Insight into the Drug Use Evaluation (DUE) Process: Assessment of Dabigatran use in Adult Inpatients at The John Hopkins Hospital

Raymond Lamore, PharmD
Emily Pherson, PharmD

The Johns Hopkins Hospital
August 27th, 2012

Overview

- Novel oral anticoagulant: dabigatran
- Overview of a drug use evaluation
- Inpatient use of dabigatran at The Johns Hopkins Hospital

ATRIAL FIBRILLATION & DABIGATRAN

Atrial Fibrillation (AF)

- Most common significant cardiac rhythm disorder
  - 5 million people in US effected
- 5-fold increase in risk of ischemic stroke
  - Ischemic stroke: 4th leading cause of death in US
- Economic burden of AF-related stroke
  - Approximately $13 billion dollars/year

J Med Econ 2012; 15:776-785.

Traditional Treatment

http://cdn.drugsdb.com/images/2012/07/Warfarin.jpg

Dabigatran (Pradaxa®)

- FDA approved October 2010
- Direct thrombin inhibitor
- Approved for prevention of stroke and systemic embolism in non-valvular AF
  - Also studied in prevention and treatment of venous thromboembolism (VTE)

- February 2012: ACCP Antithrombotic guidelines published (AT9)

AT9 Oral Anticoagulation

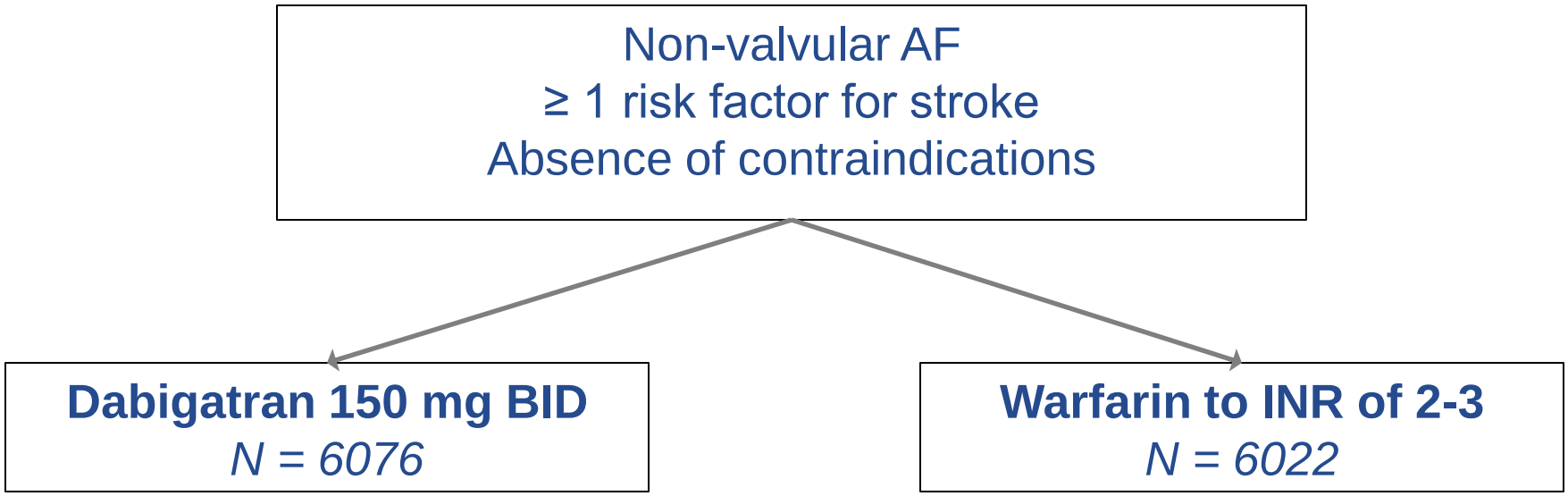
JOHNS HOPKINS MEDICINE

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range, 2.0-3.0) (Grade 2B).

4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or

CHEST 2012:141:e531-575S

RE-LY Design



Primary Efficacy Endpoint: Stroke or symptomatic embolism
Safety Endpoint: major bleeding

N Engl J Med 2009; 361:1139-51

RE-LY Efficacy

Outcomes	Dabigatran 150 mg BID	Warfarin	HR 95% CI
Stroke or systemic embolic event (%)	1.11	1.69	0.66 0.53–0.82 ***Superior***
Hemorrhagic stroke (%)	0.10	0.38	0.26 0.14–0.49

N Engl J Med 2009; 361:1139-51

RE-LY Safety

Outcomes	Dabigatran 150 mg	Warfarin	HR 95% CI
Major bleeding (%)	3.11	3.36	0.93 0.81–1.07
Gastrointestinal (%)	1.51	1.02	1.50 1.19–1.89

N Engl J Med 2009; 361:1139-51

Pharmacoeconomic Analysis

Purpose	Pharmacoeconomic comparison of warfarin, low and high-dose dabigatran in patients from the RE-LY study.
Outcomes	Quality adjusted life expectancy comparison (incremental cost-effectiveness ratio-ICER)
Cost Inclusions	Warfarin: CMS reimbursement for AC management 14 INR tests/yr (22 tests for year 1) 1 tablet/day Dabigatran: 2 capsules per day Management visits at 1 mo, 3 mo, Q3mo x 1 yr and Q4mo thereafter Additional: One-time costs of ICH, MI, CVA and TIA Monthly costs of sequelae
Patients	Incorporated: age, bleeding event, MI, stroke or death
Definitions	ICER: ratio of the change in costs to change in effects of an intervention QALY: measure of quality and quantity of life lived

Ann Intern Med 2011;154:1-11.

Pharmacoeconomic Analysis:

	Intervention	Base-Case	Ischemic Stroke: High Risk	Ischemic Stroke: Low Risk
QALY	Dabigatran 150 mg	10.84	9.36	11.23
	Warfarin	10.28	10	10.72
ICER/ QALY	Dabigatran 150 mg	$45,372	$39,680	$171,984

Ann Intern Med 2011;154:1-11.

DRUG UTILIZATION EVALUATION

A Representative Definition of Drug Utilization Evaluation

"Structured, ongoing initiatives that interpret patterns of drug use in relation to predetermined criteria, and attempt to prevent or minimize inappropriate prescribing"

- Soumerai SB, et al. N Engl J Med 1995;32:1641-5

Historical Prospective

- Facilitated by growth of prescription drug insurance programs in 1970's
  - Created impetus to manage cost and quality
  - Medicaid program among the first to routinely conduct DUEs
- Became Joint Commission requirement in 1985
- Omnibus Budget Reconciliation Act of 1990: mandated all states conduct retrospective and prospective DUEs for Medicaid enrollees

Selection of DUE Topics

- Cost
- Formulary status/procedures
  - Nonformulary medication orders / usage
- Regulatory requirements
- Adverse events
- Treatment failures
- Pharmacist interventions

Variables Assessed in a DUE

- Indications for use
- Dose
  - Too high
  - Too low
- Length of therapy
  - Examples:
    - Antibiotics
    - Stress ulcer prophylaxis
- Selection of drug
  - Formulary status/process
  - Duplicate therapy
  - Toxicity

Steps in Typical DUE Process

- Establish criteria for appropriateness
  - Evidence-based
  - Contemporary
- Identify data source
  - Electronic
  - Medical records
- Collect and analyze data
  - Identify when use is not consistent with definition of “appropriate”
- Develop improvement plan
- Re-assess

Improving Prescribing

- Problem of suboptimal prescribing is very complex
  - Economic: lack of promotion of non-profitable medications
  - Organizational/cultural: negative attitudes towards formulary systems
  - Educational/informational: failure to stay current with literature, unaware of cost
  - Psychological: impact of marketing tactics
  - Technological

Intervention Strategies

Dissemination of Information

- Can come in form of written, multimedia, group education sessions (e.g., “rounds” or seminars)
- Evidence suggests information *alone* does not have great impact on prescribing behavior
  - Small group, “academic detailing” may be more effective

Computerized Decision Support

- Can be viewed as *enabling* technology to reduce omission of recommended therapy
- Much more likely to work if prescribers are predisposed to accepting recommended therapy
- “Alert fatigue” is an issue

Formulary Changes

- Pharmacy and Therapeutics (“P&T”) Committee
- Can “restrict” medication prescribing by:
  - Geography
  - Service(s)
  - Specific providers
- Even in age of electronic prescribing systems, there are still loopholes in the system

Challenges for Future Research

- Assessing effectiveness of DUE programs to improve patient outcomes
- Determine cost:benefit of DUE programs themselves
- Learn more about determinants of suboptimal prescribing to better focus interventions

ASSESSMENT OF DABIGATRAN USE IN ADULT INPATIENTS AT THE JOHN HOPKINS HOSPITAL

Purpose and Objectives

Describe the inpatient population in whom dabigatran has been administered at The Johns Hopkins Hospital (JHH)

Detail the non-FDA approved indications for which dabigatran was used

Describe the doses prescribed, accounting for patient specific parameters:

- Renal function
- Concomitant medications (dronedarone, ketoconazole and rifampin)

Describe the techniques in transitioning from the following anticoagulants to dabigatran:

- Warfarin
- Low molecular weight heparin (LMWH)
- Heparin

Methodology

Study Design	• Retrospective chart review • March 2011 – February 2012
Inclusion Criteria	• Patients that received at least one dose of dabigatran during hospital admission
Data Collection	• Demographic data • Dabigatran dose, frequency, indication • Use of other anticoagulants • Concomitant interacting medications
Analysis	• Descriptive statistics were utilized to analyze data

Demographics

Total Patients, n	137
Age, mean, SD	60.8, 12.6
Median, IQR	60.5, 45.7 – 75.3
Gender	
Males, %	99,72.3
Weight , mean, SD	94, 25.3
Median, IQR	92, 31
Home Medication, %	84, 61.3
Primary Service	
Cardiology	106
Medicine	16
Oncology	5
Surgery	4
Neurology	4
Psychiatry	1
Rehab	1

Duration and Dosing

Overall Duration	
Days	**Patients**
1	85
1.5-7	48
>8	4

Dosing	
Dose	**Patients**
Dabigatran 75 mg PO BID	**12**
Dabigatran 150 mg PO BID	**125**

Indications for Dabigatran

Indications	Patients n (%)
Non valvular A.Fib **Cardioversion**	127 (92.7) 60 (47.2)
VTE	5 (3.6)
Valvular atrial fibrillation	2 (1.5)
Non valvular A.Fib and VTE	2 (1.5)
Unknown	1 (0.8)

$CHADS_2$ Score

$CHADS_2$ Score	Patients, n (%)
0	45 (33%)
1	48 (35%)
2	19 (14%)
3	21 (15%)
4	4 (3%)

Patient Population, n (%)	$CHADS_2$ Score, mean
All	1.2
Cardioverted	0.6
Non-cardioverted	1.7

Dabigatran Dosing*

Renal Function CrCl (ml/min)	Patients, n	Correctly Dosed	Incorrectly Dosed	
			Too high	Too low
> 50	110	104	0	6
30 – 50	13	9	0	4
< 30	2	1	1	0
Unknown	12	-	-	-

*Accounting for dronedarone (9), ketoconazole (0)

Transitioning to Dabigatran

Warfarin

- INR < 2

LMWH

- 0-2 hours before the time of next administration

IV Heparin

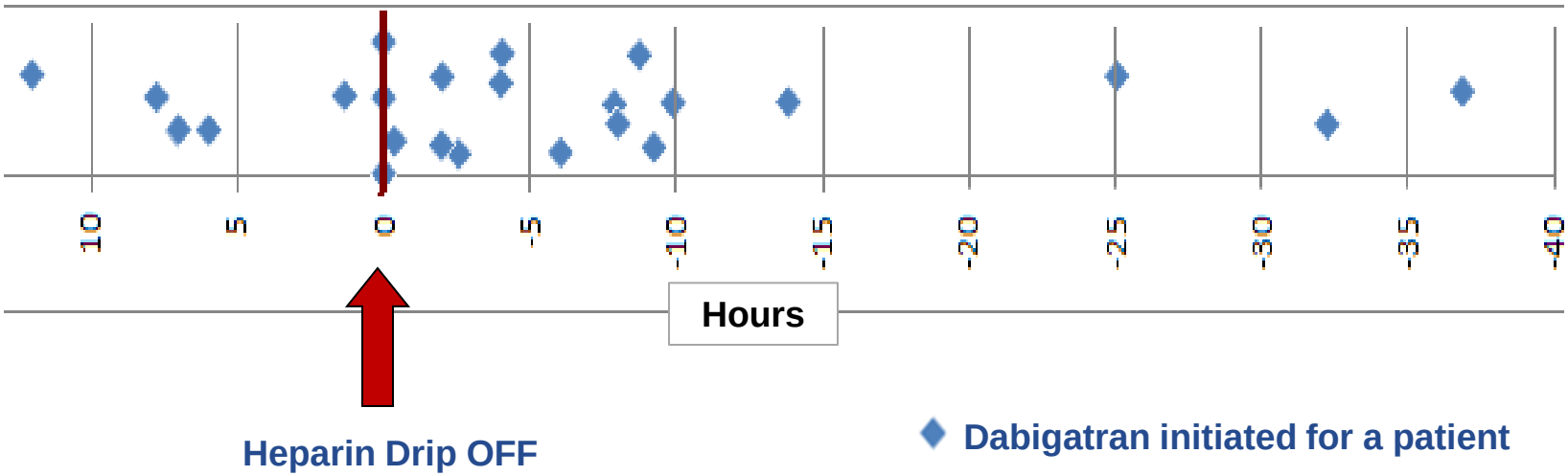
- At the time of discontinuation

Transitioning to Dabigatran

Type of Anticoagulation	Patients, n	Correctly Transitioned	Incorrectly Transitioned	
			Excess anticoagulation	No anticoagulation
Warfarin	4	4	-	-
LMWH Twice Daily	2	2	-	-
IV Heparin Infusion	27	3	7	17
Subq Heparin	5	1	4	-
TOTAL	38	10	28	

Transitioning from IV Heparin

Median difference in transition time, hours	IQR, hours
-2.6	9.5



Pharmacoeconomic Analysis for JHH

	Item	Cost
Dabigatran	75 mg capsule	$2.54
	150 mg capsule	$2.54
	DAILY COST of THERAPY	**$5.09**
Warfarin	Tablet (variable dose)	$0.15
	INR Test	$5.49
	DAILY COST of THERAPY	**$5.64**

Conclusions

- Use of dabigatran at JHH was appropriate per indications
  - A majority of use was for non-valvular Afib

- Those patients who were on therapy for Afib received short durations of therapy as they were primarily admitted for cardioversion

- Most doses were appropriately adjusted based on renal function
  - In most cases of error, doses were inappropriately low
  - Transitioning from warfarin or LMWH was done appropriately but great variability was observed in transition times associated with heparin infusions including overlap of anticoagulation

Limitations

- Retrospective, single center evaluation
- Safety analysis not completed due to small study population
- Did not capture clinical considerations that may have contributed to dosing and transitioning decisions

Recommendations and Future Directions

Systems Modifications:

- Creation of order sets to reduce potential for error in transitioning
- Addition of drug interaction alert for ketoconazole, rifampin, and dronedarone

Education:

- Provision of education to patient care team regarding package insert recommendations for appropriate indication and safe and effective transitioning from other anticoagulants
- Promotion of awareness of new recommendations regarding dose adjustments for dronedarone and ketoconazole

Acknowledgment

John Lindsley, PharmD, BCPS

David Zimmerman, PharmD

Kenneth Shermock, PharmD, PhD

Jessica Wellman, PharmD, MBA, BCPS, BCACP

Christopher Ensor, PharmD, BCPS-CV

Insight into the Drug Use Evaluation (DUE) Process: Assessment of Dabigatran use in Adult Inpatients at The John Hopkins Hospital

Raymond Lamore, PharmD
Emily Pherson, PharmD

The Johns Hopkins Hospital
August 27th, 2012