MANAGING ORAL ANTICOAGULANT-ASSOCIATED BLEEDING: Lessons from Warfarin

Jeffrey I Weitz, MD, FRCP(C), FACP

Professor of Medicine and Biochemistry
McMaster University
Canada Research Chair in Thrombosis
Heart & Stroke Foundation/ J.F. Mustard Chair in Cardiovascular Research

Disclosures

Grants/Research Support: CIHR, HSFO, CFI, ORF

Consultant: Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Janssen, and Portola

Overview

Anticoagulant conundrum

Scope of problem

NOACs versus warfarin

Warfarin reversal

The Anticoagulant Conundrum

Clotting

Bleeding

National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events In Older U.S. Adults, 2007-2009

Medication	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of Emergency Dept. Visits Resulting in Hospitalization
	No.	% (95% CI)	%
Most commonly implicated medications			
Warfarin	33,171	33.3 (28.0-38.5)	46.2
Insulins	13,854	13.9 (9.8-18.0)	40.6
Oral antiplatelet agents	13,263	13.3 (7.5-19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1-13.3)	51.8
Opioid analgesics	4,778	4.8(3.5-6.1)	32.4

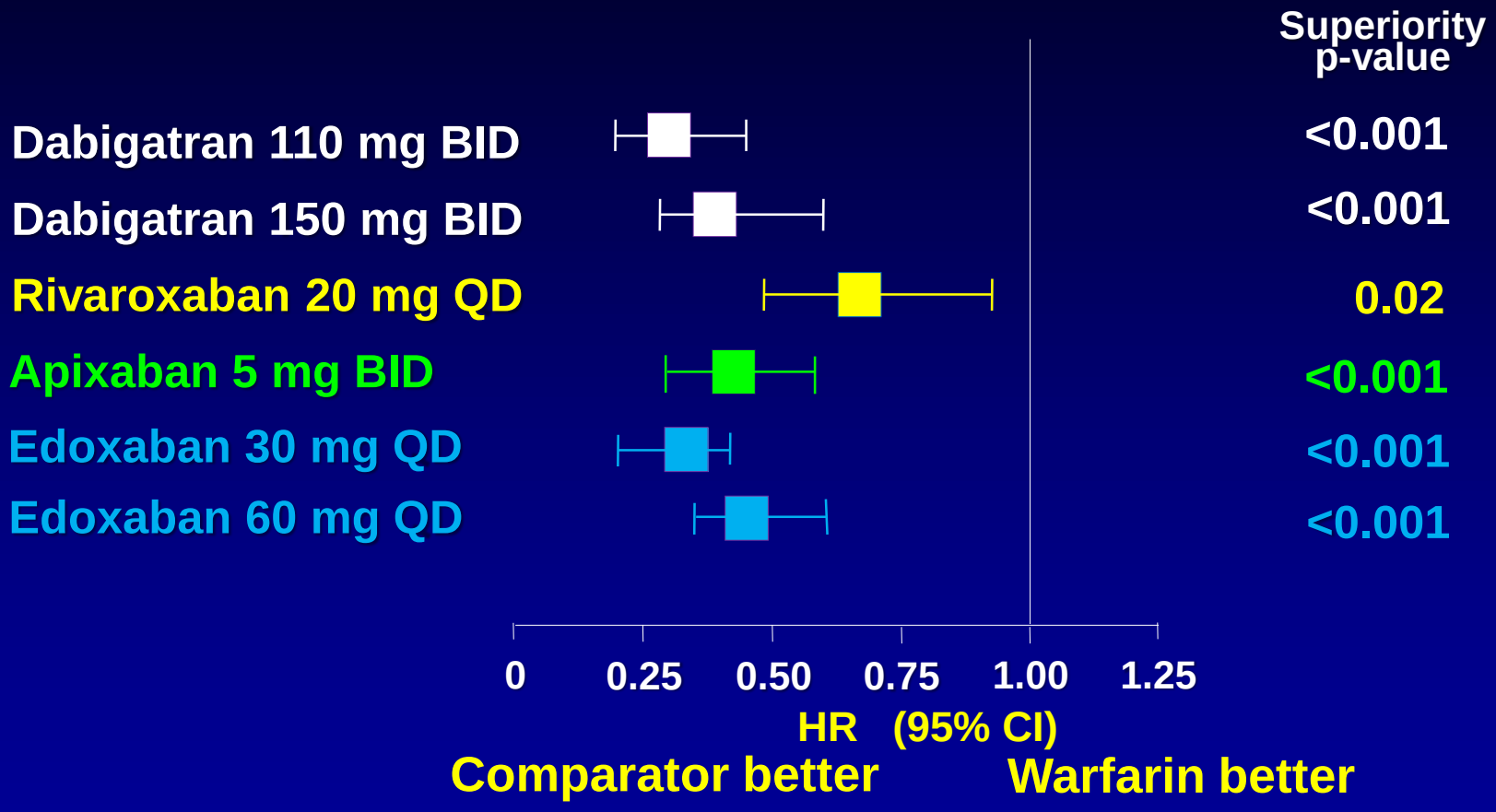
Budnitz DS et al. *NEJM*, 2011

National Estimates of Emergency Hospitalization for Common Manifestations of Adverse Drug Events in Older U.S. Adults, 2007-2009

Therapeutic category and Adverse-event manifestations	Annual National Estimate of Hospitalizations	Proportion of Emergency Dept. Visits Resulting in Hospitalization
	% (95% CI)	%
Hematologic agents		
Intracranial hemorrhage	5.6 (2.1-9.1)	99.7
Hemoptysis	2.0 (1.1-2.8)	73.6
Gastrointestinal hemorrhage	**40.8 (29.9-51.7)**	**84.7**
Genitourinary hemorrhage	4.7 (3.2-6.2)	42.4
Epistaxis	6.1 (4.3-8.0)	10.6
Skin or wound hemorrhage	6.8 (4.5-9.1)	24.5
Other type of hemorrhage	5.3 (2.7-8.0)	27.5

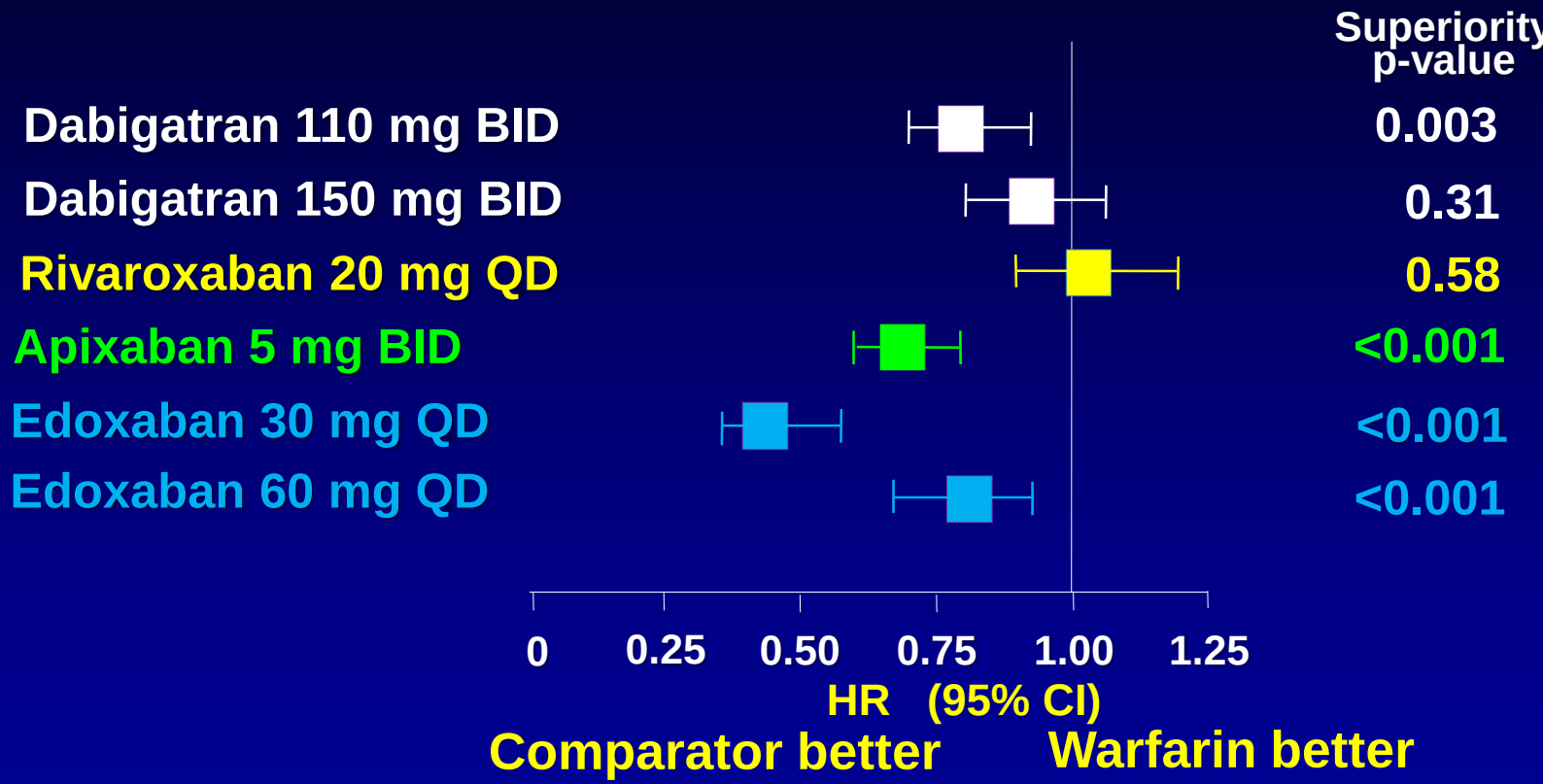
Budnitz DS et al. *NEJM*, 2011

New Oral Anticoagulants vs. Warfarin: Intracranial Hemorrhage



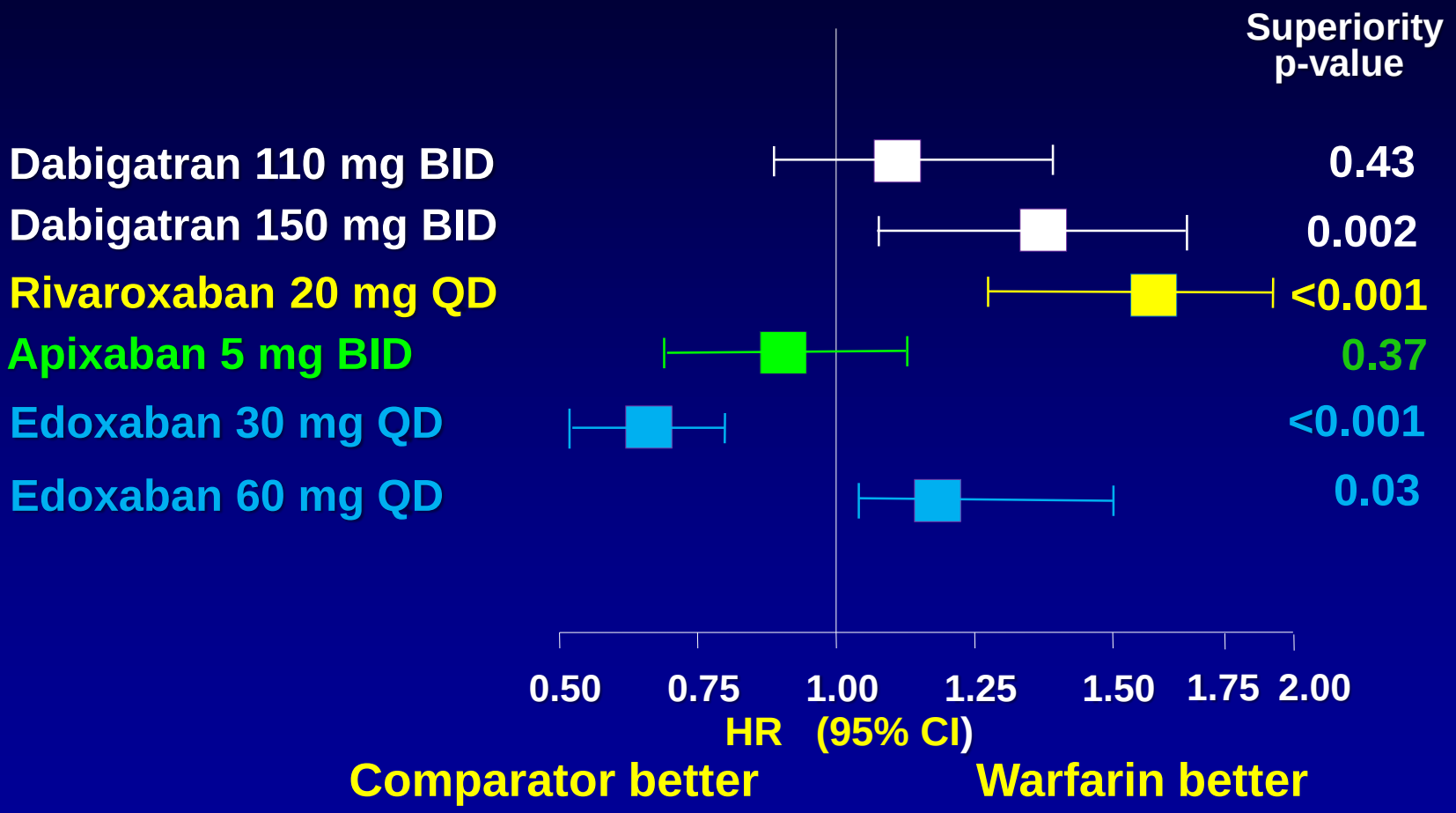
Connolly SJ, et al. *NEJM* 2009; Alexander J, et al. *NEJM* 2011; Mahaffey K, et al. *NEJM* 2011; Giugliano RP, et al. *NEJM* 2013

New Oral Anticoagulants vs. Warfarin: ISTH Major Bleeding



Connolly SJ, et al. *NEJM* 2009; Alexander J, et al. *NEJM* 2011; Mahaffey K, et al. *NEJM* 2011; Giugliano RP, et al. *NEJM* 2013

New Oral Anticoagulants vs. Warfarin: GI Bleeding



Connolly SJ, et al. *NEJM* 2009; Alexander J, et al. *NEJM* 2011; Mahaffey K, et al. *NEJM* 2011; Giugliano RP, et al. *NEJM* 2013

NOACs Versus Warfarin

NOACs are replacing warfarin for many indications

Annual rate of major bleeding with NOACs is about 3%

Warfarin Reversal

General principles

Warfarin-specific agents

Outcome

General Principles for Management of Anticoagulant-related Bleeding

1. Stop drug
2. Investigate and treat cause
3. Administer antidote
4. Test integrity of coagulation system
5. Use non-specific blood thickeners
6. Transfuse to replace deficient factors or if transfusion reverses drug
7. Consider dialysis or other maneuvers to remove drug
8. By the time all this is done, most drugs will have cleared

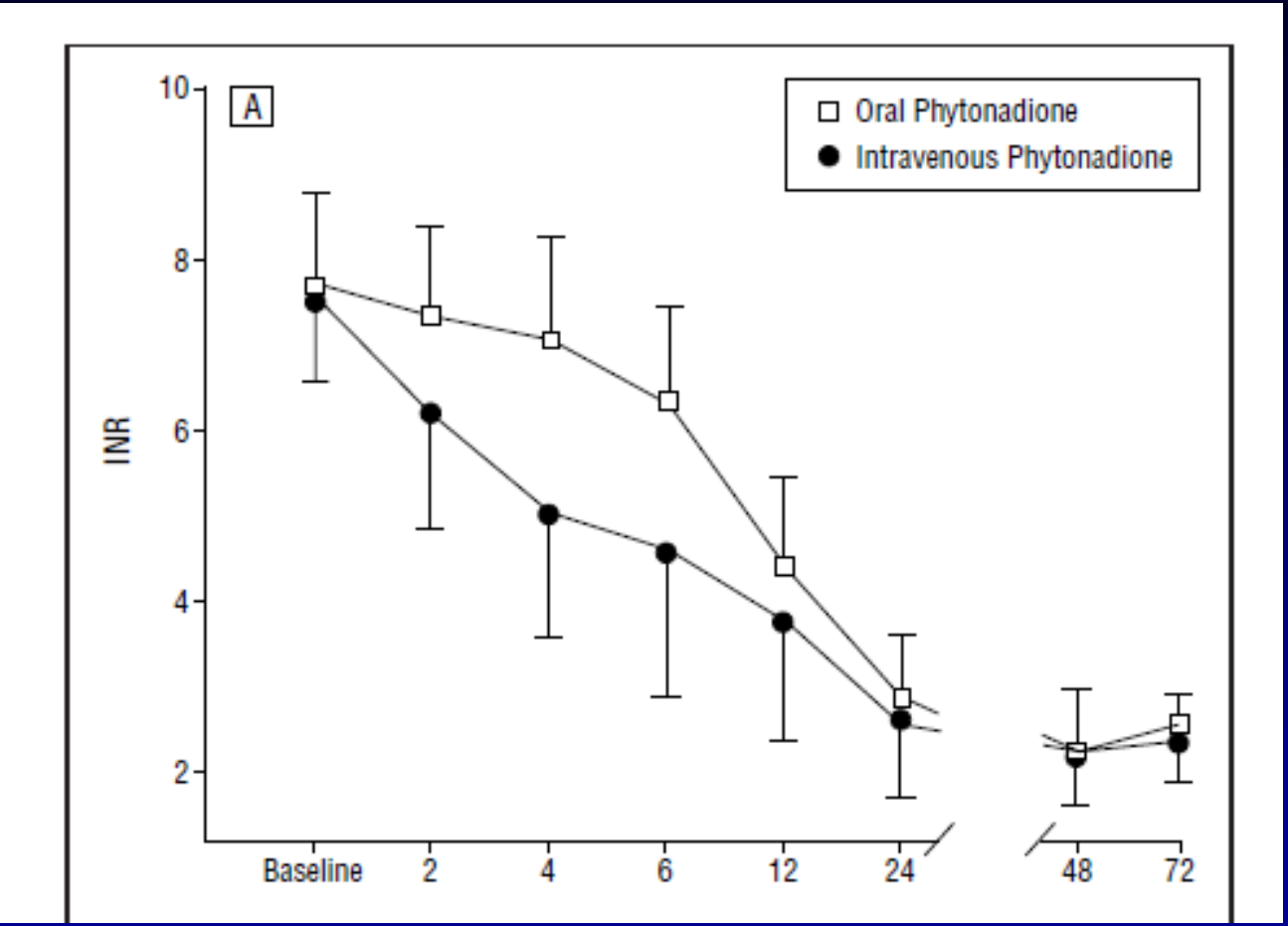
Crowther M et al, *Blood* 2008

Specific Management of Warfarin-associated Bleeding

Vitamin K (antidote to warfarin)

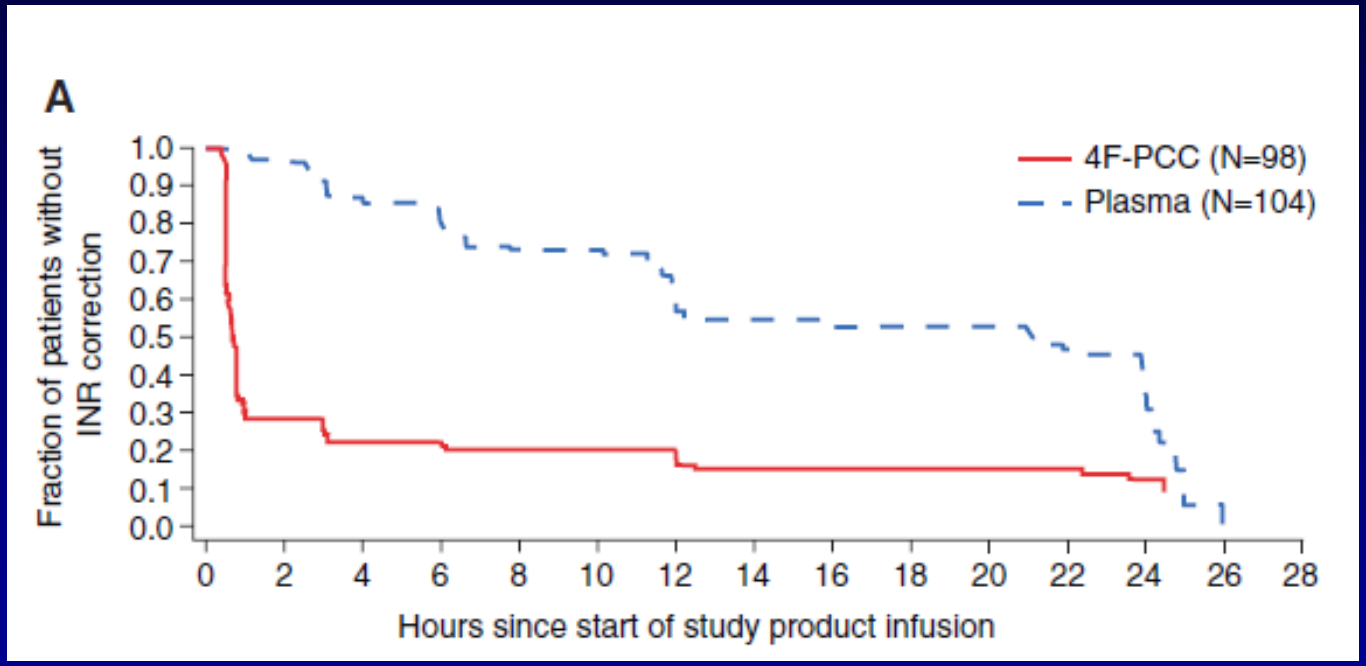
Replace vitamin K-deficient clotting factors with PCC or FFP

Oral Versus IV Vitamin K



Lubetsky A et al. *Arch Intern Med* 2003;163:2469-2473

4F-PCC versus FFP



Sarode R, et al. *Circulation* 2013;128(11):1234–43

Hemostatic Efficacy (Intention-to-Treat Efficacy Population)

Primary Rating	No. (%) of Patients [95% CI]		Difference 4F-PCC Minus Plasma, % (95% CI)
	4F-PCC (n=98)	Plasma (n=104)	
Hemostatic efficacy rating by category*			
Excellent	44† (44.9)	45 (43.3)	
Good	27 (27.6)	23 (22.1)	
Poor/none	27 (27.6)	36 (34.6)	
Noneffective	25 (25.5)	33 (31.7)	
Missing primary rating	2 (2.0)	3 (2.9)	
Effective hemostasis	71 (72.4) [63.6 to 81.3]	68 (65.4) [56.2 to 74.5]	7.1 (–5.8 to 19.9)

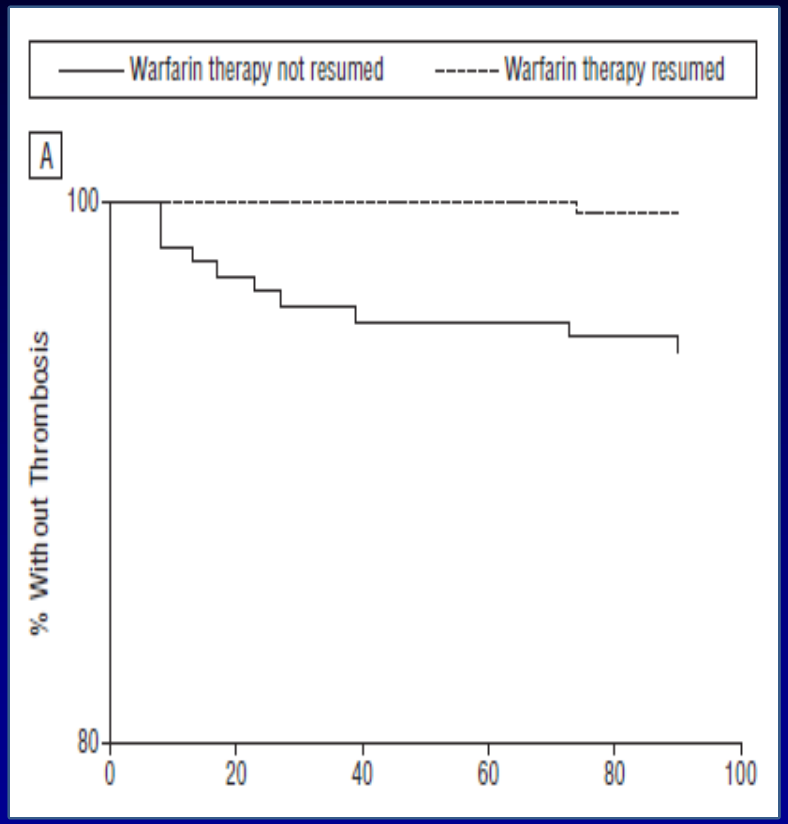
Sarode R et al, *Circulation* 2013;128:1234-1243

Hemostatic Efficacy by Time of Rating (Post Hoc Analysis; Intention-to-Treat Efficacy Population)

	Treatment Group		Difference 4F-PCC Minus Plasma, % (95% CI)*
	4F-PCC (n=98)	Plasma (n=104)	
No. of bleeds assessed for hemostatic efficacy at 4 h (visible, musculoskeletal)	23	28	
No. (%) of patients with effective hemostasis	19 (82.6)	14 (50.0)	32.6 (4.5 to 60.7; *P*=0.0200)
No. of bleeds assessed for hemostatic efficacy at 24 h (gastrointestinal, intracranial, other nonvisible)	75	76	
No. (%) of patients with effective hemostasis	52 (69.3)	54 (71.1)	–1.7 (–17.6 to 14.2; *P*=0.95)

Sarode R et al, *Circulation* 2013;128:1234-1243

Risk of VKA Reversal After GIB

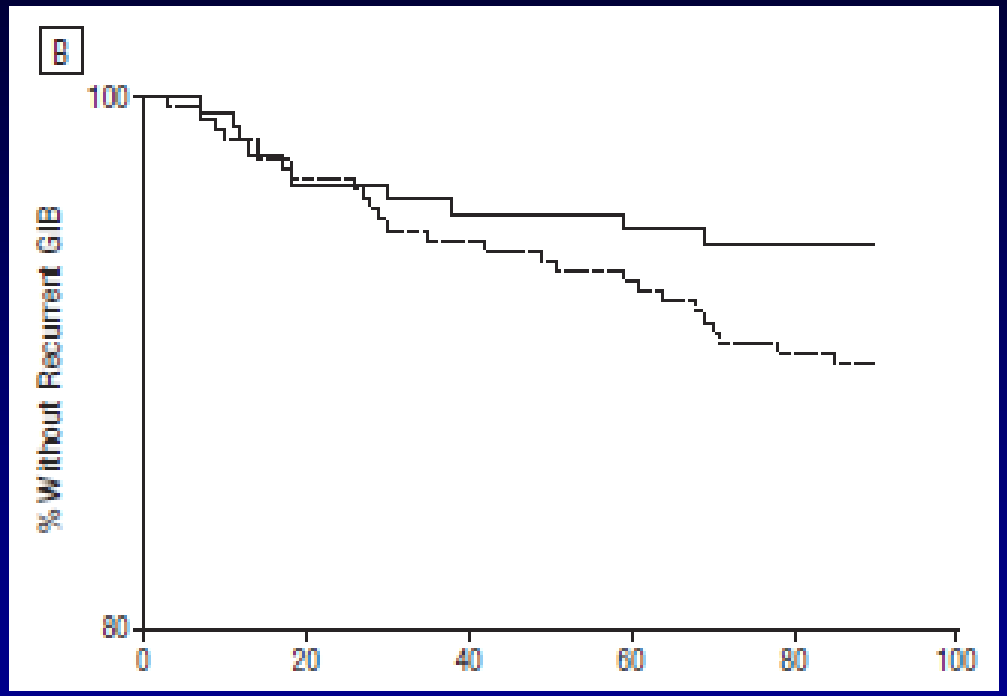


P=.002, log-rank test

(3/182 had fatal stroke)

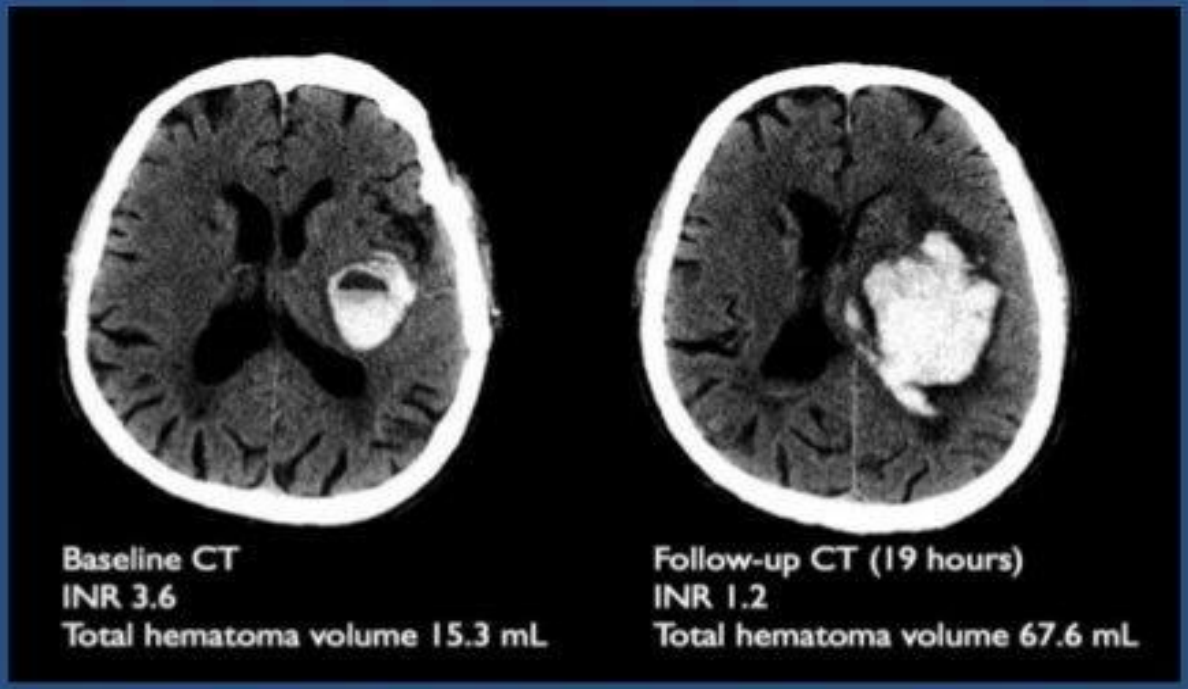
Witt DM, et al. *Arch Intern Med* 2012Oct 22;172(19):1484–91.

Benefit of VKA Reversal After GIB



Witt DM, et al. *Arch Intern Med*. 2012;172(19):1484–91

Warfarin-Associated ICH:
Poor Prognosis Despite Anticoagulation Reversal



Canadian PCC (prothrombin complex concentrate) Registry:

- N=141 anticoagulation associated intracerebral hemorrhages
- 72% with INR < 1.5 within < 1h; yet 42% mortality (50% of cases)

Dowlatshahi. *Stroke* 2012; 43: 1812

Bleeding with NOACs

Patients are different from those treated with warfarin – younger, better renal function, less ICH, and more GI bleeding

NOACs are different than warfarin – shorter half-life and more dependence on renal function, particularly dabigatran

Conclusions

Bleeding is a common complication of anticoagulant therapy

Management of major bleeding is complicated and requires a dedicated and informed team of clinicians