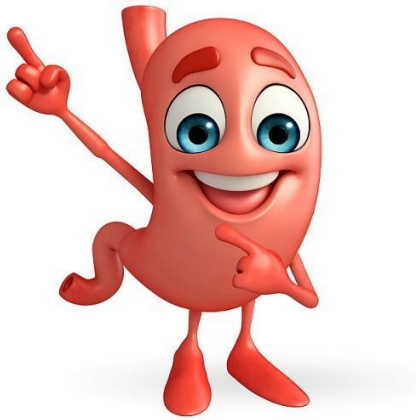
SERVIZIO SANITARIO NAZIONALE - REGIONE PIEMONTE

Azienda Sanitaria Locale “Città di Torino”

Chiusura percutanea dell’auricola sinistra: dalle LINEE GUIDA alla PRATICA CLINICA

IL PARERE DEL GASTROENTEROLOGO

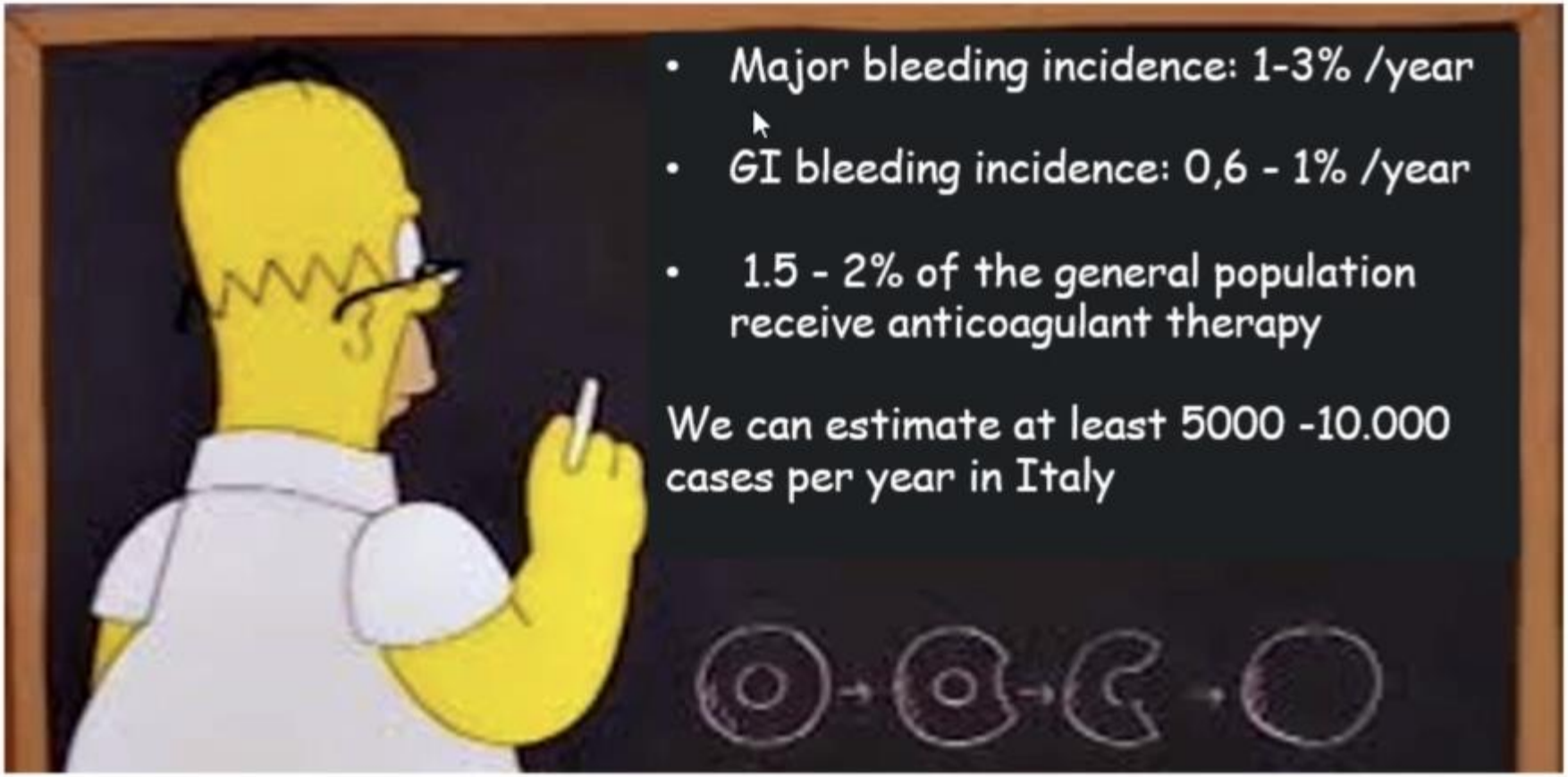


Dott.ssa Antonietta Garripoli

SC Gastroenterologia Ospedale San Giovanni Bosco

ASL Città di Torino

Burden of GI bleeding during long-term anticoagulant therapy

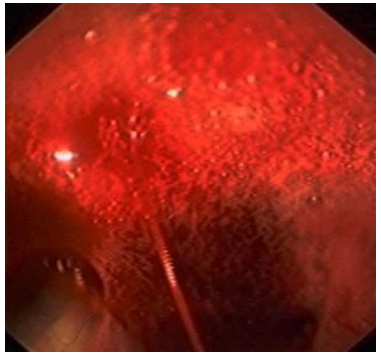


Coleman CI, Int J Clinical Practice 2012

Terapia anticoagulante nella FA: rischio di emorragia digestiva

- Nella popolazione generale = 0.1% anno
- Fibrillazione atriale = 0.3-0.5% anno
- Warfarin = x 3

Warfarin + ASA = x 2



Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies

Jay Desai[1]; Jennifer M. Kolb[2]; Jeffrey I. Weitz[3]; James Aisenberg[2]

Thrombosis and Haemostasis 110.2/2013

Sanguinamento occulto - oscuro

Sanguinamento occulto: sangue occulto feci positivo con o senza anemia microcitica

Sanguinamento oscuro: sanguinamento presente in assenza di una causa documentabile dopo

- colonscopia
- gastroscopia
- valutazione radiologica convenzionale del piccolo intestino (Rx clisma del tenue, entero TC, entero RM)

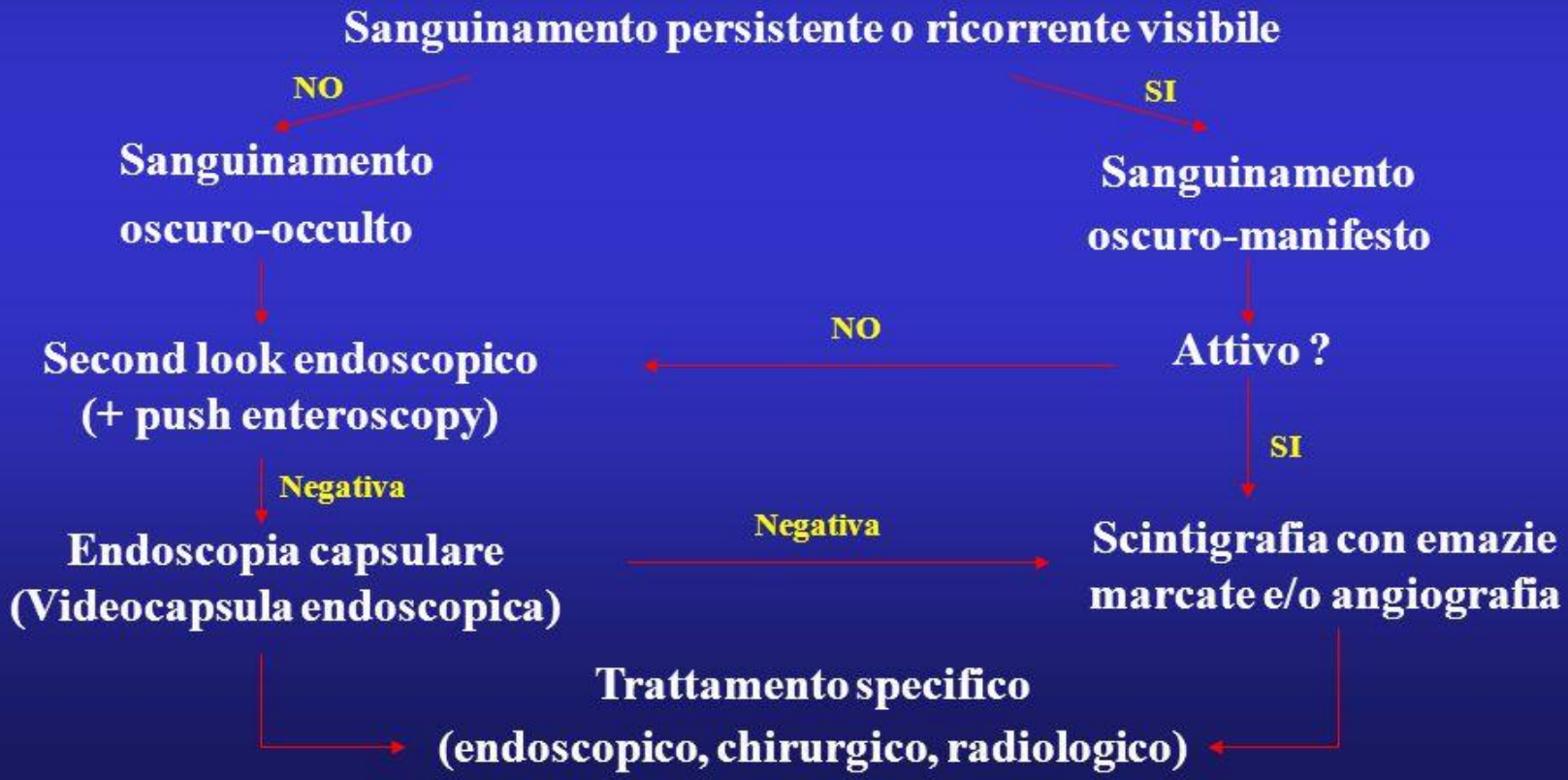
5% dei sanguinamenti digestivi

75% di origine dal piccolo intestino

EMORRAGIA DIGESTIVA

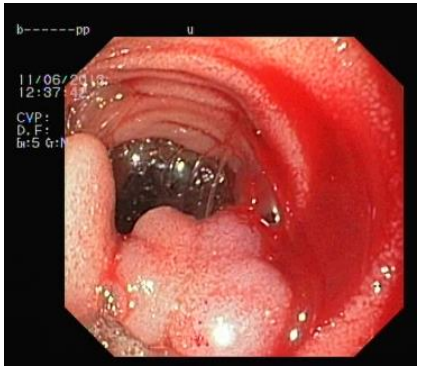
Sanguinamento oscuro

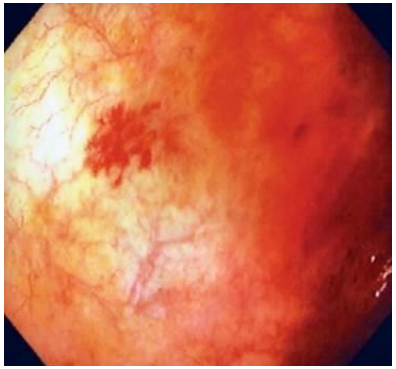
- **Sanguinamento di origine ignota che persiste o recidiva dopo endoscopia (EGDS e/o Pancolonscopia) iniziale negativa**

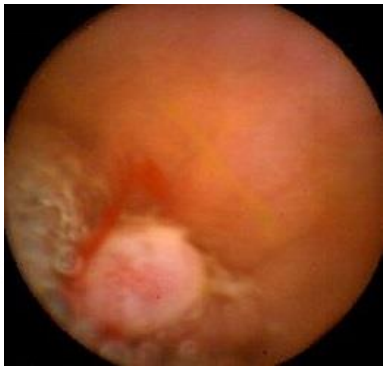


SANGUINAMENTO DALL'INTESTINO TENUE

- Lo sviluppo di tecniche endoscopiche per il piccolo intestino (videocapsula ed enteroscopia a singolo o doppio pallone) ha consentito di documentare numerose cause di sanguinamento acuto e cronico



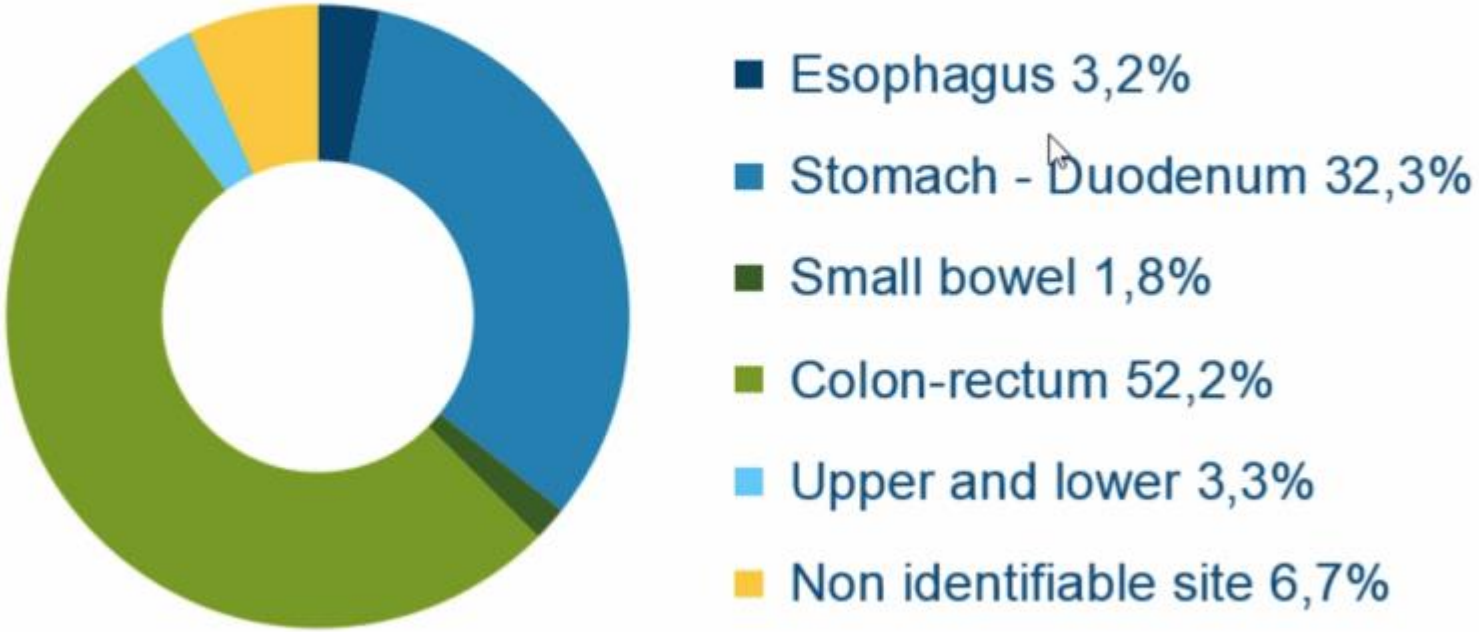




Who is most at risk?	HR (95% CI)	P value
Age (for each 5-ys increase)	1.11 (1.06–1.17)	<0.0001
Smoking history (current or former)	1.37 (1.16–1.62)	0.0002
Comorbidity		
• Hypertension (DBP, each 5mmHg decrease to <80mmHg)	1.10 (1.05–1.16)	0.0002
• Liver disease		
• Creatinine clearance (for each 5U decrease to 60ml/min)	1.06 (1.01–1.12)	0.015
• Malignancy		
• Diabetes		
Anemia at baseline	1.70 (1.41–2.04)	<0.0001
Previous GI bleeding	2.11 (1.62–2.76)	<0.0001
Concomitant medications		
• Low dose ASA	1.47 (1.26–1.72)	<0.0001
• Antiplatelet (other than ASA)	1.50 (1.02–2.21)	0.039

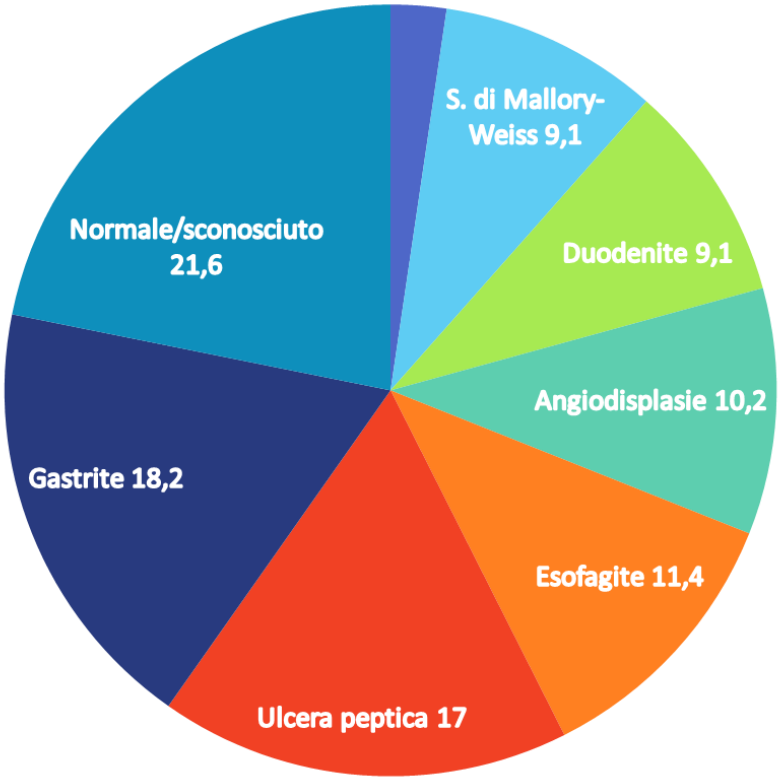
Sherwood et al. GI Bleeding in the ROCKET AF Trial. JACC 2015

Bleeding site

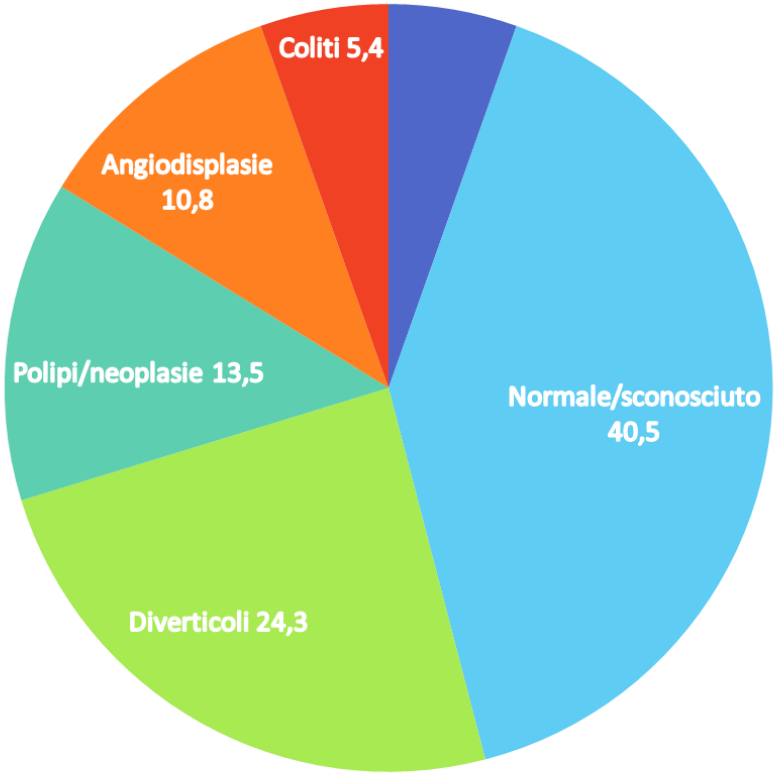


Qureshi W, Restarting Anticoagulation and Outcomes After Major Gastrointestinal Bleeding in Atrial Fibrillation. AJC 2014

CAUSE DI SANGUINAMENTO G-E IN CORSO DI TERAPIA CON WARFARIN



SUPERIORE



INFERIORE

Desai J, et al. Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies.Thrombosis and Haemostasis 110.2/2013

Endoscopic findings compared to not anticoagulated patients

	Patients taking anticoagulants	Patients not taking anticoagulants
Peptic ulcers	45%	59.4%
Gastric/duodenal erosions	10.8%	7.1%
Varices	-	13.9%
Benign and malignant tumors	7.2%	2.8%
Mallory-Weiss tears	0.9%	5%
Vascular lesions, Dieulafoy lesions	3.6%	0.9%
Other diagnosis	0.9%	2.8%
No identifiable source	29.7%	5.1%

Thomopoulos KC et al. AUGIB in anticoagulated patients, WJG 2015

Endoscopic findings according to concomitant NSAID therapy

	Previous NSAID use	No NSAID use
Peptic ulcers	**74.3%**	**32.9%**
Gastric/duodenal erosions	8.6%	11.8%
Benign and malignant tumors	5.7%	7.9%
Vascular lesions, Dieulafoy lesions	5.7%	2.6%
No identifiable source	5.7%	40.8%

Thomopoulos KC et al. AUGIB in anticoagulated patients, WJG 2015

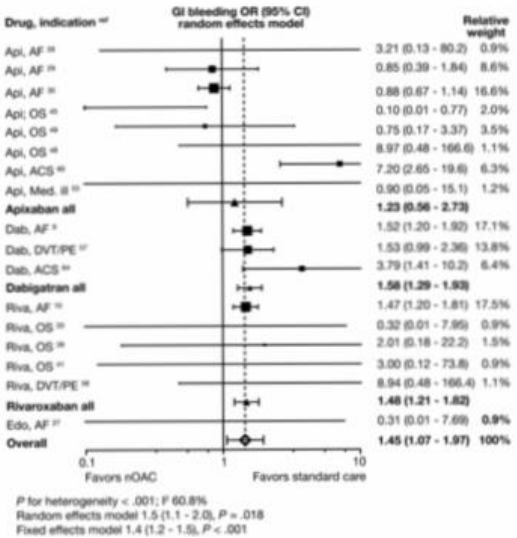
Bleeding risk according to anticoagulant agent

Boston Scientific

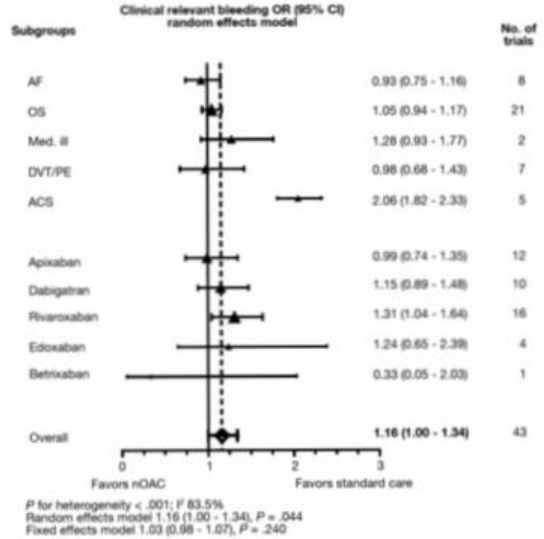
Gastroenterology. 2013 Jul;145(1):105-112.e15. doi: 10.1053/j.gastro.2013.02.041. Epub 2013 Mar 5.

New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis.

Holster IL[1], Valkhoff VE, Kuipers EJ, Tjwa ET.



Forrest plot of GIB with subgroup analysis by drug

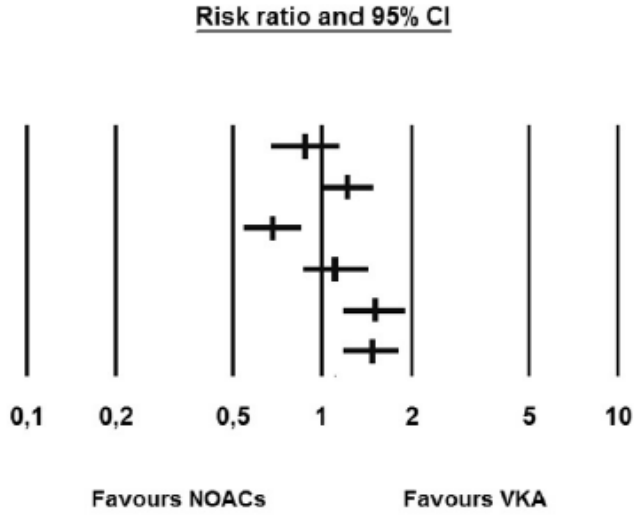


Forrest plot of clinically relevant bleeding summarized by indication and by drug

EDUCARE

Rischio di emorragia digestiva: nuovi anticoagulanti

Study name	Subgroup within study	Statistics for each study				Events / Total	
		Risk ratio	Lower limit	Upper limit	p-Value	NOAC	VKA
ARISTOTLE	apixaban	0,879	0,677	1,140	0,331	105 / 9120	119 / 9081
ENGAGE	edoxaban 60mg	1,221	1,011	1,475	0,038	232 / 7012	190 / 7012
ENGAGE	edoxaban 30 mg	0,680	0,545	0,848	0,001	129 / 7002	190 / 7012
RELY 110mg	dabigratan 110 mg	1,110	0,869	1,417	0,404	133 / 6015	120 / 6022
RELY 150mg	dabigratan 150 mg	1,503	1,197	1,888	0,000	182 / 6076	120 / 6022
ROCKET AF	rivaroxaban	1,464	1,196	1,793	0,000	224 / 6958	154 / 7004



B

NOA: Rischio di emorragia aumentato rispetto al warfarin

Short Report

Impact of new oral anticoagulants on gastrointestinal bleeding in atrial fibrillation: A meta-analysis of interventional trials

Lorenzo Loffredo*, Ludovica Perri, Francesco Violi

Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy

And in real-life settings?

Outcome	Dabigatran vs. Warfarin	Apixaban vs. Warfarin	Rivaroxaban vs. Warfarin
	Favors dabigatran / Favors warfarin	Favors apixaban / Favors warfarin	Favors rivaroxaban / Favors warfarin
Major bleeding events[a]	0.67 (0.60-0.76)	0.52 (0.41-0.67)	1.00 (0.89-1.12)
Intracranial bleeding	0.47 (0.35-0.65)	0.83 (0.52-1.34)	0.74 (0.54-1.00)
Major GI bleeding	1.17 (1.04-1.32)	0.82 (0.63-1.06)	1.00 (0.87-1.16)

Outcome	Dabigatran vs. Apixaban	Dabigatran vs. Rivaroxaban	Apixaban vs. Rivaroxaban
	Favors dabigatran / Favors apixaban	Favors dabigatran / Favors rivaroxaban	Favors apixaban / Favors rivaroxaban
Major bleeding events[a]	1.29 (0.99-1.69)	0.67 (0.58-0.78)	0.52 (0.40-0.68)
Intracranial bleeding	0.57 (0.33-0.98)[b]	0.54 (0.43-0.96)[b]	1.13 (0.66-1.93)
Major GI bleeding	1.43 (1.09-1.88)	1.17 (0.99-1.38)	0.82 (0.62-1.08)

Adeboyeje G *et al*. *JMCP* 2017;23(9):968-78

EDUCARE

Rischio di emorragia digestiva: nuovi anticoagulanti
DOSE DIPENDENTE

Studio/ farmaco	RELY/ Dabigatran			ROCKET/ Rivaroxaban		ARISOTLE / Eliquis		ENGAGE/ Edoxaban		
dose(mg)	150 x2	110 x2	warf	20mg	warf	5x2	warf	60	30	warf
% paz /year	1.51	1.12	1.02	2.0	1.24	0.7	0.86	1.51	0.83	1.23

Perché sanguinamento intestinale nei NOA?

•Erosioni gastriche e coliche sono presenti nei soggetti sani (5-15%) Gli anticoaguanti diretti attraversano in forma attiva in tratto gastro intestinale e sono eliminati con le feci

•Ciò vale anche per il Dabigatran etexilato (profarmaco) che viene convertito in Dabigatran a livello intestinale dalle esterasi intestinali (2/3)

•La quantità di farmaco attivo nel lume intestinale dipende dalla biodisponibilità, interazioni farmacologiche (P-Glicoprotein competitors)

Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies

Jay Desai[1]; Jennifer M. Kolb[2]; Jeffrey I. Weitz[3]; James Aisenberg[2]

Thrombosis and Haemostasis 110.2/2013

Antiplatelet agents and/or anticoagulants are not associated with worse outcome following nonvariceal upper gastrointestinal bleeding

Elvira Manuela Costa Moreira Teles-Sampaio1, Luís Araújo Azevedo Maia1, Paulo Sérgio Durão Salgueiro1, Ricardo Jorge Marcos-Pinto1,
Mário Jorge Dinis-Ribeiro2 and Isabel Maria Teixeira de Carvalho Pedroto1,3

Rev Esp Enferm Dig
2016, Vol. 108, N.º 11, pp. 703-708

- **Adverse outcomes were not associated with antithrombotic use.**

- **The management of nonvariceal upper gastrointestinal bleeding constitutes a challenge to clinical performance optimization and clinical cooperation.**

Controindicazioni alla terapia anticoagulante orale: il punto di vista del gastroenterologo

PATOLOGIE G-E AD ALTO RISCHIO DI SANGUINAMENTO

PATOLOGIE CON ALTO RISCHIO DI MORTALITA' IN CASO DI SANGUINAMENTO

SANGUINAMENTO OSCURO OCCULTO

Controindicazioni alla terapia anticoagulante orale: il punto di vista del gastroenterologo

- Pazienti affetti da patologie ad elevato rischio emorragico
  - Cirrosi epatica con ipertensione portale
  - Malattie infiammatorie croniche intestinali
  - Anamnesi di ulcere recidivanti helicobacter pylori negative
  - Angiodisplasie digiuno-ileali diffuse
  - Episodi di sanguinamento gastrointestinale occulto
- Pazienti che necessitano di frequenti esami endoscopici operativi
  - Poliposi Adenomatosa Familiare ed altre poliposi
  - Stenosi flogistiche

Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study.
Cerini et al
Hepatology. 2015 Aug;62(2):575-83. doi: 10.1002/hep.27783. Epub 2015 Apr 27.

CONCLUSIONS:

Factors that impact the outcome of UGIB in patients under AT are degree of multiorgan failure and comorbidity, but not AT itself.

VALUTAZIONE RISCHIO EMORRAGICO
SCORE DI RISCHIO
PAZIENTI IN TERAPIA ANTICOAGULANTE

- VTE-BLEED SCORE (tromboembolie venose)
- IMPROVE BLEEDING SCORE (tromboembolie venose)
- HAS-BLED SCORE (fibrillazione atriale)

Who needs to avoid anticoagulation??

HAS-BLED

Points			Definition
1	H	Hypertension	Sys BP > 160
1 or2 *(1pt each)*	A	Abnormal Renal and/or liver function	dialysis/transplant cirrhosis/T. Bili 2x or AST/ALT 3x normal
1	S	Stroke	
1	B	Bleeding	previous bleed/predisposition
1	L	Labile INR	< 60% in therapeutic range
1	E	Elderly (> 65 yrs)	
1 or2 *(1pt each)*	D	Drugs or alcohol excess	antiplatelet or NSAID's

A score of ≥ 3 is considered "high risk"
ESC recommends "caution" using warfarin[1]

[1]ESC Guidelines for the management of atrial fibrillation, 2011

Calculation of Rockall Score
High risk score > 5 Low risk score ≤ 5[1]

Variable	Score			
	0	1	2	3
Age	<60	60-79	>80	
Shock	No shock SBP≥100 PR<100	Tachycardia SBP≥100 PR≥100	Hypotension SBP≤100	
Co Morbidity	No major Co-morbidity		Cardiac Failure, IHD, any major co-morbidity	Renal failure, liver failure disseminated malignancy
Diagnosis	Mallory-Weiss tear, no lesion identified, no SRH or blood	All other diagnosis	Malignancy of upper GI tract	
Major SRH	None or dark spot		Blood in upper GI tract, adherent clot, visible or spurting vessel	

SBP = systolic blood in mmHg PR = pulse rate IHD=Ischaemic heart Disease
GI= gatrointestinal SRH= Stigmata recent Haemorrhage

1. Church NI, Palmer KR (2001). *Eur J Gastroenterol Hepatol* 13:1149–52.

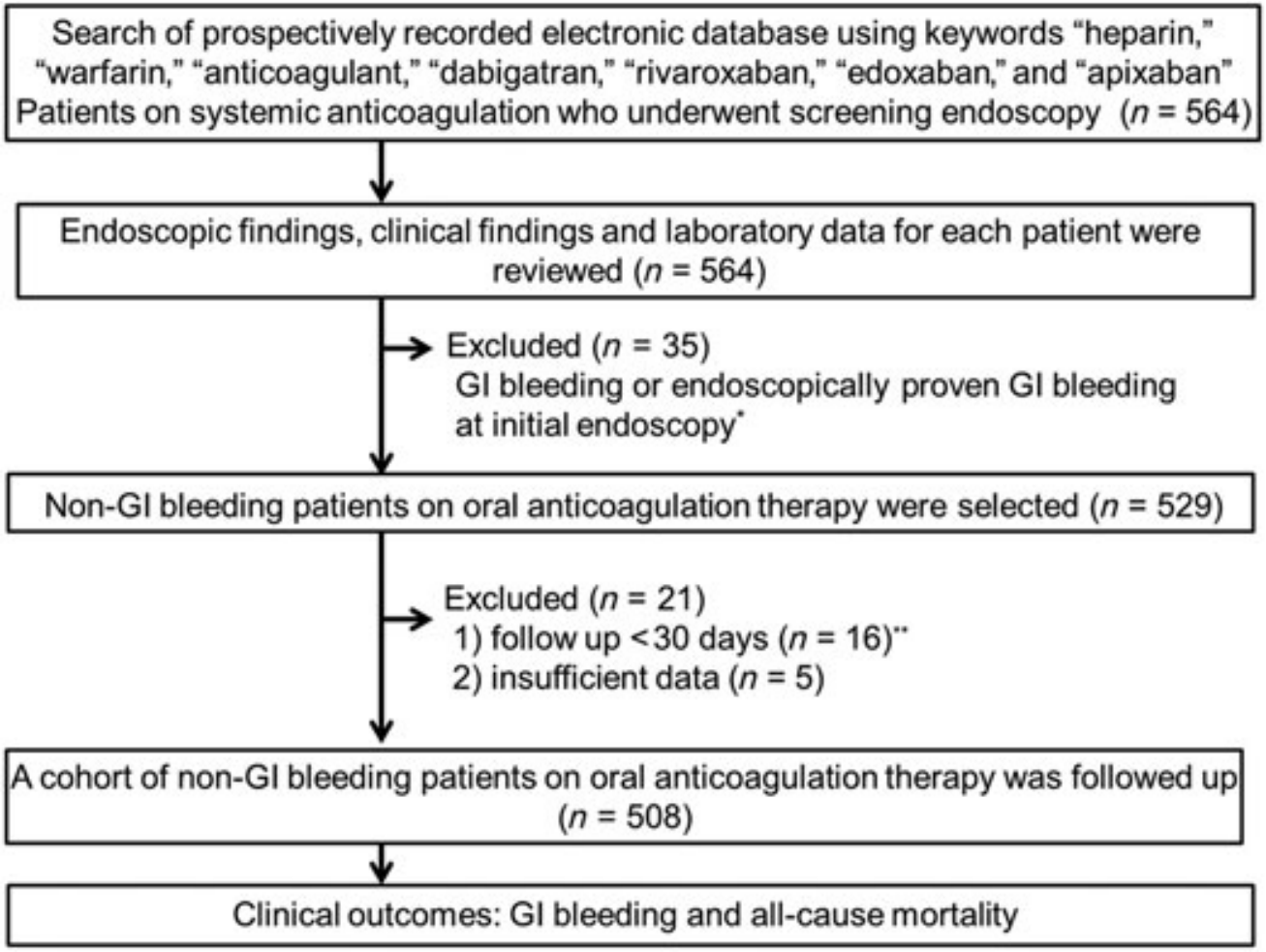
B Rockall Score

		Variable	Points
Complete Rockall Score	Clinical Rockall Score	Age	
		<60 yr	0
		60–79 yr	1
		≥80 yr	2
		Shock	
		Heart rate >100 beats/min	1
		Systolic blood pressure <100 mm Hg	2
		Coexisting illness	
		Ischemic heart disease, congestive heart failure, other major illness	2
		Renal failure, hepatic failure, metastatic cancer	3
		Endoscopic diagnosis	
		No lesion observed, Mallory–Weiss tear	0
		Peptic ulcer, erosive disease, esophagitis	1
		Cancer of upper GI tract	2
		Endoscopic stigmata of recent hemorrhage	
		Clean base ulcer, flat pigmented spot	0
		Blood in upper GI tract, active bleeding, visible vessel, clot	2

New predictive model for acute gastrointestinal bleeding in patients taking oral anticoagulants: A cohort study

Akira Shimomura,* Naoyoshi Nagata,* Takuro Shimbo,† Toshiyuki Sakurai,* Shiori Moriyasu,* Hidetaka Okubo,* Kazuhiro Watanabe,* Chizu Yokoi,* Junichi Akiyama* and Naomi Uemura‡

*Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, †Clinical Research and Informatics, Ohta Nishinouchi Hospital, Koriyama, and ‡Department of Gastroenterology and Hepatology, National Center for Global Health andMedicine, Kohnodai Hospital, Chiba, Japan



Journal of Gastroenterology and Hepatology 33 (2018) 164–

Table 2 Clinical outcomes in the patient cohort (n = 508)

Gastrointestinal bleeding episode	42 (8.3%)
Upper/lower/middle gastrointestinal tract	18 (42.8%)/21 (50.0%)/3 (7.1%)
Follow-up period, months	31.4 (19.8–57.7)
All-cause deaths	59 (11.6%)
Follow-up period, months	32.4 (21.9–59.8)

Notes: Data are presented as the median (interquartile range) or the number (proportion, %) as appropriate.

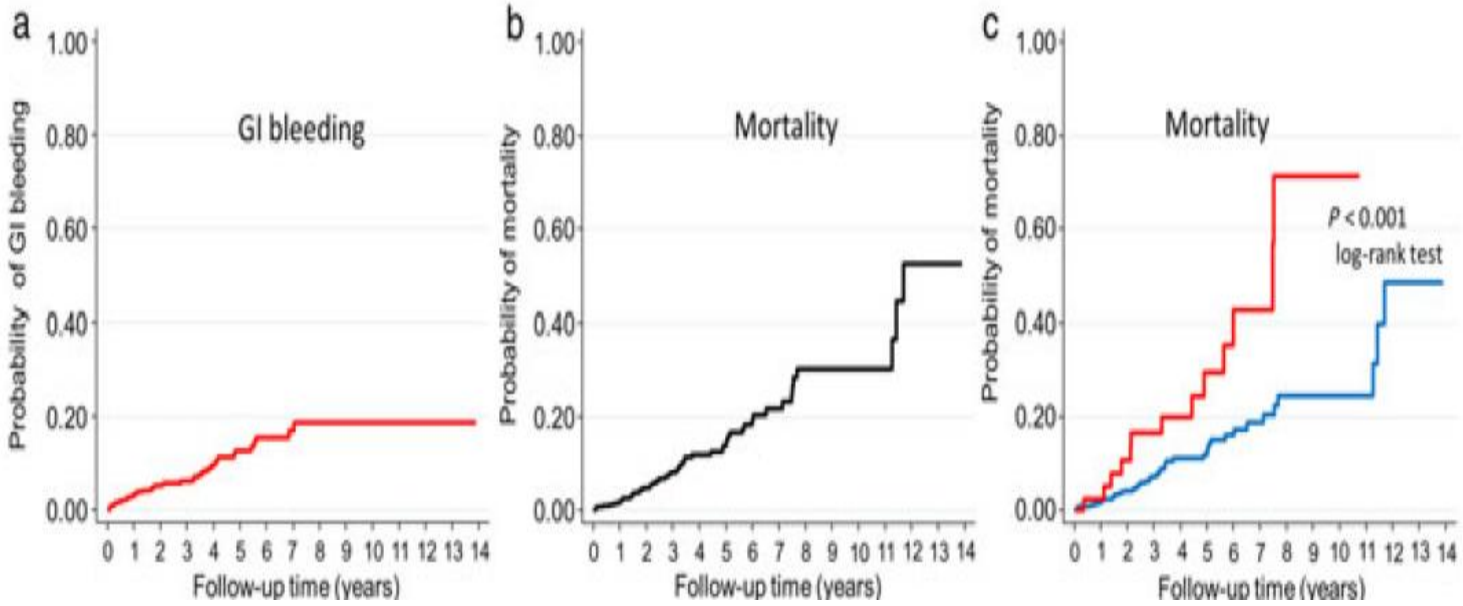


Figure 2 Cumulative probability of gastrointestinal bleeding and all-cause mortality using the Kaplan–Meier method. (a) The cumulative probability of gastrointestinal bleeding (95% confidence interval) at 1, 5, and 10 years was 3.1% (1.9–5.1%), 12.6% (8.9–17.6%), and 18.5% (12.8–26.3%), respectively. (b) The cumulative probability of mortality (95% confidence interval) at 1, 5, and 10 years was 1.9% (1.0–3.5%), 13.8% (10.0–18.7%), and 30.1% (22.2–40.4%), respectively. (c) The cumulative probability of mortality compared with the presence of gastrointestinal bleeding. Patients with gastrointestinal bleeding had significantly higher cumulative incidence of mortality than those without (log–rank test, $P < 0.001$). —, GI bleeding (+); —, GI bleeding (−). GI, gastrointestinal. [Color figure can be viewed at wileyonlinelibrary.com]

Risk factors for gastrointestinal bleeding and development of predictive scoring system

In the univariate analysis, factors associated with GI bleeding (P < 0.2) were

- PPI use (P = 0.110)
- peripheral arterial disease history (P = 0.044)
- atrial fibrillation (P = 0.086)
- Chronic kidney disease (P = 0.001)
- COPD (P = 0.023)
- peptic ulcer disease history (P = 0.041)
- cirrhosis (P = 0.005)

NEW SCORE

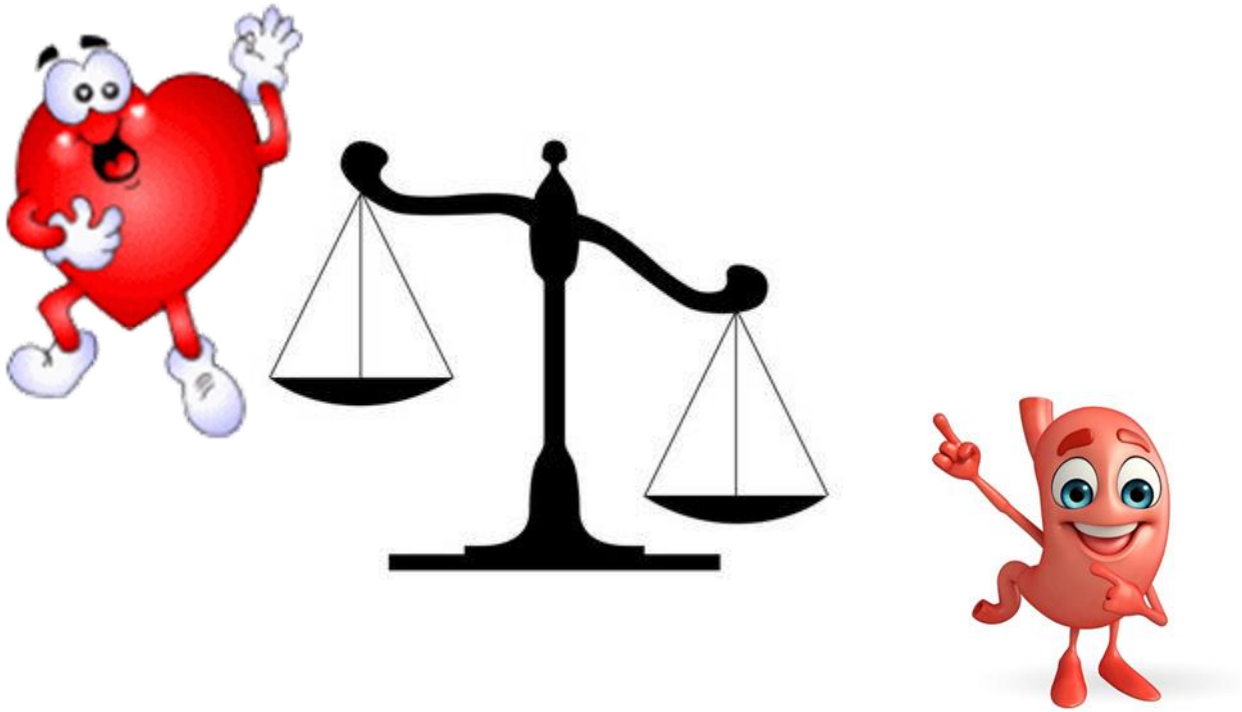
- **PPI use was assigned 1 point,**
- **Chronic kidney disease and cirrhosis 2 points each**
- **COPD and peptic ulcer disease history 1 point each.**

Table 4 Predictive ability and accuracy of the new score compared with the HAS-BLED score (n = 508)

Score	Number of bleeding/number with no bleeding episode	c-statistic (95% CI)	*P*	Hazard ratio (95% CI)	*P* for trend
New score	—	0.65 (0.58–0.72)	< 0.001	—	—
−1	4/176	—	—	1 (reference)	—
0	25/239	—	—	3.84 (1.34–11.1)	—
1	7/41	—	—	5.98 (1.75–20.5)	—
2	4/10	—	—	12.9 (3.23–51.7)	—
3	2/0	—	—	59.0 (10.7–325.8)	< 0.001
HAS-BLED score	—	0.57 (0.48–0.65)	0.145	—	—
0	2/22	—	—	1 (reference)	—
1	3/92	—	—	0.35 (0.58–2.09)	—
2	11/140	—	—	0.75 (0.17–3.40)	—
3	16/134	—	—	1.10 (0.25–4.81)	—
4	8/63	—	—	1.19 (0.25–5.62)	—
5	2/15	—	—	1.02 (0.14–7.27)	0.50

Abbreviations: CI, confidence interval; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratios [INR], Elderly, Drugs/alcohol.

…collaborazione e confronto continuo tra gastroenterologo e cardiologo…….



Valutazione del paziente

-Anamnesi familiare: neoplasia colon retto
-Anamnesi fisiologica: potus, dispepsia, alvo
-Anamnesi clinica: pregressa ulcera, pregressa emorragia digestiva, epatite-cirrosi, diverticolosi, sanguinamento rettale, sanguinamento oscuro/occulto
-Anamnesi farmacologica:
-Assunzione contemporanea di ASA o ASA + Clopidogrel
-Altri farmaci a rischio di emorragia digestiva.
-Indagini bioumorali: emocromo, creatinina, transaminasi, bilirubina, PT, aPTT
-Patologie associate
- HAS bled score

Anamnesi farmacologica

Altri farmaci responsabili di emorragie digestive:
SSRI, Alendronato, Glucocorticoidi, Antialdosteronici, Nitrati, Calcio antagonisti (Gastroenterology 2014)

Table 1—*Comparison of comparative toxicity of range of drugs with use of ibuprofen as reference for calculating relative risks*

Comparator	No of studies	Pooled relative risk	95% Confidence interval for pooled relative risk	P value (heterogeneity)
Ibuprofen	—	1.0†	—†	—†
Fenoprofen	2	1.6	1.0 to 2.5	0.310
Aspirin	6	1.6	1.3 to 2.0	0.685
Diclofenac	8	1.8	1.4 to 2.3	0.778
Sulindac	5	2.1	1.6 to 2.7	0.685
Diflunisal	2	2.2	1.2 to 4.1	0.351
Naproxen	10	2.2	1.7 to 2.9	0.131
Indomethacin	11	2.4	1.9 to 3.1	0.488
Tolmetin	2	3.0	1.8 to 4.9	0.298
Piroxicam	10	3.8	2.7 to 5.2	0.087
Ketoprofen	7	4.2	2.7 to 6.4	0.258
Azapropazone	2	9.2	4.0 to 21.0	0.832

BMJ 1996;**312**:1563–6

Percutaneous left atrial appendage closure—An alternative strategy for anticoagulation in atrial fibrillation and hereditary hemorrhagic telangiectasia?

Cardiovasc Diagn Ther. 2015 Feb; 5(1): 49–53

Results at 12 month follow-up

Variables	Results, n [%]
Complete closure	4 [80]
TIA	1 [20]
CVA	1 [20]
Systemic embolus	0 [0]
Therapy	4 [80]
Acenocoumarol	1 [20]*
Aspirin	1 [20]
No therapy	3 [60]

After implantation::
patient 1, 3 and 4 continued OAC,
patient 5 continued aspirin
patient 2 combined aspirin and clopidogrel.

At 3 month of follow-up:
All patients discontinued OAC (progressive bleeding)
4 patients switched to aspirin
patient 5 stopped the aspirin.

Values are in number [percentages (%)].
*, acenocoumarol was restarted in one patient after a TIA.
TIA, transient ischemic attack; CVA, cerebrovascular accident.

GRAZIE PER L'ATTENZIONE