HeartCare Victoria

Novel Anticoagulants: Emerging Evidence

Dr Matthew Swale
Electrophysiologist
Genesis Care

GenesisCare

Topics:

- NOAC
  - Novel Oral Anti Coagulant
    - Now
  - Non-Vit K Oral Anti Coagulant
- DOAC
  - Direct Oral Anti Coagulant

GenesisCare

Evidence vs Eminence Based??

- Is everything I'm going to tell you correct?
  - YES!! I'm a Cardiologist, I can't be wrong!!
- Will everyone else do exactly the same as me?
  - NO!! But they're Cardiologists too so they can't be wrong either!
- Why do we differ??
  - Lack of evidence – eg "Triple Therapy"
  - "Wiggle Room" within available knowledge.

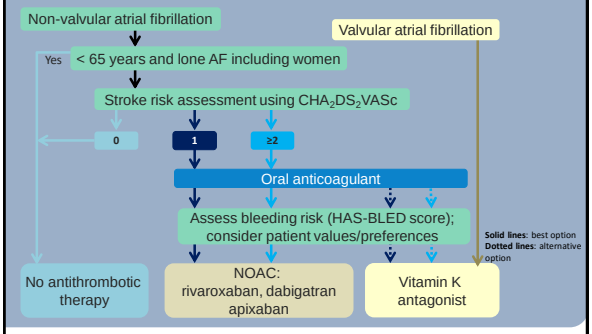
GenesisCare

Role of DOACs

ARISTOTLE (21)	Multicenter, randomized, double-blind, active-controlled, noninferiority/superiority	Patients with AF with ≥1 risk factors for stroke (N = 18,201)	Apixaban oral 2.5 or 5 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 1.8 yrs	Stroke or systemic embolism: 1.3% vs. 1.6%/yr (p = 0.01 for superiority)	Major bleeding: 2.1% vs. 3.1%/yr (p < 0.001)	Major or nonmajor clinically relevant bleeding: 4.1% vs. 6.0%/yr (p < 0.001)Major intracranial bleeding: 0.3% vs. 0.8%/yr (p < 0.001)Major GI bleeding: 0.8% vs. 0.9%/yr (p = 0.37)
ROCKET AF (32)	Multicenter, randomized, double-blind, double-dummy, active-control, noninferiority	Age ≥18 yrs with AF at moderate to high risk of stroke (N = 14,264)	Rivaroxaban oral 20 mg qd (15 mg qd in patients with CrCl 30–49 ml/min) or warfarin adjusted to maintain an INR of 2.0–3.0	Median 590 days	Stroke or systemic embolism: 1.7% vs. 2.2% (p < 0.001 for noninferiority)	Major and nonmajor clinically relevant bleeding: 14.9% vs. 14.5%/yr (p = 0.44)	Major bleeding: 3.6% vs. 3.4%/yr (p = 0.58)ICH: 0.5% vs. 0.7%/yr (p = 0.02)Fatal bleeding: 0.2% vs. 0.5%/yr (p = 0.003)GI bleeding: 3.2% vs. 2.2% (p < 0.001)
RE-LY (41)	Multicenter, randomized, single-blind, active control, noninferiority	Age ≥18 yrs with AF and ≥1 risk factors for stroke (N = 18,113)	Dabigatran etexilate oral 110 or 150 mg bid vs. oral warfarin qd (INR, 2.0–3.0)	Median 2 yrs	Stroke or systemic embolism: 1.5% and 1.1%/yr vs. 1.7%/yr (p < 0.001 for noninferiority and	Major bleeding: 2.7% and 3.1% vs. 3.4%/yr (p = 0.003 and p = 0.31 vs. warfarin)	Any bleeding: 14.6% and 16.4% vs. 18.2%/yr (p < 0.001 and p = 0.002 vs. warfarin)ICH: 0.23% and 0.30% vs. 0.74%/yr (p < 0.001 vs. warfarin)GI bleeding: 1.1% and 1.5% vs. 1.0%/year (p = 0.43 and p < 0.001 vs. warfarin)Life-

Camm AJ *et al. Eur Heart J* 2012 33: 2719–47.

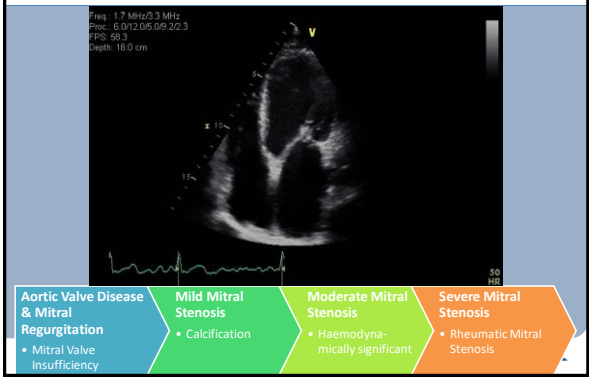
Guidelines for Anticoagulation



GenesisCare

Adapted from Camm AJ *et al. Eur Heart J* 2012 33: 2719–47.

What is VALVULAR AF?

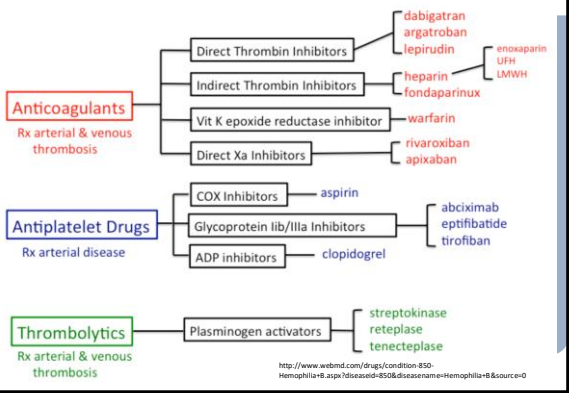


Real Issue with DOACs

- COMPLIANCE!!!
- Patient misunderstanding of bleeding risks
- Doctor misunderstanding of bleeding risks

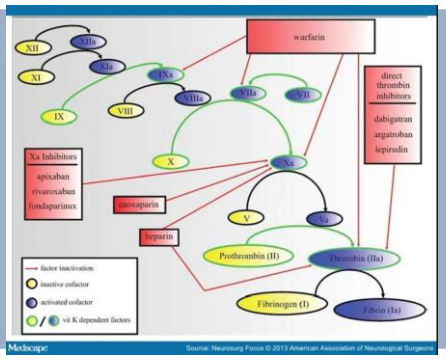
GenesisCare

Drugs Used to Treat Clotting Disorders



http://www.webmd.com/drugs/condition-850-Hemophilia+B.aspx?diseaseid=850&diseasename=Hemophilia+B&source=0

Method of Action:



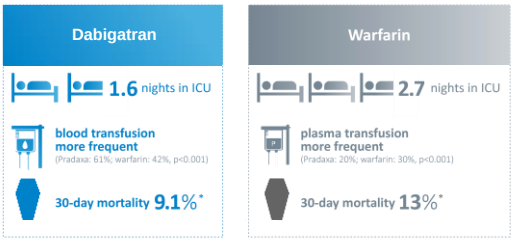
GenesisCare

Implications for each choice

	Warfarin	Dabigatran 150mg [1]	Dabigatran 110mg[1]	Apixaban 5mg[2]	Apixaban 2.5mg[2]	Rivarox. 20mg[3]	Rivarox. 15mg[3]
Monitoring REQUIRED	YES	NO		NO		NO	
Monitoring POSSIBLE	YES	YES		NO		YES	
Renal Excretion	0%	80%		27%		66%	
Half Life	36 hrs	11-13	11-13	8-15	8-15	5-13	5-13
Half Life in Renal Imp.	36 hrs	13-23	13-23	17-18	17-18	9-13	17-18
Peak : Trough	Variable	2:1		2:1		8:1	
CYP3A4	YES	NO		YES		YES	
Drug Interactions	YES	Limited		Limited		Limited	
Interaction Examples	Food Alcohol Meds	Verapamil Amiodarone		Rifampicin Ketoconzole Clarithromycin		Rifampicin Ketoconzole Clarithromycin	
Dosing	SD	BD with or without food		BD without food		SD without food	
Dialysable	NO	YES		NO		NO	
Antidote Available	VitK (?)	In development		In development		In development	

Actual Bleeding Outcomes vs Warfarin

Most major bleeding events managed with supportive care only



*pooled odds ratio for 30-day mortality 0.66 (95% confidence interval, 0.44–1.00; P=0.051).

1. Majeed A et al. *Circulation* 2013; 128: 2325–32

Need to assess anticoagulation status?

Stop NOAC + Measure NOAC Anticoagulant Effect

aPTT	TT	PT	antiXa
↑ Dabig.	↑ Dabig.	↑ Rivarox	↑ Apix.

Significant Anticoagulant Effect:
Maintain BP + urine output
Control Bleeding
Transfusion support

aPTT	TT	PT	antiXa
= Dabig.	= or (↑) Dabig.	= Rivarox	= Apix.

NOAC level LOW or ABSENT

Proceed to surgery

Discuss if surgery can be delayed?

YES for >12hrs: *Refer to Elective Surgery Strategy*

YES for 4-12hrs: *Consider Haemodialysis for Dabigatran*

NO – IMMEDIATE SURGERY REQUIRED:
Discuss with Haematology to consider Haemostatic Agent
aPCC (FEIBA) or 3F-PCC (Prothrombinex-VF)

Tran HA *et al. Med J Aust* 2013; 198: 198–9.

GenesisCare

Bleeding Management – EHRA Guidelines Europace

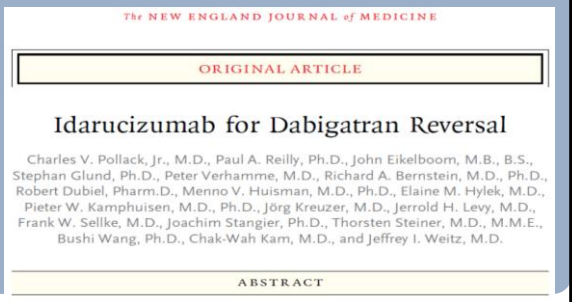
doi:10.1093/europace/euv309

Table 2 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl <30 mL/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: ~65% after 4h)[33] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, Prothrombin complex concentrate.

REVERSE-AD



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

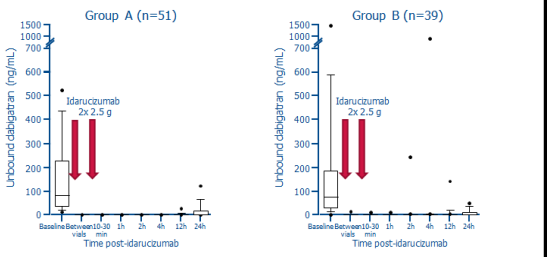
Idarucizumab for Dabigatran Reversal

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

GenesisCare

Dabigatran levels before and after treatment with idarucizumab



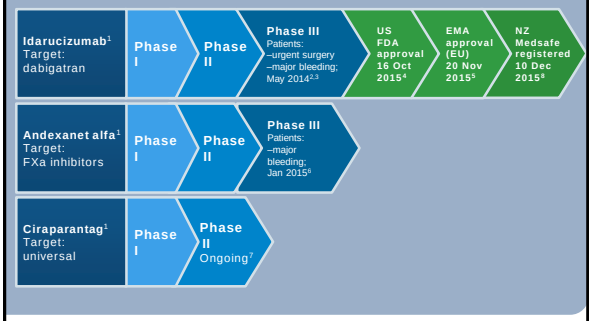
Dabigatran levels were below 20 ng/mL* in 89/90 patients already after infusion of first vial

Unbound dabigatran concentrations were below 20 ng/mL* in 77/83 and 62/78 patients at 12 and 24 hours, respectively

*A level that produces little or no anticoagulant effect

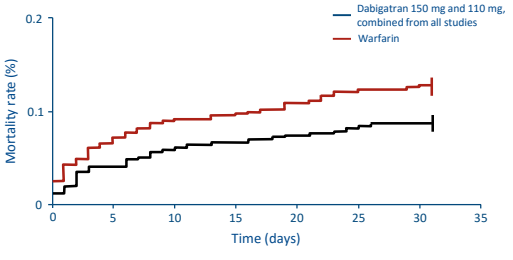
Pollack et al. NEJM 2015

NOAC reversal agents: stages of development



GenesisCare

Dabigatran associated with improved mortality outcomes vs warfarin during 30 days after major bleeding



Combined data from dabigatran 150 mg and 110 mg BID treatment groups in RE-LY®, RE-COVER™, RE-COVER™ II, RE-MEDY™, and RE-SONATE™. Only first major bleed included; analysis not adjusted for covariates

Majeed et al. Circulation 2013

GenesisCare

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 65, NO. 23, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.03.577

Changes in Renal Function in Patients With Atrial Fibrillation

An Analysis From the RE-LY Trial

Michael Böhm, MD,* Michael D. Ezekowitz, MD, CStB, DPhil,†‡ Stuart J. Connolly, MD,§ John W. Eikelboom, MBBS,§ Stefan H. Hohnloser, MD,‖ Paul A. Reilly, PhD,¶ Helmut Schumacher, PhD,# Martina Brueckmann, MD,#** Stephan H. Schirmer, MD, PhD,* Mario T. Kratz, MD,* Salim Yusuf, MD, DPhil,§ Hans-Christoph Diener, MD,†† Ziad Hijazi, MD,‡‡ Lars Wallentin, MD, PhD‡‡

BACKGROUND Vitamin K-dependent factors protect against vascular and renovascular calcification, and vitamin K antagonists may be associated with a decreased glomerular filtration rate (GFR).

OBJECTIVES This study analyzed changes in GFR during long-term treatment with warfarin or dabigatran etexilate (DE) in patients enrolled in the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial.

METHODS Of the 18,113 patients in the RE-LY study randomized to receive DE (110 mg or 150 mg twice daily) or warfarin, 16,490 patients with atrial fibrillation had creatinine values measured at baseline and at least 1 follow-up visit. Changes in GFR for up to 30 months were evaluated.

GenesisCare

RESULTS

- Renal function declined over time in all treatment groups
- After 30 months, average decline was significantly greater in the warfarin group than in either Dabigatran group
- From 18 months onward, patients were less likely to experience renal function decline (>25%) on Dabigatran
- Poor INR control (TThR>65%) exhibited faster renal function decline
- Prior warfarin use and Type 2 Diabetes was associated with more pronounced renal function decline

CONCLUSIONS Patients with atrial fibrillation receiving oral anticoagulation exhibited a decline in renal function that was greater in those taking warfarin versus DE, and it was amplified by diabetes and previous vitamin K antagonist use. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600)
(J Am Coll Cardiol 2015;65:2481-93) © 2015 by the American College of Cardiology Foundation.

Switching Drugs

Where a clinical assessment has been made to switch a patient, the following guidance is provided:

- Renal function should be calculated prior to initiation with DOACs
- From DOAC to Warfarin
  - Continue DOAC until INR >2
- From Warfarin to DOAC
  - Withhold Warfarin until INR <2 then start DOAC
  - Onset of Effect is in 2-4 hours from administration
- From Clexane to DOAC
  - Next dose substitution

1. Product information, Eliquis® (apixaban)
2. Product information, Pradaxa® (dabigatran etexilate)
3. Product information, Xarelto® (rivaroxaban)
4. ESC Guidelines: Camm AJ et al. *Eur Heart J* 2012; 33: 2719–47

GenesisCare

Important Interactions

- P-gp or CYP3A4 effects
- Verapamil and Dabigatran
  - Need to dose reduce Dabigatran
- Amiodarone and Dabigatran
  - ?need to change dose
  - Dronedarone worse
- "Azoles" – increase DOAC levels
- Rifampicin and Antiepliptics reduce available drug

1. Product information, Eliquis® (apixaban)
2. Product information, Pradaxa® (dabigatran etexilate)
3. Product information, Xarelto® (rivaroxaban)
4. ESC Guidelines: Camm AJ et al. *Eur Heart J* 2012; 33: 2719–47

GenesisCare

Important Interactions

	Warfarin	Dabigatran 150mg [1]	Dabigatran 110mg [1]	Apixaban 5mg [2]	Apixaban 2.5mg [2]	Rivarox. 20mg [3]	Rivarox. 15mg [3]
Monitoring REQUIRED	YES	NO		NO		NO	
Monitoring POSSIBLE	YES	YES		NO		YES	
Renal Excretion	0%	80%		27%		66%	
Half Life	36 hrs	11-13	11-13	8-15	8-15	5-13	5-13
Half Life in Renal Imp.	36 hrs	13-23	13-23	17-18	17-18	9-13	17-18
Peak : Trough	Variable	2:1		2:1		8:1	
CYP3A4	YES	NO		YES		YES	
Drug Interactions	YES	Limited		Limited		Limited	
Interaction Examples	Food Alcohol Meds	Verapamil Amiodarone		Rifampicin Ketoconzole Clarithromycin		Rifampicin Ketoconzole Clarithromycin	
Dosing	SD	BD with or without food		BD without food		SD without food	
Dialysable	NO	YES		NO		NO	
Antidote Available	VitK (?)	In development		In development		In development	

Anticoagulation post AF Ablation

- Observational work suggests lower stroke risks post ablation
  - 0.8 vs 5.4% at 47 months
    (Lin et,al Europace 2013; 15:676)
- Not assessed in randomised fashion
- In patients with a CHADS-VASc ≥ 1 long term anticoagulation should be continued irrespective of ablation outcome
- In CHADS-VASc 0 patients, 3 months of anti-coagulation is minimum post ablation, after this increased bleeding risk may cancel out stroke risk
  (Noseworhty et. al J Am Heart Assoc 2015:4)

GenesisCare

Perioperative Discontinuation

Table 6 Preoperative interruption of new oral anticoagulants: a suggested management approach[20,24]

Drug (doses)†	Renal function	Low bleeding risk surgery‡ (2 or 3 drug half-lives between last dose and surgery)	High bleeding risk surgery§ (4 or 5 drug half-lives between last dose and surgery)
Dabigatran (150 mg twice daily)			
Half-life, 12–17 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 13–23 h	Moderate impairment (CrCl 30–49 mL/min)	Last dose: 48–72 h before surgery	Last dose: 96 h before surgery
Rivaroxaban (20 mg once daily)			
Half-life, 5–9 h (healthy)	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 9–13 h	moderate impairment (CrCl 30–49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery
Apixaban (5 mg twice daily)			
Half-life, 7–8 h	Normal or mild impairment (CrCl ≥ 50 mL/min)	Last dose: 24 h before surgery	Last dose: 48–72 h before surgery
Half-life, 17–18 h	Moderate impairment (CrCl 30–49 mL/min)	Last dose: 48 h before surgery	Last dose: 72 h before surgery

†Estimated half-life based on calculated renal clearance using the Cockcroft–Gault equation. ‡Aiming for mild to moderate residual anticoagulant effect at surgery (<12–25%). §Aiming for no or minimal residual anticoagulant effect (<3–6%) at surgery. CrCl, creatinine clearance.

Ref: Tran et al, Internal Medicine Journal (44)2014

18 October, 2016

GenesisCare

"Triple Therapy"

- For Warfarin, WOEST trial showed Warfarin + Clopidogrel performed better than Triple Therapy
- Still under investigation for DOACs
  - RE-DUAL
  - PIONEER-AF-PCI
- We know that DAPT and Rivaroxaban reduces MACE but increases bleeding (2.1 vs 0.6%) from ATLAS-ACS TIMI 5
  - This was on doses lower than for AF (2.5 and 5mg BD)
- APPRAISE-2 with Apixaban showed increased bleeding at 1.3% vs 0.5% for placebo

WOEST: Dewilde, Willem JM et al. The Lancet , Volume 381 , Issue 9872 , 1107 – 1115

GenesisCare

2011 Consensus Statement for Warfarin (USA)

Table 1. Summary of North American Consensus Document on Triple Therapy[6]

CHADS2 Score	Stent Type	Thrombosis Risk	Bleeding Risk	Recommendation for First 12 Months	After First 12 Months
0	BMS	Any	Any	DAPT for 1 month and preferably 12 months	Warfarin monotherapy
0	DES	Any	Any	DAPT	Warfarin monotherapy
>1	BMS	Low	Low	Triple therapy for at least 1 month then oral anticoagulation plus single antiplatelet	Warfarin monotherapy
>1	DES	Low	Low	Triple therapy for at least 6 months then oral anticoagulation plus single antiplatelet	Warfarin monotherapy
>1	BMS	High	Low	Triple therapy for at least 6 months then oral anticoagulation plus single antiplatelet	Warfarin monotherapy
>1	DES	High	Low	Triple therapy	Warfarin monotherapy
>1	BMS	Any	High	Triple therapy for at least 1 month then oral anticoagulation plus single antiplatelet	Warfarin monotherapy
>1	DES	Any	High	DES not recommended	Warfarin monotherapy

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021

GenesisCare

EHRA Guidelines for Triple Therapy

doi:10.1093/europace/euv309

Hemorrhage risk	Clinical setting	Stroke risk[a]	Recommendations for antithrombotic therapy		
			Timing of treatment after PCI	Therapy	Details
Low or moderate (HAS-BLED ≤2)	Stable CAD (elective PCI)	Moderate	≥4 weeks <6 months	Triple therapy[b]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy[c]	Reduced-dose OAC + clopidogrel or Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
		High	≥4 weeks <6 months	Triple therapy[e]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel or Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
	ACS (urgent PCI)	Moderate or high	Up to 6th month	Triple therapy	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy[f]	Reduced-dose OAC + clopidogrel or Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
High (HAS-BLED ≥3)	Stable CAD (elective PCI)	Moderate	Up to 12th month	Dual therapy[c]	Reduced-dose OAC + clopidogrel
			Lifelong	Single therapy	Standard-dose OAC[d]
		High	4 weeks	Triple therapy[b]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel or Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]
	ACS (urgent PCI)	Moderate or high	4 weeks	Triple therapy[e]	Reduced-dose OAC + ASA + clopidogrel
			Up to 12th month	Dual therapy	Reduced-dose OAC + clopidogrel or Reduced-dose OAC + ASA
			Lifelong	Single therapy	Standard-dose OAC[d]

GenesisCare

Which NOAC??

- Initially all thought to be relatively equal
  - Differences in trial design and numbers may explain the differences in initial results
- Few direct comparisons
  - Some retrospective analyses appear equal
  - Recently JAMA internal Medicine and JACC suggest more bleeding with Rivaroxaban
    - But retrospective propensity matched controls not randomised
    - Dabigatran and Apixaban appear equal
    - Suggesting dosing is more important than mechanism (Direct Thrombin vs Xa inhibition)
    - JACC 2016; (Vol 67) Issue 13
    - JAMA internal medicine Online October 3
- Daily dosing of importance in adherence

GenesisCare

JACC Journals

From: DIRECT COMPARISON OF DABIGATRAN, RIVAROXABAN, AND APIXABAN FOR EFFECTIVENESS AND SAFETY IN NONVALVULAR ATRIAL FIBRILLATION
J Am Coll Cardiol. 2016;67(13_S):692-692. doi:10.1016/S0735-1097(16)30693-3

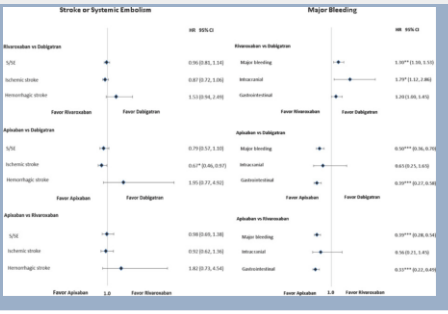


Figure Legend:

Date of download: 10/12/2016

GenesisCare

Summary

- NOACs are safe and well studied
  - Lower bleeding rates and greater predictability vs Warfarin
- Unknowns are being assessed
  - Which NOAC – early signs are BD dosing may be preferable
    - Similar stroke reduction, greater blleding
    - No randomised studies
  - Triple Therapy
- The age of Reversal Agents is upon us
  - In most clinical scenarios they will not be necessary
  - Where used the initial antidotes are highly effective

GenesisCare