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)

c/t Warfarin	Dabigatran 150mg bd	Dabigatran 110mg bd	Rivaroxaban 20/15mg	Apixaban 5/2.5mg
Ischaemic CVA	↓24%	Same efficacy	Same efficacy	Same efficacy
Major bleed	No difference	↓20%	No difference	↓31%
Intracranial bleed	↓59%	↓70%	↓33%	↓49%

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; 131:157-164.
Giugliano RP et al. ENGAGE AF-TIMI 48. Stroke. 2014;45:2372-2378.

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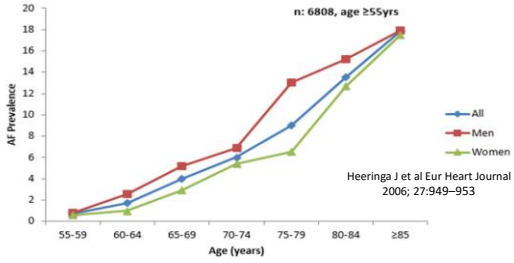
AF Prevalence
Rotterdam Study 1990-93



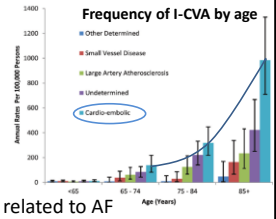
	55-59	60-64	65-69	70-74	75-79	80-84	≥85
All	0.7	1.7	4.0	6.0	9.0	13.5	17.8
Men	0.8	2.6	5.2	6.9	13.0	15.2	17.9
Women	0.6	1.0	2.9	5.4	6.5	12.7	17.5

Table: Prevalence with 95% CI of AF at baseline by gender and age. The Rotterdam Study 1990-93 (*n=6808*).

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 1st 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*[1-2]

Medical conditions and risk factors:[1-2]

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

Other:

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

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(9): 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
Thrombo-embolic events	Reference	1.86 (1.78–1.95)	1.81 (1.73–1.90)	1.14 (1.06–1.23)
Bleeding events	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.

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Vitamin K Antagonist

WARFARIN

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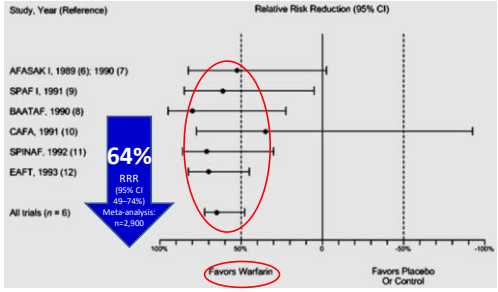
Warfarin's Efficacy vs Placebo or Control



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

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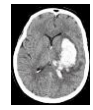
The use of VKAs for stroke prevention has significant limitations

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

ICH rate: 1%/yr



Major bleed leadings 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;133:160S–98S; 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;109:181-9
Flaherty ML. Semin Neurol. 2010;30(05):565, 572
Laurent Azoulay et al. Eur H J 2014;35:1881–1887
Tran HA et al. MJA 2013.

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NOACs

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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."

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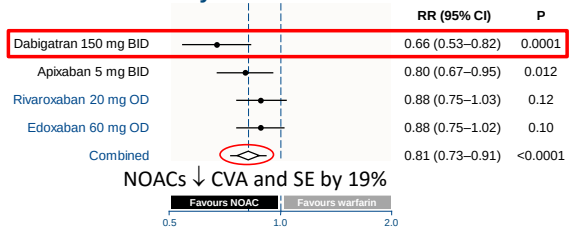
NOACs in patients with NVAF: a meta-analysis of Phase III trials

n: 42,411 NOACs; n: 29,272 Warfarin

CVA or systemic embolic events



NOACs ↓ CVA and SE by 19%

Ruff CT et al. Lancet 2014;383:955–62.

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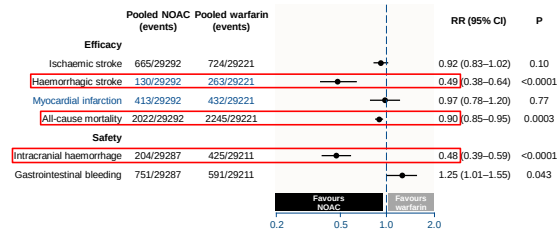
NOACs in patients with NVAF: a meta-analysis of Phase III trials

Secondary efficacy and safety outcomes: pooled analysis



Ruff CT et al. Lancet 2014;383:955–62.

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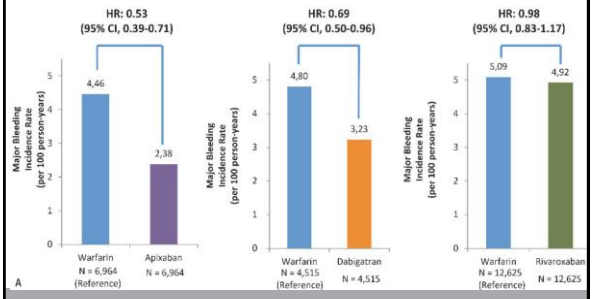
Real-world comparison of major bleeding risk among NVAF initiated on apixaban, dabigatran, rivaroxaban, or warfarin: A propensity score matched analysis



Lin G *et al*. Thromb Haemost 5 Aug 2016;116. http://dx.doi.org/10.1160/TH16-05-0403

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The first reversal agent for NOACs

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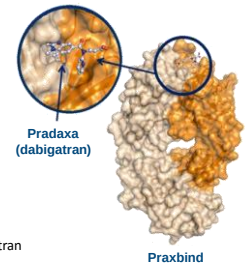
Praxbind (Idarucizumab): a specific reversal agent for anticoagulant activity of dabigatran

- 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 Haemos* 2015;113:943-51.

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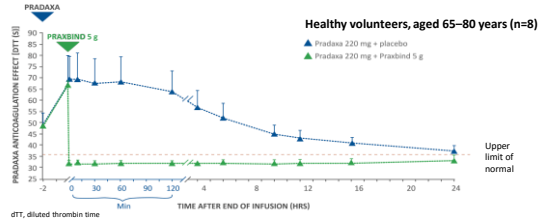
Praxbind: full reversal of Pradaxa anticoagulation – within minutes

Praxbind produced immediate, complete and sustained reversal of the anticoagulant effects of Pradaxa, and was well tolerated



Glund S *et al. Clin Pharmacokinet* DOI 10.1007/s40262-016-0417-0.
Eikelboom JW *et al. Circulation*. 2015; 132: 2412–22.

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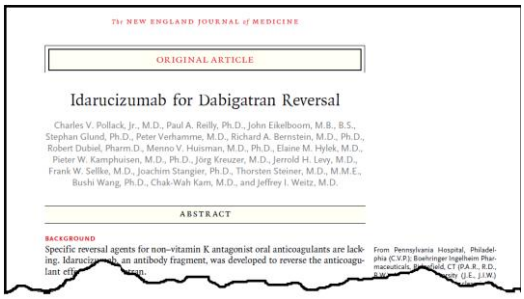
RE-VERSE AD



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., Menno V. Huisman, 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

From Pennsylvania Hospital, Philadelphia (C.V.P.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., R.D., B.W., C.-W.K.); [illegible] (J.E., 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-amlodipine 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_2DS_2-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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Summary of NOACs vs. Warfarin

(phase III data, no head-to-head data)

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