Clinical pearls and management of DOACs

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NorthShore University Health System
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• Stago Diagnostica – Research Grant
• NSUHS PI for PAUSE, Cancer HOKUSAI, CASSINI and ADAM
• BMS Speaker
• VTE Technical Advisory Panel; BMS and Janssen educational grant for DOAC discharge instruction initiative. Joint Commission
Doc, I got a Blood Clot

Which one is better for ME?!

How do I know it is working?

But, I need a surgery next month

And what if I bleed on this pill?

“Here is your DOAC, have a nice life...”
Here is your DOAC, have a nice life...

Are they really that simple?

Warfarin
Direct X inhibitors
Direct II inhibitors
Which one is better for ME?

- Stroke Prevention
- Venous Thrombo-Embolism
DABIGATRAN - RELY

Stroke rate on Warfarin: 1.69%
Stroke rate on Dabigatran 150: 1.11%
Absolute risk reduction: 0.58%
Major Bleeding on Dabigatran: 3.11%

RIVAROXABAN - ROCKET

Stroke / SE rate on Warfarin 2.2 %
Stroke rate on Rivaroxaban 1.7 %
Absolute risk reduction 0.5 %
Major Bleeding on Rivaroxaban 3.6 %

APIXABAN - ARISTOTLE

Stroke / SE rate on Warfarin    1.6 %
Stroke rate on Apixaban         1.27 %
Absolute risk reduction         0.33 %
Major Bleeding on Rivaroxaban   2.13 %

EDOXABAN - ENGAGE

Stroke / SE rate on Warfarin 1.5 %
Stroke rate on Edoxaban 60mg 1.18 %
Stroke rate on Edoxaban 60mg 1.61 %
Absolute risk reduction E60 0.32 %
Absolute risk reduction E60 -0.11 %
Major Bleeding on E60 2.75 %
Major Bleeding on E30 1.61 %

Small stroke rate differences compared to warfarin
Major differences on bleeding rate compared to other DOACs
Which one is better for **ME**?
DABIGATRAN. RECOVER

Non inferiority trial: VTE recurrence
Dabigatran 30 (2.4%) of 1274 patients
Warfarin 27 (2.1%) of 1265 patients
Major Bleeding 1.6%
Major Bleeding 1.9%

HR 1.10 (0.65 to 1.84)

Dose: 150 mg twice daily
AFTER PARENTERAL ANTICOAGUALTION FOR at least 5 d

RIVAROXABAN. EINSTEIN trials

Open-label, randomized, event-driven, non-inferiority: VTE recurrence

Rivaroxaban 36 (2.1%) of 1731 patients
Warfarin 51 (3%) of 1718 patients

Major Bleeding
Rivaroxaban 0.8%
Warfarin 1.2%

HR 0.68 (0.44 to 1.04)

Dose: 15 mg twice daily for 3 weeks, followed by 20 mg once daily

APIXABAN. AMPLIFY trials

Randomized, double-blind study: VTE recurrence

Apixaban 59 (2.3) of 2609 patients
Warfarin 71 (2.7) of 2635 patients

Major Bleeding
Apixaban 0.6%
Warfarin 1.8%

RR 0.84 (0.60 to 1.18)

Dose: 10 mg twice daily for 7 days, followed by 5 mg twice daily

EDOXABAN. HOKUSAI

Randomized, double-blind non inferiority study: VTE recurrence

Edoxaban 130 (3.2%) of 4118 patients
Warfarin 146 (3.5%) of 4122 patients

Major Bleeding

Edoxaban 1.4%
Warfarin 1.6%

Dose: 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg)

AFTER parenteral therapy at least 5 days

PE with RV dysfunction
(NT-proBNP level of ≥500 pg per milliliter)

hazard ratio, 0.52; 95% CI, 0.28 to 0.98

RV dysfunction by CT

hazard ratio, 0.42; 95% CI, 0.15 to 1.20.

<table>
<thead>
<tr>
<th>Med</th>
<th>Dabi</th>
<th>Riva</th>
<th>Apixa</th>
<th>Edoxa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Caution</td>
<td>Caution</td>
<td>NA</td>
<td>Caution</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Caution</td>
<td>Minor</td>
<td>NA</td>
<td>Caution</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Caution</td>
<td>Caution</td>
<td>NA</td>
<td>Caution</td>
</tr>
<tr>
<td>Droneradone</td>
<td>Avoid</td>
<td>Caution</td>
<td>NA</td>
<td>50%dose</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>No effect</td>
<td>Caution</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No effect</td>
<td>Minimal</td>
<td>No effect</td>
<td>Minimal</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Minimal</td>
<td>No effect</td>
<td>NA</td>
<td>No effect</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>No effect</td>
<td>Caution</td>
<td>Caution</td>
<td>NA</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>No effect</td>
<td>Minimal</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Minimal</td>
<td>Caution</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

Which one is better for ME?

- Level measurement is not necessary
- In a patient with a good TTR, a DOAC adds no value
- Antidote therapy improves bleeding outcomes
- No interactions
Doc,
I got a Blood Clot

Which one is better for ME?!

How do I know it is working?

But, I need a surgery next month

And what if I bleed on this pill?

"Here is your DOAC, have a nice life..."
How do I know it is working?

You do not...

But, can we measure it?

“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. ... What if figuring out the right dose of medicine was as simple as taking our temperature?”
Comparison of Methods to Determine Rivaroxaban anti-factor Xa activity

Suman Rathbun a,*, Alfonso Tafur a, Russell Grant b, Naomi Esmon c, Karin Mauer d, Richard A. Marlar e

a Cardiovascular section, Department of Medicine, University of Oklahoma Health Sciences Center, USA
b Labcorp of America Holdings, Research Triangle Park, NC, USA
c Oklahoma Medical Research Foundation, Oklahoma City, OK, USA
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ABSTRACT

Background and Objectives: Rivaroxaban, a new oral anti-Xa agent, has been approved for use without routine monitoring, but the lack of a predictable drug level measurement may hinder the management of anticoagulated patients. The aims of the project were to correlate an Anti-Factor Xa assay using commercial calibrators and controls (Riva Activity) with serum drug levels analyzed by HPLC-MS/MS (Riva MS) in patients currently receiving rivaroxaban, and secondly, to correlate the PT/PTT, thrombin generation (CAT assay) and Thromboelastograph (TEG) with the Riva activity and Riva MS.

Methods: Recruited patients receiving rivaroxaban prospectively had a total of 3 blood samples taken at least 2 hours apart. Plasma was divided for measurement of PT/PTT, Riva activity, rivaroxaban HPCL-MS/MS, and thrombin generation. TEG activity was measured at one random time point for each patient. Correlation and linear regression evaluations were used to compare the different assays.

Results: The cases were 22 patients on rivaroxaban, age 56 ± 12.6, and 10 healthy controls. There was a strong correlation between Riva activity compared to serum Riva MS (r = 0.99). We found a statistically significant correlation between PT/INR compared to serum measurements of Riva MS (r = 0.68) and anti-Xa activity (r = 0.69). The peak (r = -0.50) and lag time (r = 0.57) CAT correlated with Riva MS measurements. There was no correlation between Riva MS and PTT, TEG R, TEG MA, Endogenous Thrombin potential.
### Table 1 Indications for use or non-use of the antidotes

<table>
<thead>
<tr>
<th>Indications for use</th>
<th>Potential indication for use</th>
<th>Antidotes should not be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage</td>
<td>Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance</td>
<td>Elective surgery</td>
</tr>
<tr>
<td>Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome</td>
<td>Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery</td>
<td>Gastrointestinal bleeds that respond to supportive measures</td>
</tr>
<tr>
<td>Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose</td>
<td>High drug levels or excessive anticoagulation without associated bleeding</td>
<td>Need for urgent surgery or intervention in patients with acute renal failure</td>
</tr>
<tr>
<td>Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance</td>
<td>Need for surgery or intervention that can be delayed long enough to permit drug clearance</td>
<td>High drug levels or excessive anticoagulation without associated bleeding</td>
</tr>
</tbody>
</table>

**Life-threatening bleeding:** Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage

**Bleeding in a closed space or critical organ:** Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome

**Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose**
Does it matter? Edoxaban

Does it matter? Dabigatran

Does it matter?  Rivaroxaban

(A) Logistic Regression

(B) Cox Regression

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000ClinPharmR.pdf
Does it matter? Apixaban

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000ClinPharmR.pdf
What to do?

The best safety strategy is to use DOACs as they were used in the

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>No</td>
<td>20 → 15</td>
<td>5 → 2.5</td>
<td>60 → 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 → 15</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>--</td>
<td>CrCl 30-49</td>
<td>2 of 3:</td>
<td>CrCl 30–50</td>
</tr>
<tr>
<td>criteria</td>
<td></td>
<td></td>
<td>• Age ≥ 80 years</td>
<td>wgt ≤ 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• wgt ≤ 60 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Cr ≥ 1.5 mg/dL</td>
<td>• Strong P-gp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>inhibitor</td>
</tr>
</tbody>
</table>
Do patients on DOAC AND antiplatelet bleed more?

Placebo, and dabigatran 50-, 75-, 100-, and 150-mg groups bleeding risk: 2.2%, 3.5%, 4.3%, 7.9%, and 7.8% (p < 0.001 trend).

Rivaroxaban vs placebo
Non-CABG TIMI major bleeding
(2.0% vs 0.6%, P<0.001)
ICH
(0.5% vs 0.3%, P=0.019)

### Do patients on DOAC AND antiplatelet bleed more?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Edox</th>
<th>Warf</th>
<th>HR (95%CI)</th>
<th>Pint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet</td>
<td>1.42</td>
<td>1.49</td>
<td>0.94(0.77-1.15)</td>
<td>0.91</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>1.31</td>
<td>1.88</td>
<td>0.70(0.50-0.98)</td>
<td>0.14</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet</td>
<td>1.20</td>
<td>1.07</td>
<td>1.11(0.89-1.39)</td>
<td>0.17</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>0.86</td>
<td>1.19</td>
<td>0.73(0.48-1.11)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet</td>
<td>0.16</td>
<td>0.36</td>
<td>0.45(0.27-0.74)</td>
<td>0.98</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>0.40</td>
<td>0.61</td>
<td>0.66(0.36-1.20)</td>
<td>0.33</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet</td>
<td>0.53</td>
<td>0.59</td>
<td>0.89(0.65-1.22)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>0.79</td>
<td>0.94</td>
<td>0.85(0.54-1.34)</td>
<td>0.87</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet</td>
<td>2.12</td>
<td>2.61</td>
<td>0.81(0.69-0.94)</td>
<td>0.25</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>2.94</td>
<td>3.56</td>
<td>0.83(0.66-1.05)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

But still, it is a safer combination than with warfarin.
Doc, I got a Blood Clot

Which one is better for ME?!

How do I know it is working?

But, I need a surgery next month

And what if I bleed on this pill?

“Here is your DOAC, have a nice life…”
Problem # 6: Find X

\[ X = \frac{1}{\sqrt{1/2}} \]
37 YOWF with Hx extensive VTE Hx.

First event was pregnancy related with right iliac vein thrombosis. Anticoagulation eventually discontinued and had a second event in LLE: CFV, FV, POPV [well recanalized]. She had poor INR control and recurrent RLE event. Now on Rivaroxaban with no recurrence.

Poorly recanalized R Iliac, she is SP Palma procedure for RLE decompression.

Due to persistent pain and subsequent CRPS she is now listed for spinal cord stimulator. Epidural leads in April 14th, out on the 17th.

How to manage her periprocedural anticoagulation?
• **RELY**
  – 4133 (23%) PACM in 18113 pts

• **ROCKET AF.**
  – 4642 (33%) PACM in 14264 pts

Douketis et al. Thrombosis Haemostasis 2015
Sherwood et al. Circulation 2014
<table>
<thead>
<tr>
<th>Surgery</th>
<th>CAF</th>
<th>No AF</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>1255 (1.8)</td>
<td>14663 (0.6)</td>
<td>2.1</td>
</tr>
<tr>
<td>Abdom</td>
<td>101 (1.3)</td>
<td>1498 (0.3)</td>
<td>1.8</td>
</tr>
<tr>
<td>CABG</td>
<td>326 (3.1)</td>
<td>3241 (2.0)</td>
<td>1.4</td>
</tr>
<tr>
<td>Neuro</td>
<td>51 (3.1)</td>
<td>723 (0.8)</td>
<td>2.9</td>
</tr>
<tr>
<td>Ortho</td>
<td>200 (1.2)</td>
<td>3132 (0.5)</td>
<td>1.6</td>
</tr>
<tr>
<td>Vascular</td>
<td>74 (3.1)</td>
<td>1511 (1.2)</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Kaatz et al. J Thromb Haemost 2010
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O.,
Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D.,
David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A.,
David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B.,
Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D.,
for the BRIDGE Investigators*

ABSTRACT

BACKGROUND
It is uncertain whether bridging anticoagulation is necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective operation or other elective invasive procedure. We hypothesized that forgoing bridging anticoagulation would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding.

METHODS
We performed a randomized, double-blind, placebo-controlled trial in which, after perioperative interruption of warfarin therapy, patients were randomly assigned...
Does the patient need to stop anticoagulation?

Yes →

May continue anticoagulation:
- pacemaker placement
- dental extraction
- cataract surgery
- joint aspiration
- dermatologic biopsy
- venography
- radio frequency ablation

No → Proceed without interruption

Is the risk of stroke high?

Yes → Stop warfarin 5 days before the procedure no heparin bridging

No → Reasonable to consider preoperative bridging

Assess bleeding risk

Last preoperative dose of low-molecular-weight heparin is 24 hours before the intervention and ½ of the daily dose

Provide postoperative venous thromboembolism prophylaxis in all patients
Who may continue DOACs?

Prospective Dresden NOAC Registry

2179 Patients, 863 procedures

<table>
<thead>
<tr>
<th>Level</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>135</td>
<td>(16%)</td>
</tr>
<tr>
<td>Minor</td>
<td>641</td>
<td>(74%)</td>
</tr>
<tr>
<td>Major</td>
<td>87</td>
<td>(10%)</td>
</tr>
</tbody>
</table>
Who may continue DOACs?

Prospective Dresden NOAC Registry

2179 Patients, 863 procedures

- Minimal: 135 (16%)
- Minor: 641 (74%)
- Major: 87 (10%)

ANY Bleeding if NOAC continued n 187
- 1.1% (0.1 – 3.8)
- 4.8% (2.2 – 8.9)

MAJOR Bleeding if NOAC continued n 187
- 0% (0 – 2)
- 0% (0 – 2)

Who may continue DOACs?

Prospective Dresden NOAC Registry

Minimal
- Skin / Oral Surgery
- Wound revision
- Non extraction Dental

Minor
- Pacemaker
- Cataract
- Arthroscopy
- Dental Extraction
- Hernia Repair
- Pleura / Ascites puncture
- Venography

Adapted from Beyer-Westendorf et al. Eur Heart j. 2014
Feasibility and Safety of Dabigatran Versus Warfarin for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation

Results From a Multicenter Prospective Registry

Dhanunjaya Lakireddy, MD,* Yeruva Madhu Reddy, MD,* Luigi Di Biase, MD, PhD,†‡§ Subba Reddy Vanga, MD,* Pasquale Santangeli, MD,† Vijay Swarup, MD,|| Rhea Pimentel, MD,* Moussa C. Mansour, MD,¶ Andre D'Avila, MD, PhD,# Javier E. Sanchez, MD,† J. David Burkhardt, MD,† Fadi Chalhoub, MD,¶ Prasant Mohanty, MBBS, MPH,† James Coffey, MD, Naushad Shaik, MD,** George Monir, MD,† Vivek Y. Reddy, MD,# Jeremy Ruskin, MD,¶ Andrea Natale, MD†§‡‡

Kansas City, Kansas; Austin, Texas; Foggia, Italy; Phoenix, Arizona; Boston, Massachusetts; New York, New York; Kissimmee and Orlando, Florida; and San Francisco, California

Objectives

The purpose of this study was to evaluate the feasibility and safety of periprocedural dabigatran during atrial fibrillation (AF) ablation.

Background

AF ablation requires optimal periprocedural anticoagulation for minimizing bleeding and thromboembolic complications. The safety and efficacy of dabigatran as a periprocedural anticoagulant for AF ablation are unknown.
Feasibility and Safety of Uninterrupted Rivaroxaban for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation

Results From a Multicenter Prospective Registry

Dhanunjaya Lakkireddy, MD,* Yeruva Madhu Reddy, MD,* Luigi Di Biase, MD, PhD,†‡§
Ajay Vallakati, MD,* Moussa C. Mansour, MD,|| Pasquale Santangeli, MD,†
Sandeep Gangireddy, MD,¶ Vijay Swarup, MD,# Fadi Chalhoub, MD,|| Donita Atkins, RN,*
Sudharani Bommana, MPHIL,* Atul Verma, MD,∗ Javier E. Sanchez, MD,† J. David Burkhardt, MD,†
Connor D. Barrett, MD,+++ Salwa Baheiry, MD,+++ Jeremy Ruskin, MD,|| Vivek Reddy, MD,¶
Andrea Natale, MD†§

Kansas City, Kansas; Austin, Texas; Foggia, Italy; Boston, Massachusetts; New York, New York;
Phoenix, Arizona; Toronto, Ontario, Canada; and San Francisco, California
Feasibility and safety of uninterrupted periprocedural apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation: Results from a multicenter study

Luigi Di Biase, MD, PhD, FHRSA, Dhanujaya Lakireddy, MD, FHRSB, Chintan Trivedi, MD, MPH, Thomas Deneke, MD, Martin Martinek, MD, Sanghamitra Mohanty, MD, FHRSC, Prasant Mohanty, MBBS, MPH, Sameer Prakash, BS, Rong Bai, MD, FHRSD, Madhu Reddy, MD, Carola Gianni, MD, Rodney Horton, MD, Shane Bailey, MD, Elisabeth Sigmund, MD, Michael Derndorfer, MD, Anja Schade, MD, Patrick Mueller, MD, Atilla Szoellos, MD, Javier Sanchez, MD, Amin Al-Ahmad, MD, Patrick Hranitzky, MD, G. Joseph Gallinghouse, MD, Richard H. Hong, MD, FHRSD, Salwa Beheiry, RN, Helmut Pürerfellner, MD, J. David Burkhardt, MD, FHRSA, Andrea Natale, MD, FHRSD, RFA
Stroke risk in AF

Non Bridged Patients

<table>
<thead>
<tr>
<th>TE Hx +</th>
<th>CHADS2 ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE rate 0%</td>
<td>TE rate 0%</td>
</tr>
<tr>
<td>BL rate 0%</td>
<td>BL rate 0%</td>
</tr>
<tr>
<td>(n=43)</td>
<td>(n=51)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TE Hx -</th>
<th>CHADS2 &lt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE rate 1%</td>
<td>TE rate 1%</td>
</tr>
<tr>
<td>BL rate 3%</td>
<td>BL rate 3%</td>
</tr>
<tr>
<td>(n=129)</td>
<td>(n=121)</td>
</tr>
</tbody>
</table>

“To know that we know what we know, and that we do not know what we do not know, that is true knowledge.”

Confucius
## PACM in RELY

<table>
<thead>
<tr>
<th></th>
<th>Warfarin n 1424</th>
<th>Dabigatran n 2709</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bridged</td>
<td>Not Bridged</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>CHADSVASC</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Stroke / systemic</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>ANY TE</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>6.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

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*Douketis et al. Thrombosis Haemostasis 2015*
## PACM in RELY

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<tr>
<td>Stroke / systemic</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>OR 2.7</td>
<td>(0.38 – 19.3)</td>
</tr>
<tr>
<td>ANY TE</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>OR 6.4</td>
<td>(1.64 – 24.8)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>6.8</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>OR 4.6</td>
<td>(2.45 – 8.72)</td>
</tr>
</tbody>
</table>

*Douketis et al. Thrombosis Haemostasis 2015*
## PACM in ROCKET AF

<table>
<thead>
<tr>
<th></th>
<th>Warfarin n 2527 (4162 TI)</th>
<th>Rivaroxaban n 2165 (3393 TI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>PVD</td>
<td>6.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Hx Stroke</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>FEM</td>
<td>38</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BRIDGING n 483</th>
<th>NO BRIDGING n 7072</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke / systemic</td>
<td>1  0.17</td>
<td>31  0.37</td>
</tr>
<tr>
<td>ANY TE</td>
<td>5  0.86</td>
<td>67  0.82</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>5  0.91</td>
<td>69  0.88</td>
</tr>
</tbody>
</table>

Only 9% received bridging.

*Sherwood et al. Circulation 2014*
• Temporary interruptions in the ROCKET trial were associated with 0.36% of 30 day stroke incidence

• Compared to a 2.2 % / y in the overall population.

Sherwood et al. Circulation 2014
VTE post operative 90 d recurrence risk

• 3-month cumulative thromboembolism incidence rate of 1.8% (95% CI, 0.9%–2.8%).

• Pulmonary embolism was a rare event, occurring in 0.5% pts.

• Few patients with “Acute” VTE.

• Cancer was the only factor increasing the rate of incident TE.
Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism

T. VAN DER HULLE,* P. L. DEN EXTER,* J. KOOIMAN,* J. J. M. VAN DER HOEVEN,† M. V. HUISMAN* and F. A. KLOK*
*Department of Thrombosis and Hemostasis, LUMC; and †Department of Medical Oncology, LUMC, Leiden, the Netherlands


Summary. Introduction: Treatment of acute venous thromboembolism (VTE) in cancer patients is challenging, owing to a high risk of recurrent VTE and bleeding complications. The anticoagulants of choice are low molecular weight heparins (LMWHs), because of a proven higher efficacy than vitamin K antagonists (VKAs) and a similar bleeding profile. The recently introduced new oral anticoagulants (NOACs) have the potential to be alternative options for these patients, as these drugs share practical advantages with LMWH, are administered orally, and had similar efficacy to VKAs but a lower bleeding risk in phase 3 studies in the general VTE population. Methods: (RR 0.94, 95% CI 0.70–1.3). These results form a solid basis for the initiation of a head-to-head comparison of NOACs with LMWH in cancer patients.

Keywords: anticoagulants; hemorrhage; neoplasms; treatment outcome; venous thromboembolism.

Introduction

Symptomatic acute venous thromboembolism (VTE) is a common complication in cancer patients, occurring in up
Patients with cancer have more bleeding complications.

With cancer: 12.4% (95% CI 6.5%-18.2%)

Without cancer: 4.9% (95% CI 2.5%-7.4%)

Cancer effect on periprocedural thromboembolism and bleeding in anticoagulated patients

A. J. Tafur¹, W. E. Wysokinski¹*, R. D. McBane³, E. Wolny², E. Sutkowska³, S. C. Litin⁴, P. R. Daniels⁴, J. P. Slusser⁵, D. O. Hodge⁵ & J. A. Heit¹

¹Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester; ²Department of Radiotherapy, Memorial Regional Hospital, Zielona Gora; ³Division of Rehabilitation, Department of Orthopedic Surgery, University Medical School of Wroclaw, Wroclaw, Poland; ⁴General Internal Medicine, Department of Internal Medicine; ⁵Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, USA

Received 17 October 2011; revised 24 January 2012; accepted 1 February 2012

Background: Patients with active cancer are often on chronic anticoagulation and frequently require interruption of this treatment for invasive procedures. The impact of cancer on periprocedural thromboembolism (TE) and major bleeding is not known.

Patients and methods: Two thousand one hundred and eighty-two consecutive patients referred for periprocedural anticoagulation (2484 procedures) using a standardized protocol were followed forward in time to estimate the 3-month incidence of TE, major bleeding and survival stratified by anticoagulation indication. For each indication, we tested active cancer and bridging heparin therapy as potential predictors of TE and major bleeding.

Results: Compared with patients without cancer, active cancer patients (n = 493) had more venous thromboembolism (VTE) complications (1.2% versus 0.2%; P = 0.001), major bleeding (3.4% versus 1.7%; P = 0.02) and reduced survival (95% versus 99%; P < 0.001). Among active cancer patients, only those chronically anticoagulated for VTE had higher rates of periprocedural VTE (2% versus 0.16%; P = 0.002) and major bleeding (3.7% versus 0.6%; P < 0.001). Bridging with heparin increased the rate of major bleeding in cancer patients (5% versus 1%; P = 0.03) without impacting the VTE rate (0.7% versus 1.4%, P = 0.50).

Conclusions: Cancer patients anticoagulated for VTE experience higher rates of periprocedural VTE and major bleeding. Periprocedural anticoagulation for these patients requires particular attention to reduce these complications.

Key words: bleeding, malignancy, periprocedural management of anticoagulation, thromboembolism
Active Cancer as a PACM risk modifier.
3 mo. Major Bleeding Kaplan Meier curves

Survival free of major bleeding

Cancer patients
- Bridging
- No bridging
  P=0.047

All patients
- No cancer
  P<0.02

Days after procedure

Tafur A et al. Annals of Oncology 2012
HASBLED and PACM

1,000 invasive procedures

1 major bleeding (0.1%)
35 clinically relevant bleedings (3.5%)

Mechanical heart valve replacement (p< 0.01)
HAS-BLED score (p< 0.01)

> 3 HR 11.8 (5.6-24.9)
Predictors of major bleeding in peri-procedural anticoagulation management


*Mayo Clinic Thrombophilia Center, Gonda Vascular Center; †Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN; and ‡Division of Blood Disorders (MGB), National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA


Summary. Background: Appropriate periprocedural management for chronically anticoagulated patients requires assessment of patient-specific thrombosis and bleeding risks. However, predictors of post-procedure bleeding are unknown. Objectives: To determine the 3-month cumulative incidence and independent predictors of peri-procedural bleeding in chronically anticoagulated patients requiring temporary warfarin interruption for an invasive procedure. Methods: In a retrospective analysis, the cumulative incidence of peri-procedural bleeding was determined by chart review. Multivariable modeling was used to assess risk factors for bleeding. Results: Of the 644 patients evaluated, 3-month cumulative peri-procedural bleeding occurred in 11% of patients (12%), with a prevalence of 5% for major bleeding. Several predictors of peri-procedural bleeding were identified, including age ≥ 65 years, chronic kidney disease, prior bleeding, prior stroke, and use of low-molecular-weight heparin. Conclusions: The risk of peri-procedural bleeding in patients taking warfarin can be accurately predicted using a combination of patient-specific factors. These factors should be considered in the pre-procedural assessment to identify patients at high risk for peri-procedural bleeding and help guide management strategies.

Keywords: anticoagulation, bleeding, low-molecular-weight heparin, surgery, warfarin.

Introduction

Each year, nearly 10% of the more than 2.5 million chronically anticoagulated Americans require temporary warfarin discontinuation for an invasive procedure [1]. Prescribing the most appropriate peri-procedural anticoagulation management strat-
Bleed MAP and PACM

Rates of Major Bleeding

Among Bridged Patients.

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed Hx</td>
<td>2.1</td>
<td>1.1–4.1</td>
</tr>
<tr>
<td>Mitral MHV</td>
<td>2.4</td>
<td>1.1–4.9</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1.9</td>
<td>1.0–3.5</td>
</tr>
<tr>
<td>PLTpenia &lt; 150k</td>
<td>2.3</td>
<td>1.1–4.6</td>
</tr>
</tbody>
</table>

Tafur A et al J Thromb Haemost 2011
PACM Recommendation for pts on DOACs

PRE OP

Patient on DOAC Needing procedure

Needs to stop?

No

Procedure

Yes

Aim for Minimal residual effect

Hold on day – 3

IF CrCl < 50 HOLD on -5

Aim for Mild-Mod residual effect

Hold on day – 2

IF CrCl < 50 HOLD on -3

Adapted from Douketis, Current Pharmaceutical Design 2010
PACM Recommendation for pts on DOACs POST OP

Patient on DOAC POST procedure

Bleed risk HIGH?

Yes

VTE prevention
Re initiate full dose anticoagulation at 48 – 72h post op

NO

Resume day after Surgery

Adapted from Douketis, Current Pharmaceutical Design 2010
# PAUSE trial protocol

## Dabigatran:

<table>
<thead>
<tr>
<th>CrCl (mL/min)†</th>
<th>Drug Half-life, hrs (range)</th>
<th>Interval between Last NOAC Dose and Procedure Low-bleed Risk</th>
<th>High-bleed Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>14 (12-18)</td>
<td>at least 24 hrs (skip 2 doses)</td>
<td>at least 48 hrs (skip 4 doses)</td>
</tr>
<tr>
<td>≥30 to ≤50</td>
<td>18 (13-23)‡</td>
<td>at least 48 hrs (skip 4 doses)</td>
<td>at least 96 hrs (skip 8 doses)</td>
</tr>
</tbody>
</table>

## Rivaroxaban:

<table>
<thead>
<tr>
<th>CrCl (mL/min)†</th>
<th>Drug Half-life, hrs (range)</th>
<th>Interval between Last NOAC Dose and Procedure Low-bleed Risk</th>
<th>High-bleed Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>8 (7-10)</td>
<td>at least 24 hrs (skip 1 dose)</td>
<td>at least 48 hrs (skip 2 doses)</td>
</tr>
<tr>
<td>≥30 to ≤50</td>
<td>11 (9-13)‡</td>
<td>at least 24 hrs (skip 1 dose)</td>
<td>at least 48 hrs (skip 2 doses)</td>
</tr>
</tbody>
</table>

## Apixaban:

<table>
<thead>
<tr>
<th>CrCl (mL/min)†</th>
<th>Drug Half-life, hrs (range)</th>
<th>Interval between Last NOAC Dose and Procedure Low-bleed Risk</th>
<th>High-bleed Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>8 (7-10)</td>
<td>at least 24 hrs (skip 2 doses)</td>
<td>at least 48 hrs (skip 4 doses)</td>
</tr>
<tr>
<td>≥30 to ≤50</td>
<td>11 (9-13)‡</td>
<td>at least 24 hrs (skip 2 doses)</td>
<td>at least 48 hrs (skip 4 doses)</td>
</tr>
</tbody>
</table>

†Cockcroft-Gault formula (89); ‡estimated half-life range (3, 5, 93, 94)

### 9.1.2 Post-procedure NOAC resumption

See Appendix 3 for resumption by procedure type.

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Resumption of NOAC after Surgery/Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-bleed Risk</td>
</tr>
<tr>
<td>dabigatran</td>
<td>resume AM post-op day +1 (24 hrs)</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>as above</td>
</tr>
<tr>
<td>apixaban</td>
<td>as above</td>
</tr>
</tbody>
</table>
Is PAUSE a good plan?
DABIGATRAN
The analyses the regulators didn’t see
ie 17 h X 5 half lives = 85 h

85h / 24 h per day = 3.5

85h / 5 d as per ASRA = 17 h days  ???
Doc, I got a Blood Clot

Which one is better for ME?!

How do I know it is working?

But, I need a surgery next month

And what if I bleed on this pill?

“Here is your DOAC, have a nice life...”
What if I bleed?

1. The probability of bleeding is low
2. IF you bleed, the probability of death with NO antidote, is still lower than the probability of death with a major bleed on Warfarin → 0.16 / 100 patient-years (95% CI, 0.12–0.20) → RR, 0.53; 95% CI, 0.43-0.64
3. IF an antidote is not available in the nearest hospital there are reversal options

Idarucizumab
Andexanet alpha
Ciraparantag

PCC

What if I bleed?

Idarucizumab
Andexanet alpha
Ciraparantag
PCC

Patient selection
Routine monitoring is not yet justified
Perioperative discontinuation based on half life and risk
Bleeding is rare, reversal available