


**NOACs: Explore How Emerging Evidence is Influencing Treatment Considerations for Doctors and Patients**

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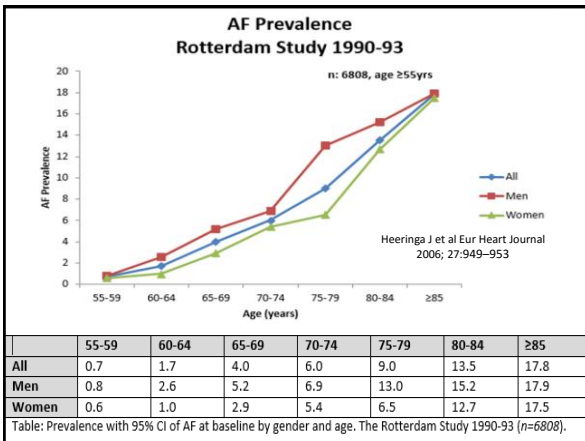
**Summary of NOACs vs. Warfarin**  
 (phase III data, no head-to-head data)

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Ischaemic CVA	↓24%	Same efficacy	Same efficacy	Same efficacy
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Dabigatran: Most extensive data on ≥75yr old (40% of study population); most extensive data on low dose (33% of study population).

Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151. Patel MR, et al. N Engl J Med. 2011;365:883-891. Granger CB, et al. N Engl J Med. 2011;365:981-992. Larsen TB, et al. AM J Med. 2014; 127:650-656. Graham DJ, et al. Circulation. 2015; 131:1557-164. Giugliano RP et al. ENGAGE AF-TIMI 48. Stroke. 2014;45:2372-2378.

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**The impact of AF on stroke incidence**  
**AF is deadly and debilitating**


**Adelaide Stroke Incidence Study**

- population: 148,000, 51% ♀,
- 20% >65yr, f/u 12 m, ICVA:109

**AF related CVA:**

- 28-day fatality: 16%
- 36% of 1<sup>st</sup> ischaemic CVA were related to AF
- 75% of AF related CVA were inadequately anticoagulated (with Warfarin)

Adelaide Stroke Incidence Study. James Leyden et al. Stroke. 2013;44:1226-1231.

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**Who are at risk of AF?**

**Demographics:**

- Birth weight, ♂, race, F/H, age<sup>1-2</sup>


**Medical conditions and risk factors:**<sup>1-2</sup>

- h/o CVA, HT, HF, valvular disease, CAD/MI, LV diastolic dysfunction, DM, OSA, thyroid disease, chronic illness, CRF, infections, postop<sup>1-2</sup>


**Other:**


- Dietary and lifestyle factors (e.g. obesity, sedentary life, low Mg levels, nicotine, high alcohol intake, stress); air pollution<sup>4</sup>
- Frequent Atrial Ectopic Beats<sup>3</sup>
- Lone fibrillators (lone AF)<sup>1</sup>

Fuster V et al. Circulation 2006; 114: e257-354. Camm J, et al. Management of Patients with Atrial Fibrillation. European Society of Cardiology, 2010. Gladstone DJ et al. Stroke. 2015;46:936-941. Link MS et al. JACC 2013;27, 62(8): 816-825.

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**ASPIRIN**




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**VKA, aspirin, VKA+Aspirin**  
 Danish National Patient Registry 1997-2008  
 n: 132,372 NVAF; f/u 12 yrs  
 (no Rx:44.5%; VKA:28.3%, ASA:18.9%, VKA+ASA:8.4%)


Relative risk (HR)	VKA	No Rx	Aspirin	VKA+Aspirin
<b>Thrombo-embolic events</b>	Reference	1.86 (1.78–1.95)	1.81 (1.73–1.90)	1.14 (1.06–1.23)
<b>Bleeding events</b>	Reference	0.84 (0.81–0.88)	0.93 (0.89–0.97)	1.64 (1.55–1.74)

**Aspirin does not work and is NOT indicated for thromboprophylaxis in NVAF.**

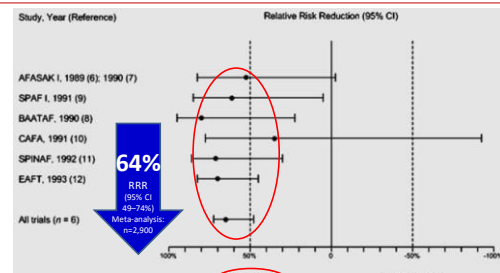
Olesen JB et al. Thromb Haemost 2011; 106: 739–749.




**Vitamin K Antagonist  
 WARFARIN**



**Warfarin's Efficacy vs Placebo or Control**



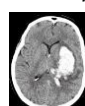
Hart RG et al. Ann Intern Med 2007;146:857-867.  
 Umer Usman MH et al. J Interv Card Electrophysiol 2008;22:129-137



**The use of VKAs for stroke prevention has significant limitations**

- Slow onset/offset of action
- Narrow therapeutic window (INR range 2–3)
- Routine coagulation monitoring
- Frequent dose adjustments


**ICH rate: 1%/yr**




**Major bleed leads to hospitalization and/or death: 1-3%/yr**

- Unpredictable response**
  - Genetic status
  - Age, (gender), race
  - Body weight, BSA
  - Co-medications, foods
  - Plasma vitamin K level
  - CHF, liver disease
  - Malignancy
- WRN; valvular, vascular and coronary calcification; osteoporosis**
- Increased stroke risk in the first month**

Ansell J et al. Chest 2008;133:1605-985; Umer Usman MH et al. J Interv Card Electrophysiol 2008;22:129-137; Nutescu EA et al. Cardiol Clin 2008;26:169-87; www.fda.gov/Drugs/DrugSafety/ucm396470.htm; Brodsky SV et al. Kidney Int 2011;119:181-9; Fishery ML. Semin Neurol. 2010;30(05):565-572; Laurent Azoulay et al. Eur H J 2014;35:1881-1887; Tran HA et al. MIA 2013.




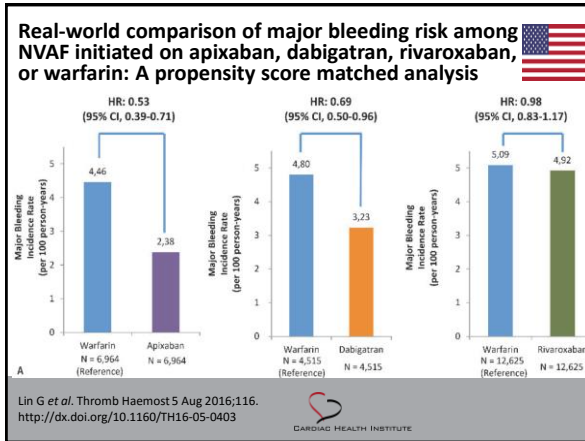
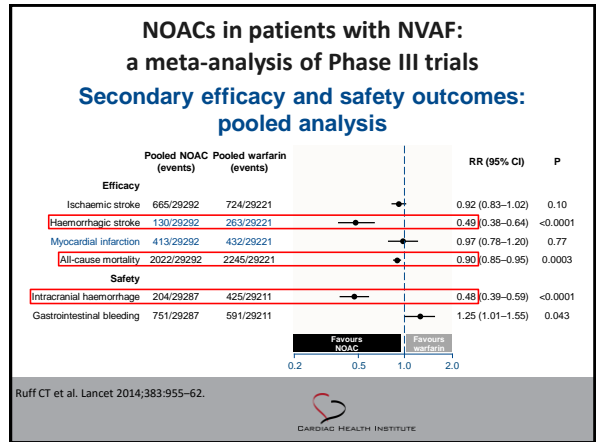
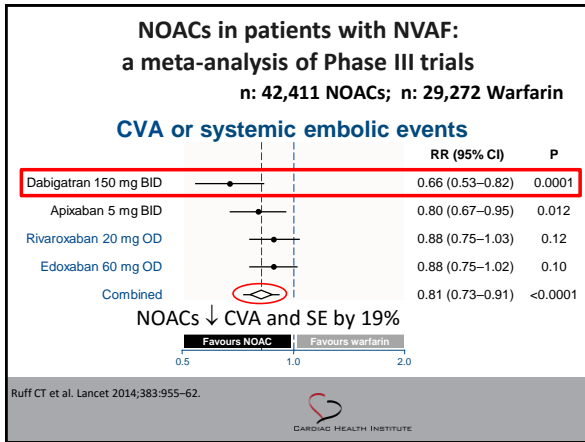
**NOACs**



**ESC GUIDELINES 2012**

- “The evidence for effective stroke prevention with aspirin in AF is weak, with a potential for harm...”
- “Given the availability of NOACs, the use of antiplatelet therapy (such as aspirin...) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.”





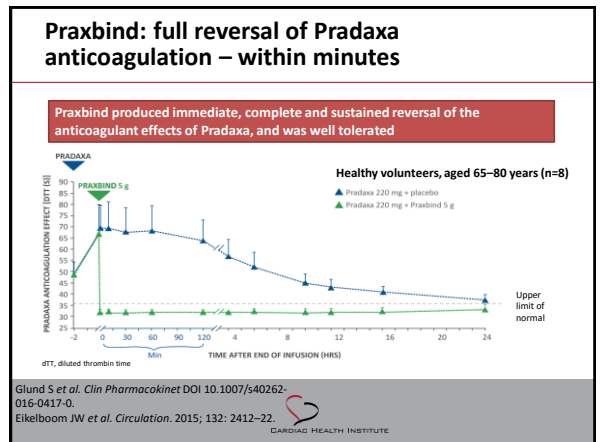
## The first reversal agent for NOACs

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### Praxbind (Idarucizumab): a specific reversal agent for anticoagulant activity of dabigatran

- Humanised Fab fragment
  - High-affinity binding specific to dabigatran
- Primarily renal excretion
- Short half-life
- No interaction with other drugs
- No intrinsic pro-coagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion
- Reduces dabigatran-induced bleeding in animal models
- Complete, and sustained reversal of dabigatran anticoagulation in healthy volunteers

Schiele F et al. Blood 2013;121:3554-62.  
Glund S et al. Thromb Haemost 2015;113:943-51.



**RE-VERSE AD**

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

**Idarucizumab for Dabigatran Reversal**

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,  
Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D.,  
Robert Dubiel, Pharm.D., Minerva V. Husman, M.D., Ph.D., Elaine M. Hylek, M.D.,  
Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D.,  
Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E.,  
Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

ABSTRACT

**BACKGROUND**  
Specific reversal agents for non-vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effect of dabigatran.


From Pennsylvania Hospital, Philadelphia (C.V.P.); Sunovion-Ingelheim Pharmaceuticals, Shelton, CT (P.A.R., R.D., B.W.K.); and the University of Illinois at Chicago (J.I.W.).

Pollack et al. *N Engl J Med* 2015; 373:511-20.




**What I do in clinical practice:**

- AF/PAF → NOACs, dabigatran 150mg preferred
- Use CHA2DS2-VASc and HAS-BLED scores
- Explain to patients (using checklist):
  - Rationale for treatment
  - Potential side effects and what to do
  - How to take the medication (patient and family)
- Communicate with the referring GP
- Periodically review symptoms, renal function etc.



**Case Study: Mrs. M.P., Age 68; retired teacher**


- h/o TIA 2 yrs ago, PAF on warfarin, HT >20yrs, DM on diet control, NSTEMI+PCI 5 yrs ago.
- Medications: warfarin, telmisartan 40mg, metoprolol 25mg bd, rosuvastatin 20mg. Frequent diclofenac, Paracetamol, occasional meloxicam for lower back pain.
- Non-smoker, 3-4 glasses red or white wine most nights. No regular exercise.
- O/E: BMI 32, 88kg, ht 168cm. BP: 160/80.
- ECG: SR 75/min, LA enlargement.



**Case Study: Mrs. M.P., Age 68; retired teacher**

Test results:

- Labile INR (last 12 month, <50% readings between 2-3)
- Abnormal LFT.
- HDL 1, LDL 2.2, TG 2.2 mmol/L. FPG: 5.9 mmol/L, fasting insulin 16 mU/L. serum Cr 98 umol/L (CrCl 67 ml/min).
- Echo: mild LVH, LA dilation and LV diastolic dysfunction, normal LV systolic function.




**Case Study: Mrs. M.P., Age 68; retired teacher**

Holistic Management:

Pharmacologic:

- warfarin → dabigatran 150mg bd
- Metoprolol 25mg bd → sotalol 80mg bd
- Telmisartan → telmisartan-amiodipine 80/5 at bedtime
- Rosuvastatin 20mg → 40mg + fenofibrate 48mg
- Metformin 500mg bid
- (magnesium supplements)




**Case Study: Mrs. M.P., Age 68; retired teacher**

Holistic Management:

Incorporate exercise and diet plans:

- Cardiac rehab program; walking exercise program >30 min/day.
- Joins nearest local gym.
- Dietician referral, counselling.

GP initiates other pain relief solutions to reduce NSAID use.  
GP monthly review for 6months, cardiac review in 3 months.



## Case Study 2: Mrs. M.P., Age 68; retired teacher

CHA<sub>2</sub>DS<sub>2</sub>-VASc Score: 7, HAS-BLED score: 6

High risk AF: deserves optimal anticoagulation → NOACs

Without labile INR (on dabigatran), achieving BP control, normalising LFT with improved glycaemic and TG profiles, minimal NSAIDs,

HAS-BLED score is recued from 6 to 2



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