Atrial Fibrillation and Stroke 2014

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Management of AF

- Why do we treat
  - Symptoms
    - Fast
    - Irregular
    - Loss of atrial contraction (10-20% of cardiac output)
  - Thromboembolism risk
  - Tachycardiomyopathy – cardiomyopathy induced by the tachycardia

AF and Stroke

- The most important things about AF in 2014 are:
  - Make the diagnosis – know your pulse campaigns and GPs and other medical personnel taking peoples pulses
  - Assessment and Management of Stroke risk
    - doesn't depend on symptoms

AF and Stroke

- The most important things about AF in 2014 are:
  - Make the diagnosis – know your pulse campaigns and GPs and other medical personnel taking peoples pulses
    - Stroke risk doesn't depend on symptoms
  - Treating appropriately with anticoagulation
    - People look for a reason not to give anticoagulation

AF and Stroke

Table 3 **Clinical events (outcomes) affected by AF**

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke.
3. Hospitalizations	Hospitalizations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation, from no effect to major reduction. AF can cause marked distress through palpitations and other AF-related symptoms.
5. Left ventricular function	Wide variation, from no change to tachycardiomyopathy with acute heart failure.

Perspective

- In the ReLY study the 1 yr mortality of newly diagnosed AF was
  - Overall 11.5%, in US 11.4%, Europe 8.2%, Africa 21.5%
  - Similar for non rheumatic and rheumatic
  - Similarly stroke risk US 3.2%, in Chia, SE Asia and Africa = 7.1, 7.8 and 9.1% unrelated to differences in RHD, CHADS2 score and OAC use

Stroke is a frequent complication of AF

- Stroke is the leading complication of AF
- AF is associated with a 5-fold higher stroke risk overall[1]
- AF doubles the risk of stroke when adjusted for other risk factors[2]
- Without preventive treatment, each year approximately 1 in 20 patients with AF (5%) will have a stroke[3]
  - When transient ischaemic attacks and clinically 'silent' strokes are considered, the rate of brain ischaemia associated with non-valvular AF exceeds 7% per year[4]
- AF is responsible for nearly one-third of all strokes,[5] and AF is the leading cause of embolic stroke[6]

1. Savelieva I et al. Ann Med 2007;39:371–91; 2. ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030; 3. Atrial Fibrillation Investigators. Arch Intern Med 1994;154:1449–57; 4. Carlson M. Medscape Cardiology 2004;8 available at http://www.medscape.org/viewarticle/487849; accessed Feb 2010; **5.** Hannon N et al. Cerebrovasc Dis 2010;29:43–9; **6.** Emmerich J et al. Eur Heart 2005); 7(Suppl C):C28–33

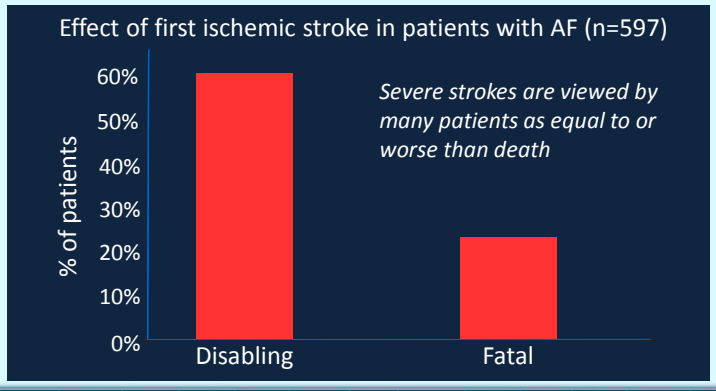
Stroke is a serious complication of AF

- Stroke in AF is associated with a heavy burden of morbidity and mortality
- AF stroke is usually more severe than stroke due to other causes[1]
- Compared with other stroke patients, those with AF are more likely to:[2]
  - Have cortical deficit (e.g. aphasia)
  - Have severe limb weakness
  - Have diminished alertness
  - Be bedridden on admission
- The mortality rate for patients with AF is double that in people with normal heart rhythm[3]

1. Savelieva I et al. Ann Med 2007;39:371–91; **2.** Dulli DA et al. Neuroepidemiology 2003;22:118–23; **3.** Benjamin EJ et al. Circulation 1998;98:946–52

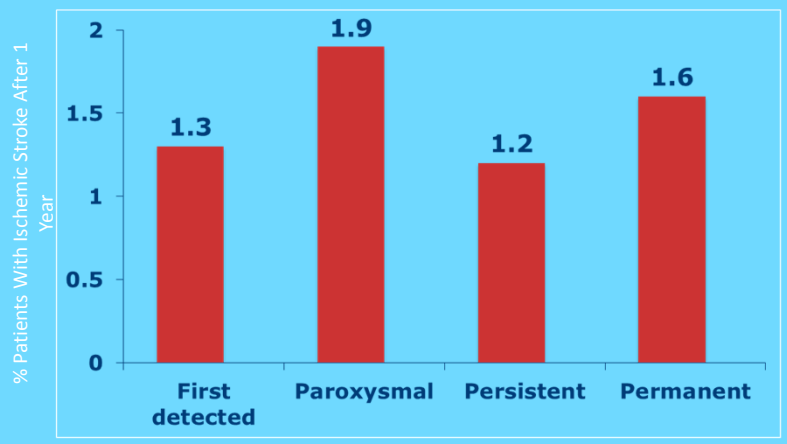
AF and Stroke

- AF is an independent risk factor for stroke
  - Increases risk of stroke by 5-fold
  - Responsible for up to 1 in 5 of all strokes
  - About 80% of AF-related strokes are ischemic



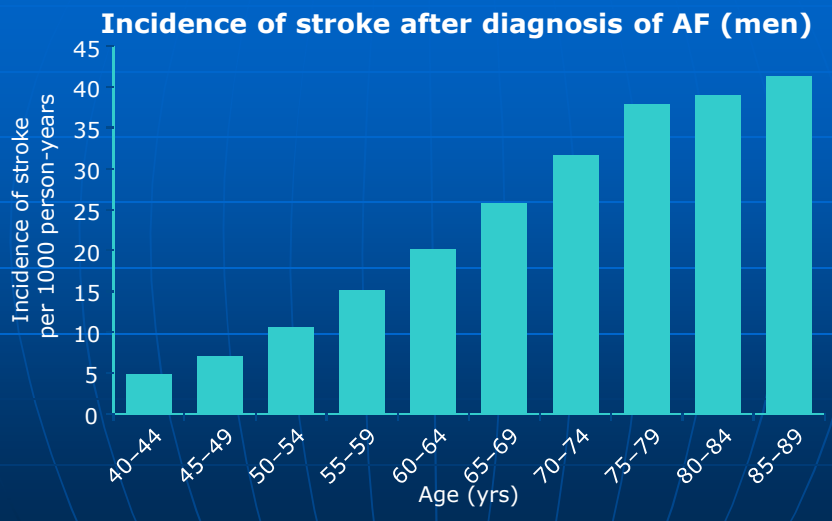
Heart and Stroke Foundation; AHA *Stroke* 1999; Gage *Arch Intern Med* 1996; Solomon *Stroke* 1994; Atrial Fibrillation Investigation Group *Arch Intern Med* 1994; Wolf et al. *Stroke* 1991; Savelieva et al, Ann Med 2007; Hart *Ann Int Med* 2007; Hylek *Stroke* 2006; Singer *Chest* 2008; Gladstone *Stroke* 2009; CCS guidelines 2004; Matchar *Am J Med* 2002; Bungard *Pharmacotherapy* 2000

Stroke Risk is Independent of Type of Atrial Fibrillation



Neuwlaat R, et al. *Eur Heart J* 2008

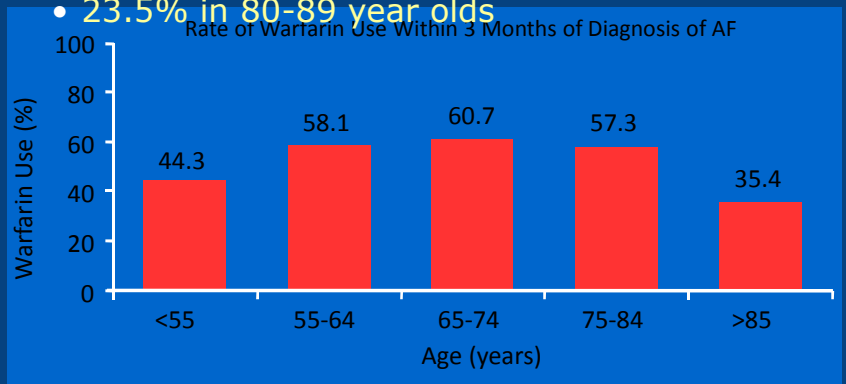
Incidence of stroke in AF patients increases with age



22-year follow-up of 75 116 men in the Danish National Registry of
Frost L et al. Neuroepidemiology 2007;28:109–15

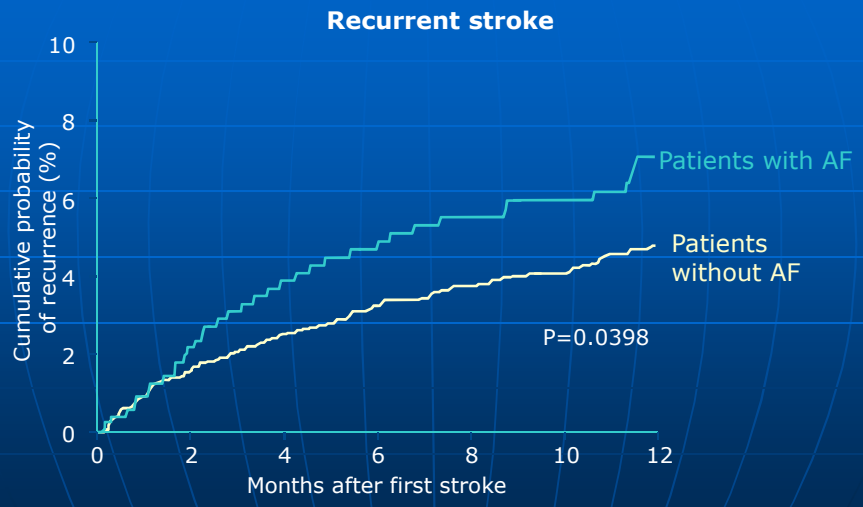
An Age-Related Treatment Paradox With Warfarin Use in SPAF

- Risk of stroke in AF patients increases with age
  - 1.5% per year in 50-59 year olds
  - 23.5% in 80-89 year olds



Go AS, et al. *Ann Intern Med* 1999; 131: 927–934

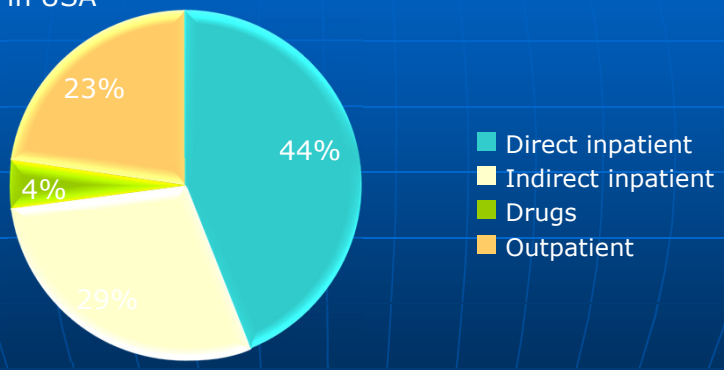
AF patients face an increased risk of recurrent stroke



Marini C et al. Stroke 2005;36:1115–9

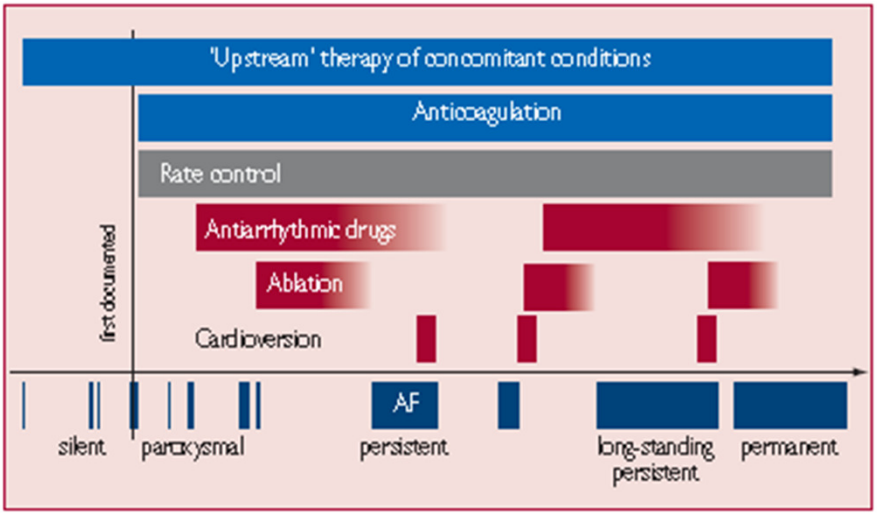
AF is associated with substantial healthcare costs

- The bulk of costs related to direct and indirect inpatient care in USA



Coyne KS et al. Value Health 2006;9:348–56

AF and Stroke



AF and Stroke

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

AF and Stroke

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

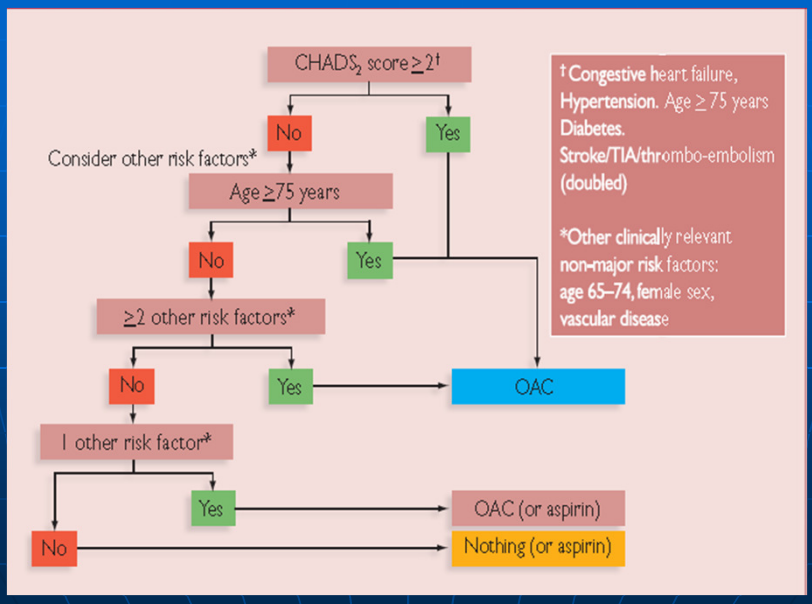
AF and Stroke

$CHADS_2$ score	Patients (n=1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
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)

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

AF and Stroke



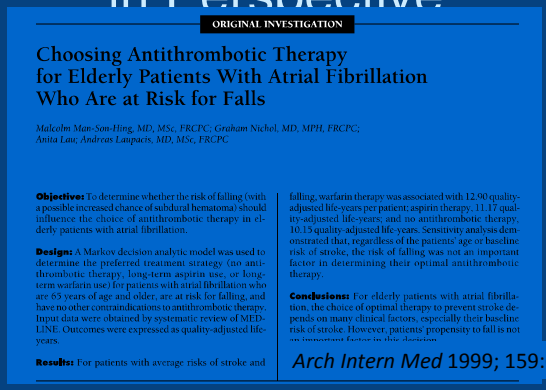
AF and Stroke

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

[a]Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non steroidal anti inflammatory drugs, or alcohol abuse, etc.
INR — international normalized ratio. Adapted from Pisters et al.[60]

Anticoagulation and the Risk of Falls in the Elderly – Putting Matters in Perspective



ORIGINAL INVESTIGATION

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

Objective: To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

Design: A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

Results: For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients' age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

Conclusions: For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients' propensity to fall is not an important factor in the decision.

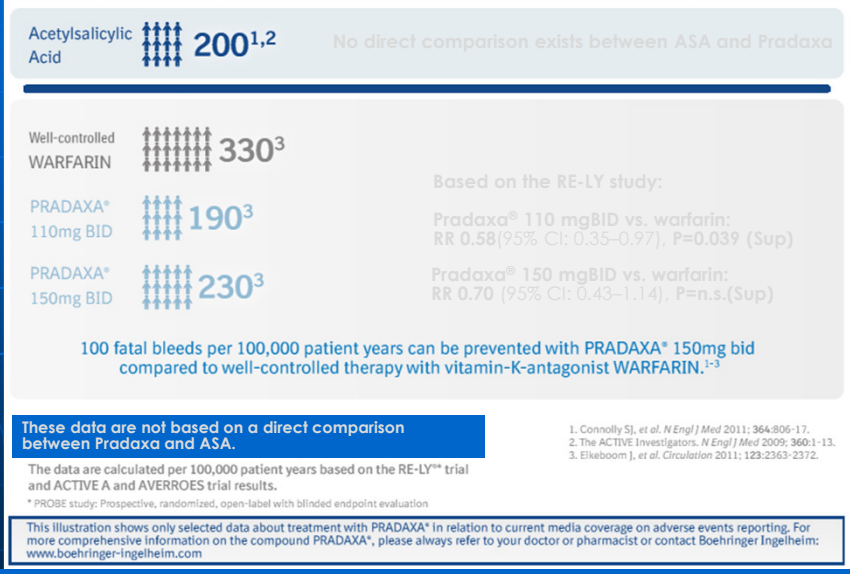
Arch Intern Med 1999; 159:677-685

- A patient with a 5% annual stroke risk from AF would need to fall 295 times in a year for the calculated risk of subdural hematoma from falling to outweigh the stroke reduction benefit of warfarin

Atrial Fibrillation – What's New

- Aspirin - ? Useless
  - Thromb Haemost 2011;106:739-749
  - Danish Registry Study
    - Metanalysis of Aspirin in AF – 19% reduction in stroke, but driven by SPAF-1, and trials had poor inclusion
    - Japanese trial showed no benefit of Aspirin
    - Warfarin showed net clinical benefit in all but CHADS-VASc score 0. (Can't comment with newer agents)
    - Net clinical benefit highest in those with highest bleeding risk (also have highest stroke risk)
    - Net clinical benefit more than with Aspirin

Fatal bleeds



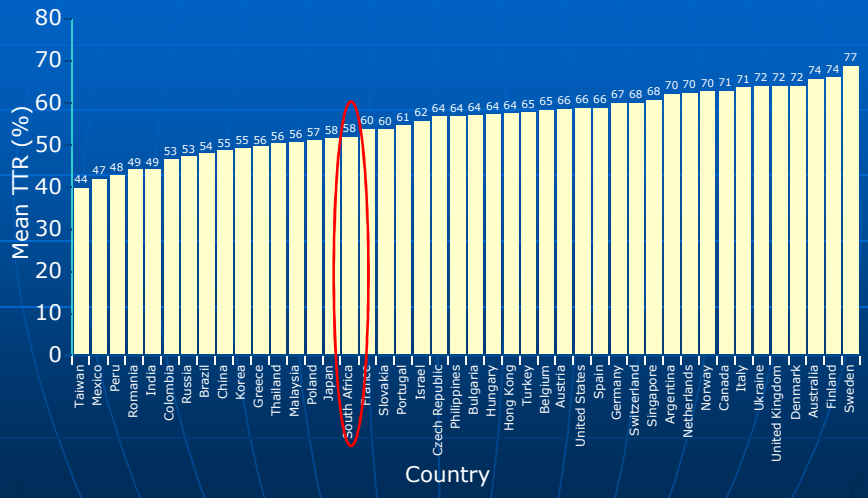
Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please refer to the full indication and local prescribing information of Pradaxa as approved in your country.

Warfarin for Stroke Prevention in AF

- Warfarin is highly effective for stroke prevention in AF –reduces risk by 64% – but its use is problematic
  - Associated with significant increase in intracranial and other haemorrhage, especially in the elderly
  - Only about 1 in 4 patients are optimally treated
    - Registries show that only 50-60% of eligible patients receive warfarin
    - Many patients who start Warfarin don't continue it – at 2 years approx. 40% still filling their scripts
    - In clinical trials, time in therapeutic range (TTR) is 60-68%; in general practice, TTR is typically <50%

Hart *Ann Int Med* 2007;146:857; Hylek *Stroke* 2006;37:1075; Singer *Chest* 2008;133:546S; Gladstone *Stroke* 2009;40:235; CCS guidelines 2004; Matchar *Am J Med* 2002;113:42; Bungard *Pharmacotherapy* 2000;20:1060

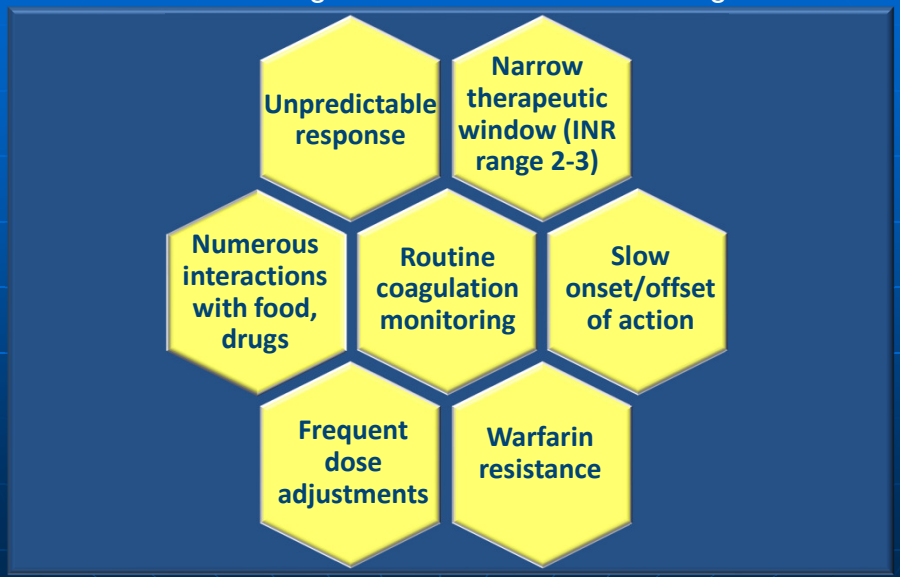
TTR subgroup analysis: mean TTR by country



Wallentin L et al. *Lancet* 2010; 376: 975–83.

Limitations of Warfarin Therapy:

Issues Making its Use a Practical Challenge



Ansell J, et al. *Chest* 2008; 133: 160S-198S; Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22: 129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26: 169-187

Key Factors in Underutilization Of VKAs in AF

- Lifestyle issues
  - Need for regular monitoring, lifestyle restrictions, compliance and other patient factors
- Resource challenges
  - Lack of availability of a coordinated anticoagulant outpatient monitoring process or clinic
- Perceived bleeding risk
  - Concern about risk of haemorrhage, not always balanced against risk of stroke

Warfarin, Aspirin and Adverse Events:

A Common Association

Number of Cases and Annual Estimate of Drugs Most Commonly Implicated in AEs Treated in the ED (United States)

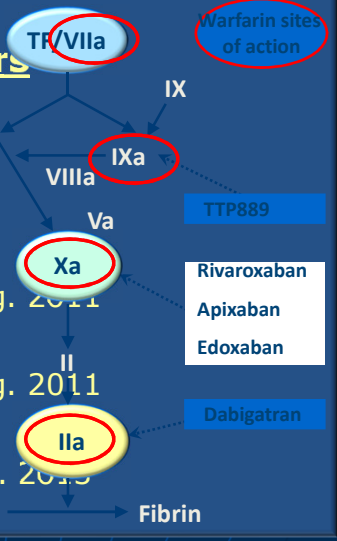
Drug	Annual Estimate	Percentage of Drug AEs Treated in ED
Insulins	55,819	8.0
Warfarin	43,401	6.2
Amoxicillin	30,135	4.3
Aspirin	17,734	2.5

AE=adverse event; ED=emergency department

DS et al. *JAMA* 2006; 296: 1858-1866

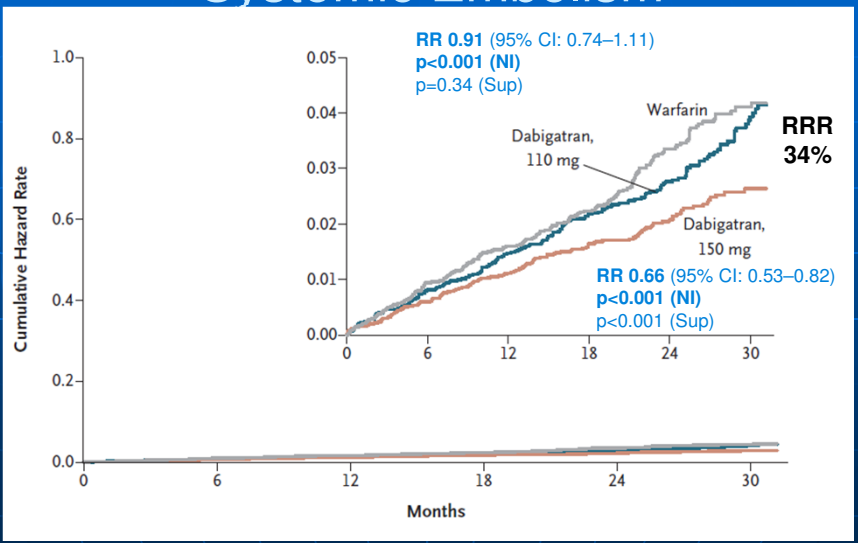
New Oral Anticoagulants for SPAF

- **Direct Thrombin Inhibitors**
  - Dabigatran
- **Factor Xa Inhibitors**
  - Rivaroxaban
    - Phase III data published Aug. 2011
  - Apixaban
    - Phase III data published Aug. 2011
  - Edoxaban
    - Phase III data expected Mar. 2013



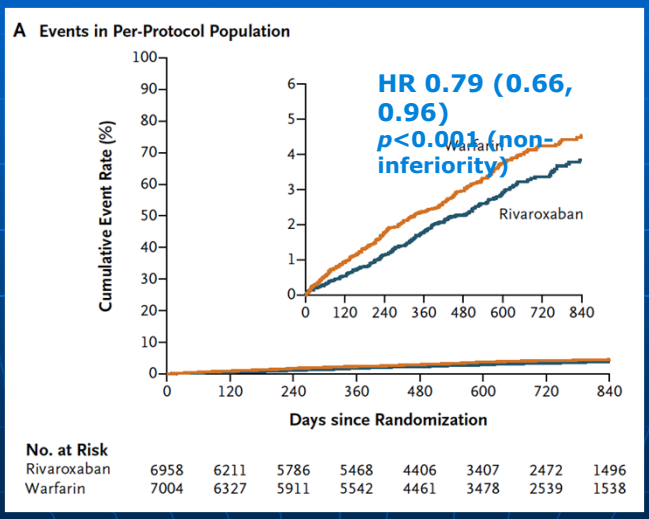
http://www.clinicaltrials.gov/ct2/search
Adapted from Turpie *Eur Heart J* 2008; 29:155

RE-LY: Dabigatran and Stroke or Systemic Embolism



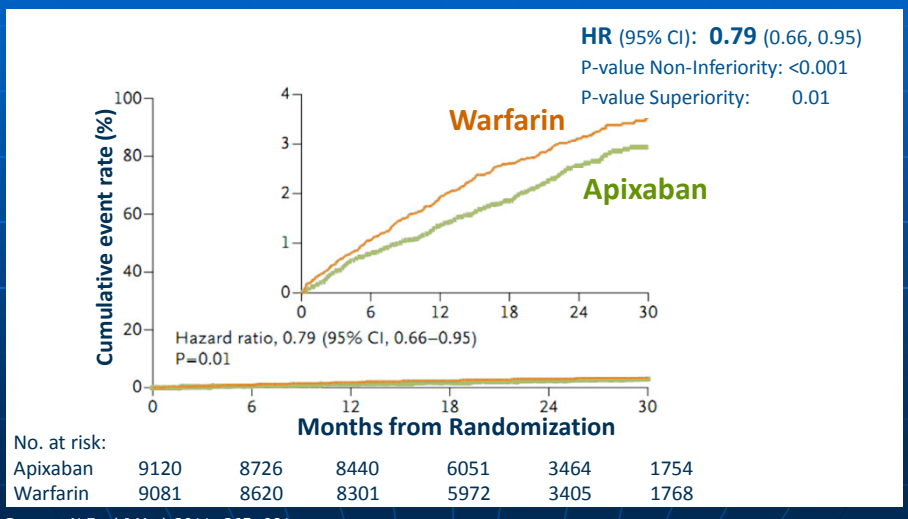
Connolly SJ., et al. *NEJM* published online on Aug 30th 2009. DOI 10.1056/NEJMoa0905561

ROCKET AF: Rivaroxaban and Stroke or Systemic Embolism



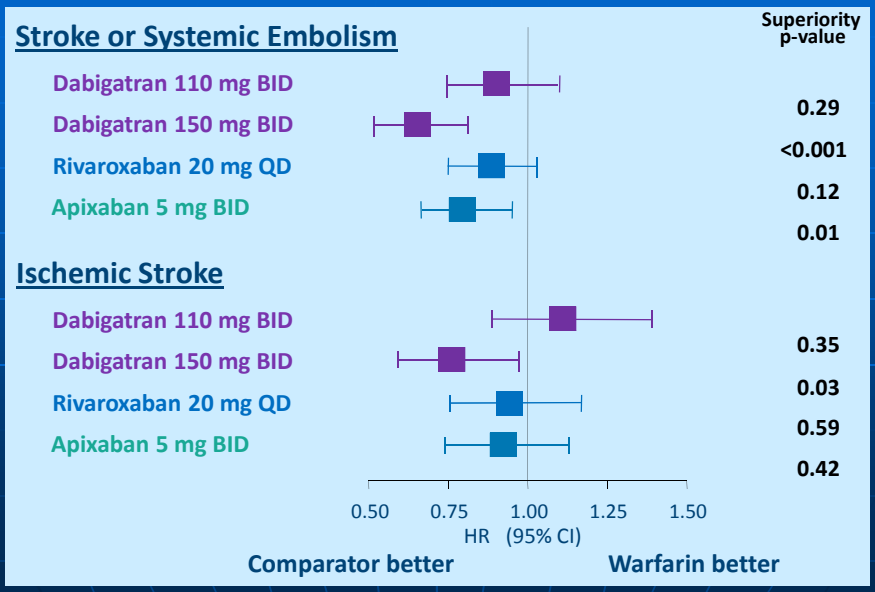
Patel *et al. N Engl J Med.* 2011; 365: 883-91

ARISTOTLE: Apixaban and Stroke or Systemic Embolism



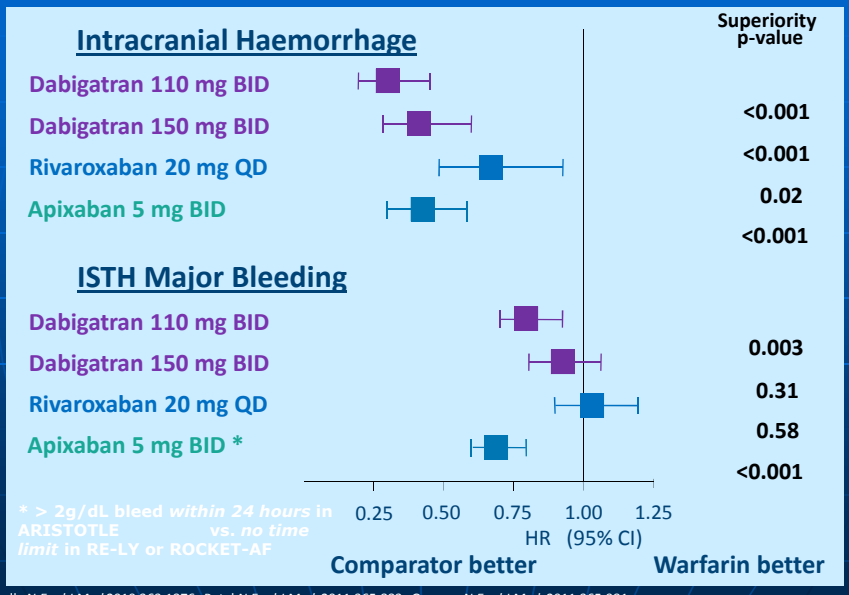
Granger *N Engl J Med* 2011; 365: 981

Prevention of Stroke



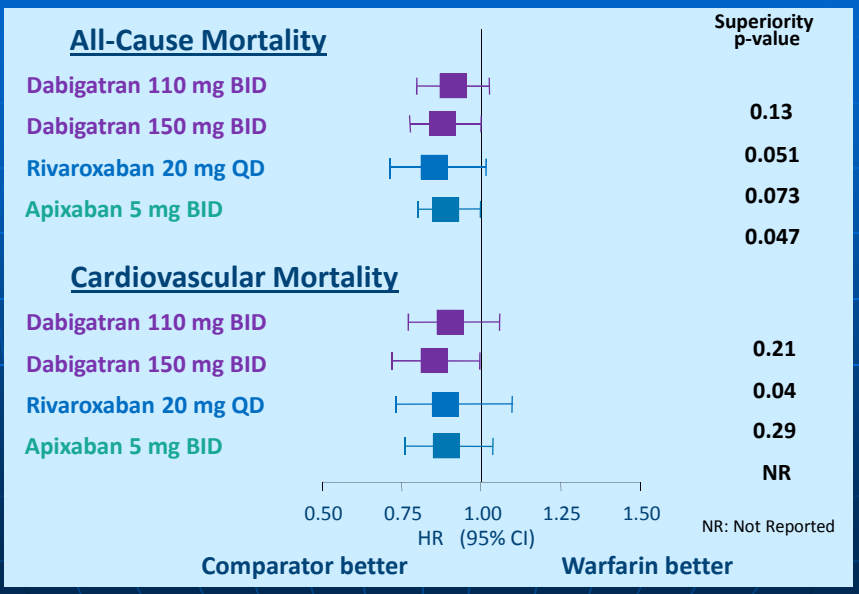
Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Reducing the Bleeding Risk



Connolly *N Engl J Med* 2010;363:1876; Patel *N Engl J Med* 2011;365:883; Granger *N Engl J Med* 2011;365:981

Mortality



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Practical Considerations:
The Importance of Patient Education

- Patient education, a key element of care, includes:
  - Education about AF stroke risk and the need to prevent it by **taking anticoagulant therapy exactly as prescribed**
  - If it is withheld (e.g., for procedures), instruction about **promptly restarting** the drug afterwards
  - Counselling about **never stopping the drug due to side effects** without prior discussion with a physician
  - Instruction about **managing a missed dose**:
    - For dabigatran, take ASAP up to 6 hours prior to the next scheduled dose; beyond 6 hours, omit the missed dose
    - For rivaroxaban, take ASAP the same day
    - Doses should never be doubled to compensate for a missed dose

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 13 June 2011 (revised); *Xarelto Product Monograph* (Canada), 11 January 2012 (revised) ; *Xarelto Product Monograph* (United States), December 2011 (revised)

Practical Considerations :
Patient Follow-up

- Patients require regular, ongoing monitoring:
  - Assess and reinforce adherence to their anticoagulant
  - Monitor renal function
    - No dabigatran if CrCl < 30 ml/min (role of 75 mg BID dose?)
    - No rivaroxaban if CrCl < 30* ml/min (15 mg OD for CrCl 30-50)

**The US (and EU) product monographs suggest a role for rivaroxaban 15 mg OD at CrCl 15-29*

"Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function"

whereas the Canadian one expressly counsels against using it below a CrCl of 30 ml/min

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 13 June 2011 (revised); *Xarelto Product Monograph* (Canada), 11 January 2012 (revised) ; *Xarelto Product Monograph* (United States), December 2011 (revised)

Practical Considerations:
Perioperative Management of Anticoagulant Therapy

- **Alteration of oral anticoagulant regimen *may not be necessary for most patients undergoing low risk procedures:***
  - Dental procedures (including extractions of up to 4 teeth), joint and soft tissue injections, arthrocentesis, cataract surgery, upper endoscopy or colonoscopy with/without biopsy
- **For other invasive and surgical procedures, oral anticoagulation needs to be withheld:**
  - Decision on whether to pursue an aggressive strategy of perioperative administration of IV heparin or SQ low molecular-weight heparin should be individualized based on an estimation of the patient's risks of thromboembolism and bleeding and the patient's preference

Douketis J, et al. Chest 2008;133:299S-339S;
Dunn AS and Turpie AGG. Arch Intern Med 2003;163:901-908

Practical Considerations:
Perioperative Management of Anticoagulant Therapy

- Determine renal function (CrCl or eGFR)
- Determine drug half-life
- Evaluate stroke and bleeding risks
  - Decide timing of temporary discontinuation
  - Consider any need for bridging therapy
  - Plan timing of resumption of therapy
- Re-evaluate after surgical or diagnostic procedure

Crowther MA & Warkentin TE. *J Thromb Haemostat* 2009;7 (Suppl 1):107-110
van Ryn J, et al. *Thromb Haemostat* 2010;103:1116-1127
Cairns et al. *Can J Card* 2011 27:74-90

Practical Considerations:
Managing Moderate/Severe Bleeding

- Stop treatment and investigate the bleeding source
- Control bleeding with pressure or surgical hemostasis
- Measure aPTT/PT: if prolonged, an OAC is on board
- Although not formally evaluated, consider:
  - Whole blood, fresh frozen plasma or platelet concentrates (with thrombocytopenia or antiplatelet drugs)
  - Activated prothrombin complex concentrates (e.g., FEIBA); recombinant Factor VIIa; concentrates of Factors II, IX, X
  - With dabigatran, adequate diuresis and consider hemodialysis/hemofiltration; rivaroxaban is unlikely to be dialyzable due to high protein binding

Based on best available information; expert recommendations; *Pradax Product Monograph (Canada)*, 26 Oct 2010 rev., 8 Nov 2010; *Xarelto Product Monograph* (United States), November 2011

Anticoagulants and Antidotes

- There is no antidote for rivaroxaban or the other new oral anticoagulants
- However, there is also no antidote for warfarin
  - Vitamin K takes time to work (far too long if the patient is presenting with an intracranial haemorrhage)
  - PCC therapy rapidly corrects INR in the majority of patients on warfarin; yet this insufficiently impacts prognosis, at least in patients with ICH among whom mortality and morbidity rates remain high

Dowlatshahi. *Stroke* 2012;43:1812

Practical Considerations:
Antithrombotic Therapy for Patients with CAD

Stable CAD

- Includes patients with a history of prior ACS and/or PCI who are without CHF, angina, etc.
- Aspirin is suggested for most patients at very low risk of stroke ($CHADS_2$=0)
- Warfarin alone, or apixaban or dabigatran or rivaroxaban +/- ASA, is suggested for most patients with $CHADS_2 \geq 1$

Recent ACS and/or PCI

- Aspirin plus clopidogrel alone is suggested for patients at low risk of stroke (CHADS2≤1)
- Triple antithrombotic therapy is suggested for patients with $CHADS_2 \geq 2$ (with warfarin the preferred oral anticoagulant?)

Based on best available information, expert recommendations, Cairns *et al*. *Can J Card* 2011 27:74-90, Skames et al. *Can J Cardiol* 2012; 28: 125-136

A Cardiologist's Perspective:
On Stroke Risk of AF and its Management

- The high risk and markedly severe outcomes of AF-related stroke need to be appreciated
- Risk is greatest in the elderly, those who are most likely to be under-treated
- Bleeding risk is present with antithrombotic therapy, but should neither be overestimated or overemphasized

A Cardiologist's Perspective:
On The Shifting Role of Warfarin

- Warfarin is an effective agent that has long served as our foundation for anticoagulation in AF
- Warfarin has important limitations that contribute to underutilization and poor INR control
  - 3 of 4 patients with AF are unprotected or poorly protected against stroke
- New agents offer important safety and efficacy advantages over warfarin
- Warfarin will continue to play an important role:
  - For other indications (e.g., prosthetic valves)
  - In patients with renal impairment (i.e., CrCl < 15 ml/min)

A Cardiologist's Perspective:
On The Evolving Treatment Paradigm for SPAF

- Compared with warfarin, each of the 3 new agents:
  - Are at least as effective in preventing stroke/systemic embolism
  - Reduce intracranial bleeding
- Differences among agents will play a role in selecting treatment strategies for individual patients, based on:
  - Patient characteristics (e.g., renal impairment, bleeding risk)
  - Patient values (e.g., preventing ischemic stroke vs. OD dosing)
- Many patients will benefit from the advantages offered by these drugs that ideally should be started by primary care/emergency department physicians rather than cardiologists