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*Collingwood - February 12, 2012*

# The Role of Warfarin in the Era of New Oral Anticoagulants

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safer healthcare now!

# Outline: Warfarin vs New Oral Anticoagulants

- Some thoughts about the new oral anticoagulants – impact of care on outcomes
- Lab monitoring
- Bleeding and emergency reversal
- Selecting an oral anticoagulant

# Approved in Canada Today

| | apixaban | dabigatran | rivaroxaban |
|---|---|---|---|
| Orthopedic prophylaxis | ● | ● | # |
| Stroke prevention in AF | Not yet | ● | ● |
| VTE treatment | No | No | No |
| ACS | No | No | No |
| Other indications | No | No | No |

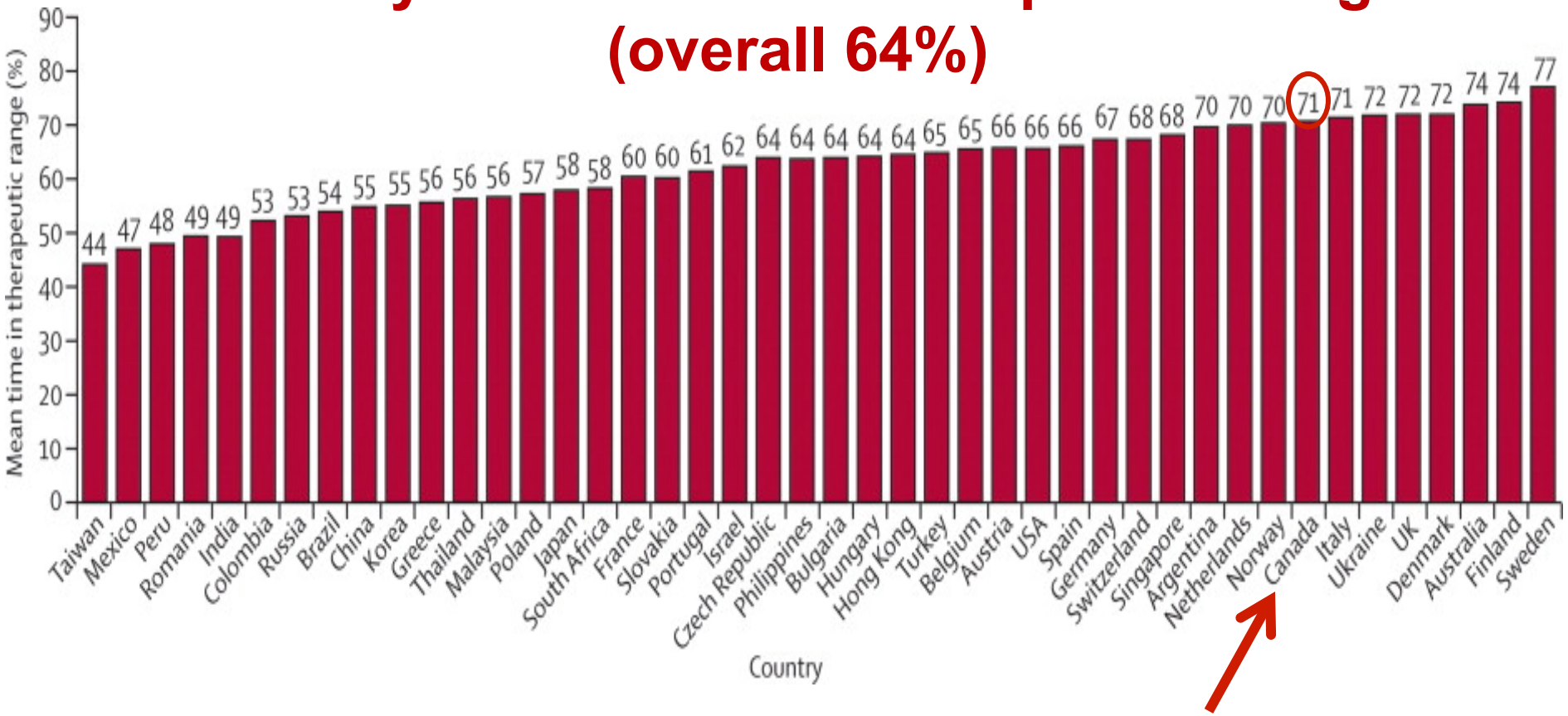
Med/surg thromboprophylaxis
Mechanical heart valves
Cancer, pregnancy

# ODB supported

| Property | dabigatran | rivaroxaban | apixaban |
|---|---|---|---|
| Target | Thrombin | Factor Xa | Factor Xa |
| Bioavailability | ≤6.5% (+ variable) | ~90% | ~66% |
| P-gp interaction | Yes | Yes | Yes |
| Time to peak | 1-2 hrs | 2-4 hrs | 1-2 hrs |
| Half-life | 12-17 hrs | 9-12 hrs | 8-15 hrs |
| Plasma prot binding | 33% | 90% | 87% |
| Dosing | Twice daily | Once daily | Twice daily |
| Hepatic metabolism | Very little | 33% (CYP3A4, 2J2) | 75% (CYP3A4) |
| Renal elimination | ≥80% | 33% active | 25% |
| Specific antidote | No | No | No |

# INR Control and Dabigatran in RE-LY

## Country Mean Time in Therapeutic Range (overall 64%)




*Wallentin – Lancet 2010;376:975*

# Warfarin vs Dabigatran & TTR

| Event | Warfarin (n=6,022) | Warfarin Q4 TTR <53% | Warfarin Q1-2 TTR >67% | Dabig 110 mg (n=6,015) | Dabig 150 mg (n=6,076) |
|---|---|---|---|---|---|
| Stroke + SE | 1.7%/yr | 2.2%/yr | 1.3%/yr | 1.5%/yr | 1.1%/yr |
| Major bleed | 3.4%/yr | 4.6%/yr | 2.7%/yr | 2.7%/yr | 3.1%/yr |
| Composite | 7.6%/yr | 11.9%/yr | 5.3%/yr | 7.1%/yr | 6.9%/yr |

**Patients on warfarin with TTR >67% did at least as well as those on dabigatran**

*Wallentin – Lancet 2010;376:975*

# Effect of *Region* on Efficacy

- *18,113 patients*

| Region | Warfarin | Dabi 110 mg | Dabi 150 mg |
|---|---|---|---|
| All | 1.7%/yr | 1.5%/yr | 1.1%/yr |
| | | | |
| N America | 1.5%/yr | 1.2%/yr | 1.1%/yr |
| S America | 1.7%/yr | 1.8%/yr | 0.9%/yr |
| W Europe | 1.4%/yr | 1.5%/yr | 1.3%/yr |
| E Europe | 1.1%/yr | 1.2%/yr | 0.8%/yr |
| S Asia | 4.0%/yr | 3.4%/yr | 0.8%/yr |

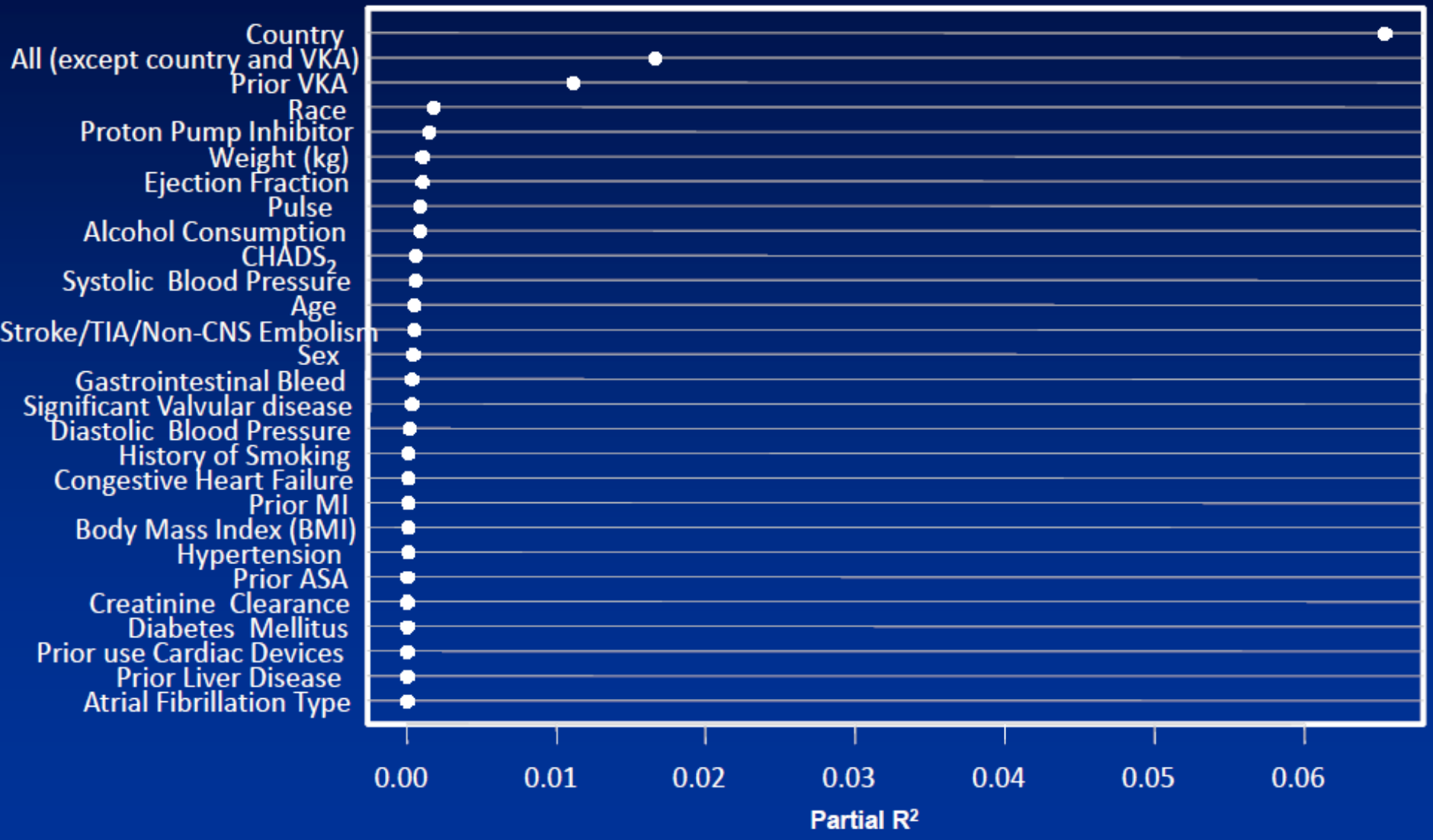
*Connolly – NEJM 2009;361:1139*

# Outcomes and Region (Rivaroxaban)

| Region | Efficacy | | Major bleeding | |
|---|---|---|---|---|
| | Rivaroxaban | Warfarin | Rivaroxaban | Warfarin |
| All | 3.8% | 4.3% | 2.7% | 3.4% |
| | | | | |
| N America | 3.5% | 3.7% | 1.5% | 2.7% |
| L America | 3.9% | 4.8% | 3.5% | 3.9% |
| W Europe | 3.8% | 4.1% | 2.7% | 3.2% |
| E Europe | 3.7% | 4.2% | 2.9% | 3.4% |
| Asian Pac | 4.3% | 5.1% | 2.9% | 4.3% |

*Patel – NEJM 2011;365:883*

# Country Strongest Predictor of TTR Regression Model in ROCKET AF




Ejection fraction is imputed at the median of non-missing values. TTR was transformed to the 1.5 power to improve the model fitting

# apixaban vs warfarin in AF trial (ARISTOTLE)

- 18,201 patients with AF

What does this mean?

| Center TTR | Stroke + systemic embolism | Death | Stroke + Syst emb + death + PE + MI |
|---|---|---|---|
| <58.0% | 1.8%/yr | 4.0%/yr | 5.3%/yr |
| 58-65% | 1.3%/yr | 3.7%/yr | 5.1%/yr |
| 65-72% | 1.2%/yr | 3.4%/yr | 4.8%/yr |
| >72% | 0.8%/yr | 3.0%/yr | 4.2%/yr |

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These were the apixaban patients!

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| >72% | 0.8%/yr | 3.0%/yr | 4.2%/yr |

**Care of the patient is very, very important!**

# Outcomes and Region (apixaban)

| Region | Stroke + syst emb | | Major bleeding | |
|---|---|---|---|---|
| | Apixaban | Warfarin | Apixaban | Warfarin |
| All | 1.3%/yr | 1.6%/yr | 2.1%/yr | 3.1%/yr |
| | | | | |
| N America | 1.0%/yr | 1.3%/yr | 2.8%/yr | 3.6%/yr |
| L America | 1.4%/yr | 1.8%/yr | 2.1%/yr | 3.5%/yr |
| Europe | 1.1%/yr | 1.1%/yr | 1.7%/yr | 2.2%/yr |
| Asian Pacific | 2.0%/yr | 3.1%/yr | 2.1%/yr | 4.1%/yr |

*Granger – NEJM 2011;365:981*

# New OACs: *Advantages*

- Rapid onset of action
  - → Eliminates need for IV/SC anticoagulant in treatment
- Less intra- and inter-individual variability than VKA
  - → Fixed dose (or limited number of doses)
- Relatively rapid offset of action
  - → May simplify pre-procedure reversal
- No routine lab monitoring
  - → More convenient for physicians and patients
- Potential for greater use in AF → ?fewer strokes

# New OACs: *Limitations of Trials*

- Selected patients:

  - low → usual TE risk

  - low → usual bleeding risk

- Careful follow-up

- Compliance data not reported BUT compliance likely greater than expected in routine practice

- Non North American care

- NOT THE REAL WORLD

# New OACs: *Disadvantages/Concerns*

- **Little real world data – Phase III trials are a good start** (patients excluded, non-North American, trial conditions)
- **Renal clearance (dabi >> riva > apix)**
- **Compliance overwhelmingly likely lower than warfarin (and lower than in RCTs) → loss of protection**
- **No proven reversal agent**
- **Greater cost**
- **Lack of "respect" for TE conditions and anticoagulant → management errors**
- **Temptation to use off-label (hip fracture, mech valves)**
- **Medical-legal hazards**

# RCT of Anticoagulation in Ablation

- Radiofrequency ablation
- Warfarin not interrupted
- Dabigatran held the morning of the procedure and restarted 3 hrs after hemostasis

| | **Warfarin (n=145)** | **Dabigatran (n=145)** | ***p*** |
|---|---|---|---|
| TE | 0 | 3 (2.1%) | *0.25* |
| Major bleeding | 1% | 6% | *0.019* |
| All bleeding | 6% | 14% | *0.031* |
| **TE + bleeding** | **6%** | **16%** | ***0.009*** |

***Lakkireddy – JACC 2012;59:***

January 12, 2012

Educating the healthcare community about safe medication practices

ISMP Medication Safety Alert! Acute Care

THE FOLLOWING ARE EXCERPTS FROM THE NEWSLETTER

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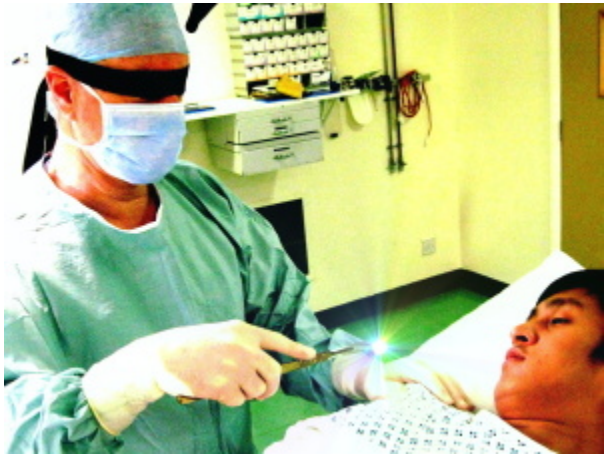
**During the 1st quarter of 2011, FDA has received:**

- **932 serious AEs linked to dabigatran**
- **505 hemorrhages (warfarin 176)**
- **120 deaths**
- **120 hemorrhagic strokes**
- **543 hospitalizations**

**"We believe FDA and the manufacturer should reevaluate dosing in the elderly or those with moderate renal impairment to determine optimal dosing and monitoring requirements."**

# New OACs: *Uncertainties*

- Uncertainties about: bioavailability, drug interactions, extremes of weight/age, effect of renal dysfunction, effect of hepatic dysfunction
- Uncertainties about patient selection: cancer, pregnancy, massive VTE, mechanical heart valves, etc
- Is a single dose for all too simplistic?
- How to manage recurrent thrombosis and bleeding
- Who to monitor, when and how?
- Peri-procedure use
- Long-term complications
- **NET SOCIETAL BENEFIT**



# Laboratory Monitoring of New Oral Anticoagulants

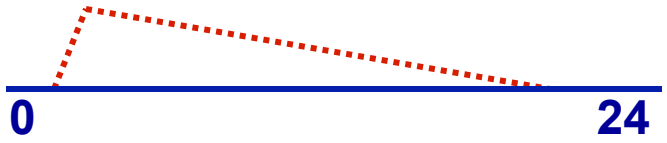
- apixaban (Eliquis®)
- dabigatran (Pradax®)
- rivaroxaban (Xeralto®)

# Lab Monitoring is Sometimes Necessary

- Bleeding event
- High risk for bleeding
- Acute thromboembolic event
- Pre-procedure safety – elective, urgent
- Extremes of weight – is the dose appropriate?
- Renal dysfunction
- Potential drug interactions
- Adherence check, education tool
- Suspected overdose

# Problems with *Monitoring* New Oral Anticoagulants

1. No validated tests
2. Each drug has unique effect on clotting tests
3. Generally poor correlation between drug levels and test results
4. Reagent - analyzer variability
5. Timing of test is critical




6. Target ranges not established

# Laboratory Monitoring

| Drug | Lab monitoring |
|---|---|
| **dabigatran** | ▪ **aPTT (poor at supratherapeutic doses)**<br>▪ ECT<br>▪ Hemoclot – linear relation<br>▪ TT (Too sensitive - is any drug present?) |
| **rivaroxaban** | ▪ **PT (INR) (riva-specific ISI)**<br>▪ AXa with specific riva calibrator |
| **apixaban** | ▪ **PT (INR) (?apix-specific ISI)**<br>▪ AXa with specific apix calibrator |

**At high concentrations**, all of the new OAC prolong both the PT and aPTT

# Laboratory Monitoring New OAC

## Assessment of "reversal"

| | |
|---|---|
| dabigatran | aPTT |
| rivaroxaban | PT |

## Monitoring of blood level

| | |
|---|---|
| dabigatran | Hemoclot test |
| Factor Xa inhibitors | Anti-Xa |

# Bleeding and Emergency Reversal of a New OAC

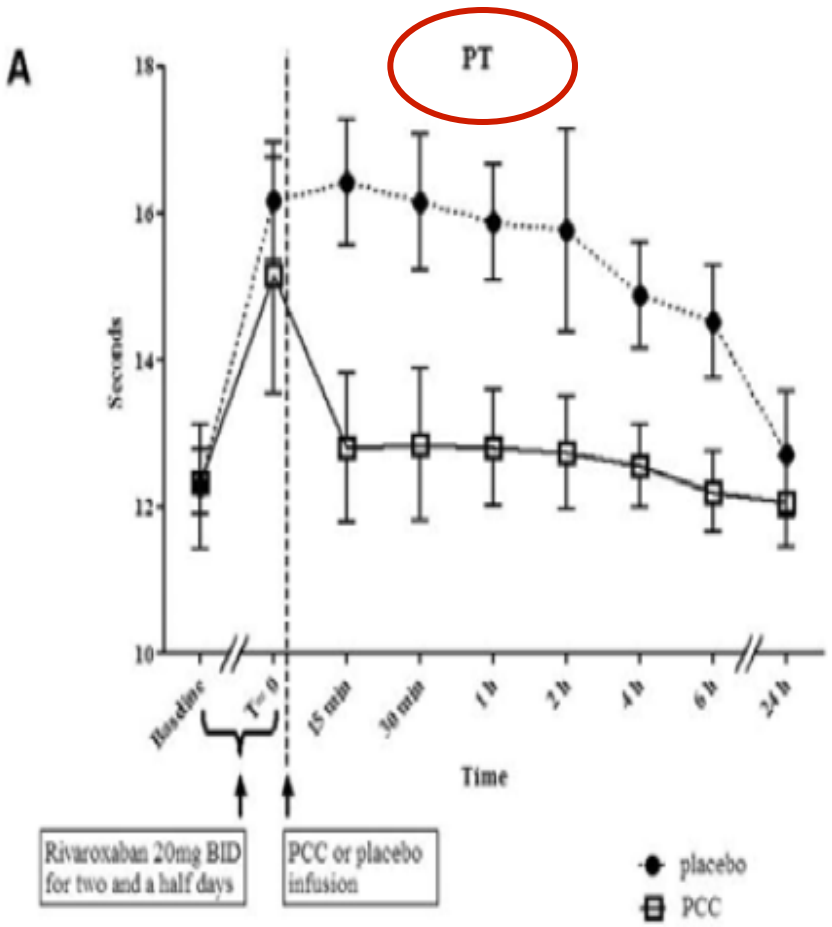
- apixaban (Eliquis®)
- dabigatran (Pradax®)
- rivaroxaban (Xeralto®)

# Management of *Bleeding* on New Oral Anticoagulants

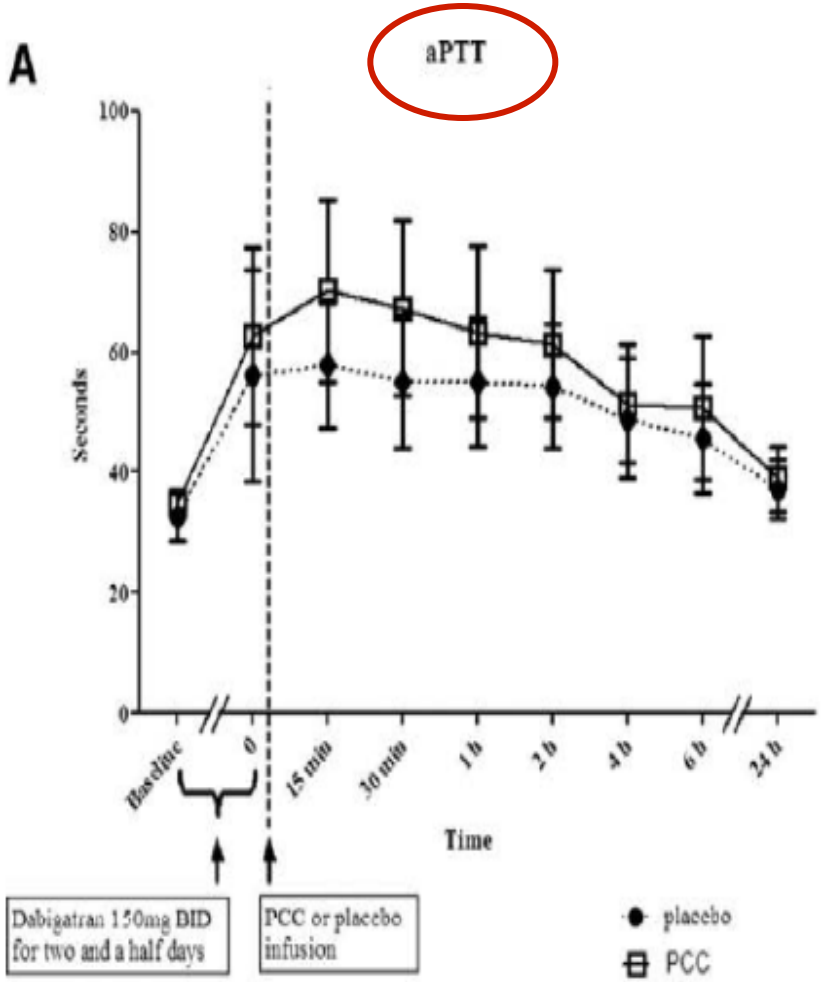
**No specific antidotes for any (yet)**

# Reversal with PCC

## rivaroxaban




## dabigatran




- dabigatran 150 mg PO BID or rivaroxaban 20 mg QD x 2½ days in 12 healthy volunteers

*Eerenberg – Circulation 2011*

# Management of *Bleeding* in Patients Receiving a New Anticoagulant

**Always:**

- Assess the source and severity of bleeding
- Assess coagulation – aPTT, PT, platelets
- Implement mechanical hemostasis if possible – packing, clipping, embolization, surgery

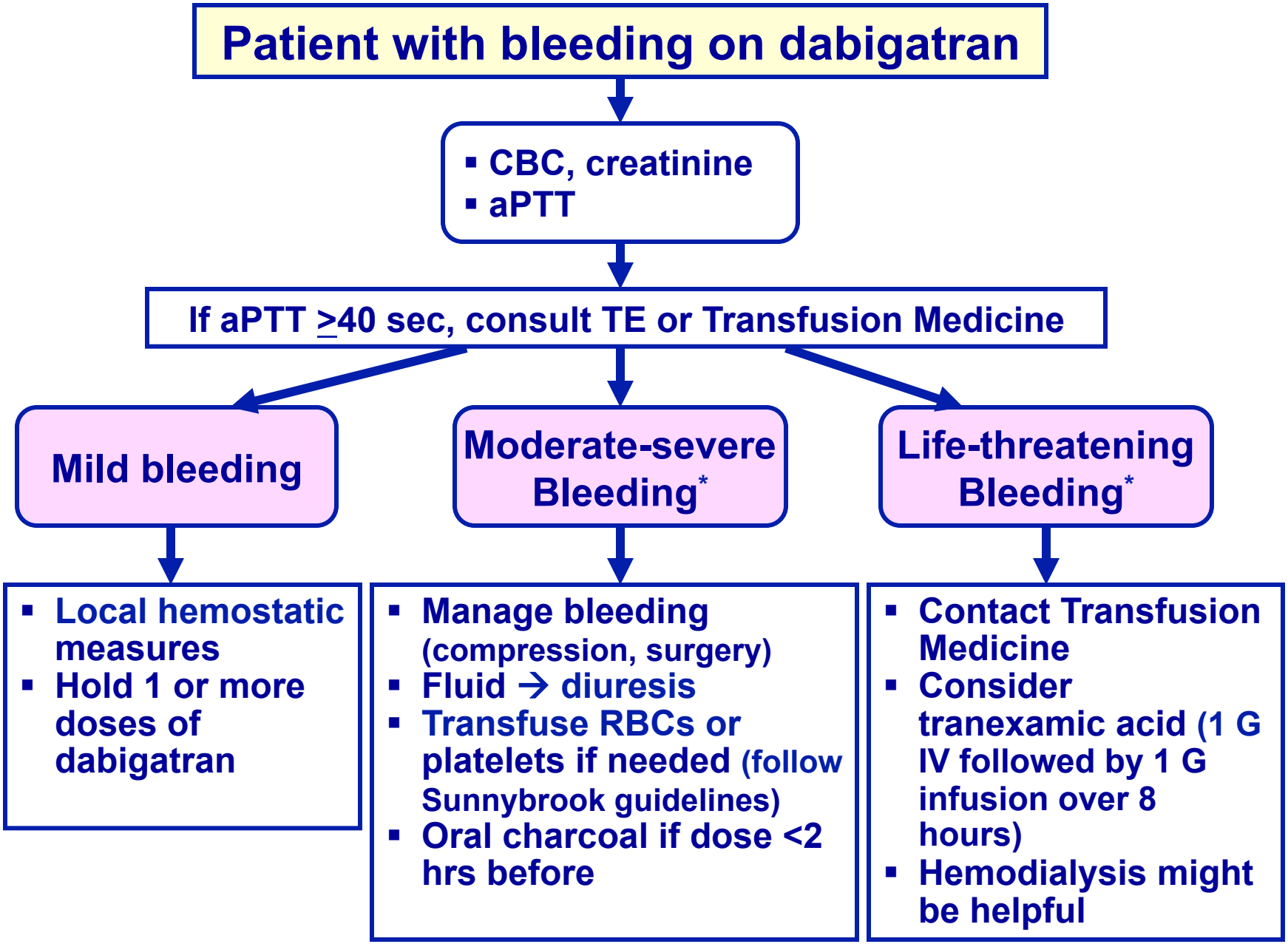
**Don't use:**

- Plasma, cryo unless factor deficiency too

**Consider:**

- Tranexamic acid
- If really desperate: hi dose PCC, FEIBA
- Removing the anticoagulant – hemodialysis (?D only)

50 IU/kg for riva




*DO NOT TRANSFUSE plasma or cryo to reverse ↑ aPTT

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# Selecting an Oral Anticoagulant 1

| Setting | Anticoagulant consideration |
|---|---|
| Good-excellent warfarin control (TTR ≥65%) | Warfarin |
| Below average warfarin control (TTR <65%) | ?? Not specifically studied |
| Severe renal dysfunction | Warfarin |
| Mechanical heart valve | Warfarin |
| Age >75 | Warfarin, ? new OAC (riva) |
| Poor compliance | Warfarin |

# Selecting an Oral Anticoagulant 2

| Setting | Anticoagulant consideration |
|---|---|
| High risk of IC bleeding | ?? (lower dose new OAC, LMWH) |
| High risk of extracranial bleeding | Warfarin or LMWH |
| Compliant, healthy patients <70 | Warf, dabi, riva |
| Cost a concern | Warfarin |