

# Stroke Prevention in Atrial Fibrillation

Which Drugs to Use?

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# Disclosure of Potential for Conflict of Interest

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*Atrial Fibrillation*

## **FINANCIAL DISCLOSURE:**

**Support provided by the Stroke Network of Southeastern Ontario**

**Other: None**

# Objectives

- Review importance of atrial fibrillation in causing stroke
- Assessing the risk of embolic stroke
- Assessing the risk of bleeding
- Choosing the best drug for your patient

# Causes of Ischemic Stroke

- Large artery atherosclerosis 30%
- Cardioembolic Stroke 25-35%
- Small vessel disease 25%
- Unknown 20%
- Unusual causes 5%

# Importance of Atrial Fibrillation

- $\frac{1}{4}$  of patients over 40 will eventually develop atrial fibrillation
- Risk of stroke averages 5% per year
- Antithrombotic therapy reduces the risk of death by  $\frac{1}{4}$  and stroke by  $\frac{2}{3}$
- Embolic strokes due to atrial fibrillation tend to be large and to have a high mortality

# Approach to Atrial Fibrillation

1. Assess the risk of stroke using the CHADS2 Score
2. Assess the risk of bleeding using the HAS BLED Score
3. Possible Choices:
  1. Aspirin
  2. Aspirin plus clopidogrel
  3. Warfarin, apixaban, dabigatran or rivaroxaban
  4. Combination antiplatelet plus antithrombotic

# Assessing the Risk of Stroke

CHADS2 Score for patients in atrial fibrillation

Risk Factor	Score
Cardiac Failure	1
Hypertension	1
Age 75 or over	1
Diabetes	1
Stroke or TIA	2

# Annual Risk of Stroke

CHADS2 Score	Annual Risk %
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2
0=Very Low Risk 1=Moderate risk 2 or more = Moderate to High Risk	



# Risk of Bleeding on Treatment

HAS BLED Risk Factors	Points
Hypertension	1
Abnormal kidney or liver function	1 or 2. One point for each.
Stroke	1
Bleeding History	1
Labile INRs	1
Elderly Over 65 years	1
Drugs (antiplatelet or NSAID) or alcohol abuse	1
<u>Maximum</u> 9 points <u>Low Risk</u> 2 or fewer, <u>High Risk</u> 3 or more	

# Risk of Bleeding

HAS BLEED Risk Factors	Points
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Drugs (antiplatelet or NSAID) or alcohol abuse	1
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# Therapies to Prevent Stroke

- Antiplatelet Drugs: aspirin, clopidogrel (Plavix),
- Oral Anticoagulant Drugs
  - Vitamin K antagonist: warfarin (Coumadin)
  - Direct Thrombin Inhibitor: dabigatran (Pradax)
  - Factor X inhibitors:
    - apixaban (Eliquis)
    - rivaroxaban (Xarelto)
    - Combinations of the above

# Risk of Bleeding with A Fib- Danish Population Study

Drug(s)	Annual Risk of Bleeding % per year
ASA alone	3.7
Warfarin	3.9
Clopidogrel	5.6
ASA + Clopidogrel	7.4
Warfarin + Aspirin	6.8
Warfarin + Clopidogrel	13.9
Warfarin + Clopidogrel + Aspirin	15.7

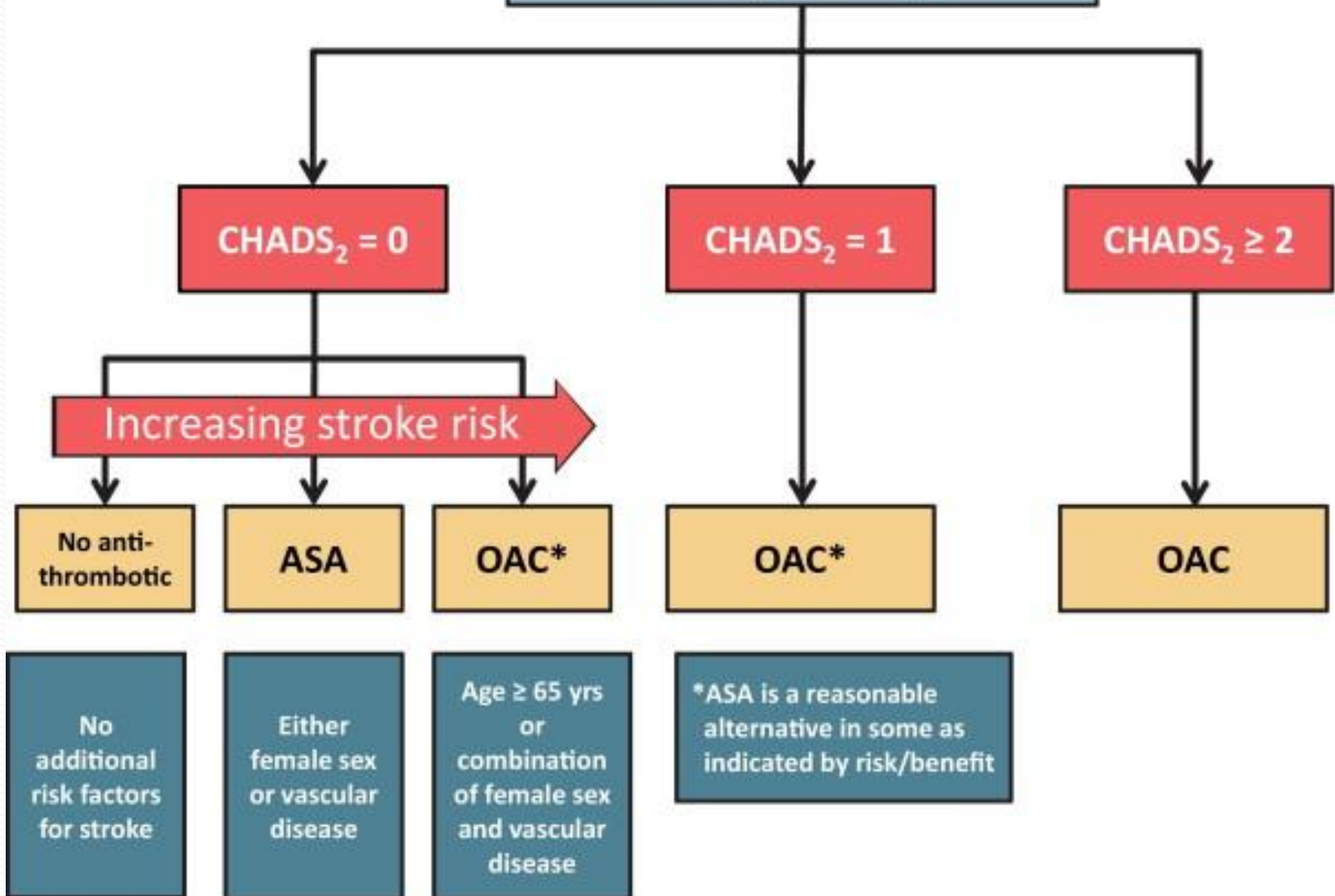
# Bleeding on Warfarin ICES

- In patients over 65 years with atrial fibrillation on warfarin the overall bleeding rate was 3.8% per year
- Highest rates were within the first 30 days
- Increased rates with CHADS2 = 4 or higher
- Mortality from bleeding 18%
- CMAJ 2013 185(2) E121-127

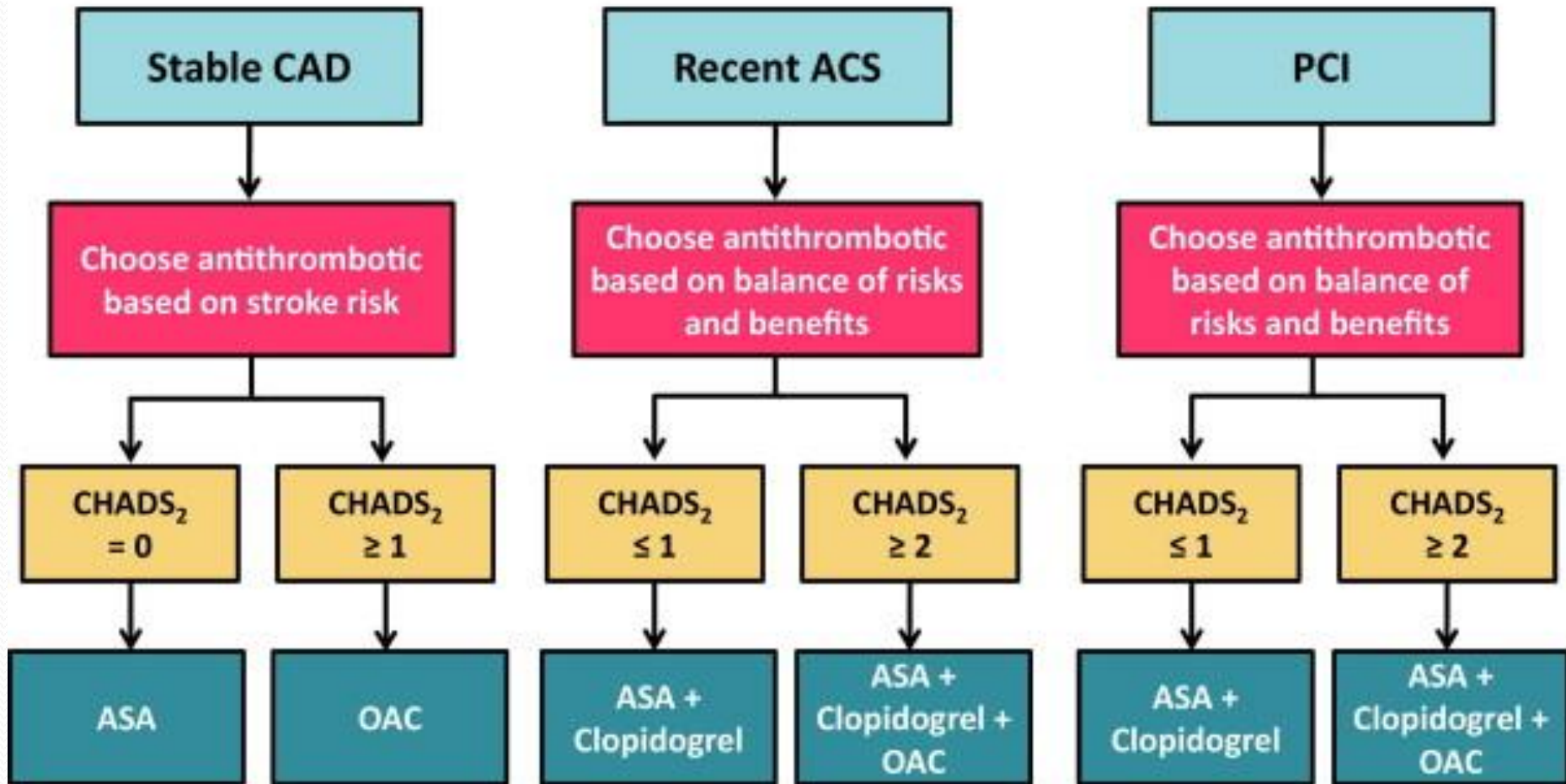
# Canadian Cardiovascular Society 2012 Guidelines

- Low risk ( $\text{CHADS}_2=0$ )
  - No drug, aspirin or oral anticoagulant according to additional risk factors
- Moderate Risk ( $\text{CHADS}_2=1$ )
  - Apixaban, dabigatran and rivaroxaban are preferred over warfarin
  - Aspirin is an option for some
- High Risk  $\text{CHADS}_2 \geq 2$ 
  - Apixaban
  - Dabigatran
  - Rivaroxaban
  - Warfarin

## Assess Thromboembolic Risk (CHADS<sub>2</sub>)



# Antithrombotic Management of AF/AFL in CAD





# Apixaban, Dabigatran and Rivaroxaban

- Approved for non-valvular atrial fibrillation (not for prosthetic valves or rheumatic heart disease)
- Estimated glomerular filtration rate (eGFR) must be over 30 ml/min.
- Need to monitor renal function periodically
- Caution with previous GI bleeding or coronary heart disease
- Apixaban dose 5 mg BID
- Dabigatran usual dose 150 mg. BID. Reduce to 110 mg. BID with moderate renal impairment, elderly or small body size.
- Rivaroxaban usual dose 20 mg. daily or 15 mg daily with impaired renal function

# Pharmacology

Drug	Dabigatran	Apixaban	Rivaroxaban
Action	Thrombin	Xa	Xa
T $\frac{1}{2}$	12-14 hours	12 hours	7-11 hours
Dose	110 or 150 mg. BID	5 mg. BID	15 or 20 mg OD
Renal Excretion	80%	25%	33%
Bioavailability	6%	60%	80%
Prodrug?	Yes	No	No
Interactions	P-gp	3A4	3A4/P-gp

# Clinical Trials

Drug	Dabigatran	Apixaban	Rivaroxaban
Trial	RE-LY	ARISTOTLE	ROCKET-AF
Design	Open-Label Warfarin	Double-Blind	Double-Blind
Participants	18,113	18,206	14,264
A F Risk Factors	1 or more	1 or more	Stroke, 2 or more
Warfarin Naïve	50%	43%	38%
% Time INR 2-3	64	62.2	55

# Comparison with Warfarin

	Dabigatran	Apixaban	Rivaroxaban
Ischemic Stroke	Better	Same	Same
Hemorrhagic Stroke	Better	Better	Better
Major Bleed	Same	Better	Same
Mortality	Same	Better	Same

# What your patients need to know about novel oral anticoagulants

1. **Compliance is essential.** Forgetting 2 or more doses will leave them unprotected.
2. **There is no antidote.** If serious bleeding occurs, only supportive treatment is available at present.
3. If they are on warfarin with a well-controlled INR there is no need to switch to dabigatran.
4. They should avoid ASA and NSAIDs while on antithrombotic agents due to the increased risk of bleeding.
5. They need renal function tested annually or during acute illnesses that could impair renal function (creatinine and eGFR).
6. If not on ODB, the cost is about \$100/month.

# Dabigatran (431) and Rivaroxaban (435)

## ODB Limited Use Criteria

- Inclusion Criteria
  - Non-valvular atrial fibrillation CHADS2 = 1 or more
  - Inadequate anticoagulation after a trial of at least 2 months on warfarin
  - Or: warfarin contra-indicated or unable to monitor INR
- Exclusions:
  - eGFR under 30 ml./min.
  - Hemodynamically significant valvular heart disease or prosthetic heart valve

# When should warfarin still be used in atrial fibrillation patients?

1. Valvular heart disease
2. Kidney disease with eGFR < 30 ml./min
3. Patients stable on warfarin
4. Patients who cannot afford \$3.00 per day
5. Patients on ODB who do not meet criteria
6. Patients in whom the lack of an antidote is a consideration
7. Significant side effects on dabigatran or rivaroxaban

# Case Example

- A 75 year-old lady has had gradually-worsening fatigue and intermittent palpitations.
- Past history of Type 2 DM, hypertension and a non-disabling stroke
- Meds: ASA, perindopril, HCTZ, metformin
- Physical exam: Pulse 100/min. irregular, BP 140/90
- Lab: eGFR 90 ml./min.
- CHADS2 =
- HAS BLED =



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- Physical exam: Pulse 100/min. irregular, BP 140/90
- Lab: eGFR 90 ml./min.
- CHADS2 = Hypertension 1 + Elderly 1 + DM 1 + Stroke 2 = 5
- HAS BLED= Hypertension 1 + Elderly 1 + Stroke 1 = 3

# Treatment Choices

- Warfarin
- Apixaban
- Dabigatran
- Rivaroxaban
- ASA + Clopidogrel (for patients who are not candidates for warfarin, apixaban, dabigatran or rivaroxaban)
  - NB Same bleeding risk as warfarin.

# Resources

- Decision Aid by Stephen LaHaye and colleagues at [www.afib.ca](http://www.afib.ca) and iPad App Afib CDA (\$4.99)
- Canadian Cardiovascular Society Guidelines at [www.ccs.ca](http://www.ccs.ca) and iPad App CCS Atrial Fibrillation Guidelines (Free)
- Canadian Best Practices for Stroke Care [www.strokebestpractices.ca](http://www.strokebestpractices.ca)



# Questions?

# Appendix: Trial Results

## Drug vs (Warfarin)

	Dabigatran	Apixaban	Rivaroxaban
Ischemic Stroke % /year	.92 (1.2)*	.97 (1.05) NS	1.34 (1.42) NS
Hem. Stroke	.10 (.38)*	.24 (.47)*	.26 (.44)*
Major Bleed	3.11 (3.36) NS	2.13 (3.09)*	3.6 (3.4) NS
Mortality	3.64 (4.13) NS	3.52 (3.94)*	1.87 (2.21)NS

All Rates are % per year. \* = significant. NS=not significant at .05