Lab monitoring of dabigatran

Why, how and when

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Why bother
Randomised Evaluation of Long-term anticoagulation therapy

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*

RE-LY

20,382 Patients in screening visit

2,269 excluded
Reasons:
417 Declined to participate
1,553 Ineligible
299 Other

18,113 Randomized

6,015 Dabigatran 110mg bid
6,076 Dabigatran 150mg bid
6,022 Warfarin
RE-LY

20,382 Patients in screening visit

2,269 excluded
   Reasons:
   417 Declined to participate
   1553 Ineligible
   299 Other

18,113 Randomized

6,015 Dabigatran 110mg bid
6,076 Dabigatran 150mg bid
6,022 Warfarin
Primary Outcome of Stroke or Systemic Embolism

Cumulative Hazard Rate

Months

Warfarin
Dabigatran, 110 mg
Dabigatran, 150 mg
Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013
Dabigatran and Postmarketing Reports of Bleeding

Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study

Rikke Sørensen,1,2 Gunnar Gislason,1,3 Christian Torp-Pedersen,4 Jonas Bjerring Olesen,1 Emil L Fosbøl,5 Morten W Hvidtfeldt,1 Deniz Karasoy,1 Morten Lamberts,1 Mette Charlot,1,6 Lars Køber,9 Peter Weeke,1 Gregory Y H Lip,7 Morten Lock Hansen1

Dabigatran and Postmarketing Reports of Bleeding

Dabigatran use in Danish atrial fibrillation patients in 2011: a
Efficacy and Safety of Dabigatran Etxilate and Warfarin in “Real-World” Patients With Atrial Fibrillation
A Prospective Nationwide Cohort Study

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Mary Rosenzweig, MSc,§ Gregory Y. H. Lip, MD¶

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

(J Am Coll Cardiol 2013;61:2264–73)
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Bleeding Events Among New Starters and Switchers to Dabigatran Compared with Warfarin in Atrial Fibrillation

Torben Bjerregaard Larsen, MD, PhD, a,b Anders Gorst-Rasmussen, MSc, PhD, a,b Lars Hvilsted Rasmussen, MD, PhD, b Flemming Skjøth, MSc, PhD, a,b Mary Roszenweig, MSc, c Gregory Y.H. Lip, MD, d

The American Journal of Medicine (2014) 127, 650-656
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Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houston, PharmD, MPH; Thomas E. Macurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMS

Circulation. 2015;131:157-164.
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Julie C. Lauffenburger, PharmD, PhD; Joel F. Farley, PhD; Anil K. Gehi, MD; Denise H. Rhoney, PharmD, FCCP, FCCM, FNCS; M. Alan Brookhart, PhD; Gang Fang, PharmD, MS, PhD

J Am Heart Assoc. 2015;4:e001798
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Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study

Hsien-Yen Chang, MeiJia Zhou, Wenze Tang, G Caleb Alexander, Sonal Singh

BMJ 2015;350:h1585
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Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

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BMJ 2015;350:h1857
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Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation

Results from the Dresden NOAC Registry

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Thromb Haemost 2015; 113:
Dabigatran ≤ warfarin risk

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Dabigatran > warfarin risk
Why
INR-guided warfarin dosing

Kurnik 2009
Hylek 2003
The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,† Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPhil,§ John W. Eikelboom, MB BS,§ Michael D. Ezekowitz, MD, PhD,|| Gerhard Nehmiz, PhD,† Susan Wang, PhD,* Lars Wallentin, MD, PhD,¶ on behalf of the RE-LY Investigators
RE-LY

Primary Outcome of Stroke or Systemic Embolism

Connolly 2009
Figure 2

Chin 2014
Figure 2

Chin 2014
How
‘Too cold’: insensitive

$r^2 = 0.49$

Chin 2014
‘Still quite cold’

$r^2 = 0.54$

Chin 2014
‘Too hot’: oversensitive

r² = 0.70

ref range
‘Just right?’

Chin 2014

$r^2 = 0.95$

Plasma dabigatran concentration (µg/L)

dTT (s)
‘Too hot’: oversensitive

$r^2 = 0.70$

Plasma dabigatran concentration (μg/L)

ref range

Chin 2014
‘Not bad?’

Target trough

r² = 0.70

Plasma dabigatran concentration (µg/L)
Table 1 Covariates of dabigatran plasma concentrations

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Mean exposure ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton-pump inhibitor [12]</strong></td>
<td>0.80 (0.67–0.95)</td>
</tr>
<tr>
<td><strong>Intestinal P-gp function</strong></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole [5]</td>
<td>2.50 (NA)</td>
</tr>
<tr>
<td>Dronedarone [6]</td>
<td>1.99 (1.79–2.21)</td>
</tr>
<tr>
<td>Verapamil [8]</td>
<td>1.71 (1.34–2.15)</td>
</tr>
<tr>
<td>Amiodarone [5]</td>
<td>1.60 (NA)</td>
</tr>
<tr>
<td>Quinidine [5]</td>
<td>1.50 (NA)</td>
</tr>
<tr>
<td>Clarithromycin [9]</td>
<td>1.49 (NA)</td>
</tr>
<tr>
<td>Ticagrelor [59]</td>
<td>1.46 (NA)</td>
</tr>
<tr>
<td>Clopidogrel, loading dose [7]</td>
<td>1.35 (1.07–1.69)</td>
</tr>
<tr>
<td>rs4148738 [13]</td>
<td>1.12 (1.08–1.17)</td>
</tr>
<tr>
<td>rs1045642 [14]</td>
<td>1.08 (NA)</td>
</tr>
<tr>
<td>Rifampicin [10]</td>
<td>0.33 (0.27–0.41)</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin, phenobarbital [10]</td>
<td>NA^c</td>
</tr>
<tr>
<td><strong>Hepatic CES1 function</strong></td>
<td></td>
</tr>
<tr>
<td>rs2244613 [13]</td>
<td>0.85 (0.81–0.90)</td>
</tr>
<tr>
<td>rs4122238 [13]</td>
<td>0.86 (0.81–0.91)</td>
</tr>
<tr>
<td>rs8192935 [13]</td>
<td>0.89 (0.85–0.93)</td>
</tr>
<tr>
<td><strong>Renal impairment [16]</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.50 (0.78–2.90)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.15 (1.63–6.08)</td>
</tr>
<tr>
<td>Severe</td>
<td>6.31 (3.54–11.25)</td>
</tr>
</tbody>
</table>
Takeaways

• Dabigatran appears to be a great advance
  − There is room for improvement

• Poor correlation between dose and concentrations
  − Uncertainty about dosing to account for covariates

• Higher [dabigatran] associated with:
  − less clots
  − more bleeds

• Dosing to [dabigatran] may improve outcomes
  − Especially by minimising bleeds