8^ edizione

Top Ten

IN GASTROENTEROLOGIA

17-18 MARZO 2017

ISEO (BS)

Iseo Lago Hotel - Via Colombera, 2

Franco Radaelli

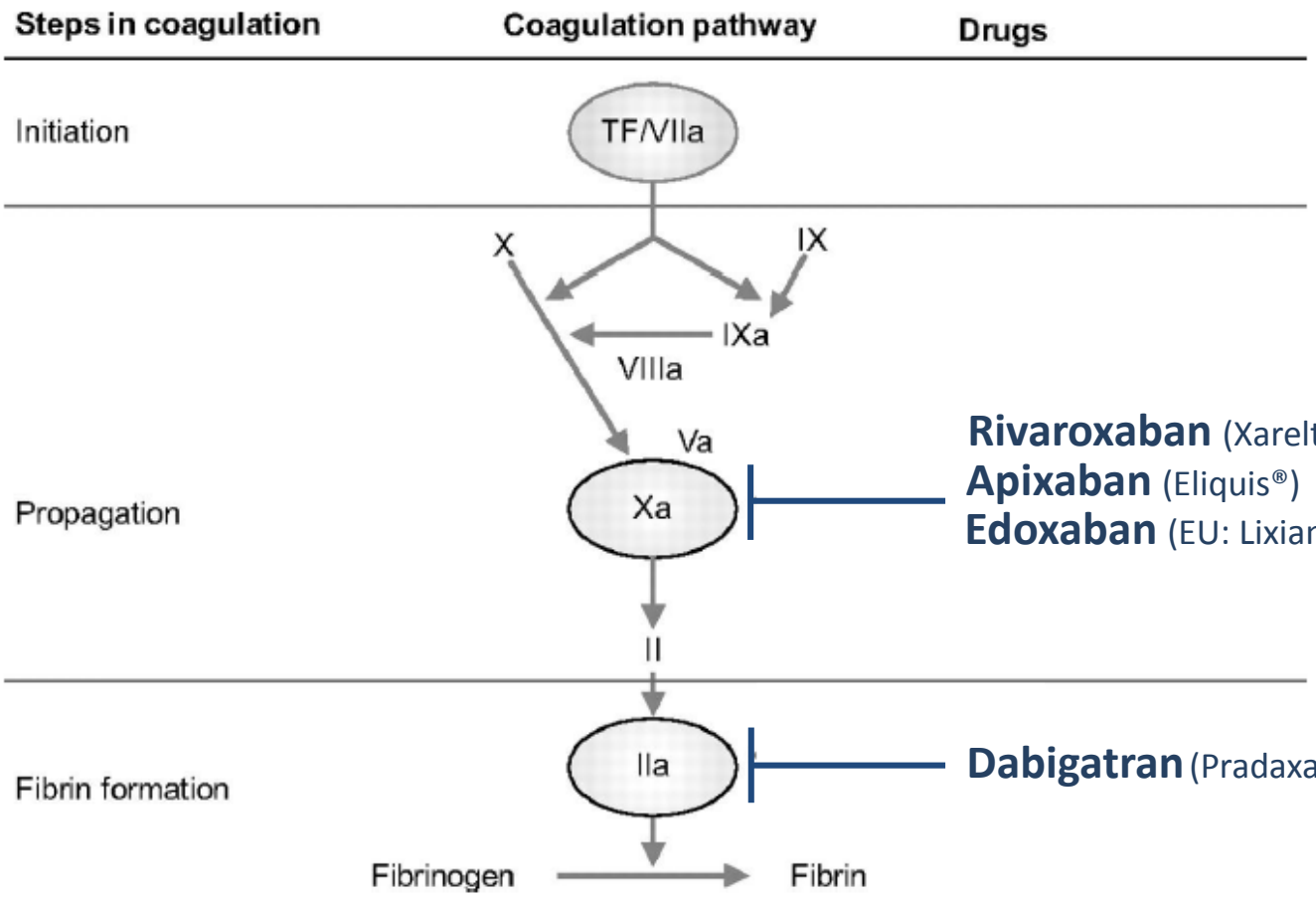
Nuovi anticoagulanti orali e procedure endoscopiche

Objectives:

1. Basics on NOACs
   - risk of GI bleeding related to NOACs

2. Management of NOACs for elective endoscopy procedures

NOACs: mechanism of action



DOACs

Direct Oral AntiCoagulants

DOACs: Approved Indications

DOAC	nv-AF	DVT/PE*	VTE prophylaxis^
Dabigatran – Pradaxa® (110mg, 150mg) BID	110-150mg bid[1]	Heparin lead-in required 5-10 days 150 mg bid	110 bid
Apixaban - Eliquis® (2.5 mg, 5 mg) BID	2.5- 5 mg bid[2]	10mg bid from day 1 to 7 5 mg bid	2.5 mg bid
Rivaraxoban - Xarelto® (10 mg, 15mg, 20mg) QD	15–20 mg qd[3]	15 mg bid from day 1 to 21 20 mg qd	10 mg qd
Edoxoban - Lixiana® (30mg, 60mg) QD	30–60 mg qd[4]	Heparin lead-in required 5 days 60 mg qd	------

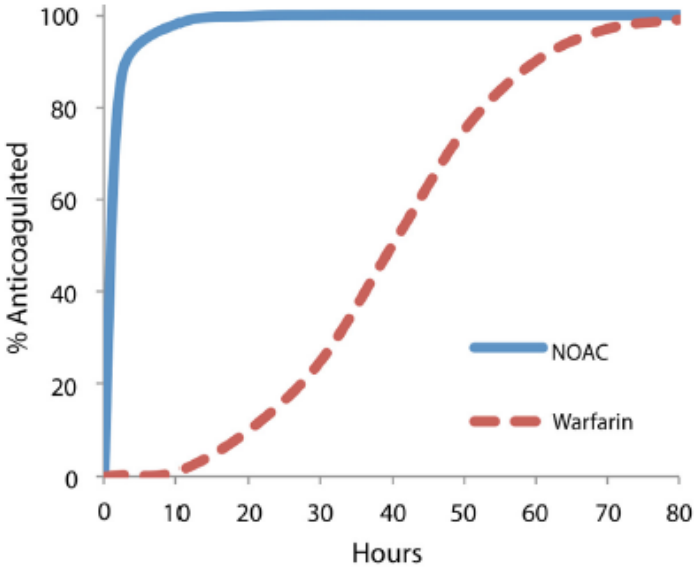
^ Indications: orthopedic surgery (hip, knee replacement)
* Extended risk reduction (recurrent DVT/PE) [150 mg bid/ 20mg qd/ 2.5mg bid]

[1] 110 mg if age ≥80; verapamil [dose to be individualized if age 75-80, CreatCL 30-49ml/min, high bleeding risk]
[2] 2.5mg if at least two criteria: age ≥80; weight < 60Kg; creatinine > 1.5mg/dL
[3] 15mg if CreatCL 15-49ml/min
[4] 30mg if CreatCL 15-49ml/min, weight < 60Kg, inhibithor Pgp (cyclosporin, eritromicine, ketoconazole, dronedarone)

DOACs: Pharmacodynamic/Kinetic properties

- Faster onset and offset of action than VKAs
- More predictable pharmacodynamic/kinetic properties than VKAs

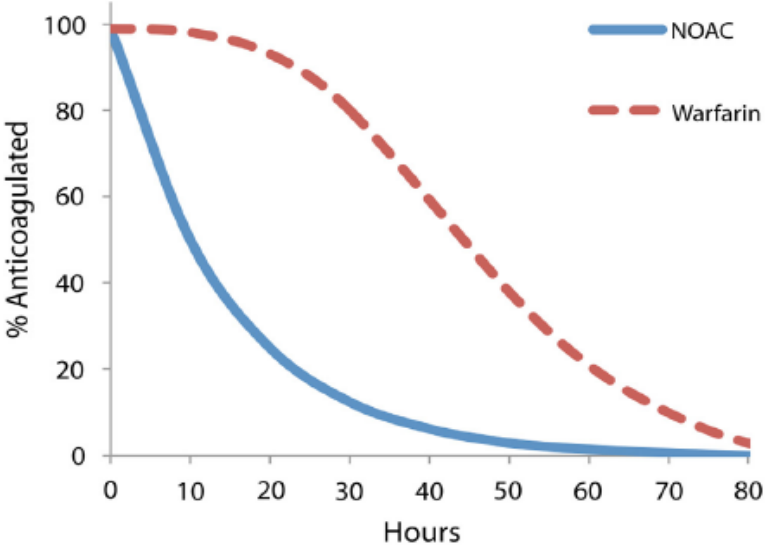
Onset of action:



Anticoagulant activity reached:

DOACs: 1-3 hours (single dose)
VKAs: days (multiple doses)

Offset of action:



Anticoagulant activity restored:

DOACs: within 24-48 hours after withdrawal
VKAs: days

Desai J, Gastrointest Endosc 2013;78:227-39

DOACs vs. VKAs: Pros and Cons

Pros

- Efficacy noninferior or superior to VKAs in phase III trials
- Less risk of ICH, fatal bleeding
- Oral fixed dose^
- Predictable dose response
  - no routine lab monitoring required
- Limited drug interactions
- No food restrictions

Cons

- Coagulation assays not routinely available
- Specific antidotes or reversal agents are not yet available
- Higher risk of GI bleeding for some
- GI tolerability
  (dabigatran: dyspepsia 5-10%)

^ dependent on indication, Creat Cl, age, concomitant medications

Hankey GJ et al, Circulation 2011; 123: 1436-1444

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Hankey GJ et al, Circulation 2011; 123: 1436-1444

Is the risk of GI bleeding with DOACs higher than with warfarin?

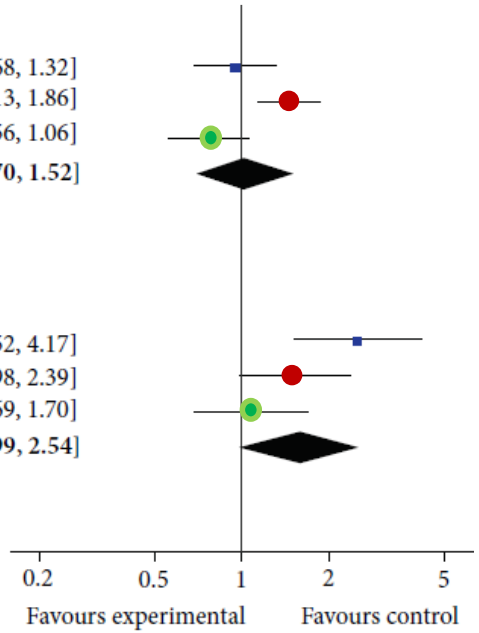
Major GI bleeding risk of DOACs *vs.* VKAs: nvAF trials

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
Study	RE-LY		ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48	
Dose	110mg bid	150mg bid	20mg	5mg bid	30mg	60mg
Risk for major GI bleeding	**NS**	**+50%**	**+61%**	**NS**	**-33%**	**+23%**
HR (95% CI)		1.49 (1.21-1.84)	1.61 (1.30-1.99)	0.89 (0-70-1.15)	0.67 (0.53-0.83)	1.23 (1.02-1.50)

Connolly SJ, NEJM 2009;361:1139-51
Patel MR, NEJM 2011:365:883-91
Granger CB, NEJM 2011;365:981-92
Giugliano RP, NEJM 2013; 369, 2093-2104

Major GI bleeding risk of DOACs *vs.* VKAs: nvAF trials

Study or subgroup		New anticoagulant Events	Total	Warfarin Events	Total	Weight	Risk ratio M-H, random, 95% CI
Upper gastrointestinal bleeding							
1. RE-LY	**Dabi**	103	12091	54	6022	11.0%	0.95 [0.68, 1.32]
2. ROCKET-AF	**Riva**	151	7131	104	7133	12.8%	1.45 [1.13, 1.86]
3. ARISTOTLE	**Apix**	66	9120	85	9081	11.2%	0.77 [0.56, 1.06]
Subtotal (95% CI)			**28342**		**22236**	**34.9%**	**1.03 [0.70, 1.52]**
Total events		320		234			
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 10.26$, df = 2 ($P = 0.006$); $I^2 = 80\%$							
Test for overall effect: $Z = 0.17$ ($P = 0.87$)							
Lower gastrointestinal bleeding							
1. RE-LY		91	12091	18	6022	7.6%	2.52 [1.52, 4.17]
2. ROCKET-AF		49	7131	32	7133	8.7%	1.53 [0.98, 2.39]
3. ARISTOTLE		39	9120	36	9081	8.5%	1.08 [0.69, 1.70]
Subtotal (95% CI)			**28342**		**22236**	**24.8%**	**1.59 [0.99, 2.54]**
Total events		179		86			
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 6.08$, df = 2 ($P = 0.05$); $I^2 = 67\%$							
Test for overall effect: $Z = 1.94$ ($P = 0.05$)							



Gomes-Outes A, Thrombosis 2013; 2013:640723

Rivaroxaban: increased risk of upper GI bleeding
Dabigatran: increased risk of lower GI bleeding
Apixaban GI bleeding not increased

GI bleeding risk of DOACs *vs.* VKAs in the *real-world*: summary of evidence

- Confliciting data from population-based cohort studies
- Dabigatran and risk of major GI bleeding *versus* warfarin:
  - downsized in most real-world studies from US, albeit consistently reported in patients >75 years
  - not reported in European studies(DE 110mg off-label)
- Rivaroxaban and risk of major GI bleeding *versus* warfarin:
  - confirmed in most real world studies, especially in elderly
- Published post-marketing data regarding major GI bleeding with edoxaban not yet available

Graham DJ, Circulation 2015; 131: 157-164
Hernandez I, JAMA Intern Med 2015; 175: 18-24
Chang HY, BMJ 2015; 350: h 1585
Abraham NS, BMJ 2015; 350: h 18571585
Graham DJ, JAMA Circulation 2016; 176: 1662-1671
Yao X, J Am Heart Assoc 2016; 13: 5

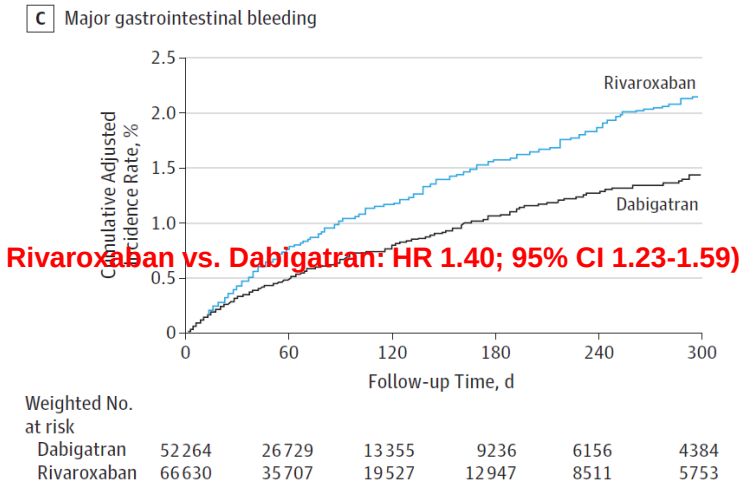
GI Bleeding in the real-world: *head to head studies*

JAMA Intern Med. 2016 Nov 1;176(11):1662-1671. doi: 10.1001/jamainternmed.2016.5954.

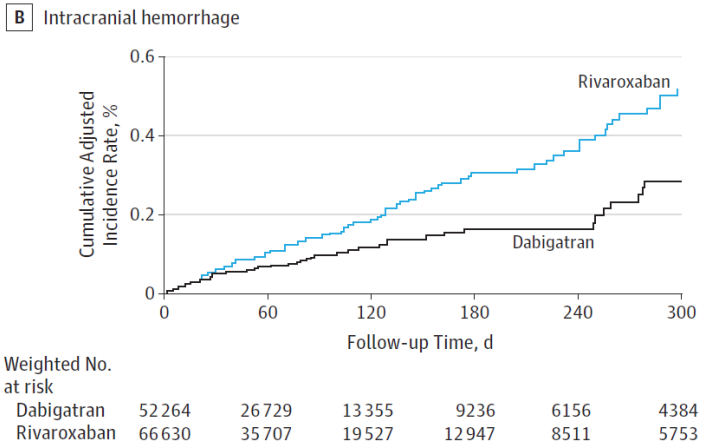
Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation.

Graham DJ[1], Reichman ME[1], Wernecke M[2], Hsueh YH[3], Izem R[3], Southworth MR[4], Wei Y[2], Liao J[2], Goulding MR[1], Mott K[1], Chillarige Y[2], MaCurdy TE[5], Worrall C[6], Kelman JA[6].

Patients with nvAF, age ≥ 65, new users, included in Medicare databaseDabigatran: n=15.524 ; Rivaroxaban n= 66.651
Propensity-score matching



Rivaroxaban vs. Dabigatran: HR 1.40; 95% CI 1.23-1.59)



Graham DJ, *JAMA Intern Med.* 2016;176:1662-1671.

GI Bleeding in the real-world: *head to head studies*

Gastroenterology. 2016 Dec 30. pii: S0016-5085(16)35532-9. doi: 10.1053/j.gastro.2016.12.018. [Epub ahead of print]

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study.

Abraham NS[1], Noseworthy PA[2], Yao X[3], Sangaralingham LR[3], Shah ND[4].

Patients with nvAF, included in OptimumLab Data Wharehouse: DE=17.426 ; Rivaroxaban = 19.201; Apixaban = 6.576)
Propensity-score matching

	Major GI Bleeding
Rivaroxaban vs. Dabigatran (n= 15787, matched 1:1)	1.20 [1.01-1.45]
Apixaban vs. dabigatran (n= 6542, matched 1:1)	0.39 [0.27-0.58]
Apixaban vs. rivaroxaban (n= 6565, matched 1:1)	0.39 [0.22-0.49]

Abraham NE, Gastroenteroloy 2017 (in press)

European Heart Journal Advance Access published February 4, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw069

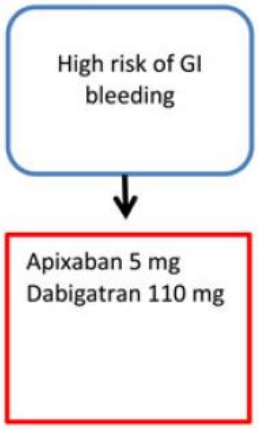
REVIEW

Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Hans-Christoph Diener[1]*, James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

Patients with a high risk of gastrointestinal bleeding



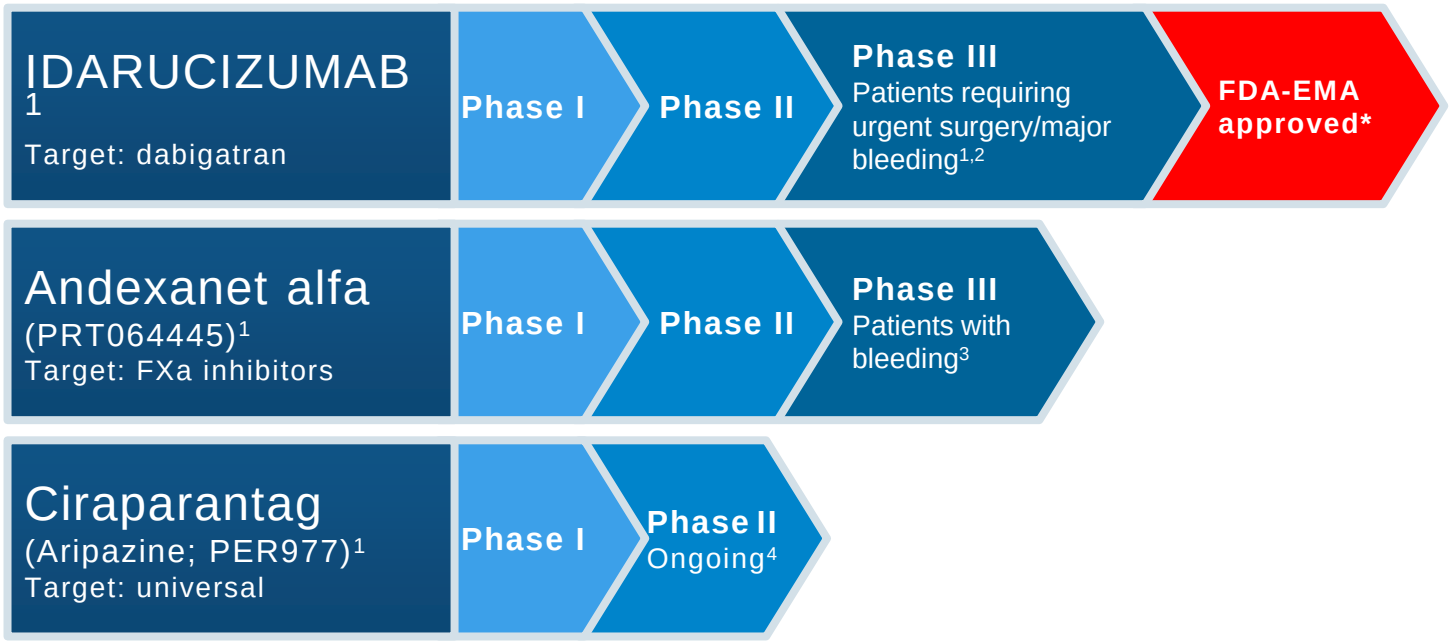
First choice

For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used

Second choice

Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily

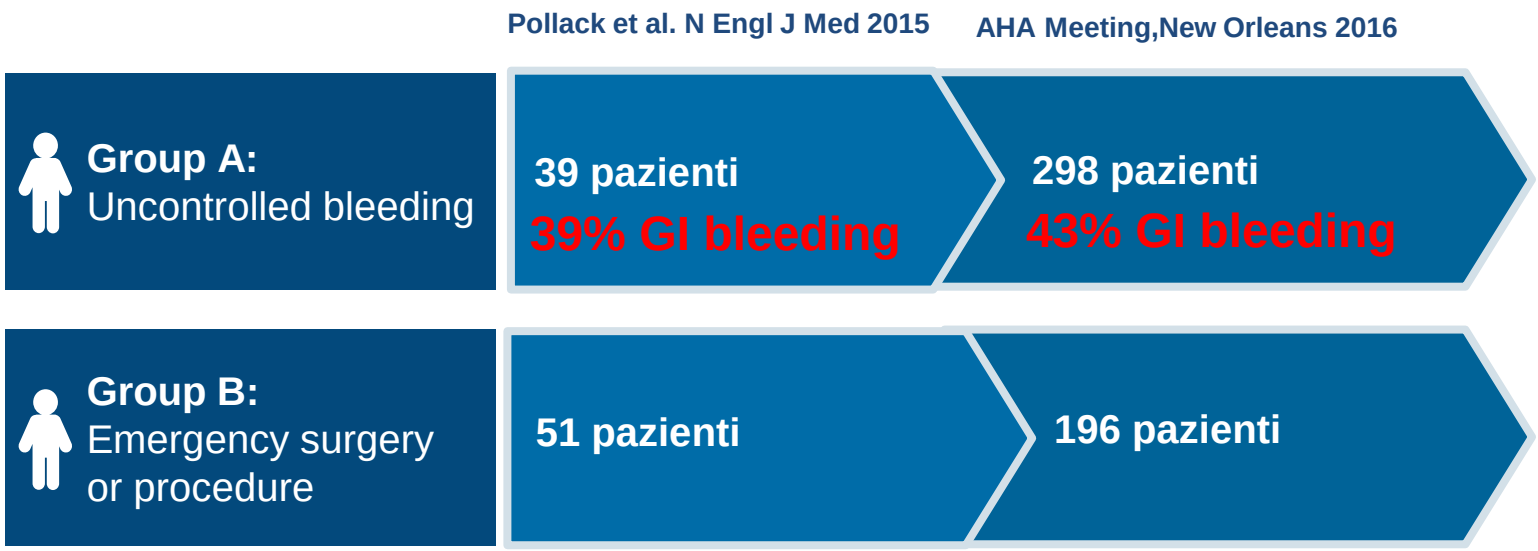
DOAC specific antidotes:



Indications: 1) need for urgent surgery **2) uncontrolled, life-threatening bleeding.**

1. Pollack et al. N Engl J Med 2015; **2.** Pollack et al. Thromb Haemost 2015; **3.** Connolly et al. N Engl J Med 2016; **4.** ClinicalTrials.gov Identifier: NCT02207257

RE-VERSE AD™:


Pollack et al. N Engl J Med 2015
AHA Meeting,New Orleans 2016
Group A:
Uncontrolled bleeding
39 pazienti
39% GI bleeding
298 pazienti
43% GI bleeding
Group B:
Emergency surgery
or procedure
51 pazienti
196 pazienti

Objectives:

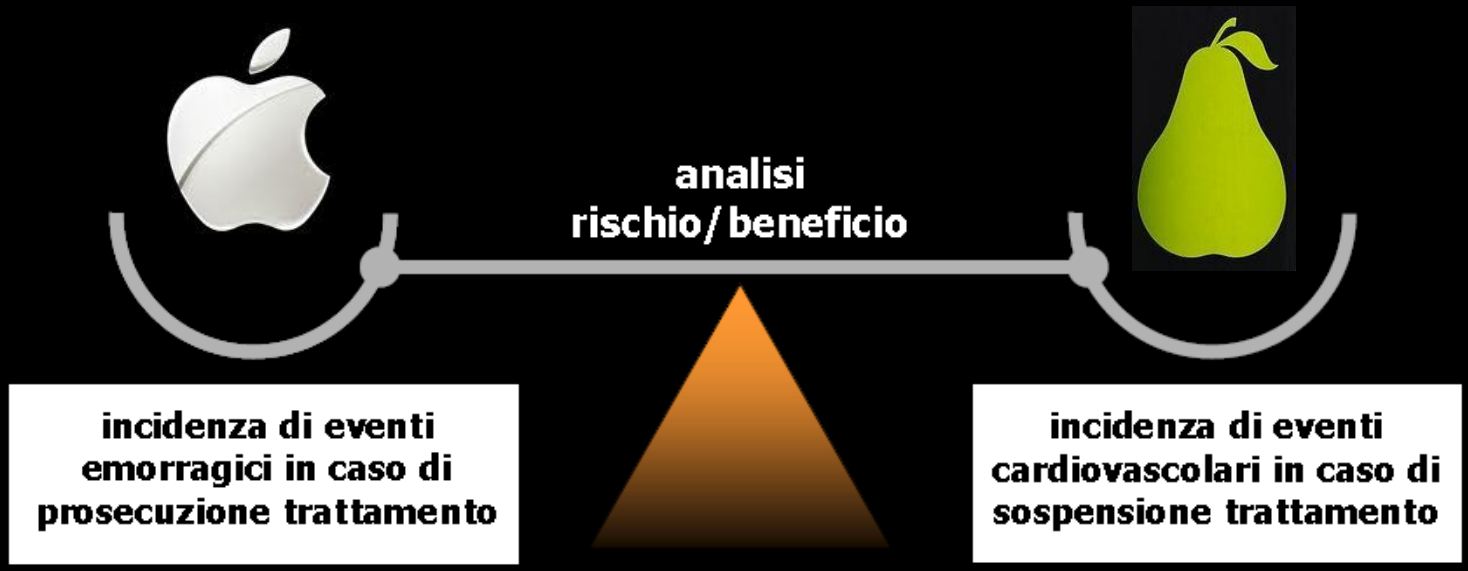
1. Basics on DOACs
2. Management of DOACs for elective endoscopy procedures

NOACs Guidelines for GI Endoscopy

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines
(Veitch A et al., Gut 2016, Endoscopy 2016)

The management of antithrombotic agents in patients undergoing GI endoscopy
(Acosta RD et al., Gastrointest Endosc 2016)

Scelta decisionale:



Evento emorragico GI:

- In genere controllabile
- Outcome spesso favorevole
- Esiti in genere assenti

Evento trombotico CV:

- Non sempre controllabile
- Outcome spesso sfavorevole
- Esiti talvolta permanenti

Scelta decisionale:

Evento emorragico GI:

- In genere controllabile
- Outcome spesso favorevole
- Esiti in genere assenti

Evento trombotico CV:

- Non sempre controllabile
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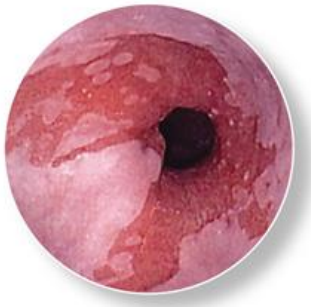
Case scenario 1



♂62 yr, nv-AF
apixaban 5mg bid (morning dose taken)
EGDS for BE surveillance (Praga C2M3)at 9.00am

Question time:

Multiple biopsies taken

Procedure rescheduled with NOAC interruption

Anticoagulants interruption for low-risk procedures

EGD, colonoscopy ± biopsy
(DA) enteroscopy ± biopsy

ERCP without sphincterotomy
EUS without FNA
Barrett ablation
Argon Plasma Coagulation (APC)

VKAs

Warfarin should be continued, but it should be ensured that the international normalised ratio (INR) does not exceed the therapeutic range:

ASGE Guidelines. Gastrointest Endosc 2009
BSG Guidelines. Gut 2008

DOACs

Biopsies on DOACs?

NO safety data

Anticoagulants interruption for low-risk procedures

EGD, colonoscopy ± biopsy
(DA) enteroscopy ± biopsy

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EUS without FNA
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Warfarin should be continued,* *but it should be ensured that the international normalised ratio (INR) does not exceed the therapeutic range:

ASGE Guidelines. Gastrointest Endosc 2009
BSG Guidelines. Gut 2008

DOACs

EHRA recommends to discontinue DOACs 24h before endoscopic biopsies

ASGE suggests continuing DOACs in patients undergoing low-risk procedures

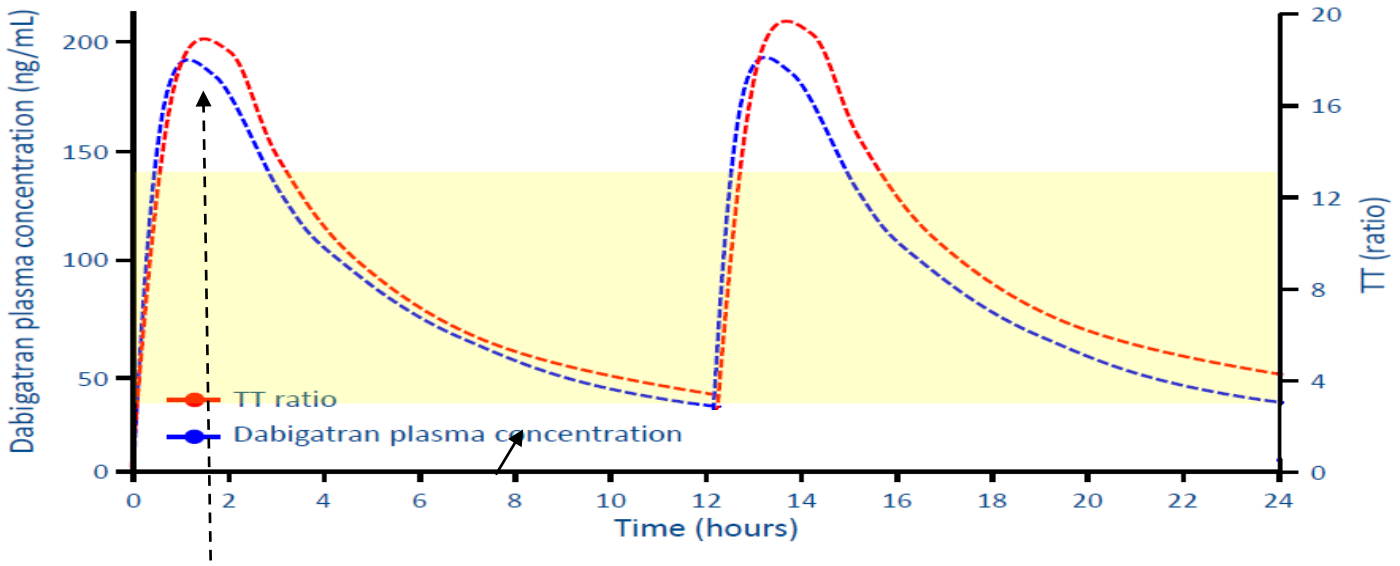
BSG/ ESGE suggest omitting the morning dose of DOACs on the day of the procedure

EHRA Guidelines, Europace 2013
Acosta RD, Gastrointest Endosc 2016
Veitch A, Gut 2016, *in press*

DOACs pharmacodynamics

Dabigatran plasma concentration and effect on coagulation

Gong IY et al. Can J Cardiol 2013: S24-S33



Peak = highest anticoagulation activity = highest risk of bleeding
dabigatran ~2h after ingestion (1-4h for other DOACs)

A relevant bleeding risk is possible for biopsies performed at peak level
Bleeding risk is minimized at trough level

Guidelines

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines

Andrew M Veitch,[1] Geoffroy Vanbiervliet,[2] Anthony H Gershlick,[3] Christian Boustiere,[4] Trevor P Baglin,[5] Lesley-Ann Smith,[6] Franco Radaelli,[7] Evelyn Knight,[8] Ian M Gralnek,[9,10] Cesare Hassan,[11] Jean-Marc Dumonceau[12]

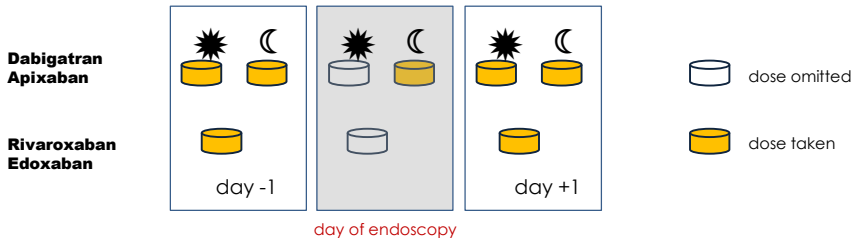
Gut 2016; 65: 374-89

Management DOACs for elective endoscopy:

Low-risk procedures:

- Diagnostic endoscopy, including mucosal biopsy
- Diagnostic push and device assisted enteroscopy
- Diagnostic EUS without FNA
- ERCP + stent placement or biliary dilation without sphincterotomy
- Argon Plasma Coagulation
- Barrett's abation
- Enteral stent deployment (controversial)

- **Omit the morning dose of DOAC on the day of the procedure**
- **Continue DOAC after the procedure (same evening for dabigatran and apixaban)**



Case scenario 2

♂75 yr., nv-AF, previous stroke, hypertension
$CHADS_2$ 5, CrCl 65ml/min,
Rivaroxaban 20mg od
ERCP for CBD stone

Question time:

No doses in the 48 hours before

No doses in the 96 hours before

Case scenario 2

♂75 yr., nv-AF, previous stroke, hypertension
$CHADS_2$ 5, CrCl 65ml/min,
Rivaroxaban 20mg od
ERCP for CBD stone

Question time:

Bridging therapy with LMWH

No bridging

Anticoagulants interruption for high-risk procedures

VKAs

Stop warfarin 5 days before endoscopy
Restart warfarin on the evening of the procedure at usual dose

Bridging therapy with LMWH in high-risk conditions:
-Mechanical valve in mitralic position
-Mechanical valve in any position and recent (<6 months) stroke or TIA
-AF and recent stroke or TIA
-AF and $CHADS_2$ 5-6
-AF and rheumatic valvular heart disease
-Recent VTE (<3 months)
-Trombophilia syndromes

ASGE Guidelines. Gastrointest Endosc 2009; 70; 1060-70
BSG Guidelines. Gut 2008; 57: 1322-29

DOACs

Stop DOACs
No bridging therapy

Considerations on heparin-bridging therapy in patients on DOACs :

- Most DOACs patients, by indication, are not at high-risk for TE events
- Heparin bridging is useless in warfarin pts not at high-risk for TE events (BRIDGE study)
  Douketis JD, New Engl J Med 2015

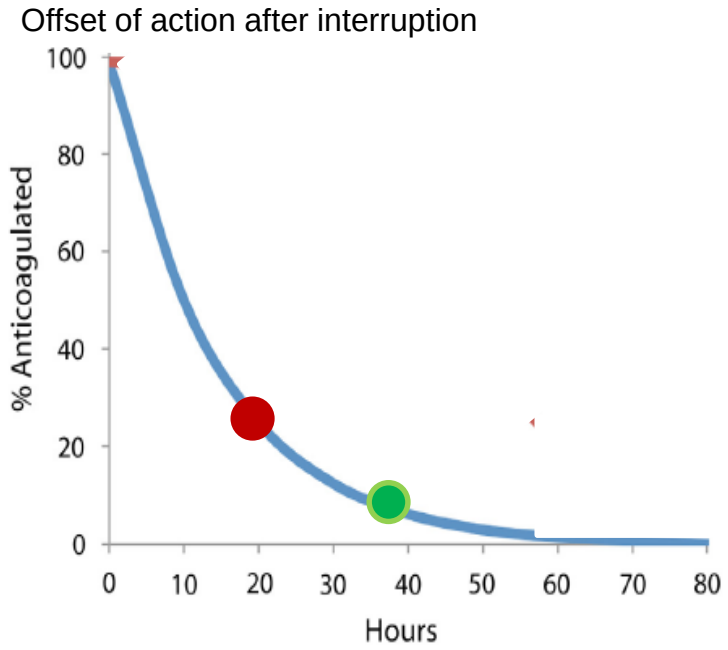
- DOACs have rapid onset and offset of action

- Bridging was harmful in Dresden (rivaroxaban)and Canadian (dabigatran) registries
  Beyern Westendorf J, Blood 2014
  Schulman S, Cirulation 2015

Consideration on DOAC interruption for elective interventional endoscopy (I):

- $t_{1/2}$ half-lives of DOACs is short (<15 hours)
- A modest residual anticoagulation effect at time of surgery/ endoscopy may be acceptable (= warfarin)

25% residual anticoagulant effect after 2 drug half-lives
10%-12% residual anticoagulant effect after 3 drug half-lives



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10%-12% residual anticoagulant effect after 3 drug half-lives

- $t_{1/2}$ half-life is significantly prolonged in case of renal impairment only for dabigatran, that has a dominant (80%) renal exctretion

DOAC interruption according to renal function (EHRA Guidelines):

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Renal Clearance %	80%	35%	25%	50%
Elimination half-life $t_{1/2}$	**12-14h** (normal renal function)	**6-12h**	**8-12h**	**9-12h**
CrCl ≥ 80ml/min	≥ 48h	≥ 48h	≥ 48h	No data
CrCl 50-80ml/min	≥ 72h	≥ 48h	≥ 48h	No data
CrCl 30-50ml/min	≥ 96h	≥ 48h	≥ 48h	No data
CrCl ≤30ml/min	Not indicated	≥ 48h	≥ 48h	No data

EHRA Guidelines, Europace 2013; 15: 625-651

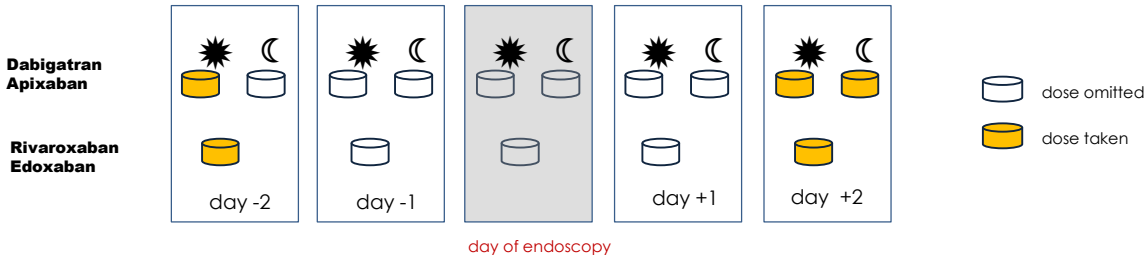
Management DOACs for elective endoscopy:

High-risk procedures:

- Polypectomy
- All other operative procedures non included in low-risk category

- Evaluation of CrCl within 1-4 weeks [Dabigatran]
- Stop DOACs
- NO bridging theapry

- **Last dose intake ≥48 hours prior the procedure**
- **DOAC resumption 48 hours after the procedure**



Consider:

- last dose intake 72-96 hours prior the procedure for patients on dabigatran with renal impairment (CrCl 30-50mL/min)
- resumption after 72-96 hours for procedures with significant risk of delayed bleeding (large EMR, ESD)

Communication from the ASGE Standards of Practice Committee

GUIDELINE

The management of antithrombotic agents for patients undergoing GI endoscopy

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

TABLE 6. Periprocedural management of dabigatran (Pradaxa)[53]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before procedure	
			Moderate procedural bleeding risk (2-3 half-lives)	High procedural bleeding risk (4-5 half-lives)
>80	1.25-3	13 (11-22)	1-1.5 days	2-3 days
50-80	1.25-3	15 (12-34)	1-2 days	2-3 days
30-49	1.25-3	18 (13-23)	1.5-2 days	3-4 days
≤29	1.25-3	27 (22-35)	2-3 days	4-6 days

TABLE 7. Periprocedural management of apixaban (Eliquis)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>60	1-3	1 or 2
30-59	1-3	3
15-29	1-3	4

TABLE 9. Periprocedural management of edoxaban (Savaysa)[99]

Creatinine clearance (mL/min)	Time to onset of action (h)	Half-life (h)	Timing of discontinuation before high-risk procedure (h)
>60	1-2	8.6	At least 24
30-60	1-2	9.4	At least 24
15-30	1-2	16.9	At least 24
≤15	1-2	No data	No data

TABLE 8. Periprocedural management of rivaroxaban (Xarelto)[54]

Creatinine clearance (mL/min)	Time to onset of action (h)	Timing of discontinuation before high-risk endoscopic procedure (day)
>90	2-4	≥1
60-90	2-4	2
30-59	2-4	3
15-29	2-4	4

Management DOACs for outpatient routine procedures:

The Management of Anticoagulants in the Periendoscopic Period for Patients with Atrial Fibrillation: A Decision Analysis

Lauren B. Gerson, MD, MSc, George Triadafilopoulos, MD, Brian F. Gage, MD, MSc

Am J Med 2004; 116: 451-9

Hold warfarin strategy cost effective for screening colonoscopy, assuming that polyps would be removed in 35% of examinations

- **Colonoscopy = high probability of operative procedure = HR procedure**
- **Upper GI endoscopy = low probability of operative procedure = LR procedure**

Periendoscopic management of DOACS: *real-life data*

Periendoscopic Management of Direct Oral Anticoagulants: A Prospective Cohort Study

NCT02734316

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Methods:

- Observational study
- Patients: All consecutive in- and outpatients on DOACs for any therapeutic indication scheduled for elective GI endoscopy, either diagnostic or therapeutic
- Data collection:
  - bespoke database, accessed by site specific, password protected website
  - demographic and clinical data (risk stratification)
  - data on DOAC management (interruption, resumption, timing)
  - early (intraprocedural) AEs
  - delayed (30-days) AEs

Study aim:

- To assess outcomes (bleeding and TE risk) of GI endoscopies in patients on DOACs:

  - major bleeding [IHTS criteria]
- To provide a «snapshot» of DOAC management in the real-world
- To evaluate bleeding outcomes for procedures performed according to ESGE guidelines (validation)

Preliminary results:

Feb 2017: 324 patients (mean age 74.7±10.8; 87% nvAF, 13% DVT/PE)
199 LR, 125 HR procedures

[69 snare polypectomies, 27 EMR (26 colon, 1 gastric), 10 biliary sphyncterotomy, 8 EUS-FNA, 3 ESD (2 gastric, 1 colon), 7 mixed indications]

1. ESGE Guideline adherence in HR: 71%
2. Bridging with LWMH: 18% pre-procedure, 11% post-procedure
3. Intraprocedural bleeding (haemostasis required):

	LR procedures	HR procedures
Overall	0.7%	8.2%
ESGE guidelines	0%	6.9%

4. 30 days-AEs: 16 [7 major bleeding, 7 minor bleeding, 1 TIA, 1 haematuria]

	LR procedures	HR procedures
Overall	0%	4.8%
ESGE guidelines	0%	7.6%

L’aderenza alle linee guida ESGE è efficace nel minimizzare il rischio sia emorragico che tromboembolico nei pazienti sottoposti ad endoscopia digestiva

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GI Bleeding in the real-world: *head to head studies*

Gastroenterology. 2016 Dec 30. pii: S0016-5085(16)35532-9. doi: 10.1053/j.gastro.2016.12.018. [Epub ahead of print]

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study.

Abraham NS[1], Noseworthy PA[2], Yao X[3], Sangaralingham LR[3], Shah ND[4].

Patients with nvAF, included in OptimumLab Data Wharehouse: DE=17.426 ; Rivaroxaban = 19.201; Apixaban = 6.576)
Propensity-score matching

	Major GI Bleeding
Rivaroxaban vs. Dabigatran (n= 15787, matched 1:1)	1.20 [1.01-1.45]
Apixaban vs. dabigatran (n= 6542, matched 1:1)	0.39 [0.27-0.58]
Apixaban vs. rivaroxaban (n= 6565, matched 1:1)	0.39 [0.22-0.49]

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8^ edizione
TopTen
IN GASTROENTEROLOGIA

European Heart Journal Advance Access published February 4, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw069

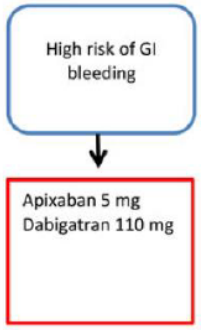
REVIEW

Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Hans-Christoph Diener[1]*, James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

Patients with a high risk of gastrointestinal bleeding



First choice

For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used

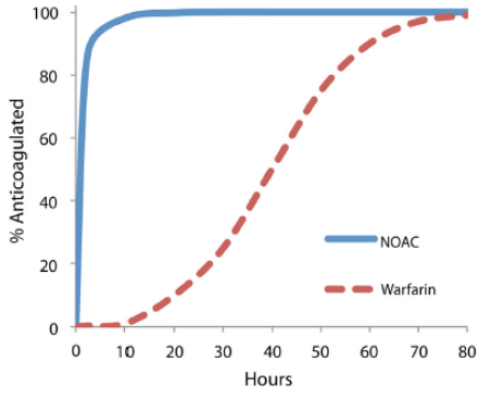
Second choice

Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily

DOACs: Pharmacodynamic/Kinetic properties

- Faster onset and offset of action than VKAs
- More predictable pharmacodynamic/kinetic properties than VKAs

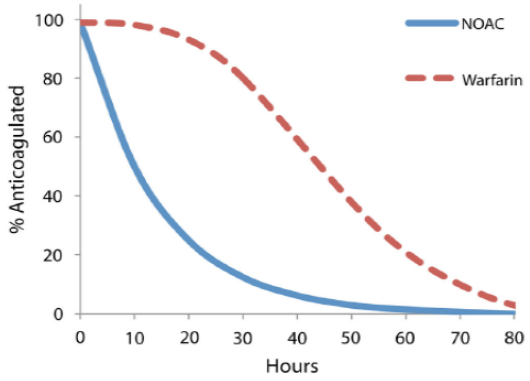
Onset of action:



Anticoagulant activity reached:

DOACs: 1-3 hours (single dose)
VKAs: days (multiple doses)

Offset of action:



Anticoagulant activity restored:

DOACs: within 24-48 hours after withdrawal
VKAs: days

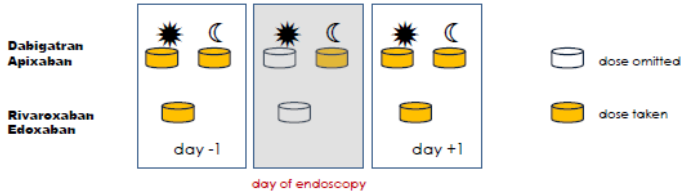
Desai J, Gastrointest Endosc 2013;78:227-39

Management DOACs for elective endoscopy:

Low-risk procedures:

- Diagnostic endoscopy, including mucosal biopsy
- Diagnostic push and device assisted enteroscopy
- Diagnostic EUS without FNA
- ERCP + stent placement or biliary dilation without sphincterotomy
- Argon Plasma Coagulation
- Barrett's abation
- Enteral stent deployment (controversial)

- **Omit the morning dose of DOAC on the day of the procedure**
- **Continue DOAC after the procedure (same evening for dabigatran and apixaban)**



DOAC interruption according to renal function (EHRA Guidelines):

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Renal Clearance %	80%	35%	25%	50%
Elimination half-life $t_{1/2}$	**12-14h** (normal renal function)	**6-12h**	**8-12h**	**9-12h**
CrCl ≥ 80ml/min	≥ 48h	≥ 48h	≥ 48h	No data
CrCl 50-80ml/min	≥ 72h	≥ 48h	≥ 48h	No data
CrCl 30-50ml/min	≥ 96h	≥ 48h	≥ 48h	No data
CrCl ≤30ml/min	Not indicated	≥ 48h	≥ 48h	No data

EHRA Guidelines, Europace 2013; 15: 625-651

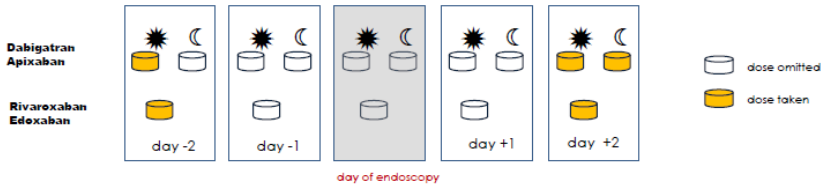
Management DOACs for elective endoscopy:

High-risk procedures:

- Polypectomy
- All other operative procedures non included in low-risk category

- Evaluation of CrCl within 1-4 weeks [Dabigatran]
- Stop DOACs
- NO bridging theapry

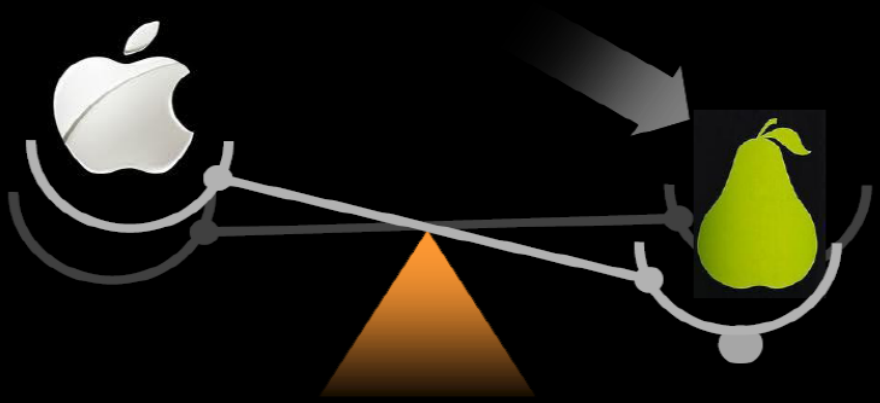
- **Last dose intake ≥48 hours prior the procedure**
- **DOAC resumption 48 hours after the procedure**



Consider:

- last dose intake 72-96 hours prior the procedure for patients on dabigatran with renal impairment (CrCl 30-50mL/min)
- resumption after 72-96 hours for procedures with significant risk of delayed bleeding (large EMR, ESD)

Scelta decisionale:



scelta decisionale

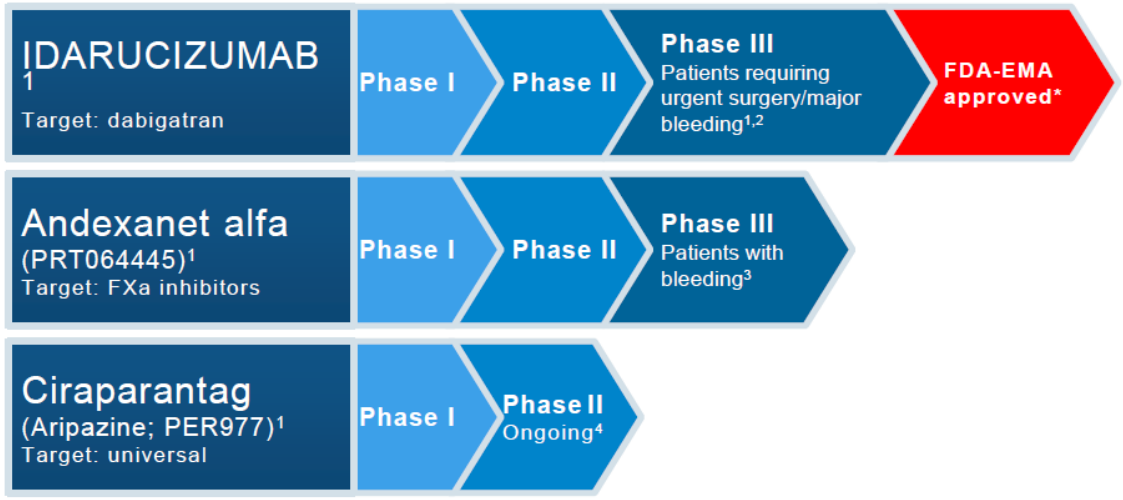
Evento emorragico GI:

- In genere controllabile
- Outcome spesso favorevole
- Esiti in genere assenti

Evento trombotico CV:

- Non sempre controllabile
- Outcome spesso sfavorevole
- Esiti talvolta permanenti

DOAC specific antidotes:



Indications: 1) need for urgent surgery **2) uncontrolled, life-threatening bleeding.**

Management DOACs for outpatient routine procedures:

The Management of Anticoagulants in the Periendoscopic Period for Patients with Atrial Fibrillation: A Decision Analysis

Lauren B. Gerson, MD, MSc, George Triadafilopoulos, MD, Brian F. Gage, MD, MSc

Am J Med 2004; 116: 451-9

Hold warfarin strategy cost effective for screening colonoscopy, assuming that polyps would be removed in 35% of examinations

- **Colonoscopy = high probability of operative procedure = HR procedure**
- **Upper GI endoscopy = low probability of operative procedure = LR procedure**

L’aderenza alle linee guida ESGE è efficace nel minimizzare il rischio sia emorragico che tromboembolico nei pazienti sottoposti ad endoscopia digestiva