

Stroke Prevention in Atrial Fibrillation: A Case-Based Discussion

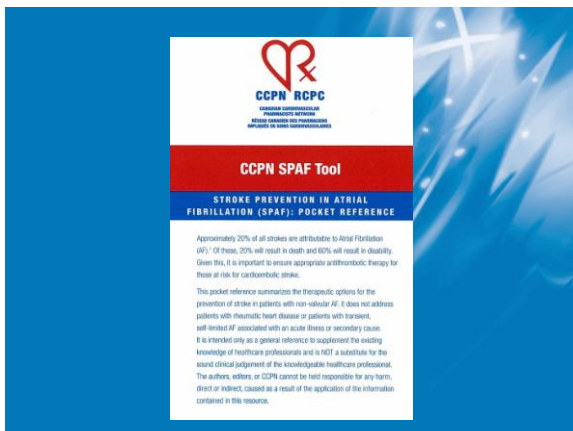
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Ontario Pharmacists' Association
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Disclosures for C.Bucci and J. Pickering

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Learning Objectives

- Understand the importance of assessing the risks of stroke and bleeding in patients with atrial fibrillation (AF)
- Be familiar with current knowledge regarding new anticoagulant treatment options for patients with AF
- Be able to discuss the risks and benefits with a patient through role playing scenarios

Atrial Fibrillation and Stroke

- AF affects approximately 200,000 to 250,000 Canadians
- AF responsible for 1 in 5 of all strokes
- The increase in risk of stroke appears similar for paroxysmal, persistent and permanent AF
- Warfarin reduces stroke in AF by 64%
- Registries show 50-60% of eligible patients receive warfarin
- In clinical trials, time in therapeutic range (TTR) is 60-68%
- In general practice, TTR is typically <50%

Step #1 :
Determine Your Patient's
Risk of Stroke

Stroke Risk in Patients with Nonvalvular AF by CHADS₂ Index Risk Score

CHADS ₂ Score - Sum Of:	Points
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 Years	1
Diabetes Mellitus	1
Prior History of Stroke / TIA	2

Risk of Stroke in National Registry of Atrial Fibrillation Participants, Stratified by CHADS ₂ Score		
CHADS ₂ Score	# Patients (n=1733)	Adjusted Stroke Rate %/yr (95% CI)
0	120	1.9 (1.2-3.0)
1	463	2.8 (2.0-3.8)
2	523	4.0 (3.1-5.1)
3	337	5.9 (4.6-7.3)
4	220	8.5 (6.3-11.1)
5	65	12.5 (8.2-17.5)
6	5	18.2 (10.5-27.4)

Gage JAMA 2001;285:2864

Step #2: Determine Your Patients Risk of Bleeding

Risk of Bleeding

HAS-BLED	Points
Hypertension (SBP > 160 mmHg)	1
Abnormal renal and liver function (1 point for each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs or alcohol	1 or 2
Maximum Score	9

Risk Factor Score	Major Bleeds (%/yr)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

HAS-BLED score of ≥ 3 suggests increased bleeding risk and warrants caution and/or regular review.

* Note: bleeding models should not be used as the sole criterion for deciding to initiate therapy

Petersen et al 2010;138:1032; Lip GYH. J Am Coll Cardiol 2011;57:173; Cairns JA. Can J Cardiol 2011;27:74-90

2010 CCS Guidelines: Recommended Antithrombotic Therapy by Risk Category

Risk Category (CHADS ₂ Score)	Recommended Therapy
≥2	Oral Anticoagulant (OAC) (dabigatran or warfarin)
1	OAC (ASA reasonable alternative in some as indicated by risk-benefit)
0	ASA or no antithrombotic therapy in select young pts with no risk factors

Cairns JA. Can J Cardiol 2011;27:74-90

Step #3: Balance the Benefits and Risks with Available Agents

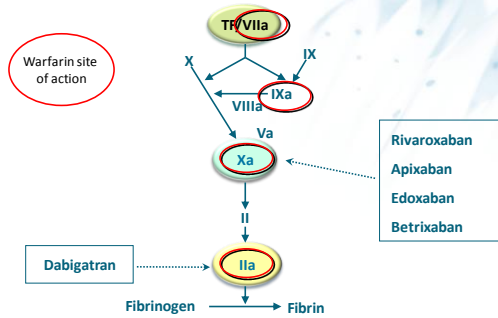
Available Therapeutic Options in AF

- ASA
- Clopidogrel in combination with ASA
- Warfarin
- Dabigatran

Pending further Health Canada approval:

- Rivaroxaban (unpublished data available in AF vs. warfarin)
- Apixaban (published data available in AF vs. ASA)

Oral Anticoagulant Agents



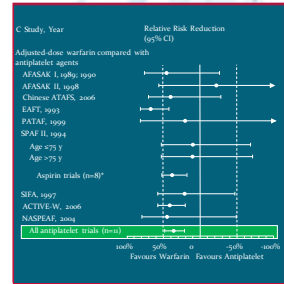
Adapted from Turpie. *Eur Heart J* 2008; 29:155

Relative Effects of Antithrombotic Therapies on All Stroke From Randomised Trials in AF

Warfarin vs Placebo
 Relative RR vs. placebo 64% (CI 49–74%)
 Absolute RR primary 2.7%/yr
 Absolute RR secondary 8.4%/yr
 Major extracranial bleeding 31 vs. 17 (0.03%/yr)

Antiplatelet vs. Placebo
 Relative RR vs. placebo 19% (CI 1–35%)
 Absolute RR primary 0.8%/yr
 Absolute RR secondary 2.5%/yr
 Major extracranial bleeding 16 vs. 15

Warfarin vs Antiplatelet
 Relative RR 37% (CI 23–48%)
 Absolute RR primary 0.9%/yr
 Major extracranial bleeding 40 vs. 22
 Intracranial haemorrhage 20 vs. 7



Hart *Ann Intern Med* 2007;146(12):857

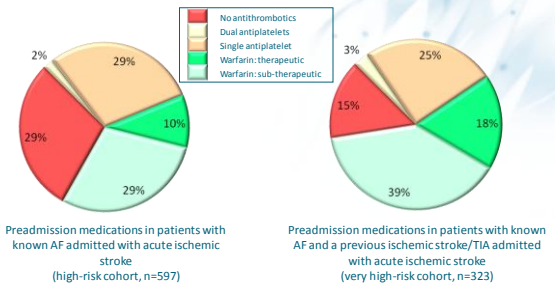
The Importance of Effective INR Control

- 3587 patients randomized to warfarin (INR 2-3) in SPORTIF III & V
- Mean follow-up (± SD) of 16.6 ± 6.3 months

	Poor Control TTR < 60% N=1190	Moderate Control TTR 60-75% N=1207	Good Control TTR > 75% N=1190
# Risk Factors (%)			
1	28.5	30.1	29.1
2	30.3	29.6	35.7
≥3	41.2	40.3	35.2
Mortality (%/year)	4.20	1.84	1.69
Stroke / systemic embolism (%/year)	2.10	1.34	1.07
Major bleeding (%/year)	3.85	1.96	1.58

White *Arch Intern Med* 2007;167:239

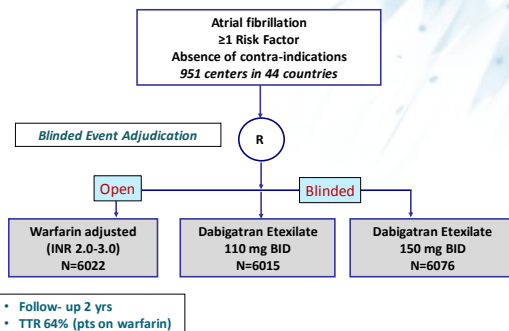
Missed Opportunities for Stroke Prevention in Atrial Fibrillation Registry of the Canadian Stroke Network 2003-2007



Need for greater efforts to prescribe and monitor appropriate antithrombotic therapy to prevent stroke in pts with atrial fibrillation

Gladstone Stroke 2009;40:235

RE-LY: A Non-inferiority Trial



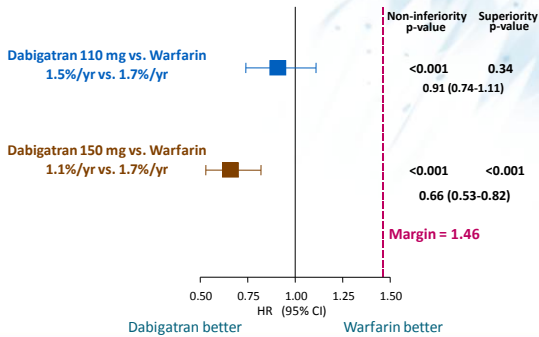
Connolly *NEJM* 2009;361:1139

Baseline Characteristics

Characteristic	Dabigatran 110 mg N=6015	Dabigatran 150 mg N= 7076	Warfarin N=6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin naïve (%)	49.9	49.8	51.4
Discontinued at 2 yrs (%)	20.7	21.1	16.6

Connolly *NEJM* 2009;361:1139

Stroke or Systemic Embolism



Connolly NEJM 2009;361:1139

Types of Stroke: Superiority Analysis

	D 110mg	D 150mg	Warfarin	D 110 mg vs. Warfarin		D 150 mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P	RR 95% CI	P
Stroke	1.4 %	1.0 %	1.6 %	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001
Hemorrhagic Stroke	0.12 %	0.10 %	0.38 %	0.31 0.17-0.56	<0.001	0.26 0.14-0.49	<0.001
Ischemic/ Unspecified	1.34 %	0.92 %	1.20 %	1.11 0.89-1.40	0.35	0.74 0.60-0.98	0.03
Non-disabling	0.50 %	0.37 %	0.58 %	0.86 0.61-1.22	0.40	0.62 0.43-0.91	0.01
Disabling or fatal	0.94 %	0.66 %	1.0 %	0.94 0.73-1.22	0.65	0.66 0.50-0.88	0.005

Connolly NEJM 2009;361:1139

Additional Clinical Outcomes

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P	RR 95% CI	P
MI	0.7%	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
MI re-adjudicated*	0.82%	0.81%	0.64%	1.29 0.96-1.75	0.09	1.27 0.94-1.71	0.12
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05
Dyspepsia	11.8%	11.3%	5.8%	Either dose vs. warfarin p<0.001			

Connolly NEJM 2009;361:1139
*Connolly NEJM 2010;363:1876

Safety Outcome: Bleeding

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P	RR 95% CI	P
Total Bleeding	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major Bleeding	2.7%	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening Major Bleed	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Fatal Bleed	0.19 %	0.23 %	0.32 %	0.60 0.36-1.00	0.05	0.72 0.44-1.17	0.19
Gastro-intestinal Major Bleed	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

Connolly NEJM 2009;361:1139

Major Bleeding: Effect of Age

Age (years):	Dabi 110 mg	Dabi 150 mg	Warfarin	Dabi 110 mg vs. Warfarin		Dabi 150 mg vs. Warfarin	
	%/year	%/year	%/year	P (interaction)	P (interaction)	P (interaction)	P (interaction)
< 65	0.76	0.79	2.32	0.0003	0.0001		
65 - 74	2.12	2.45	3.08				
≥ 75	4.21	4.81	4.09				

- Major bleeding rates increased with age
- A significant interaction between age and treatment effect attenuated dabigatran's benefits with increasing age

Healey ACC 2010; 55:Abstract 1078-120

Major Bleeding: Effect of Renal Function

	Dabi 110 mg	Dabi 150 mg	Warfarin	Dabi 110 mg vs. Warfarin		Dabi 150 mg vs. Warfarin	
	%/year	%/year	%/year	P (interaction)	P (interaction)	P (interaction)	P (interaction)
Total							
Cr Cl (ml/min): 30 - 50	5.07	4.85	5.17	0.1	0.91		
51 - 80	2.62	3.04	3.44				
> 80	1.36	1.88	2.18				
Age < 75							
Cr Cl (ml/min): 30 - 50	4.39	3.44	5.56	0.5	0.88		
51 - 80	1.85	2.17	3.20				
> 80	1.13	1.49	2.06				
Age ≥ 75							
Cr Cl (ml/min): 30 - 50	5.36	5.39	5.03	0.9	0.4		
51 - 80	3.64	4.09	3.76				
> 80	2.98	5.04	2.90				

No significant interaction between baseline renal function and treatment effect after controlling for age

Healey ACC 2010; 55:Abstract 1078-120

Conclusions

- Both dabigatran doses offer advantages over warfarin
- Dabigatran 150 mg is more effective and dabigatran 110 mg has a better safety profile
- Clinical Considerations
 - No need for INR monitoring
 - Management of bleeding/need for reversal
 - Non-compliant patients/cessation of therapy
 - Cost

Step #4: Select, Implement and Monitor Stroke Prophylaxis

Alternative Agents

Agent	Cost	Coagulation Monitoring	Drug / Food Interaction	Offset	Anti-dote	Adverse Effects
ASA	\$	No	No/No	7-10 days	No	Dyspepsia
ASA + Clopidogrel	\$\$	No	No / No	7-10 days	No	Rash Diarrhea
Dabigatran	\$\$	No	Limited / No	2-5 days*	No	Dyspepsia
Warfarin	\$	Yes**	Extensive / Extensive	3-5 days	Yes	Major bleeding occurs with all anti-thrombotic agents

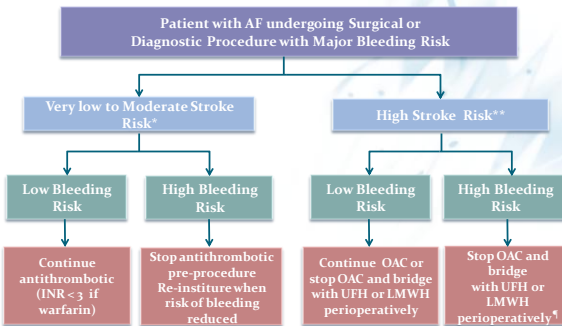
*dependent upon renal function
 **efficacy based on achieving a time in therapeutic range of at least 60% of the time

Drug Interactions

Potential ↑ in Dabigatran Concentration	Potential ↓ in Dabigatran Concentration
Amiodarone* Clarithromycin* Ketoconazole (contraindicated) Quinidine* ‡ Verapamil* ‡	Antacids ‡ Pantoprazole* ‡ Rifampin St. John's Wort Tenofovir

* no empiric dosage adjustment required however use with caution
 ‡ recommend to give 2 hours after dabigatran
 Dabigatran concentration is not affected by digoxin

Pradax[®] product monograph 2010



* CHADS₂ ≤ 2
 **mechanical valve, recent stroke or TIA, rheumatic valve disease, CHADS₂ ≥ 3
 †stop 12-24hr pre-procedure, restart when hemostasis secure and bridge to therapeutic OAC

Timing of Discontinuation After LAST Dose of Dabigatran Before Surgery

Creatinine Clearance	Timing of discontinuation after last dose of dabigatran before surgery	
	Standard risk of bleeding	High risk of bleeding
> 50 mL/min	24 hours	2 – 4 days
> 30 mL/min ≤ 50 mL/min	At least 48 hours	4 days
≤ 30 mL/min	2 – 5 days	> 5 days

To minimize risk for ischemic stroke, therapy should be restarted once hemostasis is achieved, and this should also be guided by the risk of bleeding due to the procedure.

Adapted from Van Ryn /Thomb Haemost 2010;103:1116

Cases

Key Points for Pharmacists:

- Clearly communicate the benefit of anticoagulant therapy (i.e. to prevent a stroke)
- Maintain regular follow up with the patient to ensure compliance and safety around bleeding/surgeries/drug interactions
- This is a lifestyle change for patients who are switching from warfarin to dabigatran (i.e. lack of monitoring/regular physician visits for INR dose changes)
- Encourage patients to carry a wallet card of current medications

Case: RS

- 75 year old female with paroxysmal AF



Allergies: none		Drug Coverage: Provincial		
Date	Drug	Dose Frequency	Quantity	Prescriber
1/03/2011	Ramipril	10 mg daily	90	Dr. Family
1/03/2011	Metoprolol	50 mg BID	180	Dr. Rhythm
2/14/2011	Ferrous fumarate	300 mg daily	90	Dr. Family

Prescription for dabigatran 150 mg BID by Dr. Rhythm

Case: RS

- 75 year old female with paroxysmal AF
- Lives in small community about 30 minute drive to nearest city/lab
- Meds on profile:
 - Ramipril 10 mg daily
 - Metoprolol 50 mg BID
 - Ferrous fumarate 300 mg daily



- PMHx : HTN, AF, anemia
- Additional information
 - OTC :
 - Tylenol for headaches
 - ECASA 81 mg daily

Case: RS

- What a pharmacist can discuss:
 - Ask what has been communicated to her by physician
 - Discuss person's risk of stroke and the benefits of therapy life long
 - Discuss person's risk of bleeding and communicate the signs/symptoms and what to do if they have a bleed
 - Need to take as prescribed and important not to miss doses
 - Affordability



Dabigatran 110 mg vs. 150 mg BID?

Case: LG

- 69 year old male with AF



Allergies: none		Drug Coverage: Provincial		
Date	Drug	Dose/Frequency	Quantity	Prescriber
1/03/2011	Warfarin	5 mg UD	90	Dr. Thrombo
1/03/2011	Ramipril	10 mg daily	90	Dr. Family
1/03/2011	Sotalol	80 mg BID	180	Dr. Rhythm
2/14/2011	Simvastatin	40 mg daily	90	Dr. Family
2/14/2011	Lansoprazole	30 mg daily	90	Dr. Family
10/01/2011	Warfarin	4 mg UD	90	Dr. Thrombo

"Do you think I would benefit from these new warfarins?"

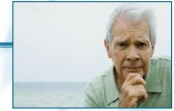
Case: LG



- 69 yr old male
- PMHx:
 - Stroke at age 62
 - AF
 - HTN
 - Dyslipidemia
 - GERD
- Social History:
 - Does not drive since stroke so hard to get to lab
 - INR checked every 2 weeks
 - No alcohol

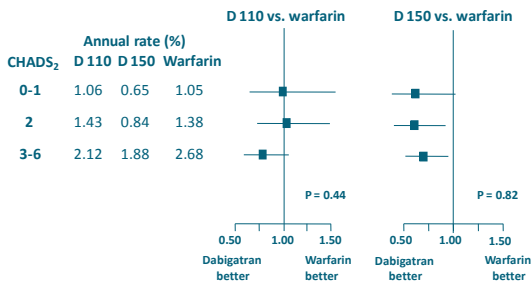
- Meds on Profile
 - Warfarin as per INR
 - Ramipril 10mg AM
 - Sotalol 80 mg BID
 - Simvastatin 40 mg daily
 - Lansoprazole 30 mg daily
- OTC
 - Tylenol #1 for occasional migraines

Case: LG



- Should discuss the following:
 - Why does he want to change?
 - INR monitoring and TTR
 - What is risk of bleeding and was this weighed?
 - History of GERD?
 - Affordability
 - Was there communication of a plan: (i.e. discuss with doctor or have doctor phone you to discuss with you or transitioning from warfarin to dabigatran)

RE-LY Subgroup Analysis: Stroke /Systemic Embolism based on CHADS₂ Score



Analysis of RE-LY to Evaluate Outcome in Relation to Centre's Average INR Control

- Efficacy: Stroke or Systemic Embolism

Centre TTR	Dabi 110 mg vs. Warfarin RR (95% CI)	Dabi 150 mg vs. Warfarin RR (95% CI)
<57.1%	1.00 (0.68-1.45)	0.57 (0.37-0.88)
57.1 – 65.5%	0.81 (0.56-1.17)	0.50 (0.33-0.77)
65.5 – 72.6%	0.89 (0.58-1.36)	0.69 (0.44-1.09)
>72.6%	0.92 (0.59-1.45)	0.95 (0.61-1.48)
Interaction	P=0.89	P=0.20

Wallentin L. *Lancet* 2010;376:975-83

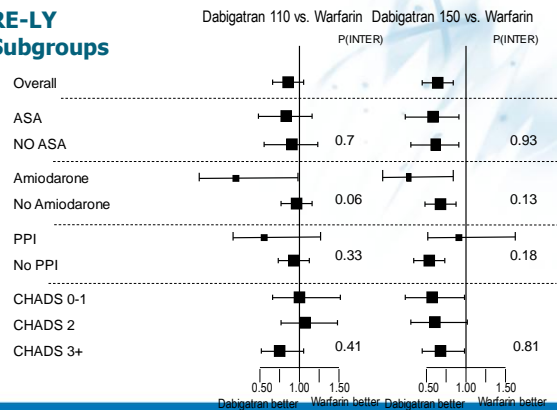
Drug-Drug Interaction with Dabigatran

Potential ↑ in Dabigatran Concentration	Potential ↓ in Dabigatran Concentration
Amiodarone*	Antacids [‡]
Clarithromycin*	Pantoprazole* [‡]
Ketoconazole (contraindicated)	Rifampin
Quinidine* [‡]	St. John's Wort
Verapamil* [‡]	Tenofovir

* no empiric dosage adjustment required however use with caution
[‡] recommend to give 2 hours after dabigatran
 Dabigatran concentration is not affected by digoxin

Pradaxa[®] product monograph 2010

RE-LY Subgroups



Case: LG

- 69 yr old male
- PMHx:
 - Stroke at age 62
 - AF
 - HTN
 - Dyslipidemia



- Meds on Profile
 - Warfarin as per INR
 - Ramipril 10mg AM, 5 mg PM

LG's has been taking dabigatran twice daily, as prescribed. He calls to inform you that he's having a colonoscopy done, and they may need to do some polypectomies. You are tasked to develop a peri-procedural management plan for LG.

Timing of Discontinuation After LAST Dose of Dabigatran Before Surgery

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To minimize risk for ischemic stroke, therapy should be restarted once hemostasis is achieved, and this should also be guided by the risk of bleeding due to the procedure.

Adapted from Van Ryn Thomb Haemost 2010;103:1116

Case: BA

- 38 year old male with persistent AF
- PMH:
 - insignificant
- Electrical engineer with a busy schedule



Is he at risk of stroke?

Antithrombotic Therapy Options –

- Nothing, this patient is too low risk for stroke
- ASA 81 mg daily
- Warfarin, INR 2.0 – 3.0
- Dabigatran
 - Dabigatran 150 mg BID
 - Dabigatran 110 mg BID
- Something else

38 years, persistent AF



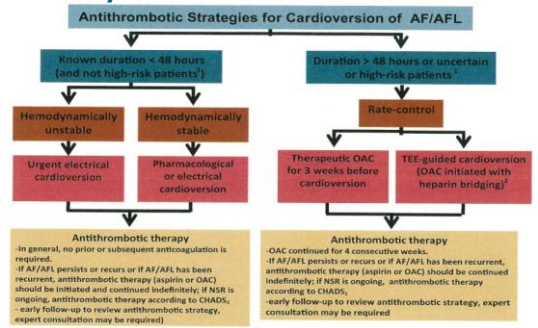
Case: BA

- 38 year old male with persistent AF
- PMH:
 - insignificant
- Electrical engineer with a busy schedule



Comes in with a script for dabigatran 150mg bid x 3 weeks. He tells you he is going to be electrically shocked and does this mean he does not require further anticoagulation?

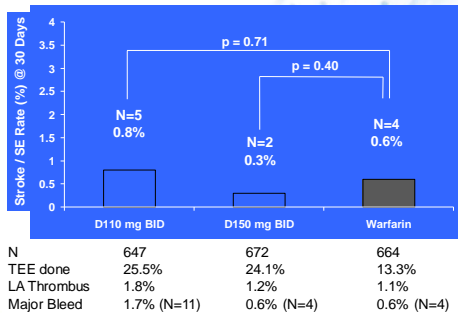
Prevention of Stroke in NVAF: Summary of 2010 CCS Guidelines



Cairns JA et al. Can J Cardiol 2011;27:74-90.

Cardioversion – Dabigatran Substudy (post-hoc)

Rate of Stroke / Systemic Embolism out to 30 days
N=1983 Cardioversions in 1270 Patients



Nagarakanti et al. Circulation 2011;123:131-136.

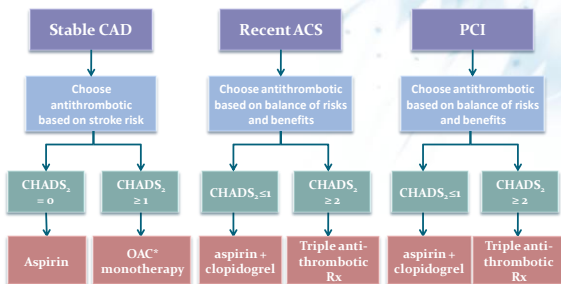
Case: RS



- 76 year old male with ST Elevation MI
 - Receives a Primary PCI with a bare metal stent
- PMH:
 - AF
 - Hypertension
 - Heart failure
- Discharge meds:
 - ASA 81 mg daily plus Plavix 150 mg daily x 4 more days then 75 mg daily
 - Ramipril 5 mg daily
 - Bisoprolol 5 mg daily
 - Atorvastatin 40 mg daily

Med Review shows patient on warfarin pre-hospital, what do you do?

Antithrombotic Management of AF/AFL in CAD Summary of CCS 2010 Guidelines



* Warfarin is preferred over dabigatran for patients at high risk of coronary events

Carre JA et al. Can J Cardiol 2011;27:74-90.

Bleeding Risk with Antithrombotic Therapy in AF Patients

- nationwide Denmark registry including 82,854 patients discharged from hospital & filling Rx for Warfarin, Aspirin or Clopidogrel; bleeding requiring admission
- mean (SD) follow-up of 3.3 ± 2.6 years, 13,573 (11.4%) had major bleeding

Variable	Patient Years	Bleed rate (%/year)	RR (95% CI)	NNH/Year (95%CI)
Warfarin	93,492	3.9	1 (reference)	1 (reference)
Aspirin	72,146	3.7	0.96 (0.95-0.96)	217 (151-388)
Clopid	1,865	5.6	1.45 (1.22-1.66)	619 (288-4102)
C + A	1,264	7.4	1.91 (1.59-2.21)	28 (20-48)
W + A	17,712	6.9	1.75 (1.71-1.79)	34 (30-39)
W + C	496	13.9	3.57 (2.88-4.22)	10 (8-14)
W + C + A	408	15.7	4.03 (3.22-4.78)	8 (7-12)

- Those having a non-fatal bleed had an increased risk of death with a HR of 2.45 (95%CI 2.37-2.57)

Arch Intern Med 2010;170(16):1433-1441.

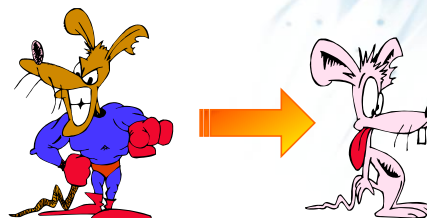
Triple Therapy – RELY Post-hoc analysis

Major Bleeding

Subgroup	D 110mg n/N (%)	D 150 mg n/N (%)	Warfarin n/N (%)	D110mg vs warfarin RR(95% CI)	D150 mg vs. warfarin RR (95% CI)
ASA + clopidogrel	29/335 (4.72%)	30/328 (4.66%)	33/339 (5.21%)	0.77 (0.50 - 1.21)	0.81 (0.52 - 1.26)
No ASA + clopidogrel	313/5677 (2.77%)	369/5747 (3.24%)	388/5681 (3.48%)	0.81 (0.61 - 0.94)	0.95 (0.82-1.10)
P Interaction				0.8727	0.5167

Eikelboom JW. Circ 2011;123: 2363

Questions?



“That’s all very well but does it kill rats?”

CBC Blogger ‘roboughlah’ response to Health Canada approval of dabigatran for stroke prophylaxis in those with atrial fibrillation Nov. 7th, 2010