IRCCS AZIENDA OSPEDALIERA UNIVERSITARIA SAN MARTINO
IST - ISTITUTO NAZIONALE PER LA RICERCA SUL CANCRO

# Il mio paziente con ESA è anticoagulato

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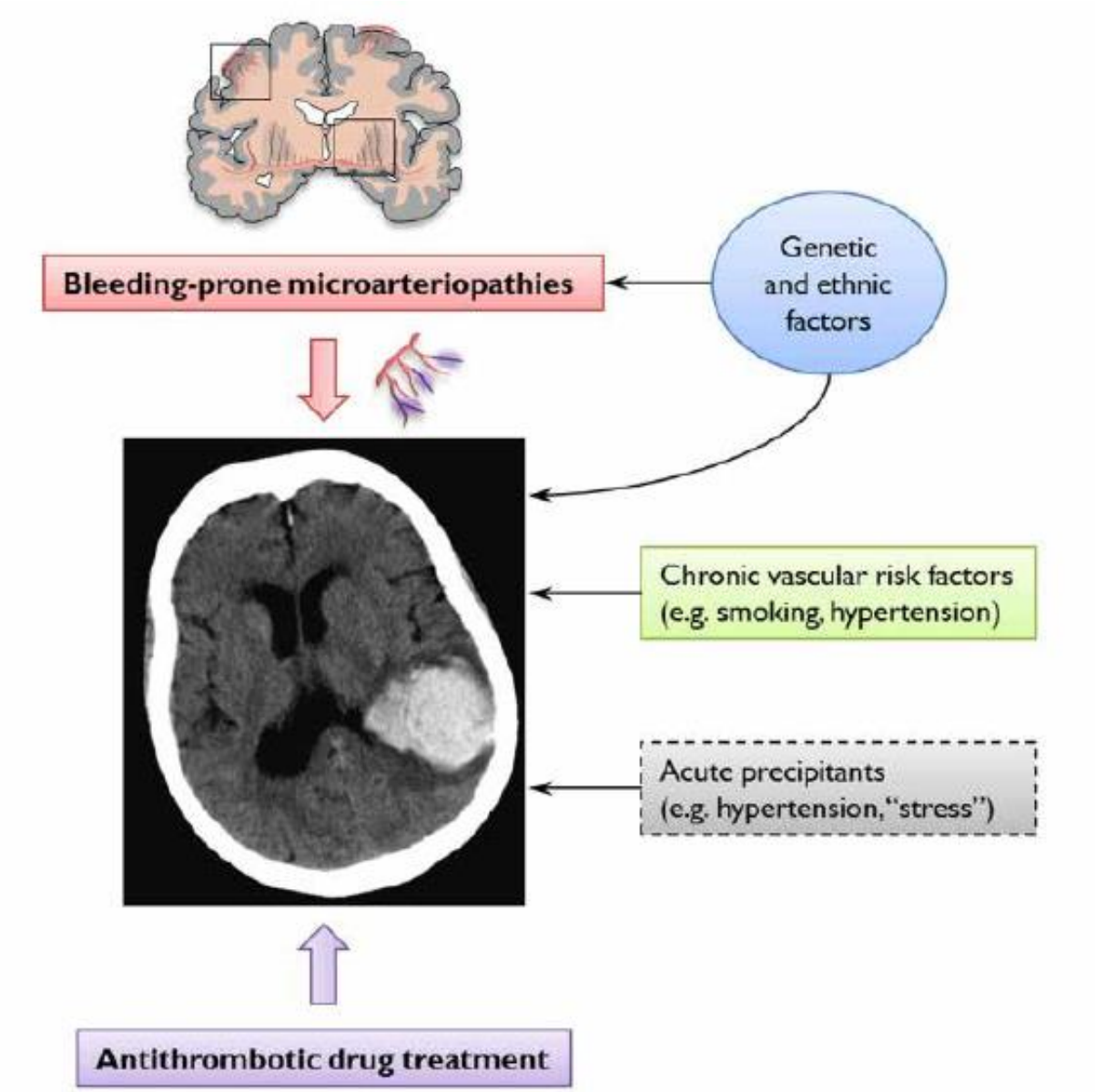
Neuro-Update Torino 9-10 Marzo 2017

# SAH – The Problem

- They occur in young people
  - 80% in 40-65 year olds
  - 15% in 20-40 year olds
- It can kill quickly
  - 25% die within 24 hours
  - 50% will be dead at 6 months
- It causes significant disability
  - Cognitive impairment
  - Neurological disability depending on size of bleed & complications encountered




Charidimou A et al. Front Neurol 2012;3(133):1-13

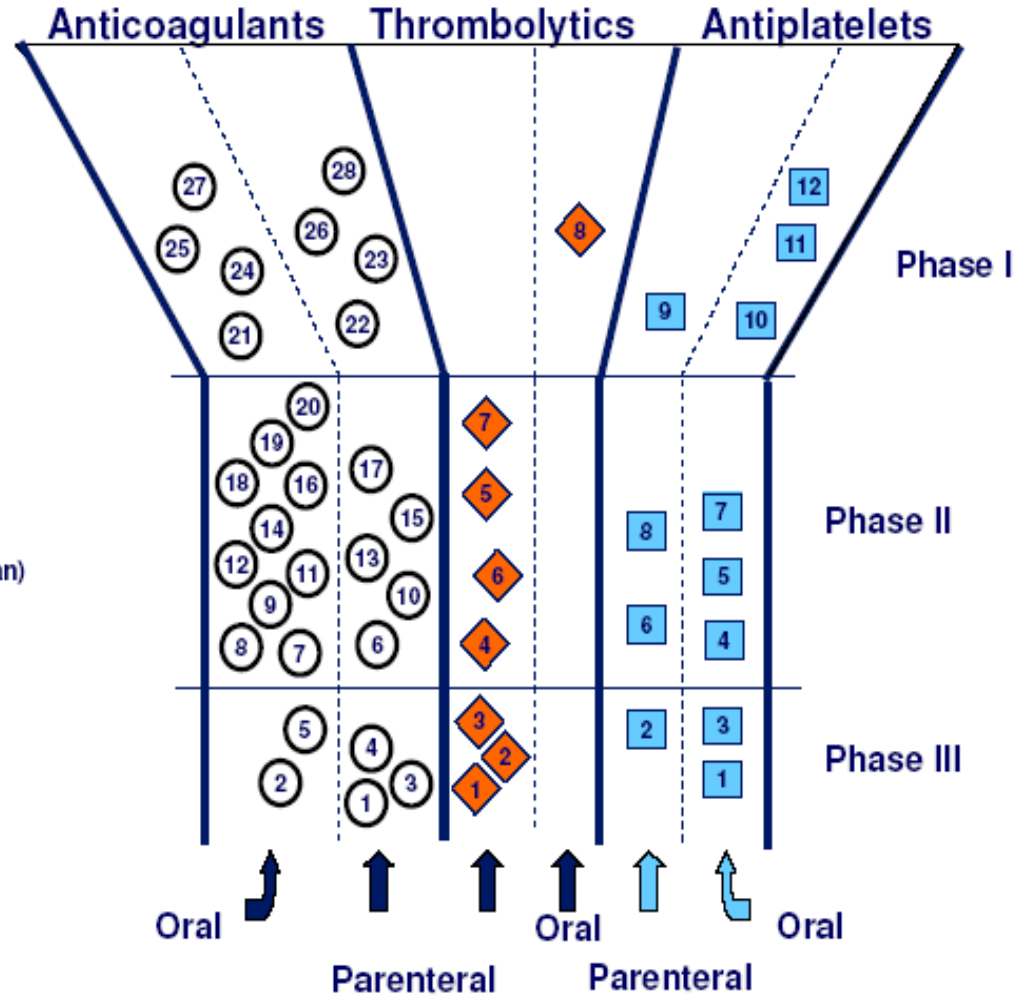
# ACs & APTs

- Stroke prevention in AF
- Treatment of thromboembolic disease
- Prevention of stent thrombosis

# Antithrombotic agents belong to one of three groups: there are three pipelines

## Anticoagulants

1 Idraparinux
2 Dabigatran
3 ART-123
4 Tifacogin
6 SR-123781
7 AZD-0837
8 MCC-977
9 SSR-182289
10 TGN-255
11 Odiparcil
12 TTP-889
13 rNAPc2
14 YM-150
15 DX-9065a
16 Rivaroxaban
17 XRP-0673 (otamixaban)
18 Apixaban (BMS)
19 LY-517717
20 DU-176b
21 TGN-167
22 AVE-5026
23 SCH-530348
24 KFA-1982
25 EMD-503962
26 SSR-126517
27 Oral heparins
28 ARC-183

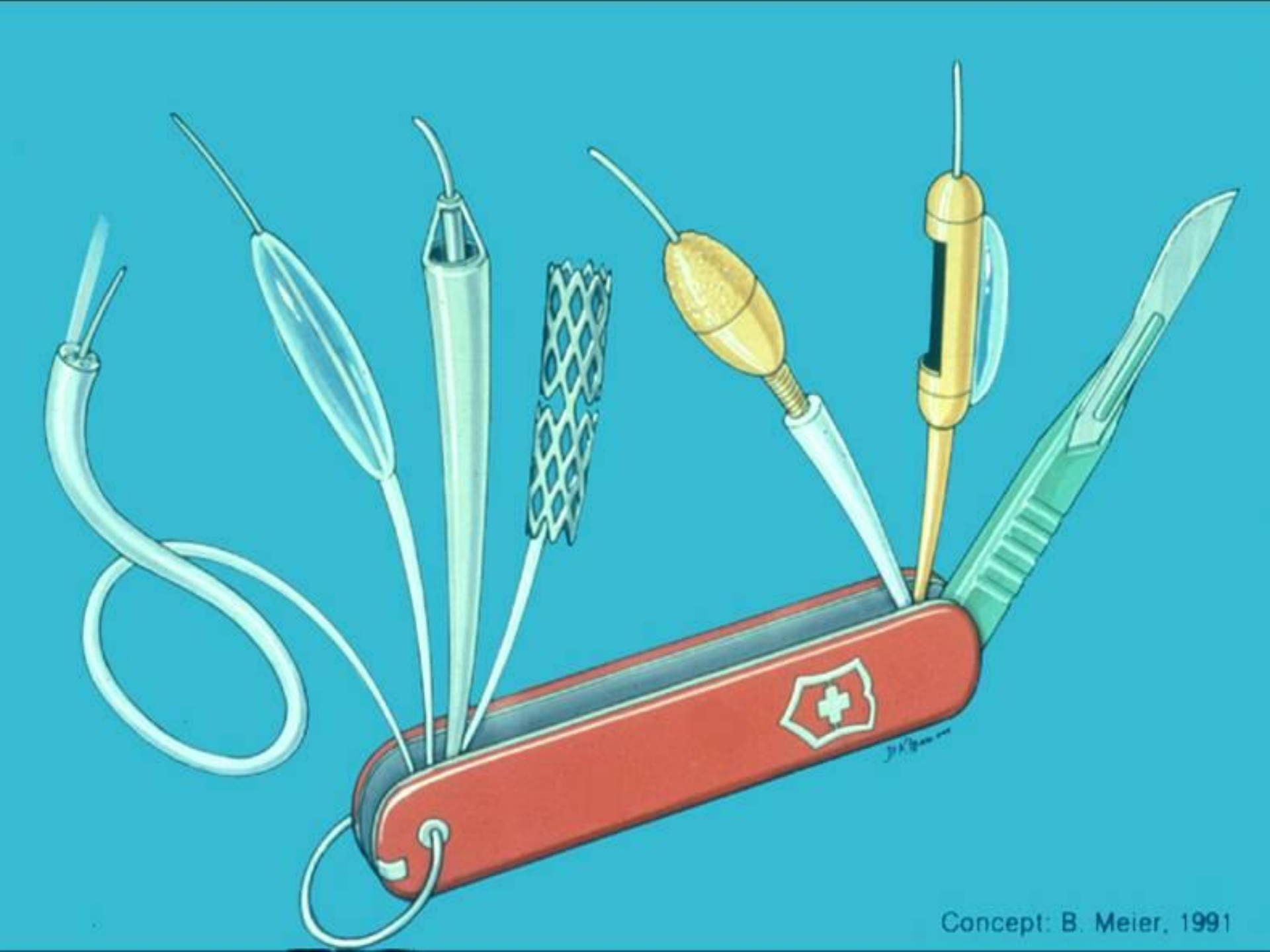


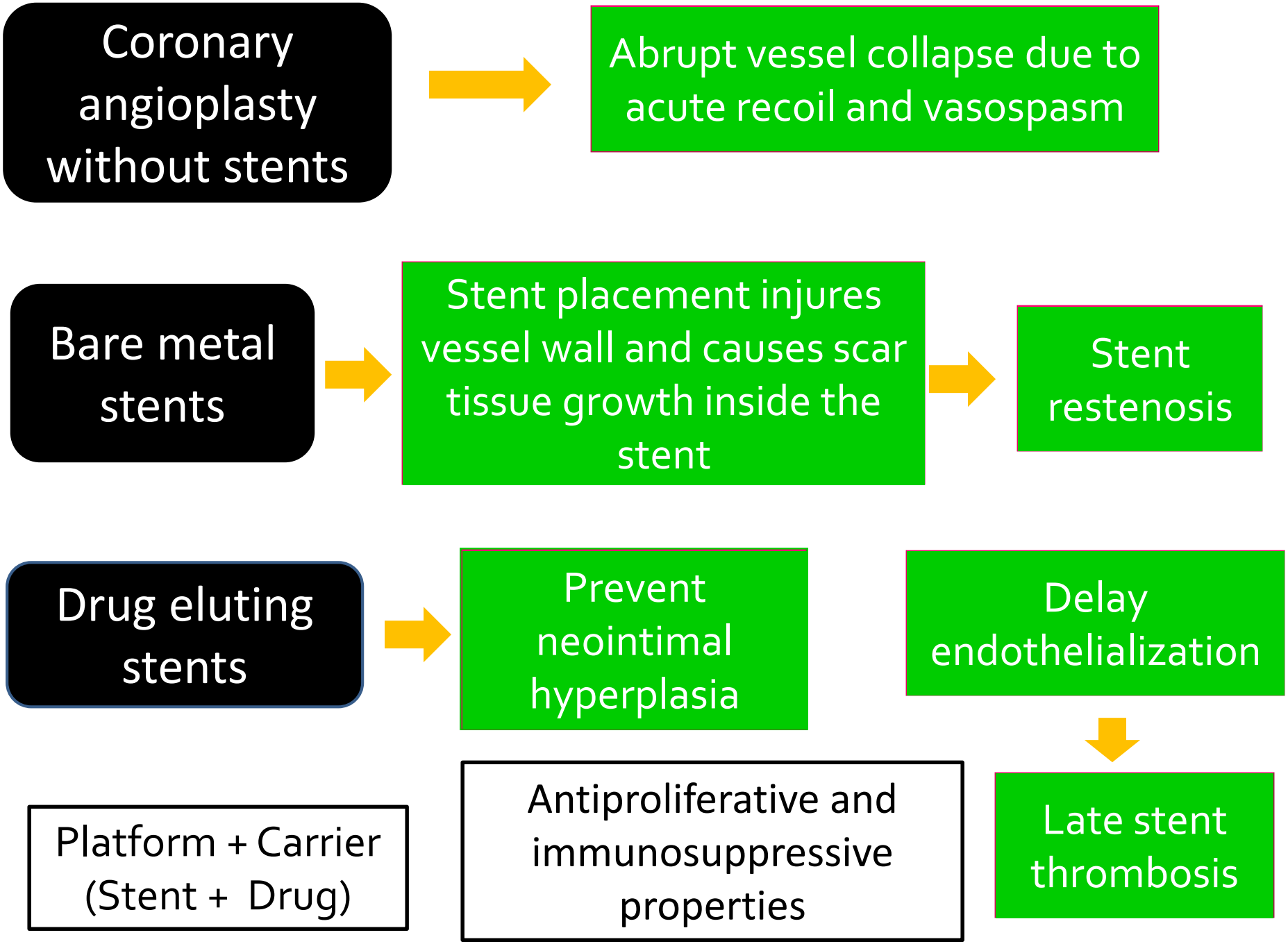

## Antiplatelets

1 Prasugrel (CS-747)
2 Ecraprost
3 S-18886
4 NCX-4016
5 AZD-6140
6 Cangrelor
7 NM-702
8 Liprostin
9 INS-50589
10 CLB-1309
11 Xemilofiban
12 SL-650472

## Thrombolytics

1 Amediplase
2 Alfimeprase
3 Desmoteplase
4 AZD-9684
5 V-10153
6 Microplasmin
7 HTU-PA (Hybrid-B PA)
8 PAI-749


Concept: B. Meier, 1991




Wessler J.D, Saldana F et al Cardiovascular Revascularization Medicine 2012

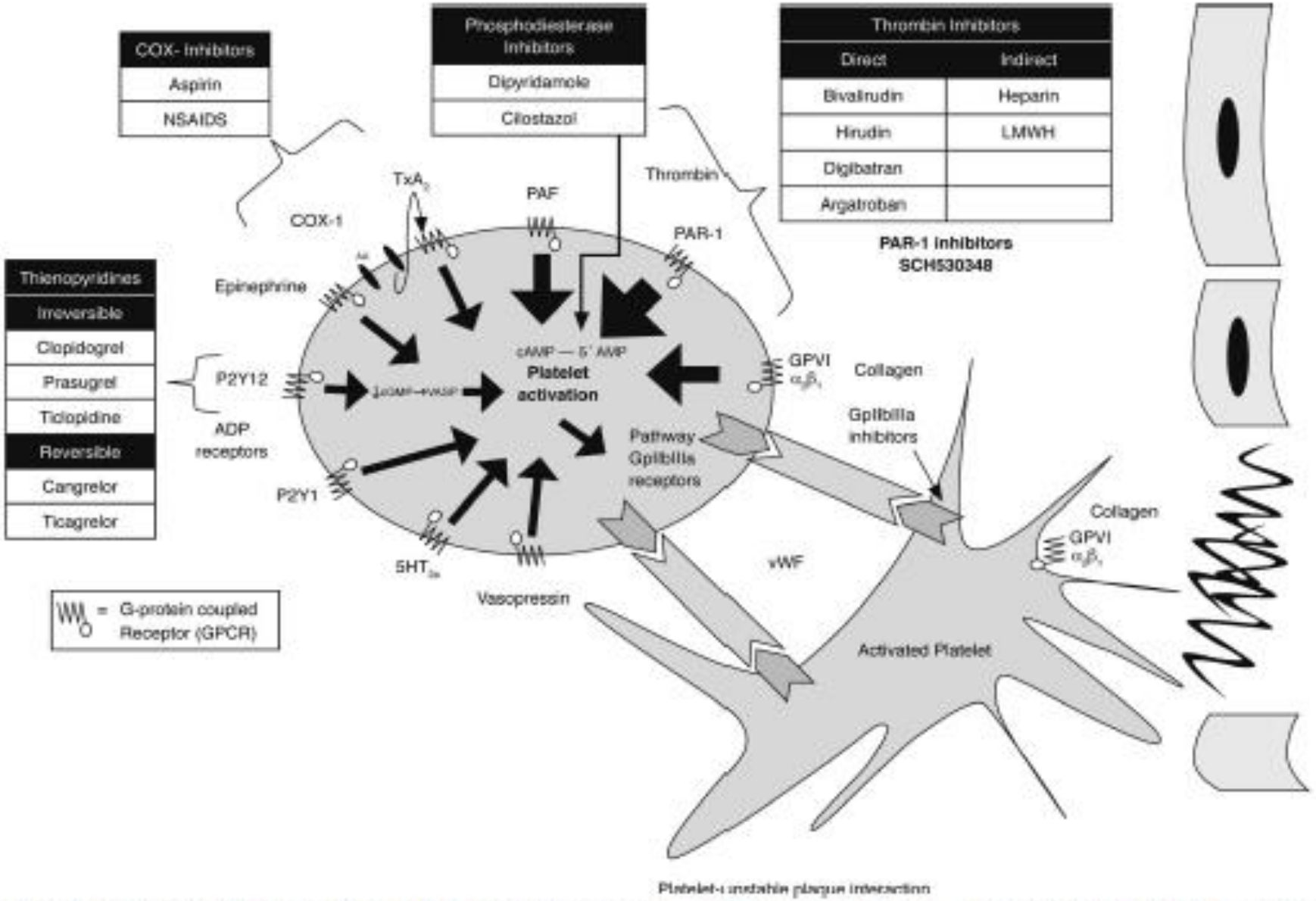



**Figure 1.** Agonists to platelet activation and antiplatelet drugs. COX = cyclooxygenase; NSAIDs = nonsteroidal antiinflammatory drugs; LMWH = low-molecular-weight heparin; $TxA_2$ = thromboxane $A_2$; PAR-1 = protease-activated receptor 1; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ADP = adenosine diphosphate; VASP = vasodilator stimulated phosphoprotein; 5HT = 5 hydroxytryptamine; vWF = von Willebrand factor; 5'AMP = 5' adenosine monophosphate; PAF = platelet aggregating factor; GP = glycoprotein; P = purinergic. (From Gladding et al.,[33] with permission.)

Curr Treat Options Cardio Med (2016) 18: 29
DOI 10.1007/s11936-016-0453-y

Cerebrovascular Disease and Stroke (N Rost, Section Editor)

# Intracranial Hemorrhage Risk in the Era of Antithrombotic Therapies for Ischemic Stroke

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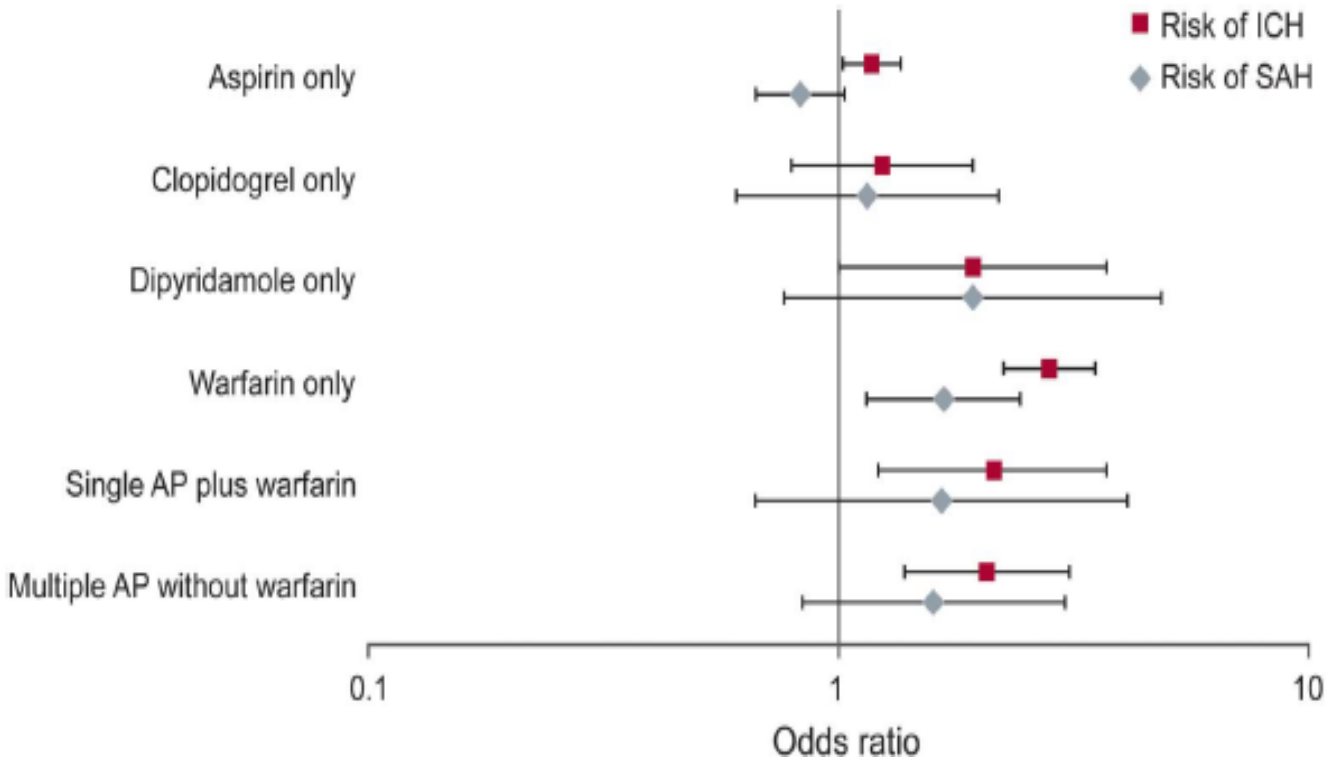
**Table 1. Antiplatelet use and intracranial hemorrhage risk in randomized controlled trials**

| Trial | Agents | Total trial population | Trial period | Intracranial hemorrhage rate |
|---|---|---|---|---|
| CAST | Aspirin | 21,106 | 4 weeks | 1.1 % (patients) aspirin vs. 0.9 % placebo, $p > 0.1$ |
| IST | Heparin, aspirin | 19,435 | Up to 14 days | 0.9 % aspirin (patients) vs. 0.8 % avoid aspirin, $p > 0.05$ |
| CAPRIE | Clopidogrel, aspirin | 19,185 | 1 to 3 years | 0.49 % aspirin (patients) vs. 0.35 % clopidogrel, $p > 0.05$ |
| ESPRIT | DP-ASA, aspirin | 2739 | 3.5 years (mean) | 0.88 % (patients) DP-ASA vs. 1.53 % aspirin, no statistical analysis |
| PRoFESS | DP-ASA, clopidogrel | 20,332 | 2.5 years (mean) | 1.4 % (patients) DP-ASA vs. 1.0 % clopidogrel, HR 1.42 (1.11–1.83) |
| MATCH | CG-ASA, clopidogrel | 7599 | 18 months | 0.85 % (patients) CG-ASA vs. 0.45 % clopidogrel, difference 0.40, 95 % CI (0.04–0.76) |
| ACTIVE W | CG-ASA, VKA | 6706 | 1.28 years (median) | 0.12 % (per year) CG-ASA vs. 0.36 % VKA, RR 0.34 (0.12–0.93), $p = 0.036$ |
| CHARISMA | CG-ASA, aspirin | 15,603 | 28 months (median) | 0.3 % (patients) CG-ASA vs. 0.3 % aspirin, RR 0.96 (0.56–1.65), $p = 0.89$ |
| ACTIVE A | CG-ASA, aspirin | 7554 | 3.6 years (median) | 0.4 % (per year) CG-ASA vs. 0.2 % aspirin, RR 1.87 (1.19–2.94), $p = 0.006$ |
| SPS3 | CG-ASA, aspirin | 3020 | 3.4 years (mean) | 0.42 % (per year) CG-ASA vs. 0.28 % aspirin, HR 1.52 (0.79–2.93), $p = 0.21$ |
| CHANCE | CG-ASA, aspirin | 5170 | 90 days | 0.3 % CG-ASA vs. 0.3 % aspirin, HR 1.01 (0.38–2.70), $p = 0.98$ |

*VKA* vitamin K antagonist, *DP-ASA* dipyridamole/aspirin, *CG-ASA* clopidogrel/aspirin

**Figure 1** **Effect of APs and warfarin on risk of ICH and SAH**




J Neurosurg 2016

Acta Neurochir (Wien) (2006) 148: 1189–1196
DOI 10.1007/s00701-006-0868-4

*Acta Neurochirurgica*
Printed in Austria

*Neurosurgical Concept*

# Low-dose aspirin before intracranial surgery – results of a survey among neurosurgeons in Germany

M. C. Korinth

Three-quarters of the respondents felt that aspirin was a risk factor for haemorrhagic complications associated with intracranial procedures, and more than half of the interviewed neurosurgeons reported having personal experience of such problems during brain surgery…

Eur Spine J (2007) 16:365–372
DOI 10.1007/s00586-006-0216-7

ORIGINAL ARTICLE

# Low-dose aspirin before spinal surgery: results of a survey among neurosurgeons in Germany

Marcus C. Korinth · Joachim M. Gilsbach · Martin R. Weinzierl

Twothirds of the respondents felt that aspirin was a risk factor for hemorrhagic complications associated with spinal procedures, and more than half of the interviewees reported having personal experience of such problems….

# Use of the $CHA_2DS_2$-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation

Deirdre A. Lane, PhD; Gregory Y.H. Lip, MD

**Table 2. Assessment of Stroke ($CHA_2DS_2$-VASc)[14] and Bleeding Risk (HAS-BLED)[15] in Atrial Fibrillation Patients**

| $CHA_2DS_2$-VASc | Score | HAS-BLED | Score |
|---|---|---|---|
| Congestive heart failure | 1 | Hypertension (systolic blood pressure >160 mm Hg) | 1 |
| Hypertension | 1 | Abnormal renal and liver function* (1 point each) | 1 or 2 |
| Age ≥75 y | 2 | Stroke | 1 |
| Diabetes mellitus | 1 | Bleeding tendency/predisposition* | 1 |
| Stroke/TIA/TE | 2 | Labile INRs (if on warfarin)* | 1 |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1 | Elderly (eg, age >65 y) | 1 |
| | | Drugs or alcohol (1 point each)* | 1 or 2 |
| Aged 65 to 74 y | 1 | | |
| Sex category (ie, female sex) | 1 | | |
| Maximum score | 9 | Maximum score | 9 |

## Table 3. Risk Factors for Bleeding on Oral Anticoagulation

- Patient-related factors
  - Age
  - History of bleeding
  - Previous stroke
  - Anemia
  - Genetic factors
  - Sex
  - Uncontrolled hypertension
  - Renal insufficiency
  - Hepatic dysfunction
  - Malignancy
- OAC treatment-related factors*
  - Inception vs OAC experience
  - Adherence
  - Intensity of anticoagulation (INR)*
  - Time in therapeutic range*
  - Dietary intake of vitamin K*
  - Management of OAC (self-monitoring, dedicated OAC clinic, usual care)*
- Concomitant medications/alcohol
  - Antiplatelet drugs
  - NSAIDs
  - Other medications affecting OAC intensity
  - Excessive alcohol intake

**CHADSVASC clinical risk estimation. Adapted from Lip et al.**

| $CHA_2DS_2VASc$ SCORE | PATIENTS (n=7329) | ADJUSTED STROKE RATE (% year) |
|---|---|---|
| 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% |

**HASBLED clinical risk estimation. Adapted from Pisters et al.**

| HAS BLED SCORE | NUMBER OF PATIENTS | NUMBER OF BLEEDING | BLEEDS PER 100 PATIENT YEARS |
|---|---|---|---|
| 0 | 798 | 9 | 1,13 |
| 1 | 1286 | 13 | 1,02 |
| 2 | 744 | 14 | 1,88 |
| 3 | 187 | 7 | 3,74 |
| 4 | 46 | 4 | 8,70 |
| 5 | 8 | 1 | 12,50 |
| 6 | 2 | 0 | 0 |
| 7 | --- | --- | --- |
| 8 | --- | --- | --- |
| 9 | --- | --- | --- |
| Total | 798 | 9 | 1,13 |

JNS

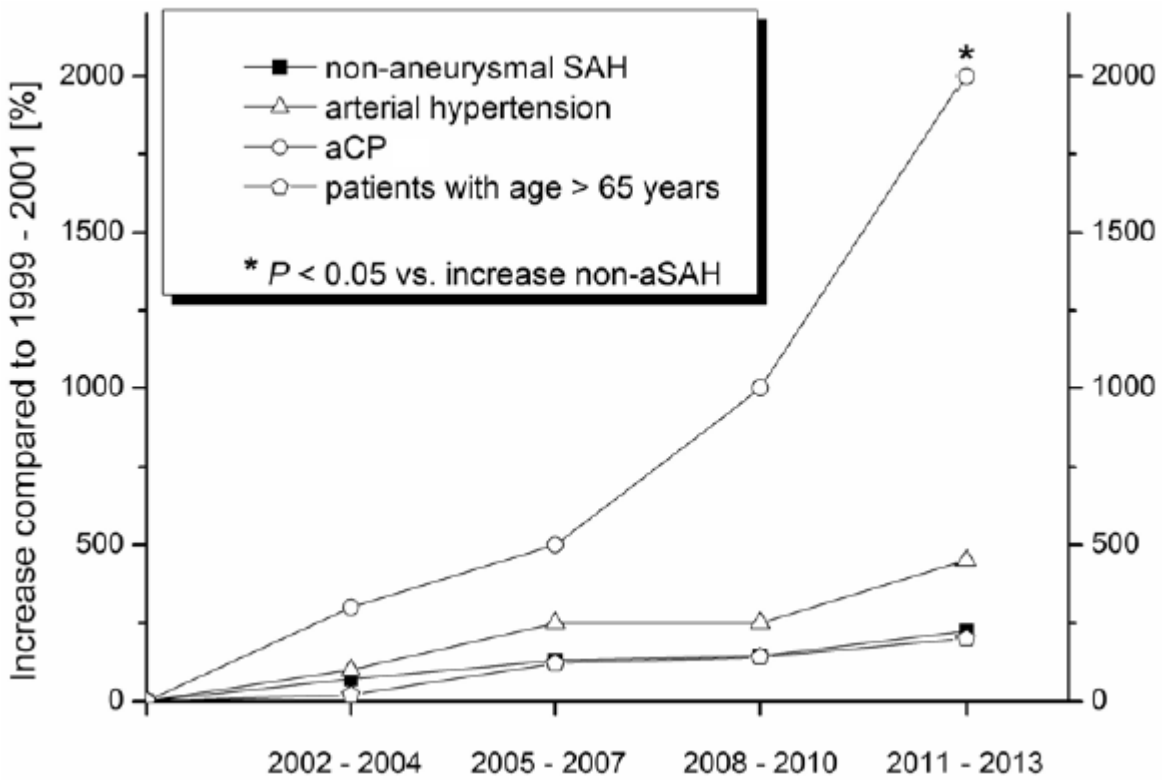
CLINICAL ARTICLE

J Neurosurg 124:1731–1737, 2016

# Increasing numbers of nonaneurysmal subarachnoid hemorrhage in the last 15 years: antithrombotic medication as reason and prognostic factor?

**Juergen Konczalla, MD, Sepide Kashefiolasl, MD, Nina Brawanski, MD, Christian Senft, MD, PhD, Volker Seifert, MD, PhD, and Johannes Platz, MD**

Department of Neurosurgery, Goethe University Hospital, Frankfurt, Germany



HIGH LIGHT
CME

# The increasing incidence of anticoagulant-associated intracerebral hemorrhage

M.L. Flaherty, MD; B. Kissela, MD; D. Woo, MD; D. Kleindorfer, MD; K. Alwell, BSN; P. Sekar, MS; C.J. Moomaw, PhD; M. Haverbusch, BSN; and J.P. Broderick, MD

NEUROLOGY 68 January 9, 2007

***Table 2*** *Age-stratified annual stroke incidence rates in the Greater Cincinnati/Northern Kentucky area**

| | 1988 | 1993–1994 | 1999 |
|---|---|---|---|
| All ICH | | | |
| Overall | 16.5 (14.1–18.9) | 22.1 (19.4–24.8) | 24.6 (21.8–27.4) |
| Age 0–49 | 2.2 (1.3–3.2) | 3.2 (2.1–4.3) | 5.0 (3.6–6.5) |
| Age 50–69 | 26.4 (19.6–33.2) | 41.0 (32.7–49.4) | 39.0 (31.1–47.0) |
| Age 70–79 | 76.0 (55.4–96.6) | 103.4 (80.1–126.6) | 99.6 (77.0–122.3) |
| Age 80+ | 140.5 (102.0–178.9) | 156.6 (118.2–195.0) | 207.0 (164.6–249.4) |
| AAICH | | | |
| Overall | 0.8 (0.3–1.3) | 1.9 (1.1–2.7) | 4.4 (3.2–5.5) |
| Age 0–49 | 0.2 (0–0.5) | 0.1 (0–0.3) | 0.3 (0–0.7) |
| Age 50–69 | 0.9 (0–2.2) | 3.7 (1.1–6.3) | 5.5 (2.5–8.6) |
| Age 70–79 | 5.7 (0.1–11.4) | 12.3 (4.2–20.4) | 24.3 (12.9–35.6) |
| Age 80+ | 2.5 (0–7.4) | 13.0 (1.5–24.6) | 45.9 (25.6–66.2) |
| Ischemic stroke caused by atrial fibrillation | | | |
| Overall | NA | 22.0 (19.3–24.7) | 20.6 (18.1–23.2) |
| Age 0–49 | NA | 0.3 (0–0.7) | 0.1 (0–0.3) |
| Age 50–69 | NA | 20.0 (14.1–25.9) | 15.5 (10.5–20.6) |
| Age 70–79 | NA | 117.1 (92.9–142.8) | 95.1 (72.9–117.3) |
| Age 80+ | NA | 298.7 (245.4–351.9) | 324.8 (272.1–377.4) |

REVIEW

# Antithrombotic treatment and intracerebral haemorrhage: between Scylla and Charybdis

J Hofmeijer,[1,2] L J Kappelle,[3] C J M Klijn[3]

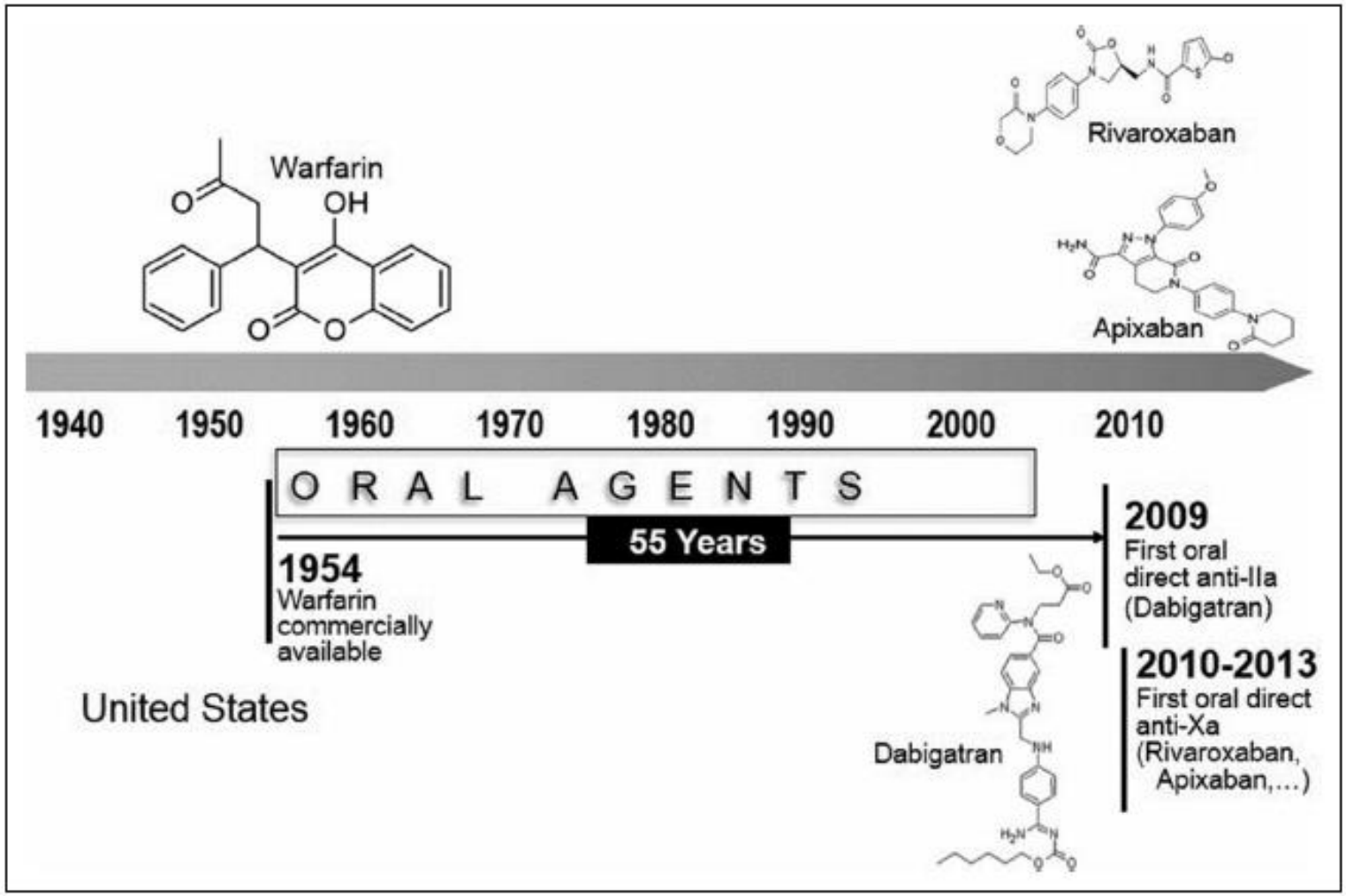
Hofmeijer J, *et al*. *Pract Neurol* 2015;**15**:250–256. doi:10.1136/practneurol-2015-001104

# Oral Anticoagulants and Status of Antidotes for the Reversal of Bleeding Risk

Clinical and Applied Thrombosis/Hemostasis
2015, Vol. 21(2) 105-114

DOI: 10.1177/1076029614545211
cat.sagepub.com
SAGE

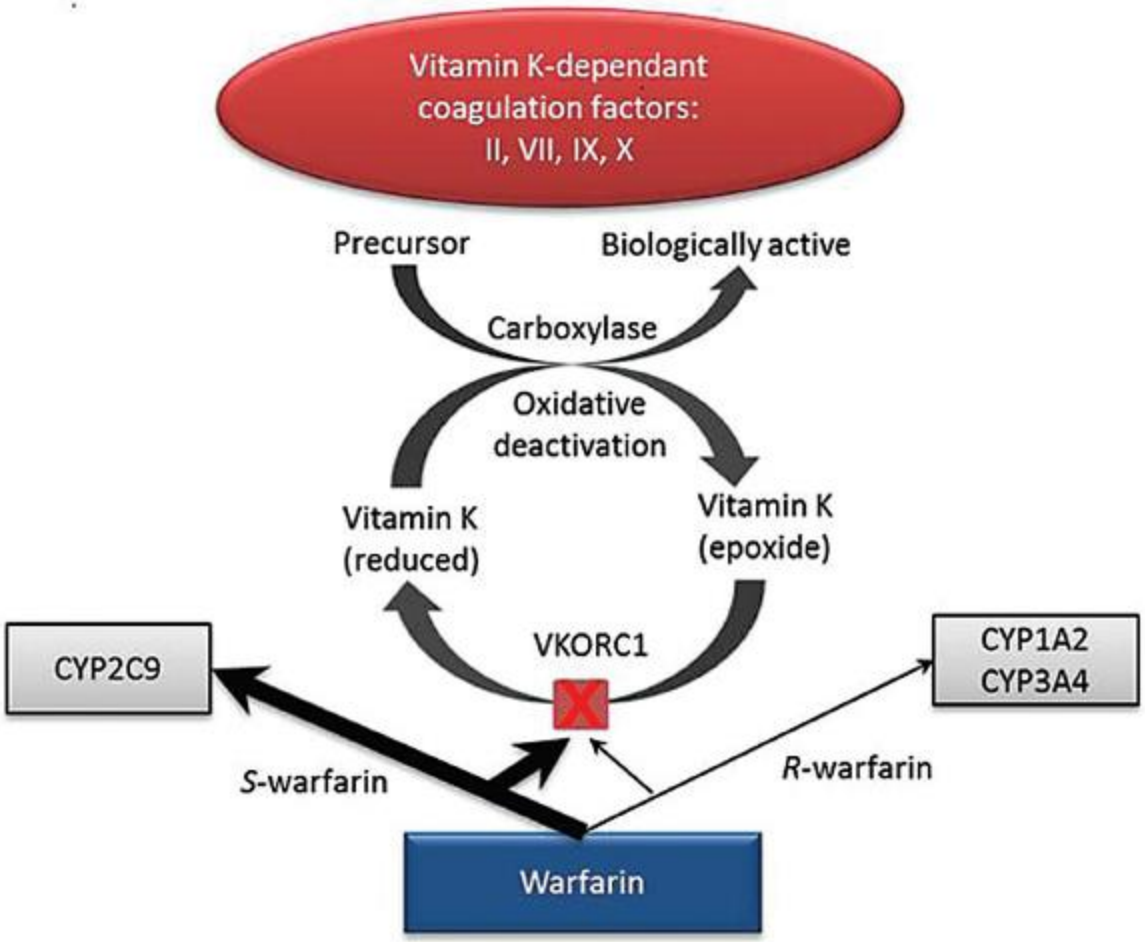
**Joseph Ebright, PharmD[1], and Shaker A. Mousa, PhD, MBA, FACC, FACB[1]**



# The king is dead (warfarin): direct thrombin and factor Xa inhibitors: the next Diadochian War?

Hans-Christoph Diener[1]*, John Eikelboom[2], Christopher B. Granger[3], and Werner Hacke[4]


International Journal of Stroke © 2012 World Stroke Organization Vol 7, February 2012, 139–141


Vitamin K-dependant coagulation factors: II, VII, IX, X
Precursor
Biologically active
Carboxylase
Oxidative deactivation
Vitamin K (reduced)
Vitamin K (epoxide)
VKORC1
CYP2C9
CYP1A2
CYP3A4
S-warfarin
R-warfarin
Warfarin

Thrombosis Research 129 (2012) 392–400

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

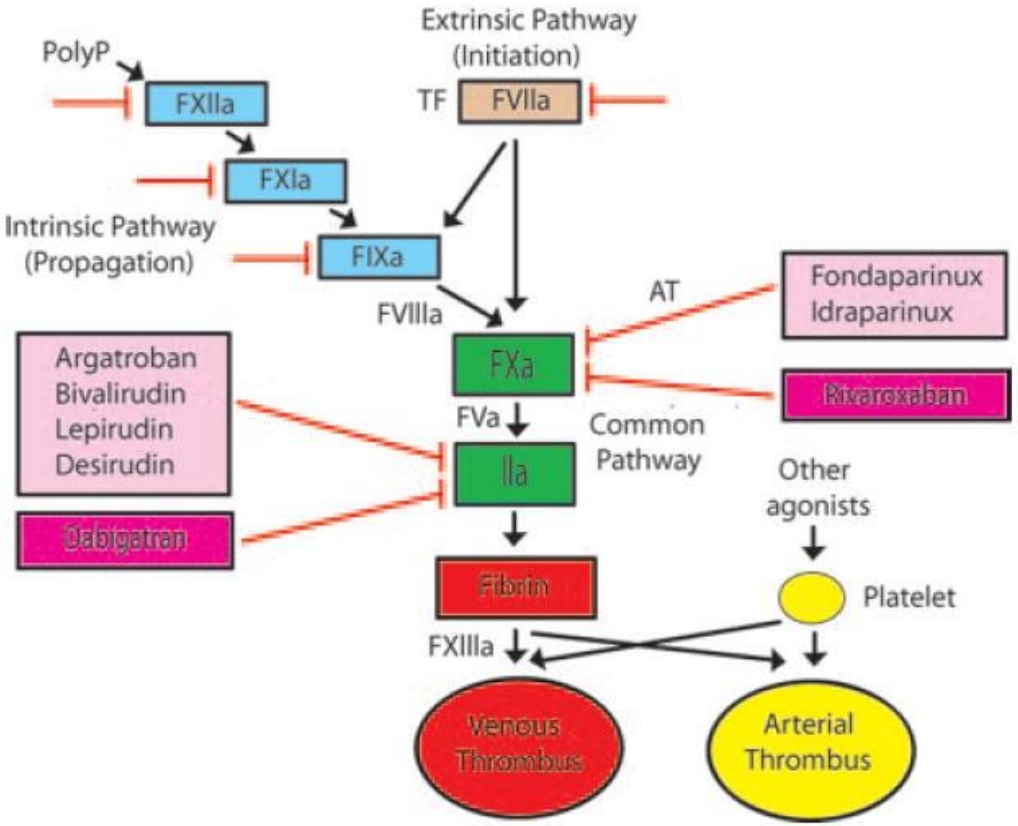
Review Article

# Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: A review of the literature

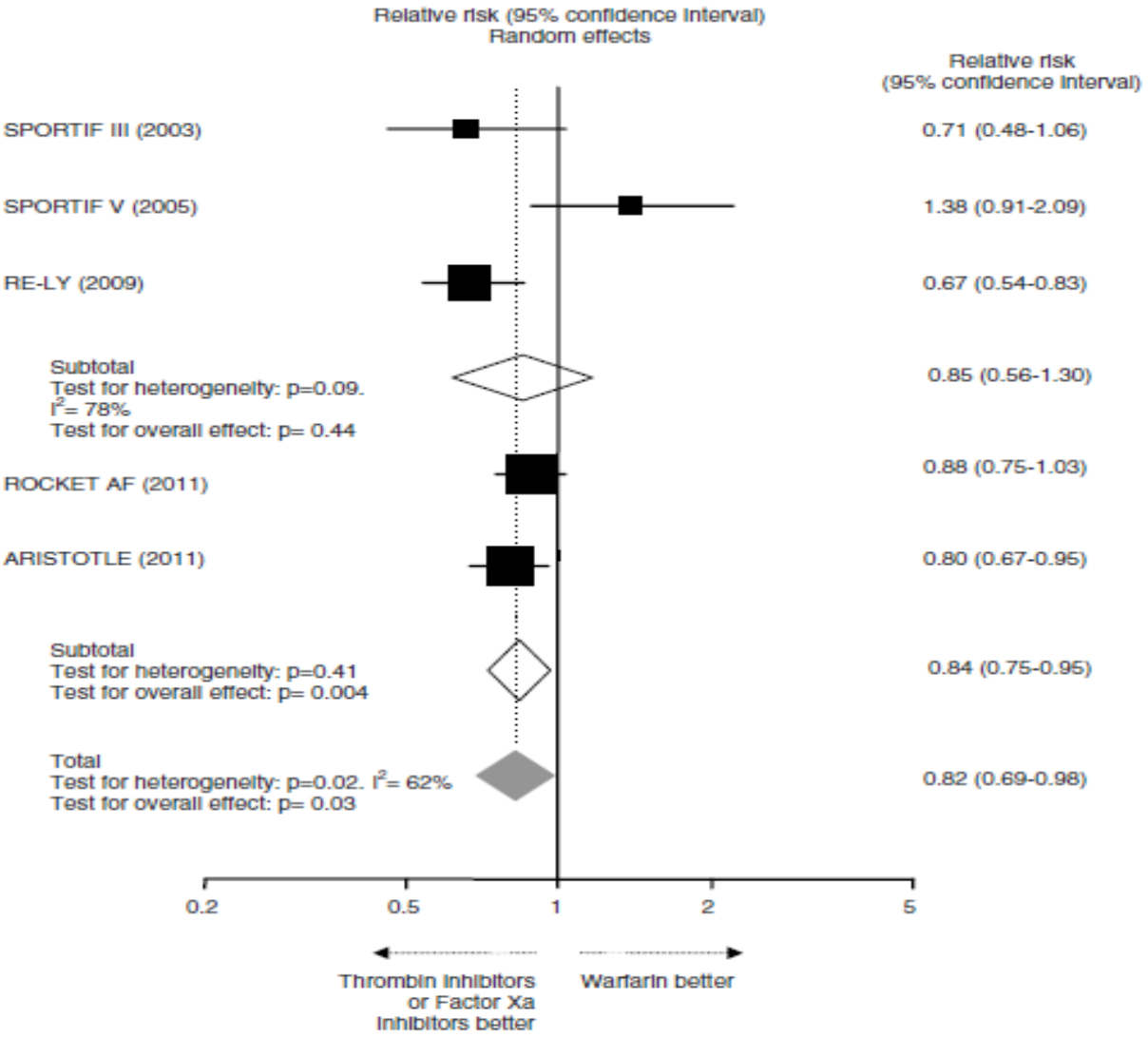
Cecilia Becattini *, Maria Cristina Vedovati, Giancarlo Agnelli

*Internal and Cardiovascular Medicine & Stroke Unit, University of Perugia, Italy*

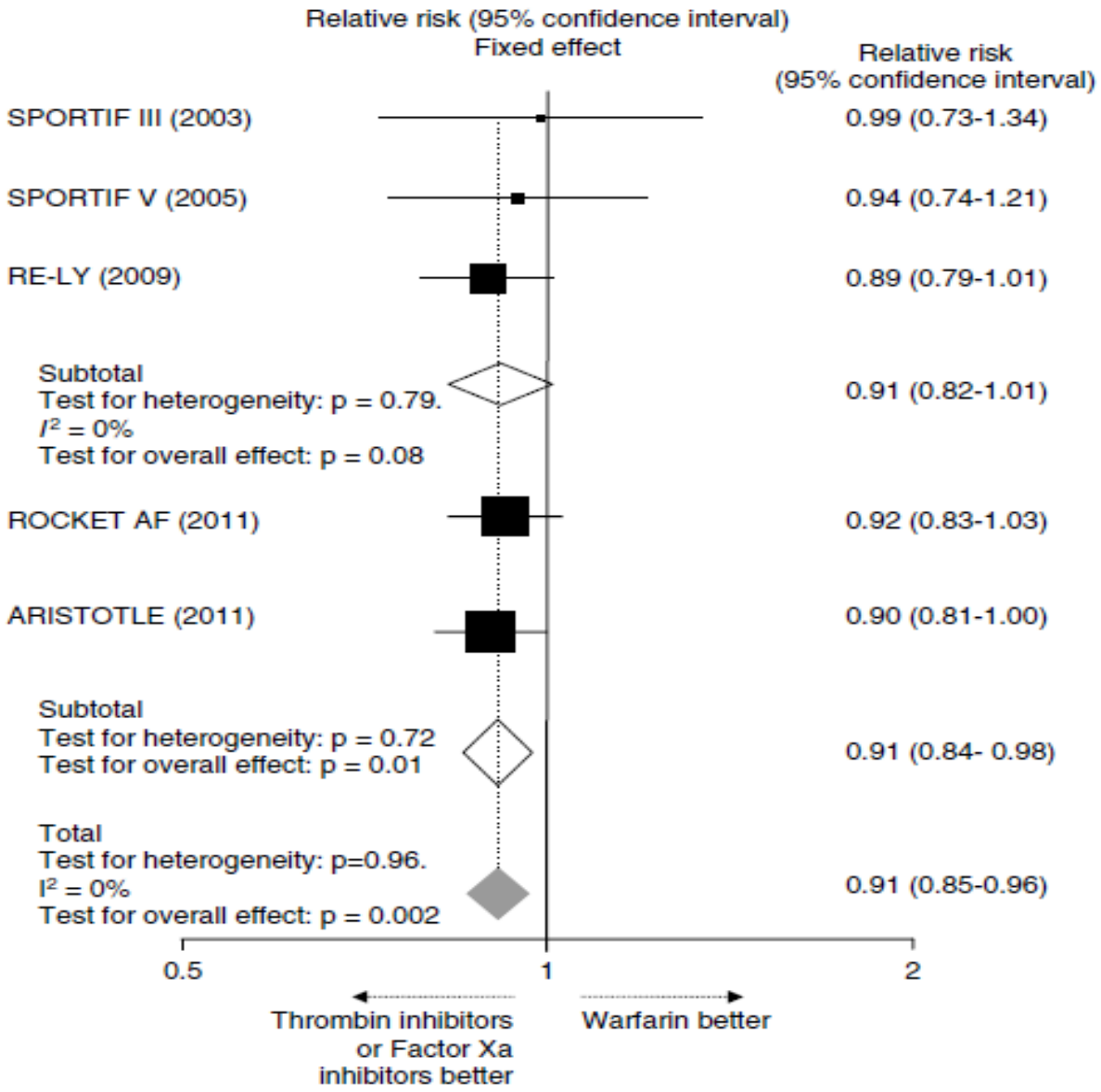
- Direct thrombin inhibitors
  - argatroban
  - bivalirudin
  - dabigatran
    - FXa-inhibitors
  - rivaroxaban
  - apixaban



# Risk of stroke or systemic embolism



# Death from any cause



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EMERGENCY MEDICINE PRACTICE

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# Intracerebral Hemorrhage In Anticoagulated Patients: Evidence-Based Emergency Department Management

December 2015
Volume 17, Number 12

Authors

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## Table 1. Common Etiologies And Risk Factors For Intracerebral Hemorrhage

- Coagulopathy: hereditary or medication/drug-induced
- Structural: mass, arteriovenous malformation, aneurysm
- Acquired: amyloid angiopathy
- Traumatic: intraparenchymal hemorrhage, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage
- Advanced age
- Hypertension
- Race

## Table 2. Randomized Controlled Trials Of Novel Oral Anticoagulants In Atrial Fibrillation

| Trial | Number of Patients | Annual Incidence of Stroke | Annual Risk of ICH |
|---|---|---|---|
| RE-LY® (warfarin vs dabigatran) | 18,113 | Dabigatran: 1.69%<br>Warfarin: 1.53% | Dabigatran: 0.12%<br>Warfarin: 0.38% |
| ARISTOTLE (warfarin vs apixaban) | 18,201 | Apixaban: 1.27%<br>Warfarin: 1.6% | Apixaban: 0.24%<br>Warfarin: 0.47% |
| ROCKET AF (warfarin vs rivaroxaban) | 14,264 | Rivaroxaban: 1.7%<br>Warfarin: 2.2% | Rivaroxaban: 0.5%<br>Warfarin: 0.7% |
| ENGAGE AF-TIMI 48 (warfarin vs edoxaban) | 21,105 | Edoxaban: 1.18%<br>Warfarin: 1.5% | (Major bleeding)<br>Edoxaban: 2.75%<br>Warfarin: 3.43% |

J Neurosurg 116:1093–1096, 2012

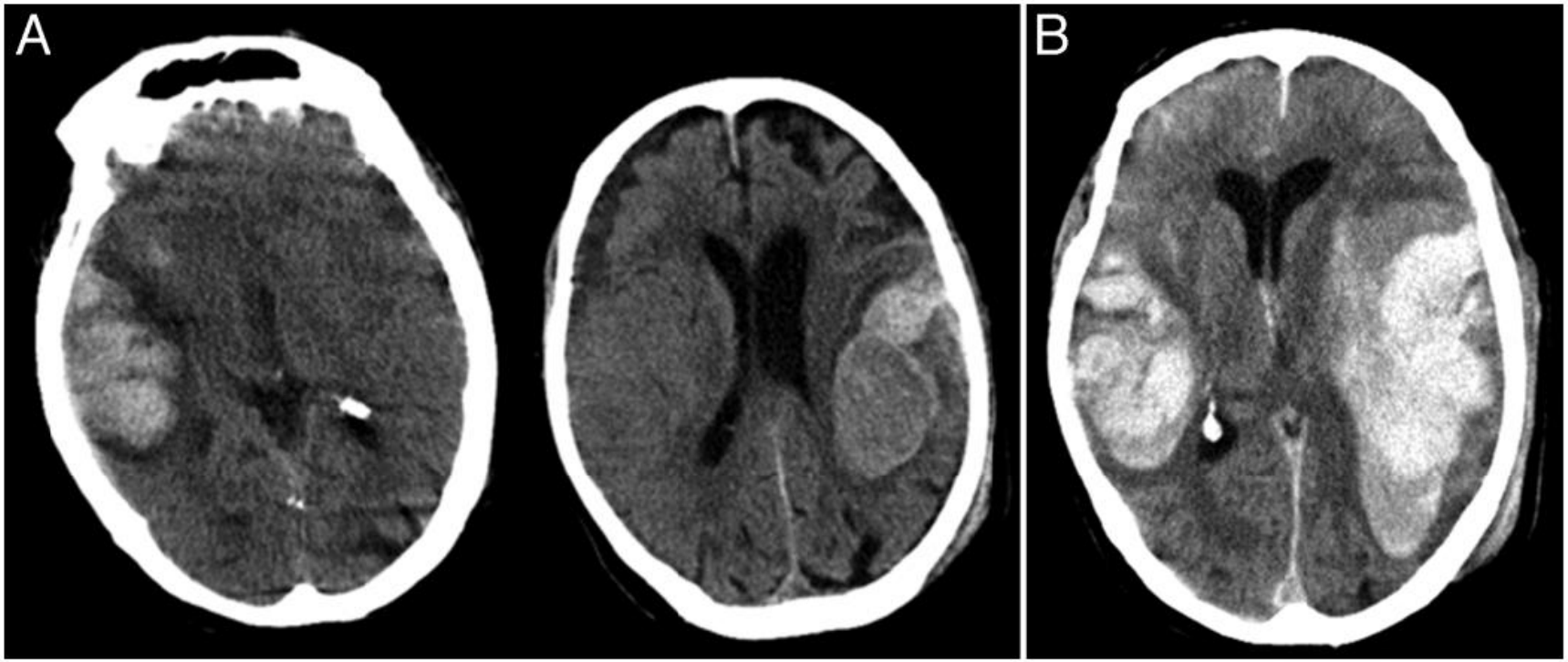
# Neurosurgical complications of direct thrombin inhibitors—catastrophic hemorrhage after mild traumatic brain injury in a patient receiving dabigatran

Case report

SARAH T. GARBER, M.D., WALAVAN SIVAKUMAR, M.D., AND RICHARD H. SCHMIDT, M.D., PH.D.

*Department of Neurosurgery, University of Utah, Salt Lake City, Utah*

Neurosurgical complications of direct thrombin inhibitors



# Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013

**Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.***

| Analysis | Dabigatran | | | Warfarin | | |
|---|---|---|---|---|---|---|
| | No. of Patients | No. of Events | Incidence (no. of events/ 100,000 days at risk) | No. of Patients | No. of Events | Incidence (no. of events/ 100,000 days at risk) |
| **Gastrointestinal hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 10,599 | 16 | 1.6 | 43,541 | 160 | 3.5 |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 12,195 | 19 | 1.6 | 119,940 | 338 | 3.1 |
| **Intracranial hemorrhage** | | | | | | |
| Analysis with required diagnosis of atrial fibrillation | 10,587 | 8 | 0.8 | 43,594 | 109 | 2.4 |
| Sensitivity analysis without required diagnosis of atrial fibrillation | 12,182 | 10 | 0.9 | 120,020 | 204 | 1.9 |

We believe that the large number of reported cases of bleeding associated with dabigatran provides a salient example of stimulated reporting. In this case, such reporting provided a distorted estimate of the comparative bleeding rates associated with dabigatran and warfarin in clinical practice.

Weber effect

Lantigua et al. Critical Care (2015) 19:309
DOI 10.1186/s13054-015-1036-0

CRITICAL CARE

RESEARCH Open Access

# Subarachnoid hemorrhage: who dies, and why?

Hector Lantigua[1†], Santiago Ortega-Gutierrez[2†], J. Michael Schmidt[1], Kiwon Lee[3], Neeraj Badjatia[4], Sachin Agarwal[1,5], Jan Claassen[1,5], E. Sander Connolly[5] and Stephan A. Mayer[6*]

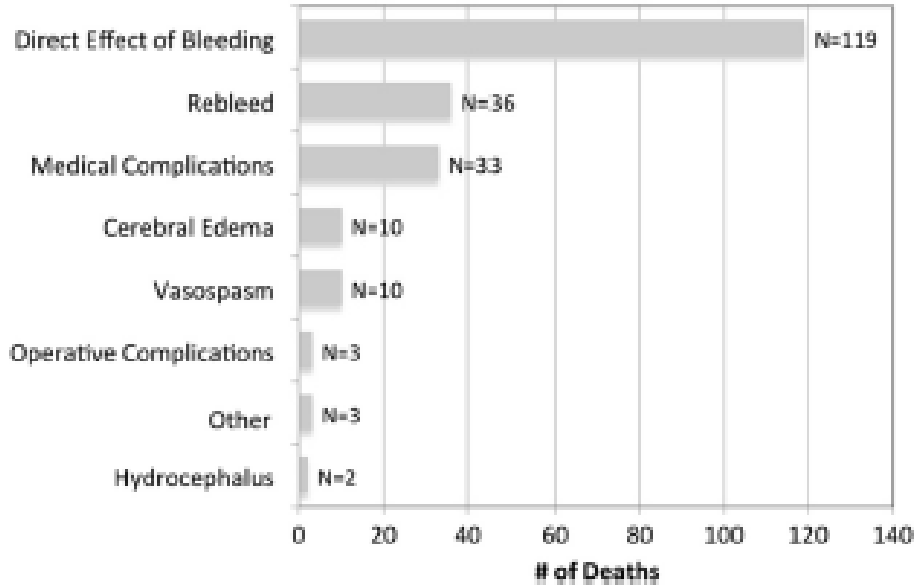



**Fig. 3** Adjudicated causes of death or neurological devastation leading to withdrawal of support. "Other" causes included prolonged coma after refractory status epilepticus, internal carotid artery rupture due to balloon angioplasty, and hemorrhagic conversion of infarct

# Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

Brett Cucchiara, MD; Steven Messe, MD; Lauren Sansing, MD;
Scott Kasner, MD; Patrick Lyden, MD; for the CHANT Investigators

*Stroke* November 2008

**Table 4. Univariate Predictors of Mortality (n=303)**

| | OR (95% CI) | *P* Value |
|---|---|---|
| Age, per year | 1.06 (1.04–1.09) | <0.001 |
| Male sex | 1.53 (0.82–2.88) | 0.18 |
| Hypertension | 1.18 (0.54–2.59) | 0.67 |
| Diabetes | 0.94 (0.47–1.90) | 0.87 |
| Ischemic heart disease | 2.16 (1.06–4.39) | 0.03 |
| Prior stroke | 2.26 (1.03–4.95) | 0.04 |
| Oral anticoagulant therapy | 8.13 (3.19–20.69) | <0.001 |
| Prior antiplatelet use | 0.89 (0.46–1.73) | 0.73 |
| Atrial fibrillation | 3.04 (1.29–7.16) | 0.01 |
| ICH volume, per 10 cc | 1.54 (1.34–1.76) | <0.001 |
| Presence of IVH | 3.23 (1,81–5.78) | <0.001 |
| Lobar location | 3.56 (1.82–6.96) | <0.001 |

# Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

Brett Cucchiara, MD; Steven Messe, MD; Lauren Sansing, MD;
Scott Kasner, MD; Patrick Lyden, MD; for the CHANT Investigators

(*Stroke*. 2008;39:2993-2996.)

| | SICH (n=267) | OAT ICH (n=18) | *P* Value |
|---|---|---|---|
| ICH volume change, median (IQR) | 0.9 mL (0–5.4) | 9.6 mL (0–19.4) | 0.03 |
| >33% ICH expansion | 26% | 56% | 0.006 |
| Any ICH expansion | 65% | 78% | 0.27 |
| | SICH (n=282) | OAT ICH (n=21) | *P* Value |
| Mortality | 17% | 62% | <0.001 |
| mRS 4–6 | 50% | 90% | 0.001 |

*British Journal of Anaesthesia* **113** (S2): ii17–ii25 (2014)
doi:10.1093/bja/aeu397

BJA

# Intracranial haemorrhage: therapeutic interventions and anaesthetic management

P. Fogarty Mack

**Table 1** Determination of the ICH score. GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using ABC/2 method; and IVH, presence of any IVH on initial CT. Reproduced from [15], with permission

| Component | ICH score points |
|---|---|
| GCS score | |
| 3–4 | 2 |
| 5–12 | 1 |
| 13–15 | 0 |
| ICH volume (ml) | |
| ≥30 | 1 |
| <30 | 0 |
| IVH | |
| Yes | 1 |
| No | 0 |
| Infratentorial origin of ICH | |
| Yes | 1 |
| No | 0 |
| Age (yr) | |
| ≥80 | 1 |
| <80 | 0 |
| Total ICH score | 0–6 |

*British Journal of Anaesthesia* **113** (S2): ii17–ii25 (2014)
doi:10.1093/bja/aeu397

BJA

# Intracranial haemorrhage: therapeutic interventions and anaesthetic management

P. Fogarty Mack

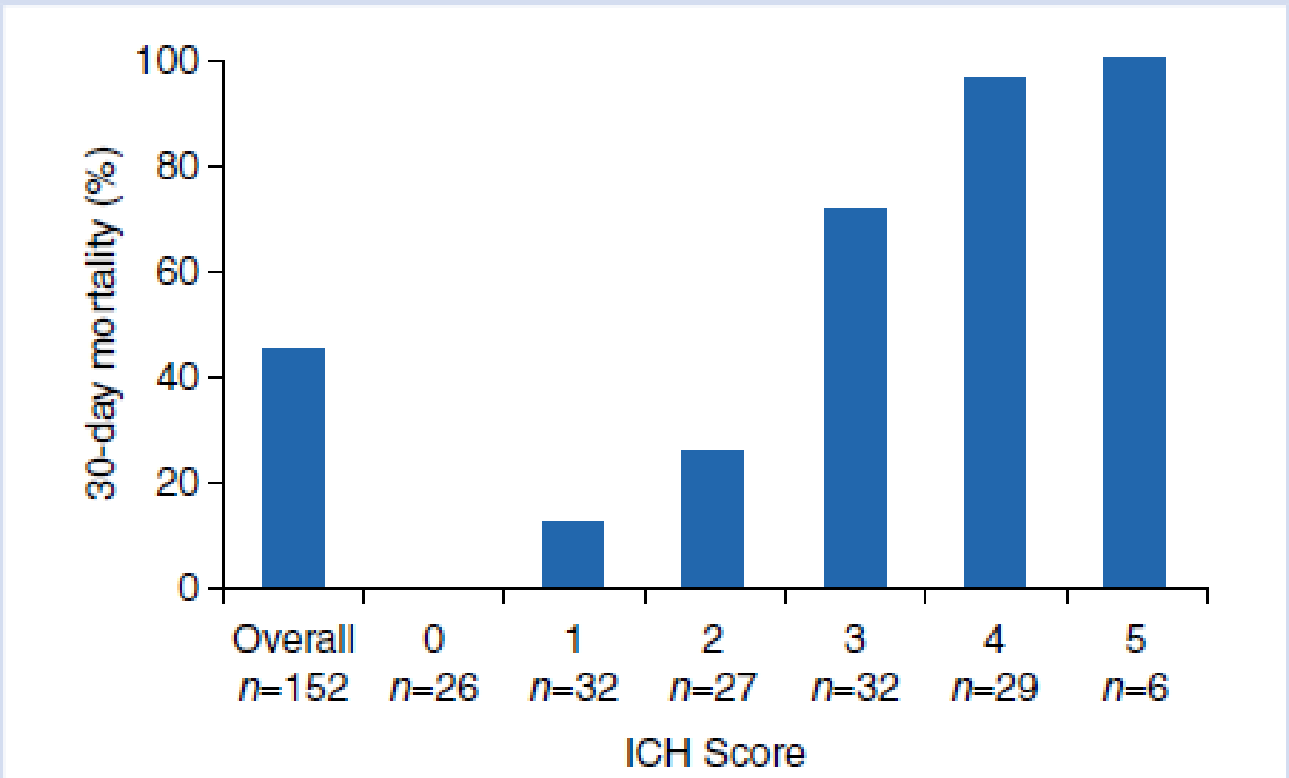



**Fig 1** ICH score and mortality. Reproduced from [15], with permission

J Neurosurg (Suppl) 121:1–20, 2014


# Race against the clock: Overcoming challenges in the management of anticoagulant-associated intracerebral hemorrhage

PETER LE ROUX, M.D.,[1] CHARLES V. POLLACK JR., M.A., M.D.,[2] MELISSA MILAN, M.D.,[3,4] AND ALISA SCHAEFER, PH.D.[3]

- Pt with anticoagulation therapy
  - Any type of intracranial hemorrhage
    - Subdural hematoma
    - Epidural hematoma
    - Subarachnoid hemorrhage
    - Intracerebral hemorrhage
    - Urgent correction of coagulopathy
      - Expansion
      - Limit tissue damage
      - Facilitate surgical intervention

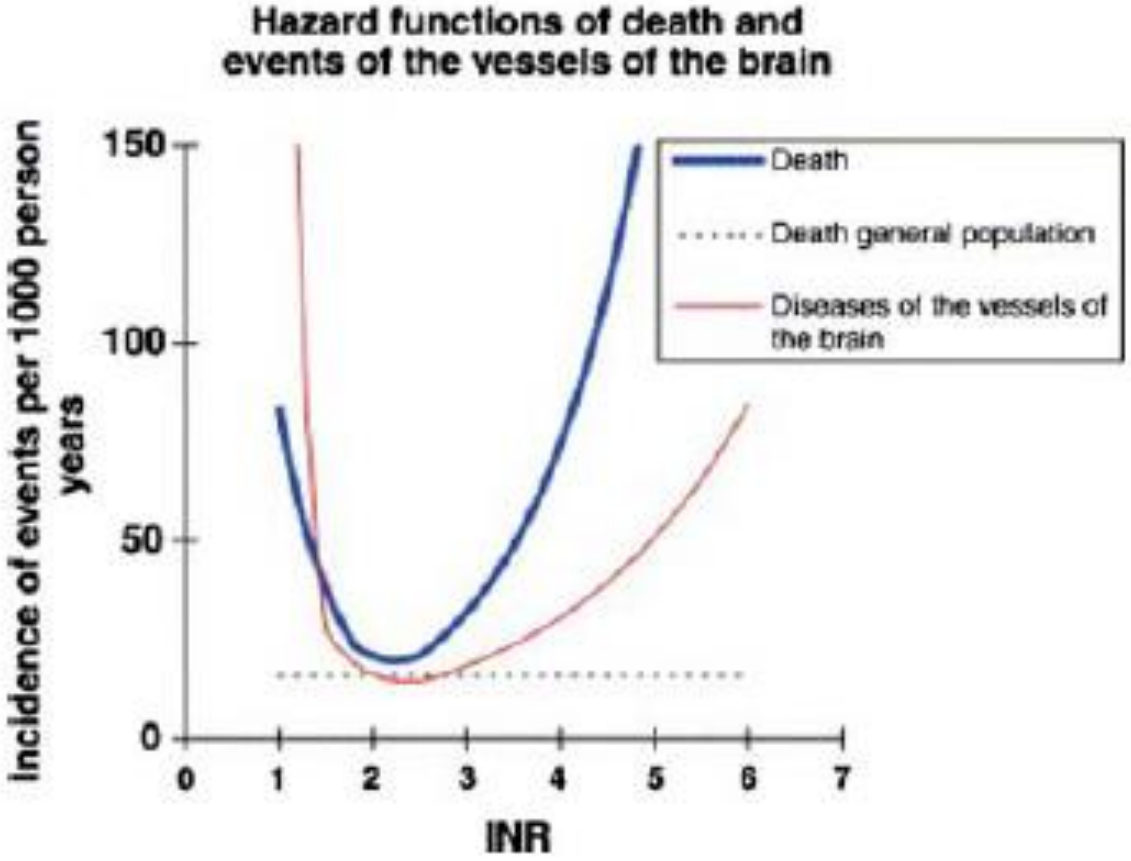



**Fig. 1** Relationship between INR and death and events of vessels of the brain in the 21,967 Swedes with atrial fibrillation. The nadir of the U-shaped curves occurred at 2.2 for death and 2.4 for cerebral vascular events. From Oden et al. [8] with permission

Original Investigation

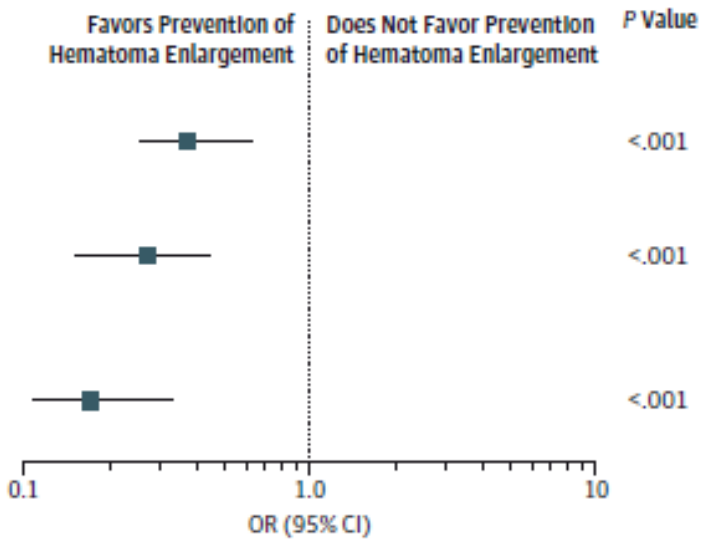
# Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

Joji B. Kuramatsu, MD; Stefan T. Gerner, MD; Peter D. Schellinger, MD; Jörg Glahn, MD; Matthias Endres, MD; Jan Sobesky, MD; Julia Flechsenhar, MD; Hermann Neugebauer, MD; Eric Jüttler, MD; Armin Grau, MD; Frederick Palm, MD; Joachim Röther, MD; Peter Michels, MD; Gerhard F. Hamann, MD; Joachim Hüwel, MD; Georg Hagemann, MD; Beatrice Barber, MD; Christoph Terborg, MD; Frank Trostdorf, MD; Hansjörg Bäzner, MD; Aletta Roth, MD; Johannes Wöhrle, MD; Moritz Keller, MD; Michael Schwarz, MD; Gernot Reimann, MD; Jens Volkmann, MD; Wolfgang Müllges, MD; Peter Kraft, MD; Joseph Classen, MD; Carsten Hobohm, MD; Markus Horn, MD; Angelika Milewski, MD; Heinz Reichmann, MD; Hauke Schneider, MD; Eik Schimmel, MD; Gereon R. Fink, MD; Christian Dohmen, MD; Henning Stetefeld, MD; Otto Witte, MD; Albrecht Günther, MD; Tobias Neumann-Haefelin, MD; Andras E. Racs, MD; Martin Nueckel, MD; Frank Erbguth, MD; Stephan P. Kloska, MD; Arnd Dörfler, MD; Martin Köhrmann, MD; Stefan Schwab, MD; Hagen B. Huttner, MD

*JAMA*. 2015;313(8):824-836. doi:10.1001/jama.2015.0846

**Figure 3. Adjusted Graphical Regression Analysis of Combined Associations of INR Reversal, Systolic Blood Pressure, and Timing With Hematoma Enlargement**

| | No. of Patients | Patients With Hematoma Enlargement, No. (%) | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| INR <1.3 | | | | |
| Achieved | 432 | 116 (26.9) | 0.37 (0.26-0.59) | <.001 |
| Did not achieve | 421 | 191 (45.4) | | |
| INR <1.3 within 4 hours | | | | |
| Achieved | 217 | 43 (19.8) | 0.27 (0.15-0.43) | <.001 |
| Did not achieve | 636 | 264 (41.5) | | |
| INR <1.3 within 4 hours and systolic BP <160 mm Hg within 4 hours | | | | |
| Achieved | 193 | 35 (18.1) | 0.17 (0.11-0.33) | <.001 |
| Did not achieve | 498 | 220 (44.2) | | |



European Heart Journal (2013) **34**, 489–500
doi:10.1093/eurheartj/ehs408

REVIEW

*New drugs*

# Acute management of bleeding in patients on novel oral anticoagulants

**Deborah M. Siegal[1] and Mark A. Crowther[1,2]***

[1]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Ont., Canada; and [2]Laboratory Medicine, St Joseph's Healthcare and Hamilton Health Sciences, Hamilton

**Table 2** Effect of novel oral anticoagulants on commonly used coagulation tests

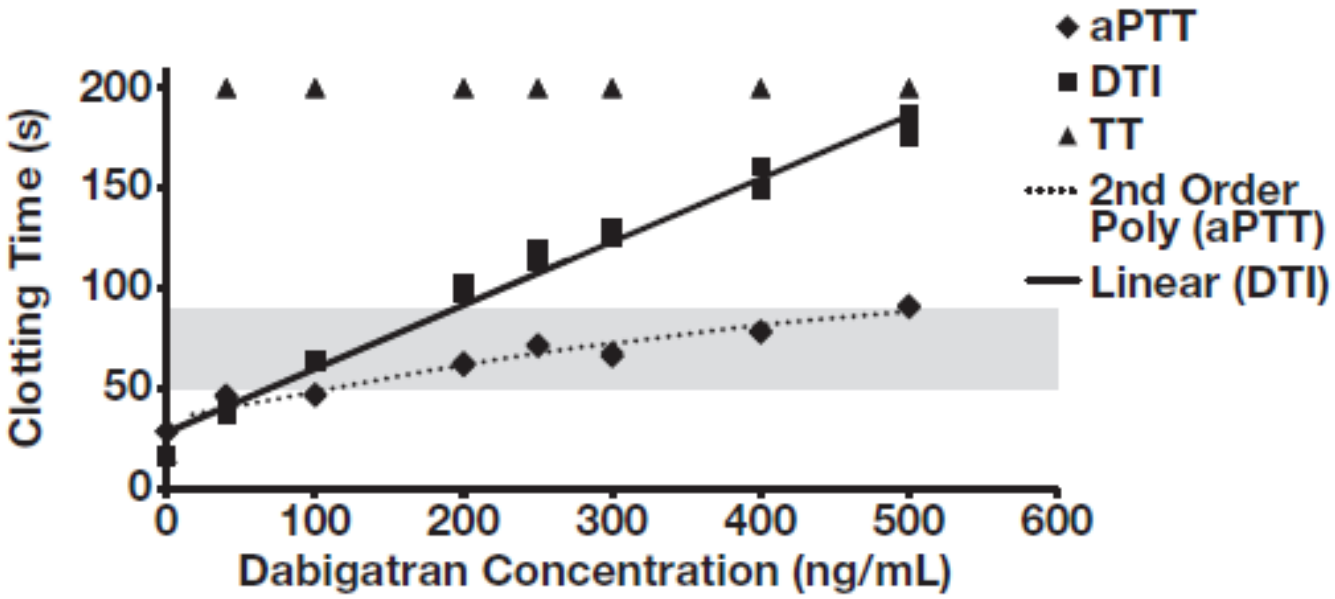
| Novel anticoagulant | Prothrombin time (PT) | Activated partial thromboplastin time (aPTT) | Thrombin clotting time (TCT) | Ecarin clotting time | Haemoclot assay | Anti-factor Xa activity | |
|---|---|---|---|---|---|---|---|
| | | | | | | Clot-based | Chromogenic |
| Dabigatran | ↑ or no change (low sensitivity, varies with reagents) | ↑ (varies with reagents) | ↑ | ↑ | ↑[a] | ↑ | ND |
| Rivaroxaban | ↑ or no change (not sensitive at low concentrations, varies with reagents) | ↑ or no change (less sensitive than PT) | — | — | — | ↑ | ↑[a] (sensitive and specific when calibration curve used) |
| Apixaban | ↑ or no change (other tests more sensitive, may vary with reagents) | ↑ or no change (other tests more sensitive, may vary with reagents) | — | — | — | ↑[a] | ↑[a] |

ND, no data.
[a]Preferred test. Adapted from previously published review articles.[41,59]

# Plasma-Diluted Thrombin Time to Measure Dabigatran Concentrations During Dabigatran Etexilate Therapy

*Scott T. Avecilla, MD, PhD,[1,2] Chris Ferrell, MT(ASCP),[1] Wayne L. Chandler, MD,[1,3] and Morayma Reyes, MD, PhD[1]*

*Am J Clin Pathol* 2012;137:572-574
DOI: 10.1309/AJCPAU7OQM0SRPZQ



Journal of Clinical Neuroscience 20 (2013) 1350–1356

Contents lists available at SciVerse ScienceDirect

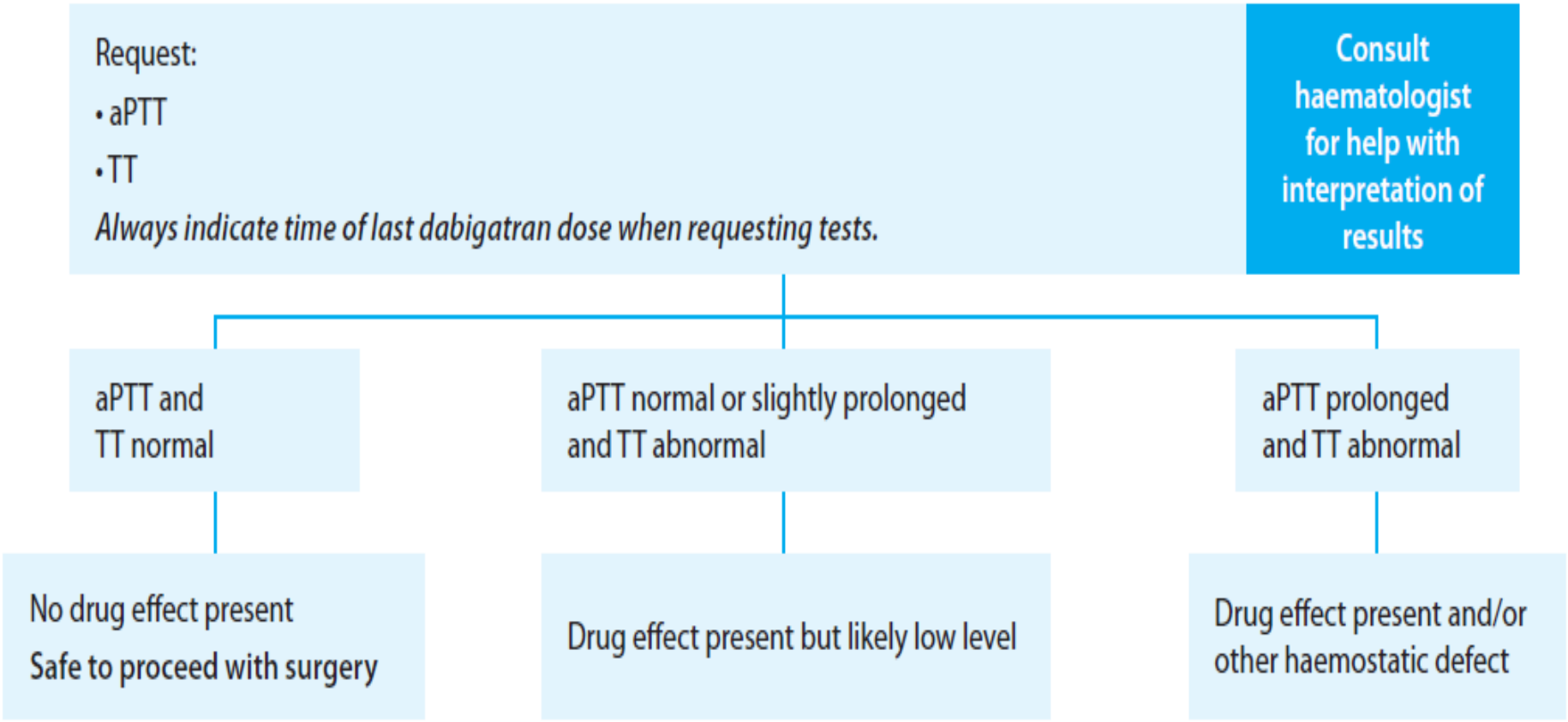
Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

# New-generation oral anticoagulants for the prevention of stroke: Implications for neurosurgery

Tarek Y. El Ahmadieh [a], Salah G. Aoun [b], Marc R. Daou [a], Najib E. El Tecle [a], Rudy J. Rahme [a], Randall B. Graham [a], Joseph G. Adel [a], H. Hunt Batjer [b], Bernard R. Bendok [a,*]



# Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: Executive Summary. A Statement for Healthcare Professionals From the Neurocritical Care Society and the Society of Critical Care Medicine

Jennifer A. Frontera, MD, FNCS[1]; John J. Lewin III, PharmD, MBA, FASHP, FCCM, FNCS[2]; Alejandro A. Rabinstein, MD, FNCS[3]; Imo P. Aisiku, MD, MBA, FCCP[4]; Anne W. Alexandrov, PhD, RN, ANVP-BC, FAAN[5,6]; Aaron M. Cook, PharmD, BCPS[7]; Gregory J. del Zoppo, MD, MS[8]; Monisha Kumar, MD[9]; Ellinor I. B. Peerschke, PhD, FAHA[10]; Michael F. Stiefel, MD, PhD[11]; Jeanne S. Teitelbaum, MD[12,13]; Katja E. Wartenberg, MD[14]; Cindy L. Zerfoss, MSN, RN, ACNP-BC[15]

Critical Care Medicine December 2016 • Volume 44 • Number 12

| Antithrombotic | Reversal Agent |
|---|---|
| Vitamin K antagonists | If INR ≥ 1.4:<br>vitamin K 10 mg IV, plus 3- or 4-factor PCC IV (dosing based on weight, INR, and PCC type) or fresh frozen plasma 10–15 mL/kg IV if PCC not available |
| Direct factor Xa inhibitors | Activated charcoal (50 g) within 2 hr of ingestion, activated PCC (FEIBA) 50 U/kg IV or 4-factor PCC 50 U/kg IV |
| DTIs | For dabigatran reversal:<br>Activated charcoal (50 g) within 2 hr of ingestion, and idarucizumab 5 g IV (in two 2.5 g/50 mL vials)<br>Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration<br>For other DTIs:<br>Activated PCC (FEIBA) 50 U/kg IV or<br>4-factor PCC 50 U/kg IV |
| Unfractionated heparin | Protamine 1 mg IV for every 100 units of heparin administered in the previous 2–3 hr (up to 50 mg in a single dose) |
| LMWHs | Enoxaparin:<br>Dosed within 8 hr: protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose)<br>Dosed within 8–12 hr: protamine 0.5 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose)<br>Minimal utility in reversal > 12 hr from dosing<br>Dalteparin, nadroparin, and tinzaparin:<br>Dosed within 3–5 half-lives of LMWH: protamine 1 mg IV per 100 anti-Xa units of LMWH (up to 50 mg in a single dose) or<br>rFVIIa 90 µg/kg IV if protamine is contraindicated |
| Danaparoid | rFVIIa 90 µg/kg IV |
| Pentasaccharides | Activated PCC (FEIBA) 20 U/kg IV or rFVIIa 90 µg/kg IV |
| Thrombolytic agents (plasminogen activators) | Cryoprecipitate 10 units IV or antifibrinolytics (tranexamic acid 10–15 mg/kg IV over 20 min or ε-aminocaproic acid 4–5 g IV) if cryoprecipitate is contraindicated |
| Antiplatelet agents | Desmopressin 0.4 µg/kg IV × 1<br>If neurosurgical intervention: platelet transfusion (one apheresis unit) |

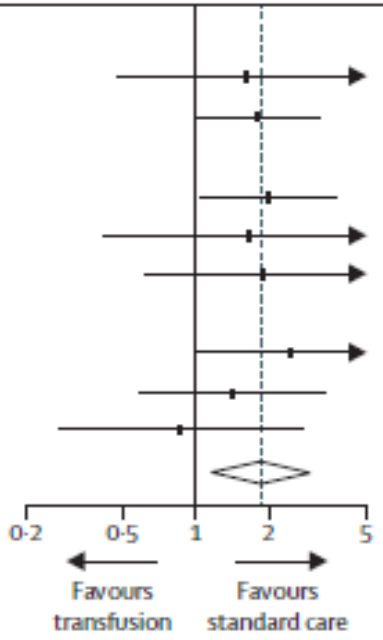
DTI = direct thrombin inhibitor, FEIBA = factor eight inhibitor bypassing activity, INR = international normalized ratio, LMWH = low molecular weight heparin, PCC = prothrombin complex concentrates, rFVIIa = recombinant factor VIIa.

# Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

*M Irem Baharoglu*, Charlotte Cordonnier*, Rustam Al-Shahi Salman*, Koen de Gans, Maria M Koopman, Anneke Brand, Charles B Majoie, Ludo F Beenen, Henk A Marquering, Marinus Vermeulen, Paul J Nederkoorn, Rob J de Haan, Yvo B Roos, for the PATCH Investigators†*

*Lancet* 2016; 387: 2605–13

| | n/N | OR (95% CI) | p value |
|---|---|---|---|
| **Type of antiplatelet therapy** | | | 0·78 |
| Dual antiplatelet therapy | 35/189 | 1·62 (0·48–5·45) | |
| Single antiplatelet therapy | 154/189 | 1·80 (1·02–3·18) | |
| **Country** | | | 0·94 |
| Netherlands | 120/190 | 1·97 (1·03–3·77) | |
| UK | 31/190 | 1·63 (0·42–6·31) | |
| France | 39/190 | 1·88 (0·61–5·74) | |
| **Haematoma volume** | | | 0·14 |
| Haematoma volume ≤7 mL | 67/183 | 2·46 (1·02–5·94) | |
| Haematoma volume >7 to 30 mL | 65/183 | 1·40 (0·58–3·39) | |
| Haematoma volume >30 mL | 51/183 | 0·87 (0·27–2·76) | |
| **Unadjusted overall estimate** | | **1·84 (1·10–3·08)** | |




**Interpretation** Platelet transfusion seems inferior to standard care for people taking antiplatelet therapy before intracerebral haemorrhage. Platelet transfusion cannot be recommended for this indication in clinical practice.

J Thromb Thrombolysis
DOI 10.1007/s11239-013-0933-9

# Dabigatran-associated subdural hemorrhage: using thromboelastography (TEG®) to guide decision-making

Ron Neyens · Nicole Bohm · Madelyne Cearley · Charles Andrews · Julio Chalela



**Originalien**

Anaesthesist 2012 · 61:948–953
DOI 10.1007/s00101-012-2091-4
Received: 7 May 2012
Revised: 30 August 2012
Accepted: 7 September 2012
Published online: 7. Oktober 2012


M. Casutt · C. Konrad · G. Schuepfer
Department of Anaesthesiology and Intensive Care, Kantonsspital Lucerne, Lucerne 16

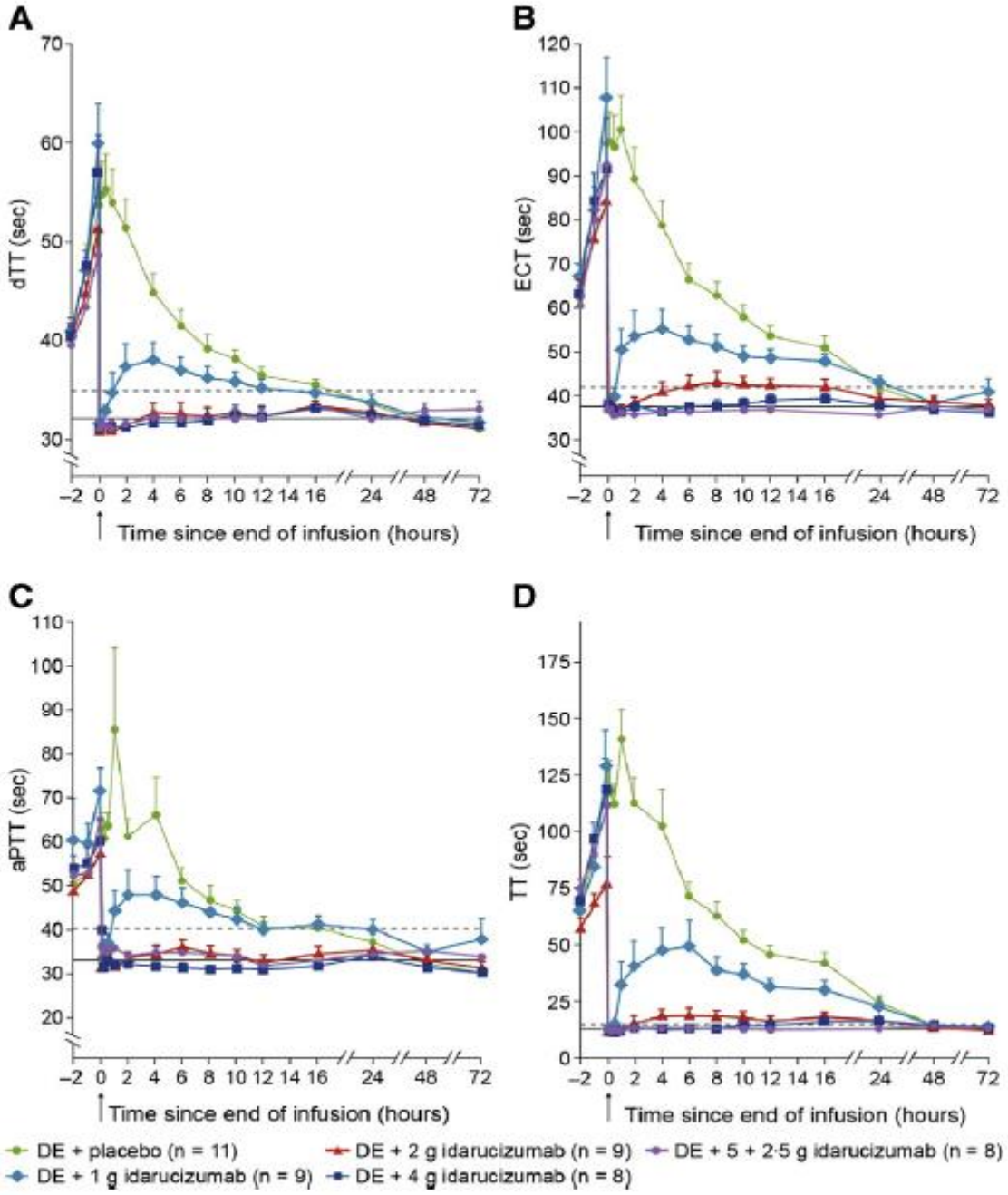
# Effect of rivaroxaban on blood coagulation using the viscoelastic coagulation test ROTEM™

J Thromb Thrombolysis (2017) 43:306–317
DOI 10.1007/s11239-017-1476-2

# Real-life experience with the specific reversal agent idarucizumab for the management of emergency situations in dabigatran-treated patients: a series of 11 cases

Milan R. Vosko[1] · Christof Bocksrucker[2] · Rafał Drwiła[3] · Petr Dulíček[4] · Tomas Hauer[5] · Johannes Mutzenbach[6] · Christoph J. Schlimp[7] · David Špinler[8,9] · Thomas Wolf[10] · Daša Zugwitz[11]

Published online: 16 February 2017


A
dTT (sec)
70
60
50
40
30
–2 0 2 4 6 8 10 12 14 16 24 48 72
Time since end of infusion (hours)
B
ECT (sec)
120
110
100
90
80
70
60
50
40
30
–2 0 2 4 6 8 10 12 14 16 24 48 72
Time since end of infusion (hours)
C
aPTT (sec)
110
100
90
80
70
60
50
40
30
20
–2 0 2 4 6 8 10 12 14 16 24 48 72
Time since end of infusion (hours)
D
TT (sec)
175
150
125
100
75
50
25
0
–2 0 2 4 6 8 10 12 14 16 24 48 72
Time since end of infusion (hours)
DE + placebo (n = 11)
DE + 2 g idarucizumab (n = 9)
DE + 5 + 2·5 g idarucizumab (n = 8)
DE + 1 g idarucizumab (n = 9)
DE + 4 g idarucizumab (n = 8)

ARTICLES

nature medicine

# A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa

Genmin Lu[1], Francis R DeGuzman[2], Stanley J Hollenbach[2], Mark J Karbarz[1], Keith Abe[2], Gail Lee[2], Peng Luan[1], Athiwat Hutchaleelaha[3], Mayuko Inagaki[3], Pamela B Conley[1], David R Phillips[1] & Uma Sinha[1]

VOLUME 19 | NUMBER 4 | APRIL 2013 NATURE MEDICINE

Vascular Health and Risk Management

Dovepress

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Open Access Full Text Article

REVIEW

# Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa, and idarucizumab

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
17 February 2016
Number of times this article has been viewed

# Single-Dose Ciraparantag Safely and Completely Reverses Anticoagulant Effects of Edoxaban

JE Ansell et al. Thromb Haemost 117 (2), 238-245. 2016 Nov 17. more

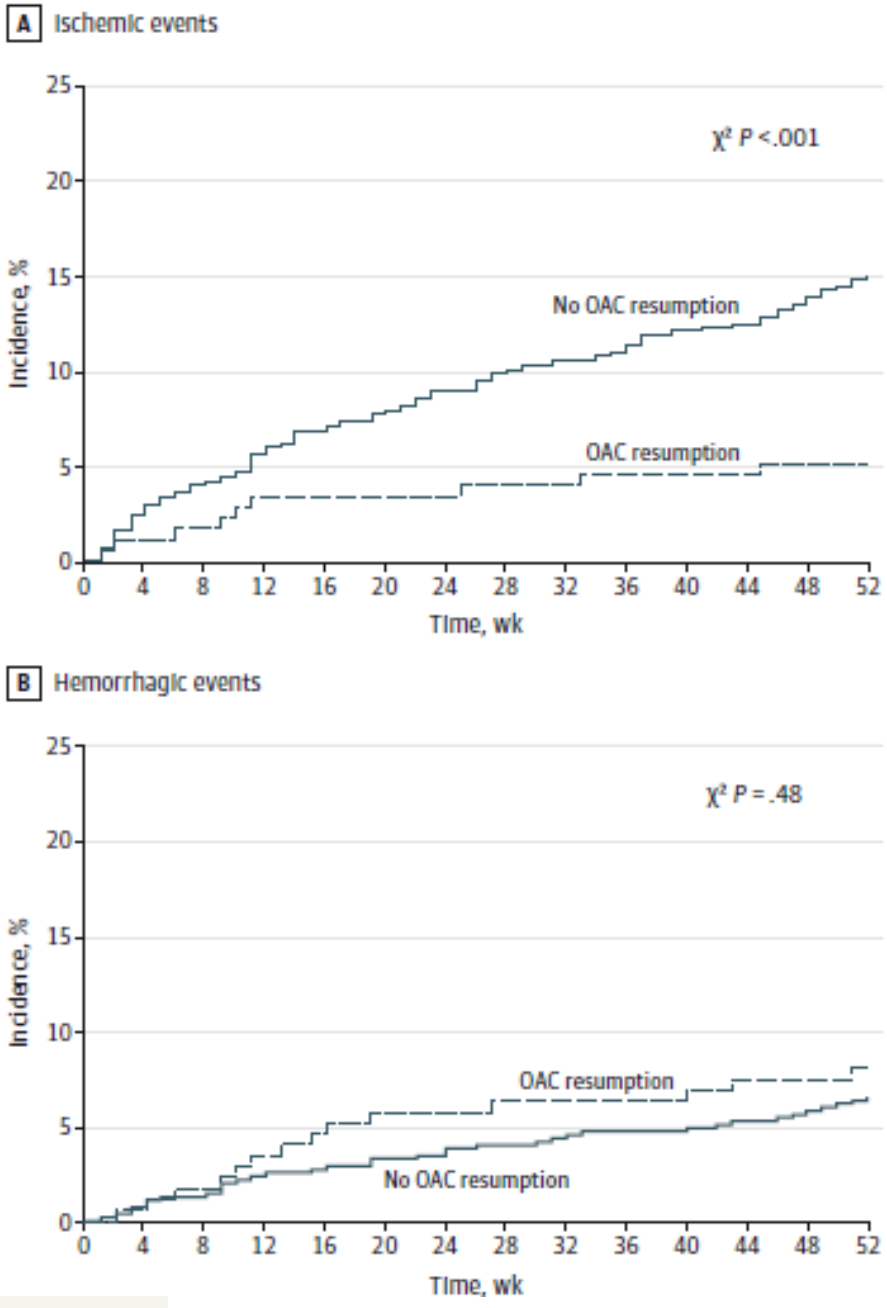
blood
2012 120: 2954-2962
Prepublished online August 28, 2012;
doi:10.1182/blood-2012-06-415943

**How I treat anticoagulated patients undergoing an elective procedure or surgery**

Alex C. Spyropoulos and James D. Douketis

## Table 5. Postoperative resumption of new oral anticoagulants: a suggested management approach

| Drug | Low bleeding risk surgery | High bleeding risk surgery |
|---|---|---|
| Dabigatran | Resume on day after surgery (24 h postoperative), 150 mg twice daily | Resume 2-3 days after surgery (48-72 h postoperative), 150 mg twice daily* |
| Rivaroxaban | Resume on day after surgery (24 h postoperative), 20 mg once daily | Resume 2-3 days after surgery (48-72 h postoperative), 20 mg once daily† |
| Apixaban | Resume on day after surgery (24 h postoperative), 5 mg twice daily | Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily† |




*JAMA*. 2015;313(8):824-836. doi:10.1001/jama.2015.0846