et al, PLOS ONE 2015

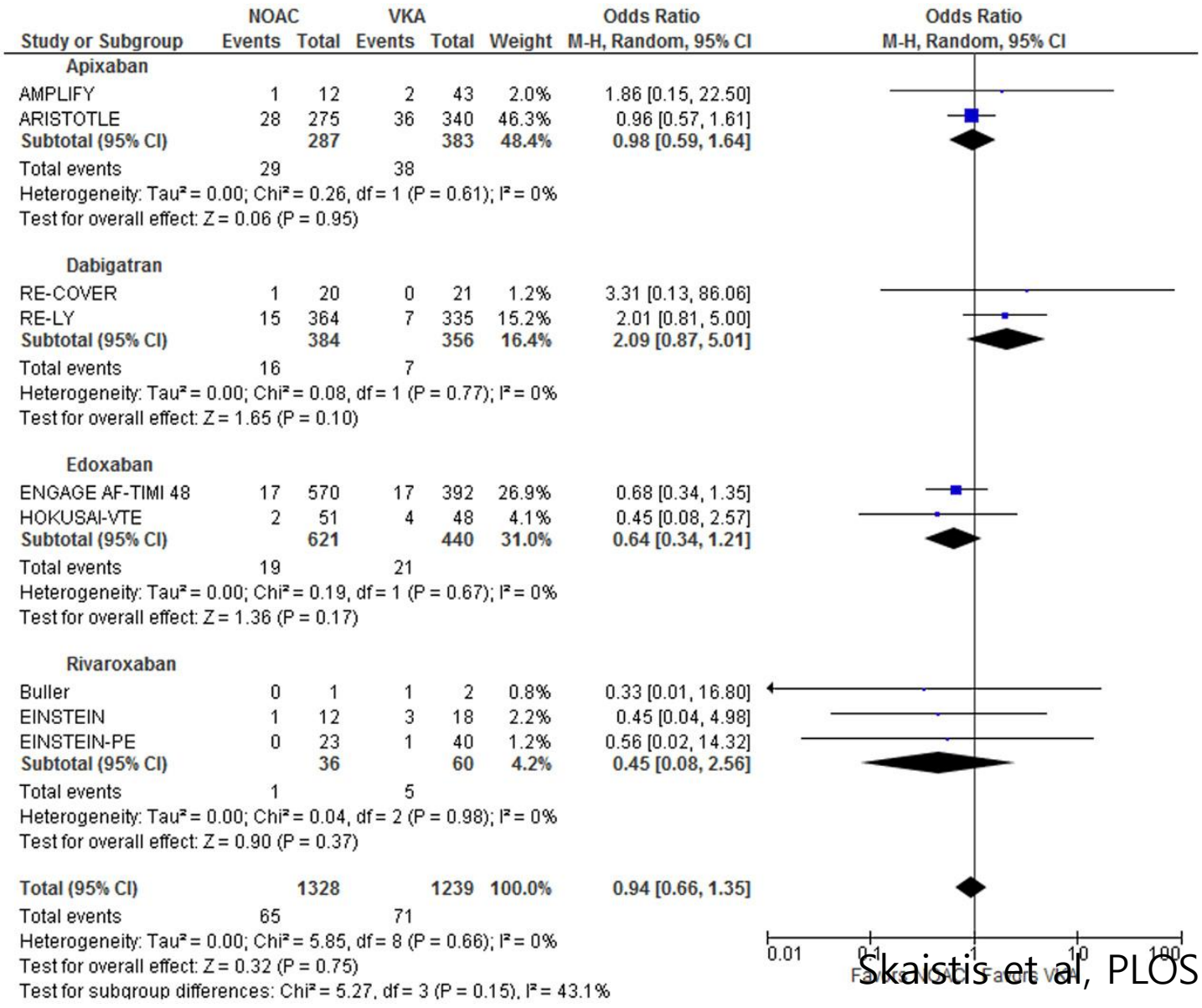
odds that ICH events will lead to fatal bleeding events.






Skaistis et al, PLOS ONE 2015

odds that **major extracranial bleeding** events will lead to fatal bleeding events.




Skaistis et al, PLOS ONE 2015