STAIR VIII

Accelerating the Evolution of Stroke Therapies

New Oral Anticoagulants in AF Unresolved issues

Sheraton Pentagon City Hotel
March 9, 2013

Agenda

1. Monitoring anticoagulant effects
2. Reversal agents
3. Compliance
4. Concomitant use of reperfusion therapies
5. Phase 4 observations

Why measure levels?

Assess adherence

Detect accumulation / overdose

Diagnose cause of stroke

Decide on use of thrombolysis

Diagnose cause of bleeding

Plan timing of urgent surgery

How can levels be estimated?

Test		Dabigatran	Rivaroxaban	Apixaban
Specific Assay*	Drug specific	Hemoclot	Anti-Xa	Anti-Xa
	aPTT	↑↑↑	↑	↑
Non-specific assays	PT	↑	↑↑	↑↑
	TT	↑↑↑↑	No effect	No effect

*Mass spectrometry can be used to measure drug levels

What are the unresolved issues?

- Specific tests to estimate drug levels are not widely available
- Uncertain normal range of drug levels
- Uncertain relation between coagulation test results and drug levels
- Uncertain relation between drug levels and clinical outcomes

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Do we need reversal agents?

Urgent surgery

Management of life-threatening bleeding

What are the lessons from the trials? Dabigatran vs. warfarin

Surgery	Dabigatran 110, %	Dabigatran 150, %	Warfarin, %
Urgent	17.8%	17.7%	21.6%
Elective	2.8%	3.8%	3.3%
Major	6.1%	6.5%	7.8%
Minor	1.9%	3.2%	1.8%

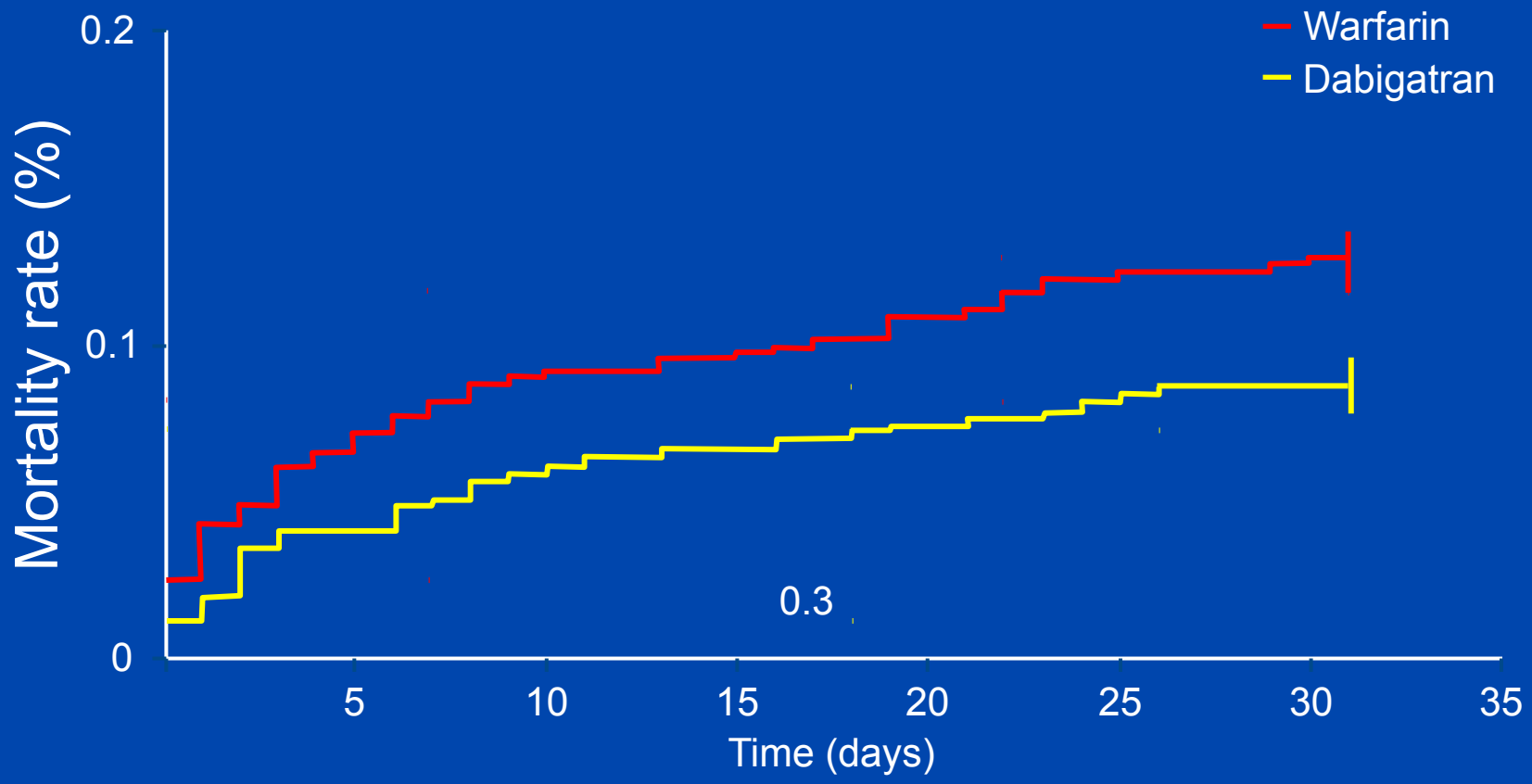
Healey JS, et al. Circulation 2012; 126: 343-8.

Mortality by treatment after ICH in RE-LY

Intracranial bleeding	Warfarin	Dabigatran 150 mg bid	Dabigatran 110 mg bid
All	36% (32/90)	35% (13/37)	41% (11/27)
Intracerebral	41% (19/46)	64% (7/11)	64% (9/14)
Subdural	28% (10/36)	21% (5/24)	20% (2/10)
Subarachnoid	38% (3/8)	50% (1/2)	0% (0/3)

Hart RG, et al. Stroke 2012; 43: 1511-7.

Mortality after a major bleed: dabigatran vs. warfarin (>1000 bleeds)



The Kaplan–Meier analysis suggest a reduced risk for death with dabigatran vs warfarin during 30 days after the bleeding (P=0.052)

Majeed A, et al. Presented at ASH meeting, December 2012

Reversal of new oral anticoagulants

General measures	Specific antidotes	
	Anti-IIa	Anti-Xa
Activated charcoal, hemofiltration & hemodialysis		
3- and 4-factor PCCs (e.g., Profilnine, Octaplex)		
Activated PCCs (e.g., FEIBA)	Fab fragment	Factor Xa decoy (PRT4445)
Recombinant factor VIIa (Novoseven)		
Antifibrinolytic agents (e.g., TXA)		

What are the unresolved issues?

- Uncertain efficacy and safety of reversal agents
- Uncertainty about the best choice of non-specific reversal agent in patients with life-threatening bleeding
- Uncertainty about the optimal approach to test efficacy and safety of reversal agents in a timely and affordable manner

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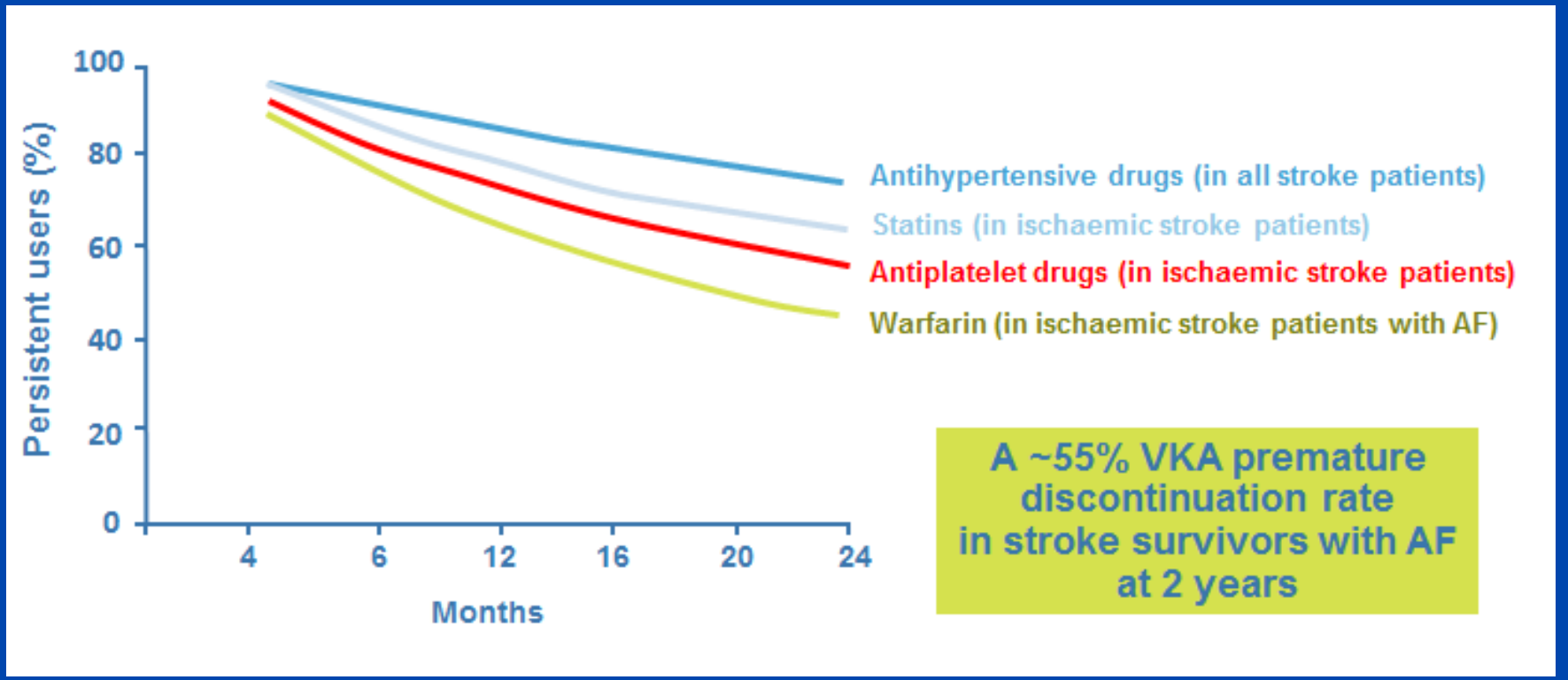
Warfarin has higher discontinuation rates than BP, statin and antiplatelet drugs

Swedish Stroke Survivors with Atrial Fibrillation

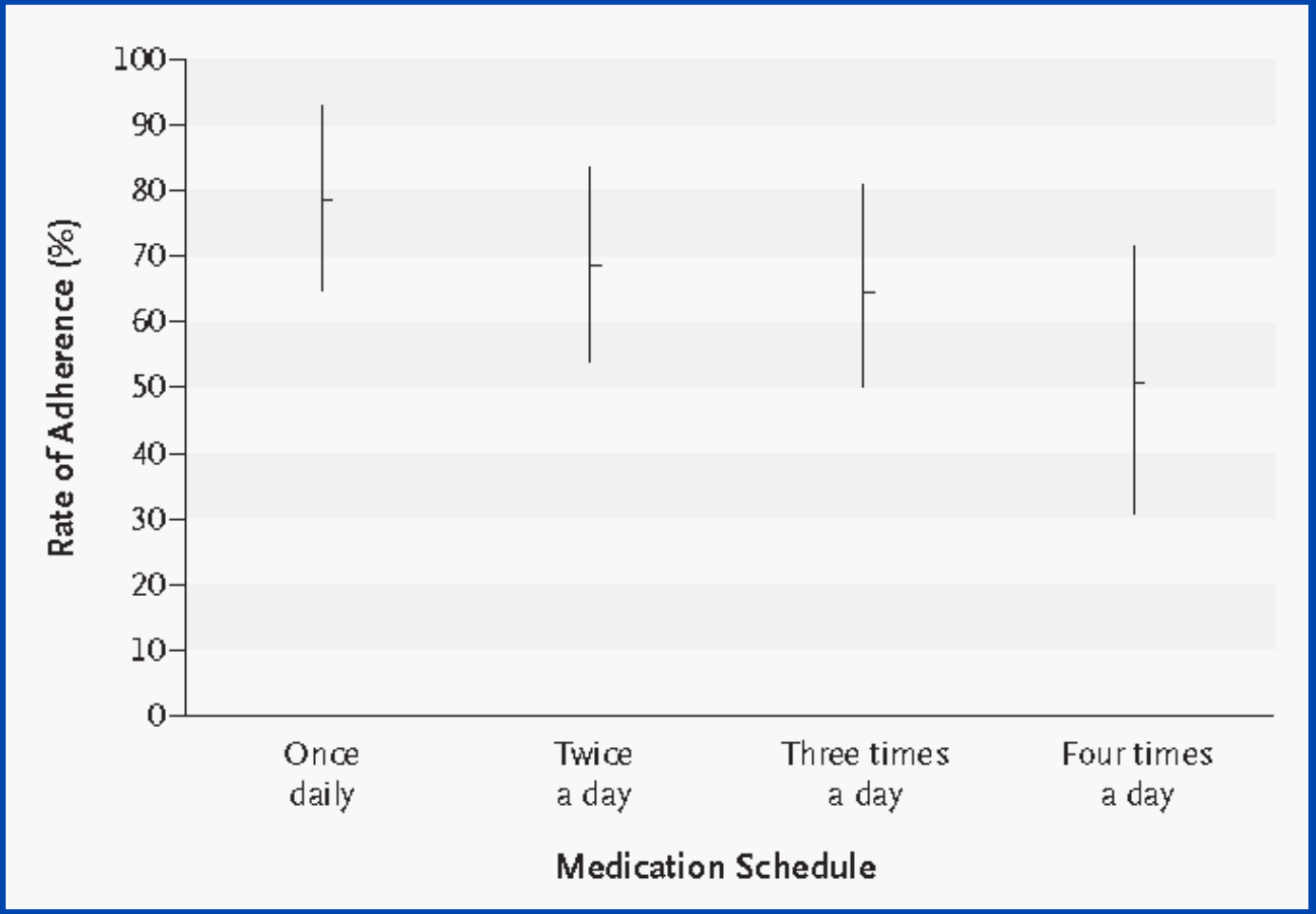


Glader E-L et al. Stroke 2010;41:397–401

Adherence and dosing frequency

Meta-analysis of 76 trials using electronic monitors

Inverse relation between adherence and frequency of dosing



Claxton AJ, et al. Clin Ther 2001; 23: 1296-1310.

Will new oral anticoagulants be associated with better or worse compliance than VKA?

Reduced compliance?

No laboratory monitoring to determine compliance

Twice daily administration (dabigatran, apixaban)

Improved Compliance?

No need for routine monitoring

No dietary restrictions

Low propensity for drug-drug interactions

No need to take “rat poison”

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What are the unresolved issues?

- Compliance with new oral anticoagulants compared with warfarin (and impact on outcome)
- Compliance with once daily compared with twice daily new oral anticoagulants (and impact on outcome)
- Methods to improve compliance

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Thrombolysis in patients with acute stroke receiving new OACs

- Key variables
  - Time of last dose of drug
  - Blood drug levels
  - Severity of stroke
- Available human data
  - Case reports
  - Stroke physician surveys

Unresolved Issues

- Timing of thrombolysis in relation to last dose of the new oral anticoagulant
- Methods to rapidly determine blood levels of the new orals in patients with acute stroke
- Drug level below which pharmacological reperfusion therapies can be safely administered

Pragmatic approach

- Warfarin treated patients
  - thrombolysis if INR <1.7
- New oral anticoagulants:
  - Consider thrombolysis if:
    - At least 3 half lives have elapsed since last dose
    - Estimated blood levels <25% of mean steady satet trough levels

    OR

    - Only if TT (or Hemoclot) is normal

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Why do we need phase 4 surveillance?

Appropriate use of new oral anticoagulants

Efficacy and safety in real world

Relation between drug levels, coagulation measures and outcome

Experience with reversal agents

Results with reperfusion therapies

Detection of rare adverse events

What phase 4 methods of surveillance have been put in place?

- Pharmaceutical company initiatives
  - Registries (e.g., GLORIA, GARFIELD)
  - Pharmacovigilance data collection and reporting
- Regulatory agencies
  - E.g., Mini-sentinel
- Investigator-driven
  - E.g., hospital electronic databases, Canadian Stroke registry