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School of Medicine

New Agents for Atrial Fibrillation: How Will They Affect Intracerebral Hemorrhage Management?



Charles R. Wira, III, MD
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YNHH Stroke Program



Disclosures

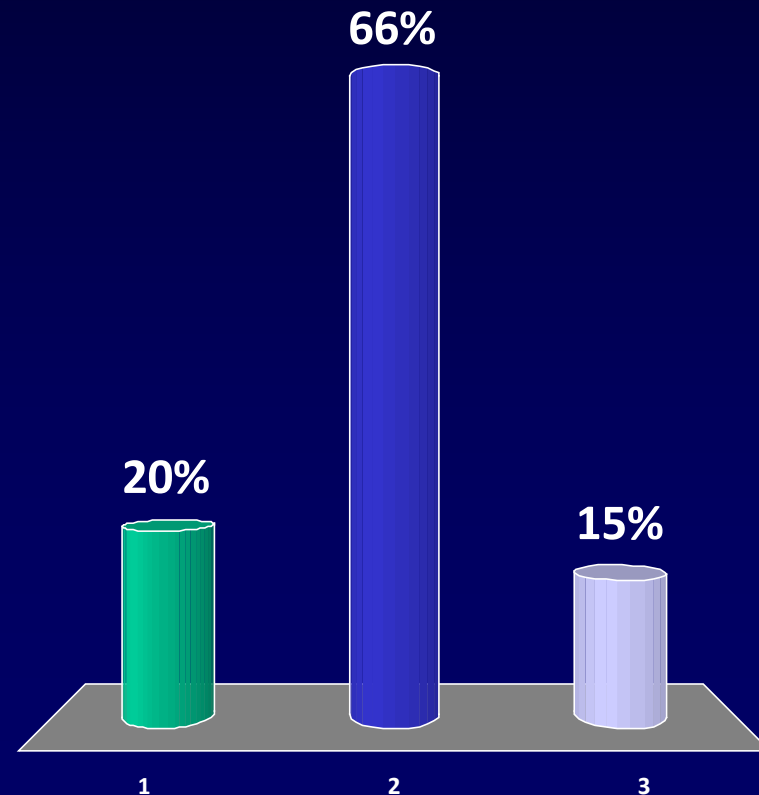
- Charles R. Wira, III, MD
- Assistant Prof. of Emer. Medicine
- YNHH Stroke Service
- No Disclosures



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School of Medicine

Has your institution managed ICH in a patient on either Dabigatran or Apixaban?

1. Yes
2. No
3. Unsure



Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage

S.M. Davis, MD; J. Broderick, MD; M. Hennerici, MD; N.C. Brun, MD; M.N. Diringer, MD; S.A. Mayer, MD; K. Begtrup, MSc; and T. Steiner, MD, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators

Abstract—Background: Although volume of intracerebral hemorrhage (ICH) is a predictor of mortality, it is unknown whether subsequent hematoma growth further increases the risk of death or poor functional outcome. **Methods:** To determine if hematoma growth independently predicts poor outcome, the authors performed an individual meta-analysis of patients with spontaneous ICH who had CT within 3 hours of onset and 24-hour follow-up. Placebo patients were pooled from three trials investigating dosing, safety, and efficacy of rFVIIa (n = 115), and 103 patients from the Cincinnati study (total 218). Other baseline factors included age, gender, blood glucose, blood pressure, Glasgow Coma Score (GCS), intraventricular hemorrhage (IVH), and location. **Results:** Overall, 72.9% of patients exhibited some degree of hematoma growth. Percentage hematoma growth (hazard ratio [HR] 1.05 per 10% increase [95% CI: 1.03, 1.08; $p < 0.0001$]), initial ICH volume (HR 1.01 per mL [95% CI: 1.00, 1.02; $p = 0.003$]), GCS (HR 0.88 [95% CI: 0.81, 0.96; $p = 0.003$]), and IVH (HR 2.23 [95% CI: 1.25, 3.98; $p = 0.007$]) were all associated with increased mortality. Percentage growth (cumulative OR 0.84 [95% CI: 0.75, 0.92; $p < 0.0001$]), initial ICH volume (cumulative OR 0.94 [95% CI: 0.91, 0.97; $p < 0.0001$]), GCS (cumulative OR 1.46 [95% CI: 1.21, 1.82; $p < 0.0001$]), and age (cumulative OR 0.95 [95% CI: 0.92, 0.98; $p = 0.0009$]) predicted outcome modified Rankin Scale. Gender, location, blood glucose, and blood pressure did not predict outcomes. **Conclusions:** Hematoma growth is an independent determinant of both mortality and functional outcome after intracerebral hemorrhage. Attenuation of growth is an important therapeutic strategy.

NEUROLOGY 2006;66:1175–1181



Figure 3. Rapid Expansion of Hematoma.

The first CT scan (Panel A) was obtained one hour after the patient presented and was followed by neurologic deterioration and expansion of the hematoma visible on the CT scan obtained six hours after presentation (Panel B).



Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage

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Abstract—Background: Although volume of intracerebral hemorrhage (ICH) is a predictor of mortality, it is unknown whether subsequent hematoma growth further increases the risk of death or poor functional outcome. **Methods:** To

Oral Anticoagulation COAGULOPATHY

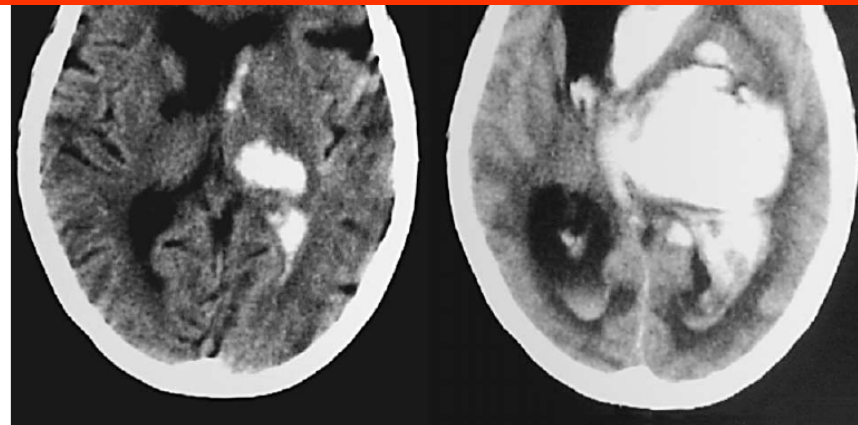
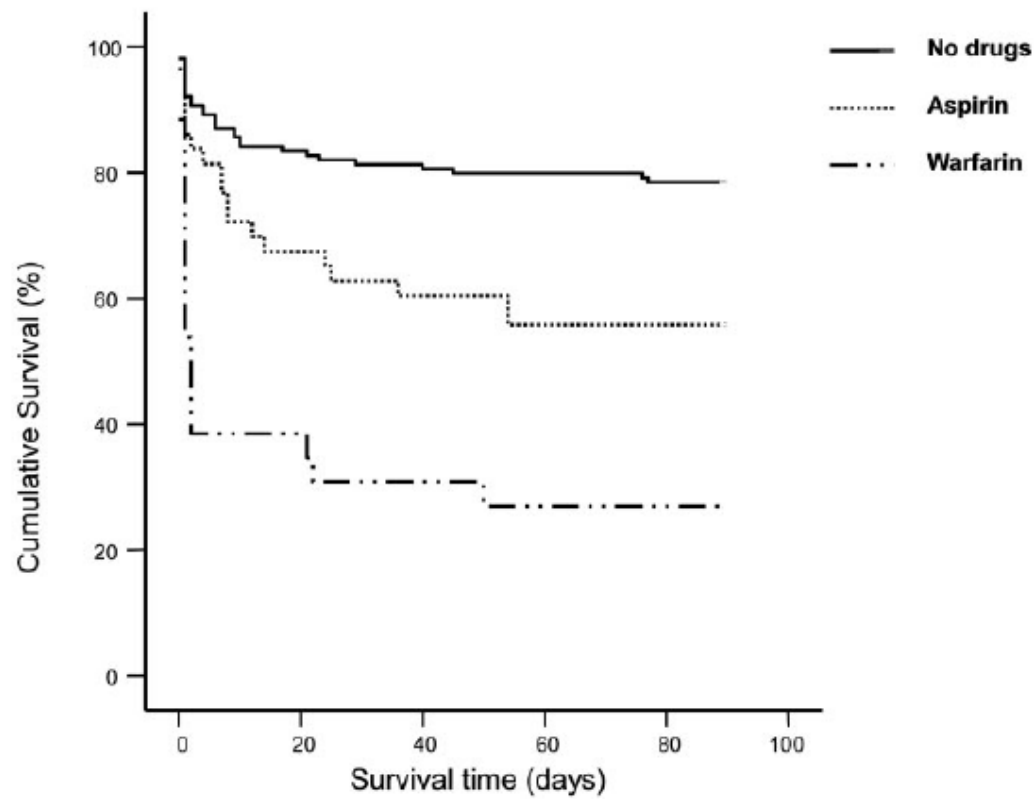


Figure 3. Rapid Expansion of Hematoma.

The first CT scan (Panel A) was obtained one hour after the patient presented and was followed by neurologic deterioration and expansion of the hematoma visible on the CT scan obtained six hours after presentation (Panel B).



Three-month survival of 208 subjects with ICH according to use of aspirin or warfarin (nonusers of aspirin/warfarin, n=138; aspirin users, n=44; warfarin users, n=26).

Timing of Fresh Frozen Plasma Administration and Rapid Correction of Coagulopathy in Warfarin-Related Intracerebral Hemorrhage

Joshua N. Goldstein, MD, PhD; Stephen H. Thomas, MD, MPH; Virginia Frontiero; Annelise Joseph; Chana Engel, BA; Ryan Snider, BA; Eric E. Smith, MD, MPH; Stephen M. Greenberg, MD, PhD; Jonathan Rosand, MD, MSc

Background and Purpose—Anticoagulation-related intracerebral hemorrhage (ICH) is often fatal, and rapid reversal of anticoagulation is the most appealing strategy currently available for treatment. We sought to determine whether particular emergency department (ED) interventions are effective in reversing coagulopathy and improving outcome.

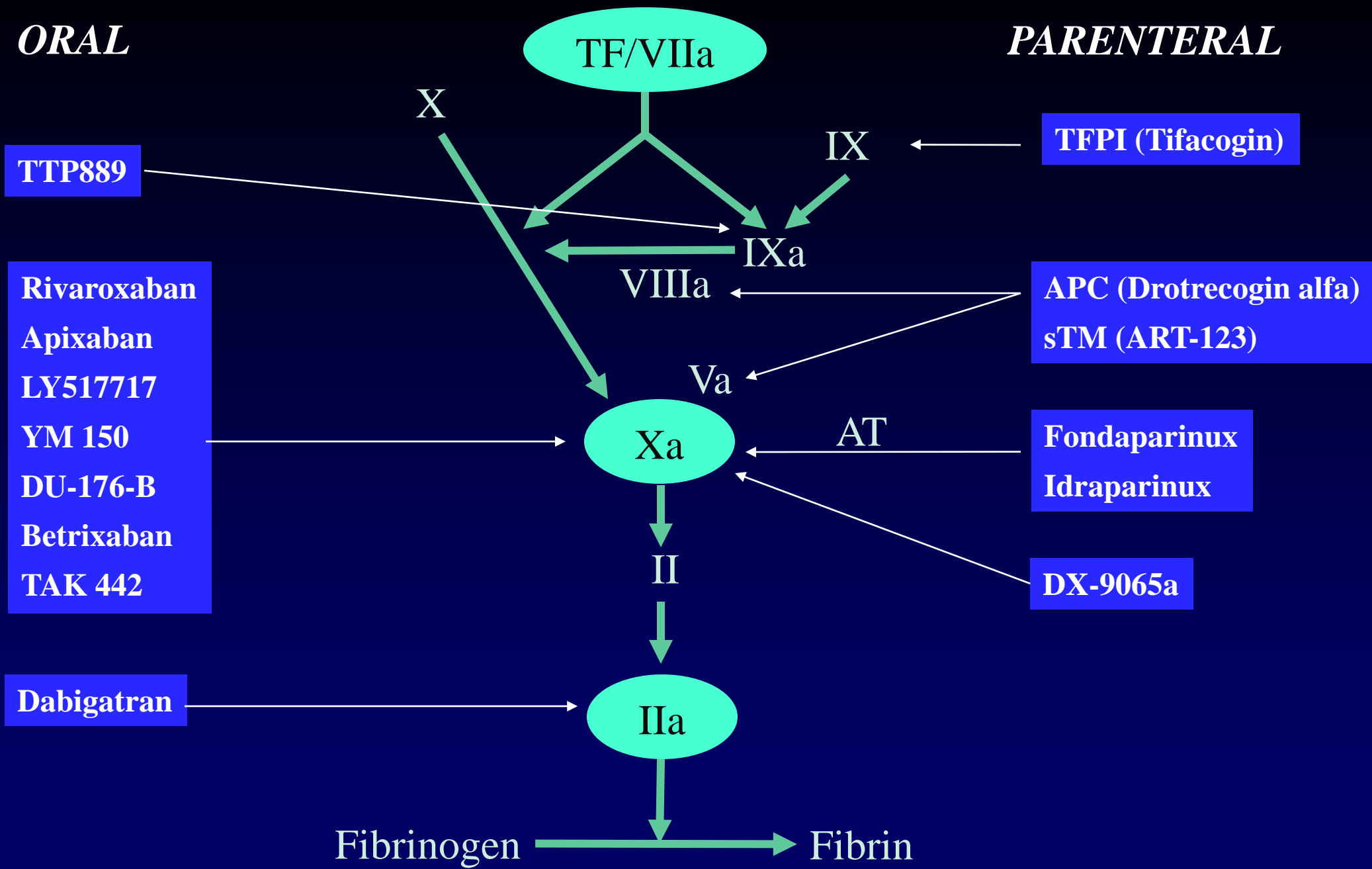
Methods—Consecutive patients with warfarin-related ICH presenting to an urban tertiary care hospital from 1998 to 2004 were prospectively captured in a database. ED records were retrospectively reviewed for dose and timing of fresh-frozen plasma (FFP) and vitamin K, as well as serial coagulation measures. After excluding patients with incomplete ED records, do-not-resuscitate orders established in the ED, initial international normalized ratio (INR) ≤ 1.4 , and for whom no repeat INR was performed, 69 patients were available for analysis. The primary outcome was a documented INR ≤ 1.4 within 24 hours of ED presentation.

Results—Patients whose INR was successfully reversed within 24 hours had a shorter median time from diagnosis to first dose of FFP (90 minutes versus 210 minutes; $P=0.02$). In multivariable analysis, shorter time to vitamin K, as well as FFP, predicted INR correction. Every 30 minutes of delay in the first dose of FFP was associated with a 20% decreased odds of INR reversal within 24 hours (odds ratio, 0.8; 95% CI, 0.63 to 0.99). Dosing of FFP and vitamin K had no effect. No ED intervention was associated with improved clinical outcome.

Conclusions—Time to treatment is the most important determinant of 24-hour anticoagulation reversal. Although additional study is required to determine the clinical benefit of rapid reversal of anticoagulation, minimizing delays in FFP administration is a prudent first step in emergency management of warfarin-related ICH. (*Stroke*. 2006;37:151-155.)

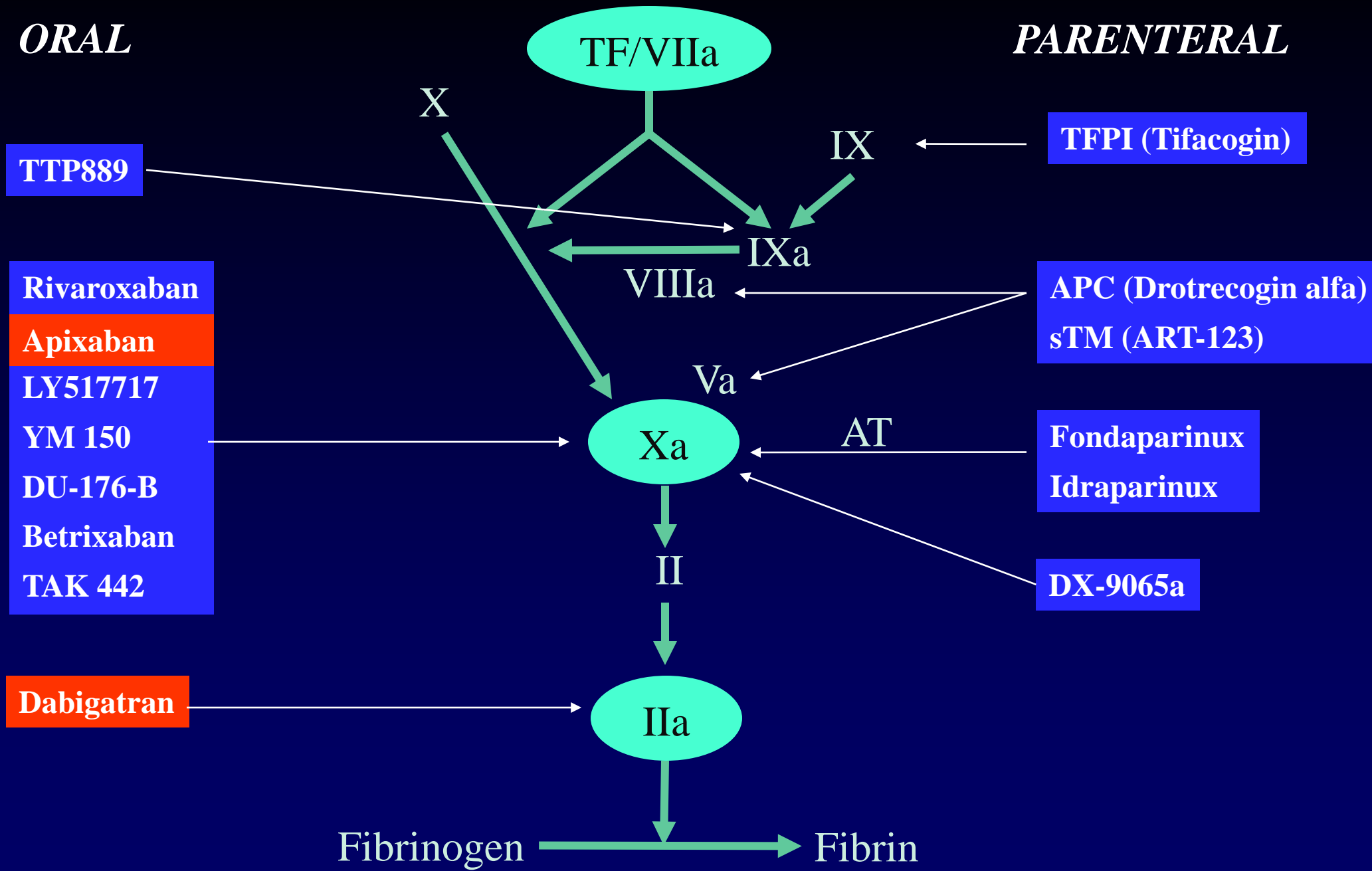
ORAL

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ORAL

PARENTERAL



Deaths prompt dabigatran safety advisory in Japan

AUGUST 17, 2011 Shelley Wood



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8 COMMENT READ LATER PRINT FONT SIZE CITE

Tokyo, Japan - The Japanese **Ministry of Health, Labor, and Welfare** has issued a safety advisory in that country warning of the potential for adverse events with **dabigatran** (Prazaxa in Japan; Pradaxa elsewhere, Boehringer Ingelheim), following the deaths of five patients. The advisory notes that there have been 81 cases of serious side effects, including gastrointestinal bleeding, since the launch of dabigatran; the drug has been used in around 64 000 people since its launch in Japan in January 2011.

"Within this group, treatment with Prazaxa could not be completely ruled out as a cause of death in five patients, one of whom had kidney failure (a contraindication) and four of whom were aged over 80," Boehringer Ingelheim spokesperson **Dr Reinhard Malin** confirmed to **heartwire** in an email.

According to Malin, the Japanese branch of the company has advised physicians to carefully monitor for signs of anemia and bleeding and emphasized the need for an immediate response if these side effects develop. "Physicians in Japan are recommended to perform renal-function tests before and during treatment, with doses to be reduced or treatment stopped upon signs of renal impairment or bleeding."

Treatment With New Anticoagulation Agents

THE FAR SIDE

By GARY LARSON



"C'mon, c'mon — it's either one or the other."

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 17, 2009

VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RELY: Complications

Event	Dabigatran 110mg (N=6015)		Dabigatran 150mg (N=6076)		Warfarin (N=6022)	
	No. of Patients	%/yr	No. of Patients	%/yr	No. of Patients	%/yr
Major Bleeding	322	2.71	375	3.11	397	3.36
Life Threatening	145	1.22	175	1.45	212	1.8
Non-Life Threatening	198	1.66	226	1.88	208	1.76
Gastrointestinal	133	1.12	182	1.51	120	1.02
Major or Minor Bleeding	1740	14.62	1977	16.42	2142	18.15
Intracranial Bleeding*	27	0.23	36	0.3	87	0.74

*P<0.001

Connolly et al, NEJM, 2009

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SEPTEMBER 15, 2011

VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	<i>no.</i>	<i>%/yr</i>	<i>no.</i>	<i>%/yr</i>		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

**INCLUSION
CRITERIA**

EXCLUSION CRITERIA

	Prior Stroke	All Ages	Severe Stroke (<6mos)	Stroke within 7-14 days	Renal Dz	ASA
RELY	+/-	Yes	Yes	Yes	Yes	No
ARISTOTLE	Yes	Yes	No	Yes	Yes	Yes

ORIGINAL ARTICLE

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D., Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D., Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D., Danny Liaw, M.D., Ph.D., Steen E. Husted, M.D., Jose Lopez-Sendon, M.D., Raffaele De Caterina, M.D., Petr Jansky, M.D., Harald Darius, M.D., Dragos Vinereanu, M.D., Jan H. Cornel, M.D., Frank Cools, M.D., Dan Atar, M.D., Jose Luis Leiva-Pons, M.D., Matyas Keltai, M.D., Hisao Ogawa, M.D., Ph.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Witold Ruzyllo, M.D., Rafael Diaz, M.D., Harvey White, M.D., Mikhail Ruda, M.D., Margarida Gerales, Ph.D., Jack Lawrence, M.D., Robert A. Harrington, M.D., and Lars Wallentin, M.D., Ph.D., for the APPRAISE-2 Investigators*

ABSTRACT

BACKGROUND

Apixaban, an oral, direct factor Xa inhibitor, may reduce the risk of recurrent ischemic events when added to antiplatelet therapy after an acute coronary syndrome.

METHODS

We conducted a randomized, double-blind, placebo-controlled clinical trial comparing apixaban, at a dose of 5 mg twice daily, with placebo, in addition to standard antiplatelet therapy, in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events.

RESULTS

The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80 to 1.11; $P=0.51$). The primary safety outcome of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; $P=0.001$). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

CONCLUSIONS

The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events. (Funded by Bristol-Myers Squibb and Pfizer; APPRAISE-2 ClinicalTrials.gov number, NCT00831441.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Alexander at Duke Clinical Research Institute, Duke University Medical Center, DUMC Box 3850, Durham, NC 27715, or at john.h.alexander@duke.edu.

*The investigators in the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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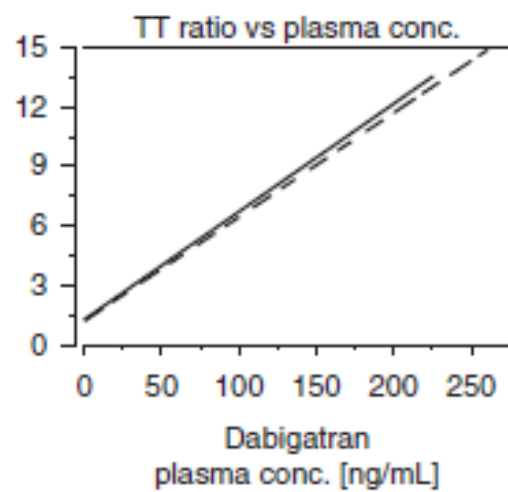
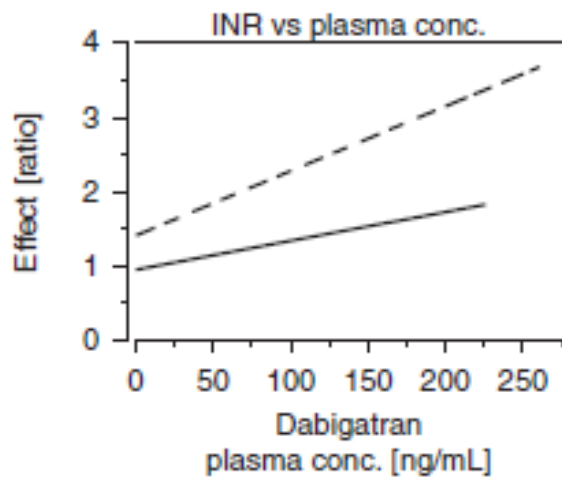
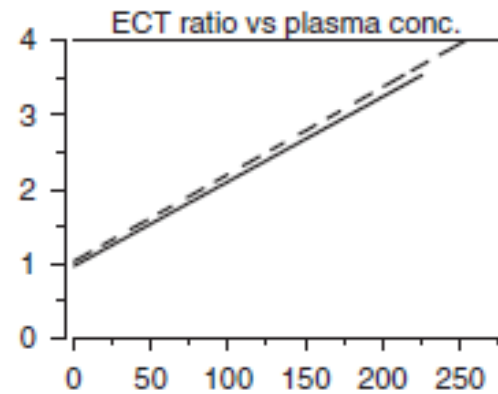
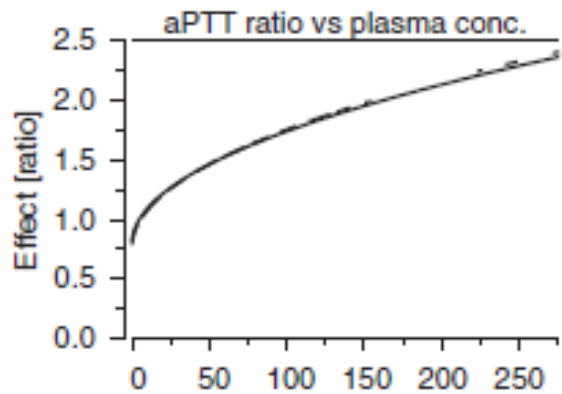
“The study was prematurely terminated...because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events.”

“The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events.”

	Apixaban		Placebo			
Safety: bleeding†	3673 (100)		3642 (100)			
TIMI criteria						
Major bleeding	46 (1.3)	2.4	18 (0.5)	0.9	2.59 (1.50–4.46)	0.001
Major or minor bleeding	80 (2.2)	4.2	29 (0.8)	1.5	2.79 (1.83–4.27)	<0.001
ISTH criteria						
Major bleeding	98 (2.7)	5.1	40 (1.1)	2.0	2.48 (1.72–3.58)	<0.001
Major or clinically relevant non-major bleeding	117 (3.2)	6.2	45 (1.2)	2.3	2.64 (1.87–3.72)	<0.001
GUSTO criteria						
Severe bleeding	36 (1.0)	1.8	12 (0.3)	0.6	3.05 (1.59–5.86)	0.001
Severe or moderate bleeding	83 (2.3)	4.3	25 (0.7)	1.3	3.37 (2.16–5.27)	<0.001
Fatal bleeding	5 (0.1)	0.3	0	NA	NA	NA
Intracranial bleeding	12 (0.3)	0.6	3 (0.1)	0.2	4.06 (1.15–14.38)	0.03
Any bleeding	679 (18.5)	40.1	305 (8.4)	14.4	2.36 (2.06–2.70)	<0.001
Net clinical outcomes						
Cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, or fatal bleeding	295 (8.0)	14.0	299 (8.1)	14.3	0.98 (0.83–1.15)	0.80
Death, myocardial infarction, or ischemic or hemorrhagic stroke	327 (8.8)	15.5	328 (8.9)	15.6	0.99 (0.85, 1.15)	0.90

Can Levels be Tested?

Can These Agents be Rapidly
Reversed?



— Healthy subjects (N=12) — — — Liver impaired patients (N=12)

Nephrol Dial Transplant (2004) 19: 1552–1558

DOI: 10.1093/ndt/gfh203

Advance Access publication 19 March 2004

Original Article

**Nephrology
Dialysis
Transplantation**

Factor Xa-activated whole blood clotting time (Xa-ACT) for bedside monitoring of dalteparin anticoagulation during haemodialysis

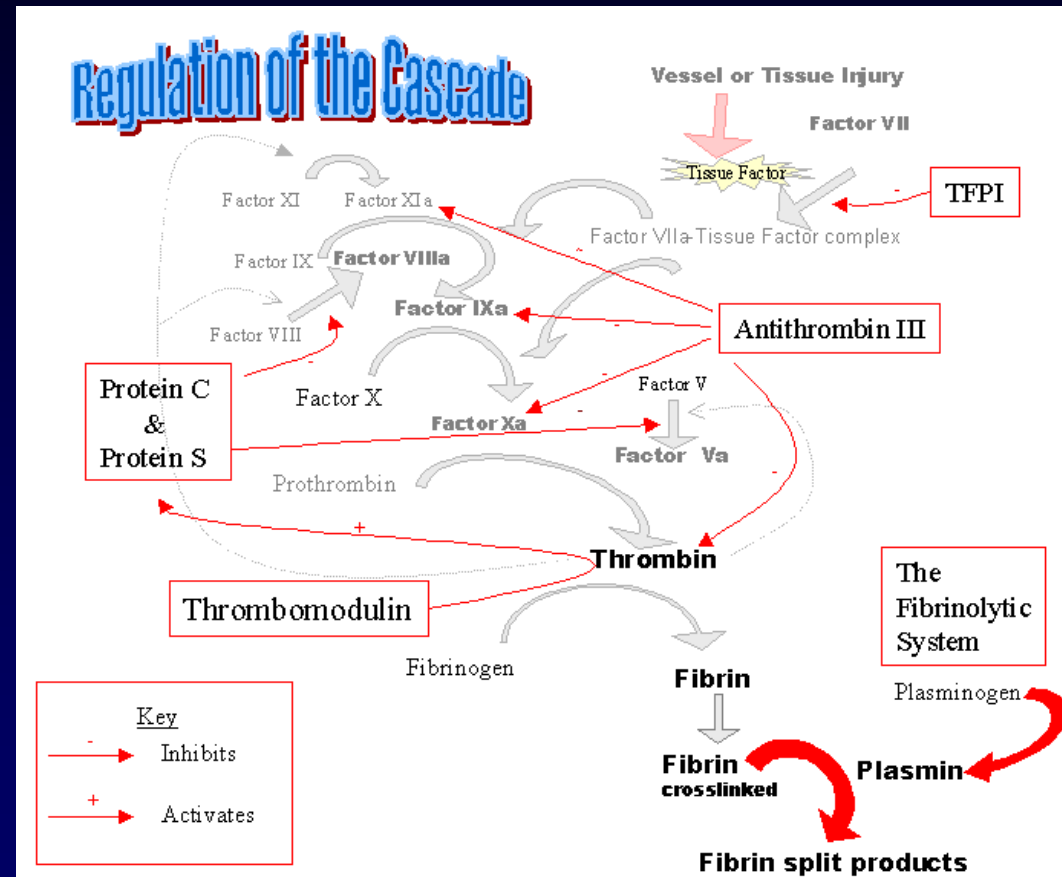
Rolf Dario Frank, Vincent M. Brandenburg, Regina Lanzmich and Jürgen Floege

Department of Nephrology and Clinical Immunology, University Hospital Aachen, Germany

Management of Bleeding

Factor Replacement For Coagulopathies

- FFP:
 - Contains all coagulation factors and fibrinogen (2-5mg/cc)
- Recombinant Factor VIIa
- Prothrombin Complex Concentrate (PCC):
 - Factors II, VII (not in all PCC products), IX, X
 - Protein C/S/Z
 - Heparin (40-200IU in most preparations)
- FEIBA
 - Factors II, VII, IX, X
 - Factor VIII antigen
 - No heparin
- Cryoprecipitate:
 - Fibrinogen (140-300 mg/U), vWF, XIII, fibronectin
- ProPlex-T
 - Factor IX



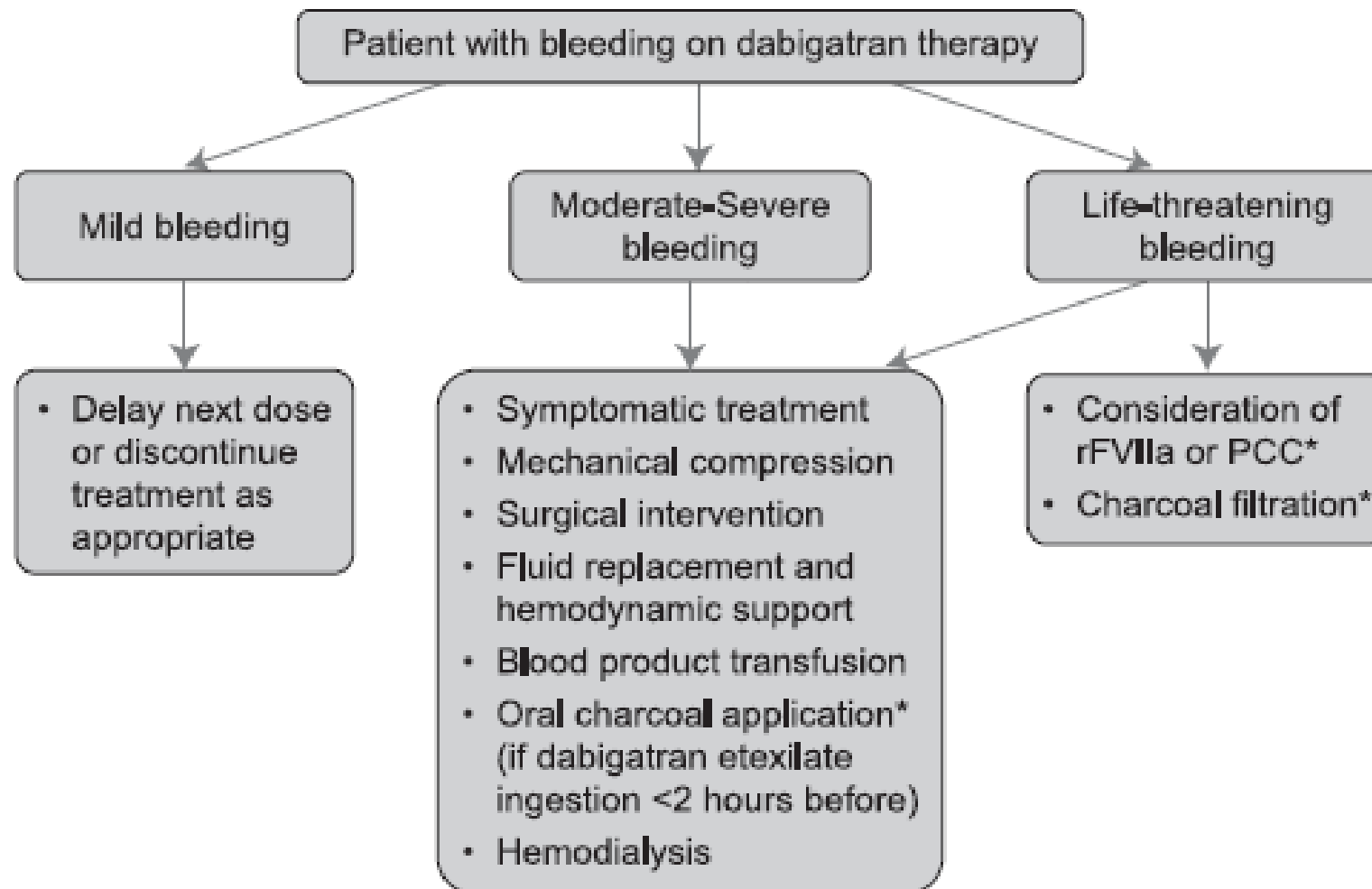
****Other considerations: Volume, Type and Screen, Hemostatic vs. clinical effect**

Medication	Mechanism	Cl.	Duration of Action	Monitoring	Reversal
Heparin	Thrombin inhibitor; Inhibits activated IX, X, XI, XII, and plasmin; prevents conversion of fibrinogen to fibrin.	L/K	6 hrs	PTT	Protamine Sulfate
Warfarin	Inhibits the Vitamin K epoxide reductase complex 1, thus reducing the hepatic synthesis of II, VII, IX, X, and Protein C and S.	L	2-5 days	PT, INR	Vitamin K, FFP, PCC, rFVIIa
Enoxaparin	Inhibits Factor Xa (some IIa inhibition)	L	12 hrs	Factor Xa	Protamine Sulfate (60% effective)

Hirsh, 2008; www.aventis.com Blech, 2008
 Connolly, 2009 Raghaven, 2008 Lu, 2008

Medication	Mechanism	Cl.	Duration of Action	Monitoring	Reversal
Dabigatran	Thrombin (IIa) inhibitor; prevents cleavage of fibrinogen to fibrin, inhibits activation of factors V, VIII, XI, and XIII.	K/F	T ½ 12-17 hours; 28 hours in severe CKD	PTT >2.5x may indicate overanticoagulation; ECT, TT.	rFVIIa, FFP? Charcoal, Hemodialysis

Hirsh, 2008; www.aventis.com Blech, 2008
 Connolly, 2009 Raghaven, 2008 Lu, 2008



*Recommendation based only on limited non-clinical data, there is no experience in volunteers or patients

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc;
Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

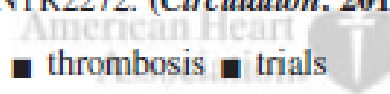
Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8 ± 1.3 versus 12.3 ± 0.7 seconds at baseline; $P < 0.001$) that was immediately and completely reversed by PCC (12.8 ± 1.0 ; $P < 0.001$). The endogenous thrombin potential was inhibited by rivaroxaban ($51 \pm 22\%$; baseline, $92 \pm 22\%$; $P = 0.002$) and normalized with PCC ($114 \pm 26\%$; $P < 0.001$), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Clinical Trial Registration—URL: <http://www.trialregister.nl>. Unique identifier: NTR2272. (*Circulation*. 2011;124:00-00.)

Key Words: anticoagulants ■ coagulation ■ hemorrhage ■ thrombosis ■ trials



Medication	Mechanism	Cl.	Duration of Action	Monitoring	Reversal
Apixaban	Xa inhibitor	K/F	T ½ 12.7hrs	Factor Xa, +/- PT	FFP, rFVIIa, PCC (rfXa studies) Protamine NOT effective

Hirsh, 2008;

www.aventis.com

Blech, 2008

Connolly, 2009

Raghaven, 2008

Lu, 2008

50th ASH Annual Meeting and Exposition Online Program and Abstracts

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AMERICAN SOCIETY OF HEMATOLOGY

Last updated October 26, 2010. Please note that this site represents the latest program changes and differs from the print version in some details.

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983 Recombinant Antidote for Reversal of Anticoagulation by Factor Xa Inhibitors

Oral and Poster Abstracts

Poster Session: Antithrombotic Therapy Poster I

Saturday, December 6, 2008, 5:30 PM-7:30 PM

Hall A (Moscone Center)

Poster Board I-88

Genmin Lu, PhD^{*}, Francis R. DeGuzman^{*}, Sanjay Lakhota, PhD^{*}, Stanley J Hollenbach^{*}, David R Phillips, PhD and Uma Sinha, PhD

Portola Pharmaceuticals Inc, South San Francisco, CA

Conclusion

Questions?

Testing

- **Activated Partial Thromboplastin Time**
 - aPTT is functional determination of the intrinsic pathway of coagulation (factors XII, XI, IX, VIII, V, II, I, prekallikrein, high molecular weight kininogen). This pathway is initiated by the interaction of Factor XII with a negatively charged surface.
- **International Normalized Ratio (INR)**
 - measures of the extrinsic pathway of coagulation
- **Factor Levels (ie: Xa)**

Testing

- **Ecarin clotting time (ECT)**

- a laboratory test used to monitor anticoagulation during treatment with hirudin, an anticoagulant medication which was originally isolated from leech saliva. Ecarin, the primary reagent in this assay, is derived from the venom of the saw scaled viper

- **Thrombin time (TT, TCT)**

- measures the time it takes for a clot to form in the plasma of a blood sample anticoagulant to which an excess of thrombin has been added. This test is repeated with pooled plasma from normal patients. The difference in time between the test and the 'normal' indicates an abnormality in the conversion of fibrinogen to fibrin