CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

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ICTUS ISCHEMICO ed EMORRAGICO

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SC Neurologia

ASST Cremona

Sistema Socio Sanitario

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Regione Lombardia

ASST Cremona

No dislosures

Outline

Residual embolic risk & hemorrhagic risk
- warfarin
- DOACs

Ischemic event in anticoagulated patients
- thrombolysis & warfarin
- thrombolysis & DOACs
- thrombolysis & dabigatran
- stop or resume anticoagulation

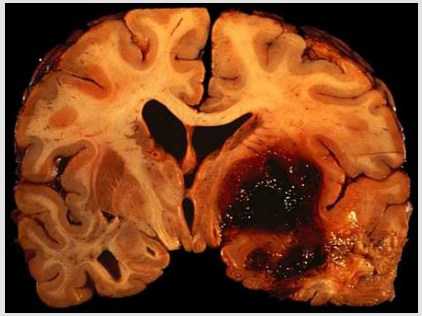
Hemorrhagic event in anticoagulated patients
- if and when to resume anticoagulation

Warfarin - residual risks

A meta-analysis of 8 randomized controlled trials (RCTs), investigating the safety and efficacy outcomes in AF patients treated with warfarin for stroke prevention, found that current use of warfarin was associated with **a low rate of residual stroke or systemic embolism estimated to be 1.66% per year** *(Agarwal S, et al. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. Arch Intern Med. 2012;172:623–631)*

Stroke rates are higher on OACs with some patient clinical characteristics, that is, **older age, female sex, previous stroke/transient ischemic attack, vitamin K-antagonist naive status, renal impairment, previous aspirin use, and higher CHADS2 score** (*Albertsen IE et al. Risk of Stroke or Systemic Embolism in Atrial Fibrillation Patients Treated With Warfari:n A Systematic Review and Meta-analysis. Stroke. 2013;44:1329-1336)*

First ever stroke: non-significant increase in intracranial haemorrhage (0.4% vs 0.2%) or major extracranial bleeding (2.1% vs 1.2% per year; RR 1.66, 0.82–2.35)
Recurrency: non-significant increase in major bleeding (2.8% vs 0.7% per year; HR 3.20, 0.91–11.3). (*Alberts, Lancet Neurology 2012)*



Factors associated with worst prognosis in ICH

- Lower level of consciousness at the Glasgow Coma Scale
- **Initial hematoma volume** → physical disruption of adjacent tissue
  - seems not to be significantly different compared with non-OAT-ICH until INR <3.0;
  - it is larger in OAT-ICH with INR > 3.0;
  - nonlinear relationship between hematoma volume and INR suggest there may be a threshold for the effect of INR on hematoma volume;
- Intraventricular bleeding
- Hematoma enlargement
- Oedema

CME

Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage

J.J. Flibotte, BA; N. Hagan, BA; J. O'Donnell, RN; S.M. Greenberg, MD, PhD; and J. Rosand, MD, MS

Warfarin was the sole predictor of expansion (OR 6.2, 95% CI 1.7 to 22.9) and expansion in warfarin patients was detected later in the hospital course compared with non-warfarin patients ($p < 0.001$). ICH expansion showed a trend toward increased mortality (OR 3.5, 95% CI 0.7 to 8.9, $p = 0.14$) and reduced the marginal effect of warfarin on ICH mortality

***Table 4** ICH expansion in patients with two or more CT scans, n = 70*

Characteristic	OR (95% CI)
Onset to baseline CT scan, h	0.99 (0.94–1.03)
Warfarin	6.22 (1.69–22.88)
Antiplatelet agent	0.42 (0.12–1.46)
Hypertension	0.31 (0.07–1.32)
ICH volume per 10 mL	0.84 (0.60–1.17)
IVH volume per 10 mL	1.12 (0.55–2.30)
Lobar location	1.02 (0.32–3.23)
GCS < 9	1.42 (0.25–8.16)
Glucose per 10 mg/dL	1.00 (0.81–1.22)
APOE ε4	0.46 (0.09–2.52)*
APOE ε2	5.13 (0.30–90.70)*

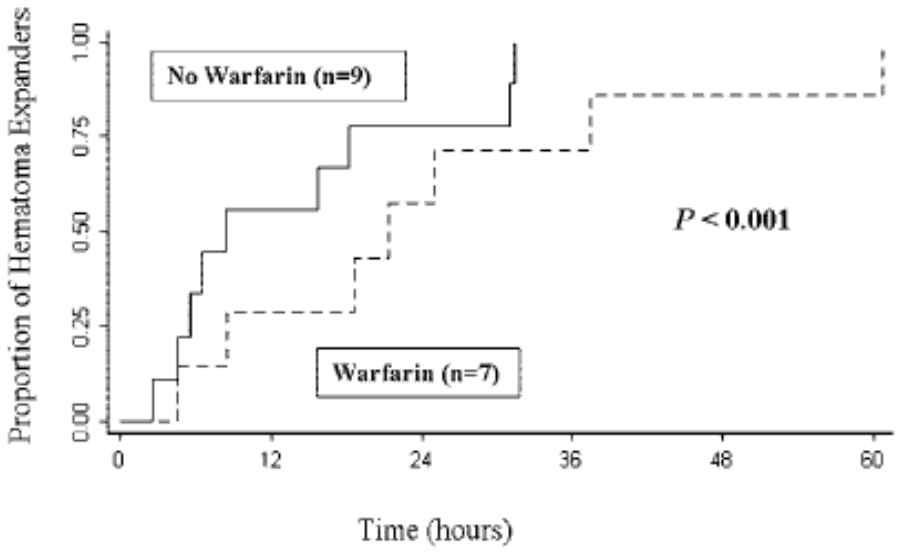


Figure 2. Kaplan-Meier estimate of rate of hemorrhage expansion among subjects with hematoma expansion.

16/70 had ICH expansion (23%)

*7/13 [54%] vs 9/57 [16%], *p=0.007*

Neurology 2004;63:1059–1064

Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

Brett Cucchiara, MD; Steven Messe, MD; Lauren Sansing, MD;
Scott Kasner, MD; Patrick Lyden, MD; for the CHANT Investigators

Table 2. Hemorrhage Expansion and Clinical Outcome by Group

	SICH (n=267)	OAT ICH (n=18)	*P* Value
ICH volume change, median (IQR)	0.9 mL (0–5.4)	9.6 mL (0–19.4)	0.03
>33% ICH expansion	26%	56%	0.006
Any ICH expansion	65%	78%	0.27
	SICH (n=282)	OAT ICH (n=21)	*P* Value
Mortality	17%	62%	<0.001
mRS 4–6	50%	90%	0.001

Stroke 2008;39:2993-2996

DOAC: ischemic stroke residual risk

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

N Engl J Med 2009;361:1139-51.

Clinical endpoint	CrCl 30–49 mL/min			CrCl ≥50 mL/min			P-value for interaction
	Rivaroxaban 15 mg (n = 1474)[a]	Warfarin (n = 1476)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	Rivaroxaban 20 mg (n = 5637)[a]	Warfarin (n = 5640)[a]	Hazard ratio (95% CI), rivaroxaban vs. warfarin	
Principal efficacy endpoint (stroke and systemic embolism)	2.32	2.77	0.84 (0.57–1.23)	1.57	2.00	0.78 (0.63–0.98)	0.76
Stroke, systemic embolism, vascular death	4.64	4.83	0.96 (0.73–1.27)	2.76	3.32	0.83 (0.70–0.98)	0.38
Stoke, systemic embolism, MI, vascular death	5.58	6.54	0.85 (0.67–1.09)	3.55	4.16	0.85 (0.73–0.99)	0.98
Stroke							
Ischaemic	1.98	1.78	1.11 (0.71–1.73)	1.20	1.34	0.90 (0.69–1.16)	0.41
Haemorrhagic	0.29	0.52	0.56 (0.21–1.51)	0.26	0.42	0.62 (0.37–1.03)	0.88
Undetermined	0.05	0.09	0.51 (0.05–5.67)	0.07	0.10	0.68 (0.24–1.90)	0.84

[a]Event rates per 100 patient-years of follow-up.

European Heart Journal (2011) 32, 2387–2394

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	no.	%/yr		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

N Engl J Med 2011;365:981-92.

Events, %/y	Warfarin (n=7036)	Edoxaban High Dose (n=7035)	Edoxaban High Dose vs Warfarin Hazard Ratio	Edoxaban High Dose vs Warfarin P Value	Edoxaban Low Dose (n=7034)	Edoxaban Low Dose vs Warfarin Hazard Ratio	Edoxaban Low Dose vs Warfarin P Value
All stroke	1.69%	1.49%	0.88	0.11	1.91%	1.13	0.12
Hemorrhagic	0.47%	0.26%	0.54	<0.001	0.16%	0.33	<0.001
Fatal	0.21%	0.14%	0.57	0.002	0.14%	0.33	<0.001
Disabling, nonfatal*	0.07%	0.03%	0.36	0.081	0.02%	0.36	0.079
Nondisabling†	0.19%	0.09%	0.35	<0.001	0.08%	0.26	<0.001
Ischemic‡	1.25%	1.25%	1.00	0.97	1.77%	1.41	<0.001
Fatal	0.24%	0.28%	1.15	0.50	0.33%	1.35	0.12
Disabling, nonfatal*	0.25%	0.26%	1.06	0.79	0.42%	1.70	0.004
Nondisabling†	0.82%	0.73%	0.89	0.32	1.06%	1.28	0.019
TIA (symptoms <24 h)	0.50%	0.56%	1.11	0.45	0.79%	1.56	<0.001
Ischemic stroke or TIA	1.73%	1.76%	1.02	0.81	2.48%	1.43	<0.001
All stroke or TIA	2.17%	2.00%	0.92	0.27	2.62%	1.21	0.005
New definition of stroke[14] (includes events resolving <24 h with infarct on brain imaging)							
New stroke	1.77%	1.54%	0.87	0.077	1.99%	1.12	0.13
New ischemic stroke	1.33%	1.30%	0.98	0.79	1.85%	1.39	<0.001

Stroke. 2014;45:2372-2378.

DABI 110	1.34
DABI 150	0.92
RIVA 15	1.98
RIVA 20	1.2
APIXA	0.97
EDOXA 60	1.25
EDOXA 30	1.77

DOAC: hemorrhagic risk

Table 3. Safety Outcomes, According to Treatment Group.*

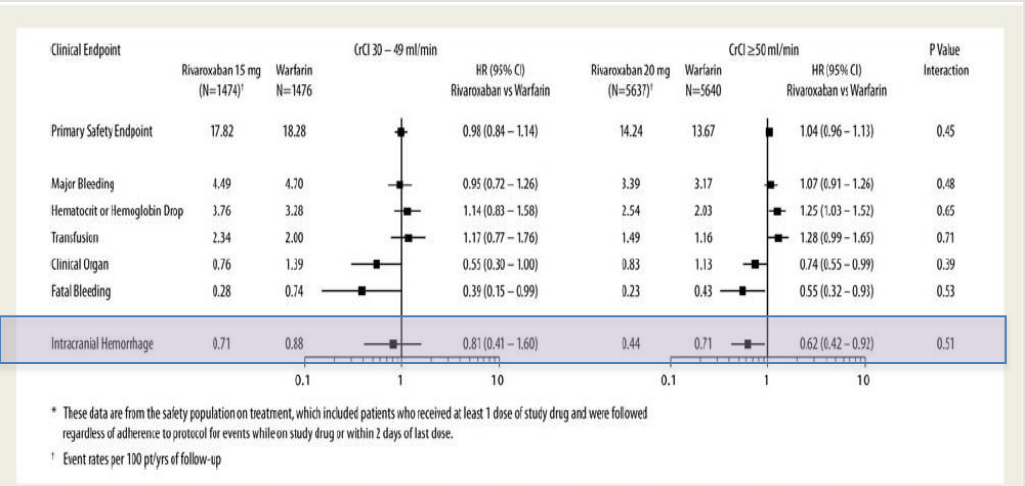
Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

N Engl J Med 2009;361:1139-51.

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	no.	%/yr		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

European Heart Journal (2011) **32**, 2387–2394



* These data are from the safety population on treatment, which included patients who received at least 1 dose of study drug and were followed regardless of adherence to protocol for events while on study drug or within 2 days of last dose.

† Event rates per 100 pt/yrs of follow-up

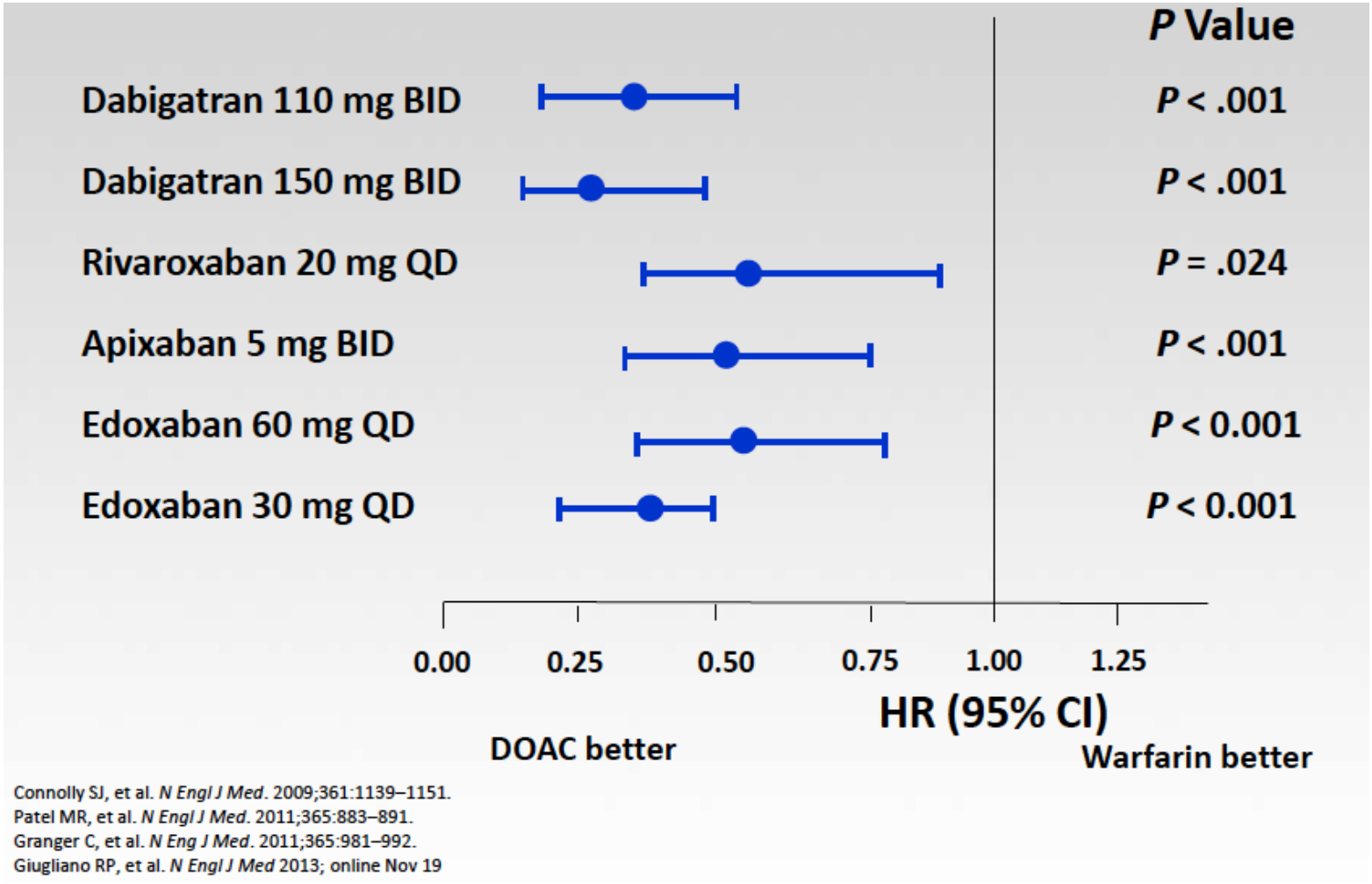
N Engl J Med 2011;365:981-92.

Table 3. Safety and Net Clinical End Points.*

Outcome	Warfarin (N=7012)		High-Dose Edoxaban (N=7012)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7002)		Low-Dose Edoxaban vs. Warfarin	
					Hazard Ratio (95% CI)	P Value			Hazard Ratio (95% CI)	P Value
	no. of patients with event	% of patients/yr	no. of patients with event	% of patients/yr			no. of patients with event	% of patients/yr		
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Bleeding into a critical organ or area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
Overt bleeding with blood loss of ≥2 g/dl	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Any intracranial bleeding	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal intracranial bleeding	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal bleeding	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper gastrointestinal tract	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower gastrointestinal tract	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Bleeding in other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001
Bleeding during transition to open-label oral anticoagulation therapy										
Day 1–14	6	—	4	—	—	—	5	—	—	—
Day 15–30	5	—	6	—	—	—	13	—	—	—
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
Clinically relevant nonmajor bleeding	1396	10.15	1214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001
Minor bleeding	714	4.89	604	4.12	0.84 (0.76–0.94)	0.002	533	3.52	0.72 (0.65–0.81)	<0.001
Major or clinically relevant nonmajor bleeding	1761	13.02	1528	11.10	0.86 (0.80–0.92)	<0.001	1161	7.97	0.62 (0.57–0.67)	<0.001
Any overt bleeding	2114	16.40	1865	14.15	0.87 (0.82–0.92)	<0.001	1499	10.68	0.66 (0.62–0.71)	<0.001
Net clinical outcome†										
Primary	1462	8.11	1323	7.26	0.89 (0.83–0.96)	0.003	1248	6.79	0.83 (0.77–0.90)	<0.001
Secondary	987	5.23	883	4.64	0.88 (0.81–0.97)	0.008	837	4.38	0.83 (0.76–0.91)	<0.001
Tertiary	1123	6.02	999	5.30	0.88 (0.81–0.96)	0.003	1010	5.37	0.89 (0.82–0.97)	0.007

Stroke. 2014;45:2372-2378.

NAO vs warfarin: ICH



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Giugliano RP, et al. *N Engl J Med* 2013; online Nov 19

Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism

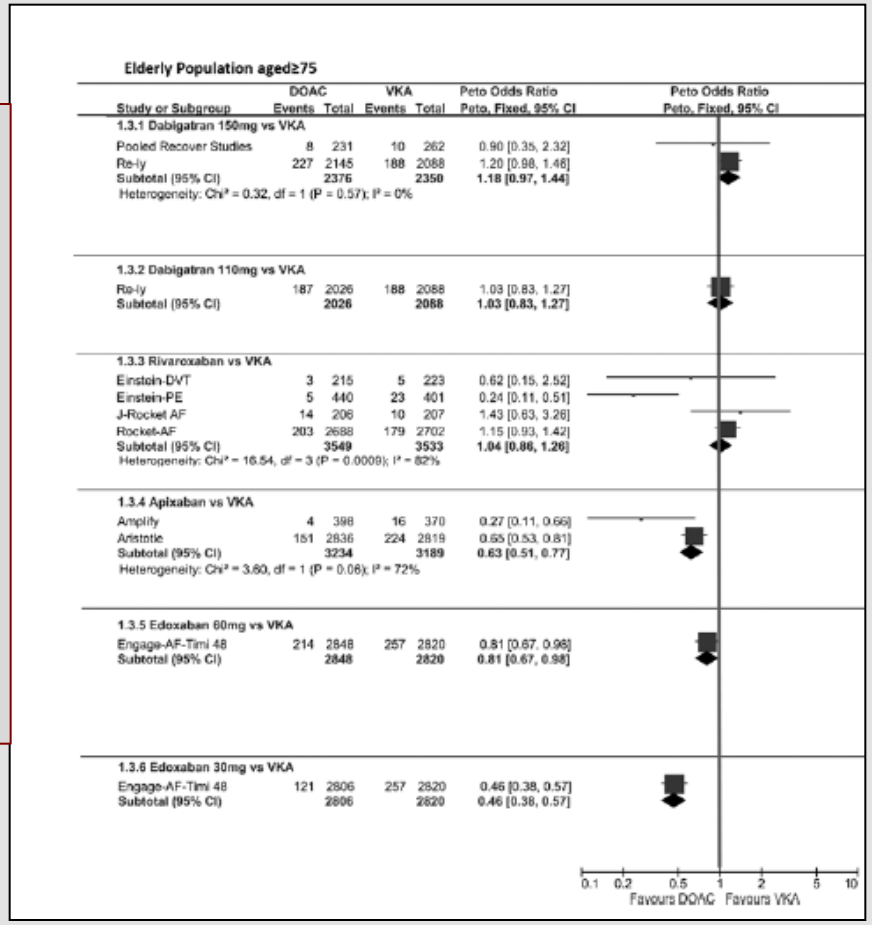
Systematic Review and Meta-Analysis

31418 pz > 75aa da tutti i trials fase II e III con DOAC in pz con FA / VTE con warfarin as comparator

<u>Major bleedings in pz > 75aa</u>:
non significant higher risk for dabi 150 x 2
similar risk for dabi 110 x 2
similar risk for rivaroxa
significant reduction for apixaban, edoxaban 30/60

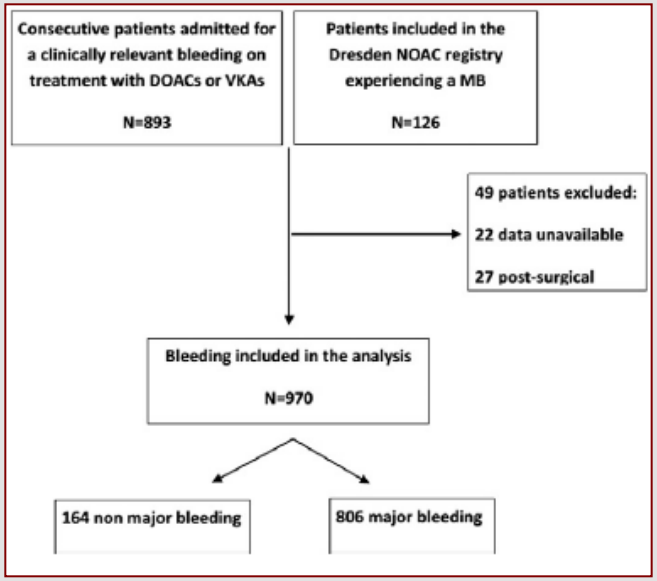
<u>Gastrointestinal</u>
Significant increase x dabi 110 e 150
No data x gli altri

<u>Intracranial</u>
Significant reduction for dabi 110 e 150 e apixa
Non significant reduction for riva
No data for edoxaban



Sharma M et al. Circulation. 2015:132; 194-204

Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life



MBs	TOT (N = 806)	DOAC (N = 191)	VKA (N = 615)	OR 95% CI	p
Intracranial, n (%)	354 (44)	41 (21)	313 (51)	0.26 0.18–0.39	<0.001
Gastrointestinal, n (%)	239 (30)	88 (46)	151 (25)	2.62 1.87–3.68	<0.001
Soft/muscle, n (%)	80 (10)	11 (6)	69 (11)	0.48 0.25–0.93	0.027
Retroperitoneal, n (%)	33 (4)	2 (1)	31 (5)	0.20 0.05–0.84	0.015
Genito-urinary, n (%)	27 (3)	15 (8)	12 (2)	4.28 1.97–9.32	<0.001
Pleural/pericardial/ peritoneal, n (%)	21 (3)	5 (3)	16 (3)	1.01 0.36–2.78	ns
Articular, n (%)	18 (2)	9 (5)	9 (1)	3.33 1.30–8.51	0.008
Upper airways, n (%)	15 (2)	9 (5)	6 (1)	5.02 1.76–14.29	0.001
Ocular, n (%)	9 (1)	9 (5)	0	–	<0.001
Spinal, n (%)	5 (1)	0	5 (1)	–	ns
Other, n (%)	5 (1)				

	Death rates (%)		HR (95% CI)	aHR[b] (95% CI)
	VKA	DOAC		
Overall study population	18	9	1.78 (1.08–2.93)	1.67 (1.00–2.79)
Patient with ICH[a]	26	24	1.05 (0.54–2.02)	0.92 (0.47–1.81)
Patients with gastrointestinal bleeding	7	11	1.46 (0.57–3.74)	1.76 (0.65–4.76)
Patients with other major bleeding	10	3	3.42 (0.78–15.03)	1.71 (0.31–9.47)
Exclusion of patients on treatment for valvular diseases	19	9	2.07 (1.25–3.43)	–
Non traumatic major bleeding	19	9	2.13 (1.20–3.76)	1.84 (1.01–3.32)
Non traumatic ICH[a]	31	39	1.05 (0.54–2.03)	1.08 (0.54–2.13)

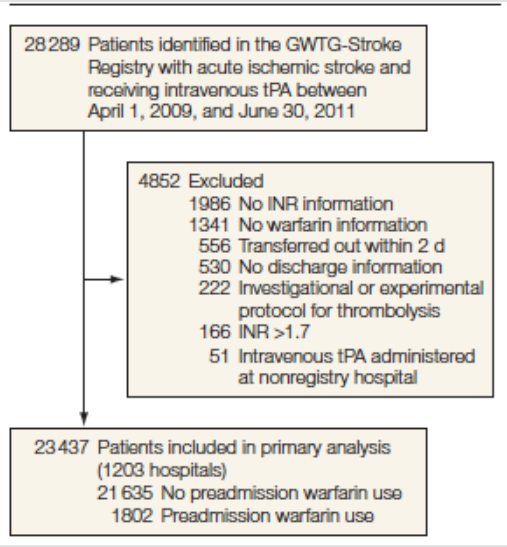
Becattini C et al. Int J Cardiol 2017;227:261-266

Outline

Ischemic event in anticoagulated patients

- thrombolysis & warfarin
- thrombolysis & DOACs
- thrombolysis & dabigatran
- stop or resume anticoagulation

Risks of Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Receiving Warfarin and Treated With Intravenous Tissue Plasminogen Activator



The baseline INR levels were higher in warfarin-treated patients (median, 1.20 [IQR, 1.07-1.40] vs 1.00 [IQR, 1.00-1.10]; $P<.001$). Nearly 15% (269/1802) of warfarin-treated patients presented with INRs between 1.5 and 1.7. Time from

hemorrhage. This definition is based on the criteria for sICH established in the National Institute of Neurological Disorders and Stroke (NINDS) tPA trials.[3]

Table 3. Primary and Secondary Outcomes Measures According to Preadmission Warfarin Use

Outcome	No. of Events/Total No. of Patients (%)		OR (95% CI)		*P* Value
	Preadmission Warfarin Use	No Preadmission Warfarin Use	Unadjusted	Adjusted	
Symptomatic intracranial hemorrhage	102/1802 (5.7)	1005/21 635 (4.6)	1.22 (0.99-1.51)	1.01 (0.82-1.25)[a]	.94
Life-threatening or serious systemic hemorrhage	16/1802 (0.9)	199/21 635 (0.9)	0.99 (0.62-1.56)	0.78 (0.49-1.24)[a]	.29
Any tPA complication[b]	191/1802 (10.6)	1824/21 635 (8.4)	1.29 (1.10-1.52)	1.09 (0.93-1.29)[a]	.30
In-hospital mortality[c]	202/1772 (11.4)	1676/21 304 (7.9)	1.50 (1.29-1.75)	0.94 (0.79-1.13)[d]	.50
Discharge to skilled nursing facility[e]	414/1406 (29.5)	3720/18 464 (20.1)	1.60 (1.43-1.80)	1.16 (1.02-1.32)	.02
Discharge to inpatient rehabilitation facility[e]	518/1406 (36.8)	6113/18 464 (33.1)	1.19 (1.06-1.33)	1.09 (0.97-1.22)	.16

Xian Y at al. JAMA 2012;307(24):2600-2608

Safety of Intravenous Thrombolysis for Ischemic Stroke in Patients Treated with Warfarin

Methods: We analyzed data from 45,074 patients treated with IV tPA enrolled in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Register. A total of 768 patients had baseline warfarin treatment with INR ≤ 1.7. Outcome measures were SICH, arterial recanalization, mortality, and functional independence at 3 months.

TABLE 2. Outcomes by Warfarin Group, Unadjusted Analysis

Outcome	Warfarin, INR ≤ 1.7, n = 768			No Warfarin, n = 43,651	
	No./Total	Value	*p*	No./Total	Value
SICH SITS-MOST	15/751	2.0	0.60	744/42,728	1.7
SICH ECASS II	57/744	7.7	0.001	2,131/42,647	5.0
SICH NINDS	79/746	10.6	0.001	3,140/42,511	7.4
HI	87/746	11.7	0.005	3,762/42,163	8.9
PH	61/746	8.2	0.02	2,663/42,163	6.3
PHr	27/746	3.6	0.55	1,363/42,156	3.2
mRS 0–1, 3 months	169/582	29.0	<0.001	13,628/21,099	39.2
mRS 0–2, 3 months	259/582	44.5	<0.001	19,056/34,727	54.9
Dead, 3 months	155/594	26.1	<0.001	5,325/35,310	15.1
Recan CTA/MRA	18/30	60.0	0.42	776/1,475	52.6
Recan dHMCAS	91/150	60.7	0.16	3,901/7,099	55.0

Mazya MV et al. Ann Neurol 2013;74:266–274

TABLE 3. Outcomes in Warfarin-Treated Patients, Adjusted Analysis

Outcome	Warfarin, INR ≤ 1.7, n = 768, OR (95% CI) Value	*p*
SICH SITS-MOST	1.23 (0.72–2.11)	0.46
SICH ECASS II	1.26 (0.82–1.70)	0.24
SICH NINDS	1.13 (0.90–1.37)	0.35
HI	1.03 (0.75–1.31)	0.40
PH	1.08 (0.82–1.35)	0.41
PHr	1.06 (0.70–1.62)	0.78
mRS 0–1, 3 months	0.95 (0.76–1.17)	0.61
mRS 0–2, 3 months	1.01 (0.81–1.24)	0.96
Dead, 3 months	1.05 (0.83–1.33)	0.66

Multivariate logistic regression analysis. ORs for SICH and radiological hemorrhage types are adjusted for age, stroke severity, blood glucose, systolic blood pressure, diabetes mellitus, hypertension, use of aspirin, onset-to-treatment time > 3 hours, visible infarct signs on baseline imaging, and baseline HMCAS. HMCAS is not adjusted for in SICH per SITS-MOST and ICH type PHr, where it is not a risk factor.[29] ORs for mRS and mortality are adjusted for all the above, plus atrial fibrillation, congestive heart failure, and previous stroke. Probability values are for significance versus stroke thrombolysis patients without warfarin.

Mazya MV et al. Ann Neurol 2013;74:266–274

Trombolisi & VKA – linee guida

- *AHA 2013*

  Exclusion criteria within 3 hrs: current use of anticoagulant with INR>1.7 or PT>15 sec

  Relative exclusion criteria within 3 and 4,5 hrs: taking an oral anticoagulant regardless INR

- *ISO-SPREAD 2015*

  Il trattamento con r-tPA entro 4,5 ore dall'esordio è indicato nei pazienti in terapia con anticoagulanti orali con AVK e INR ≤ 1.7 (grado D)

- *Scheda tecnica Actilyse*

  Controindicazioni: pazienti che ricevono un trattamento efficace con un anticoagulante orale, ad esempio warfarin sodico.

  Speciali avvertenze e precauzioni per l'uso: L'uso di Actilyse può essere preso in considerazione qualora il dosaggio o il tempo intercorso dall'ultima assunzione di un trattamento anticoagulante renda improbabile la conferma dell'efficacia residua di quest'ultimo con appropriato/i test dell'attività anticoagulante per il/i prodotto/i interessato/i, non mostrando attività clinica rilevante sul sistema della coagulazione (ad es. INR ≤ 1,3 per gli antagonisti della vitamina K o altro/i test rilevante/i per altri anticoagulanti orali entro il rispettivo limite superiore di normalità).

thrombolysis & DOAC – case reports

	N°	Male	Approriate coagulation tests*	ICH	sICH	Outcome
DABIGATRAN	17	10	No	4	2	2 decessi 1 invariato 12 good 2 nr
RIVAROXABAN	8	5	No	2	0	Good
APIXABAN	2	2	No	0	0	Good

* dTT/ECT for dabi; anti-Xa for riva/edoxa

Cappellari M et al. Thromb Haemost 2015; 113: 440–444

Trombolisi & DOAC - Linee guida

- **AHA/ASA 2013**

Exclusion criteria: Current use of direct thrombin inhibitor or direct Factor Xa inhibitors with elevated sensitive laboratory tests such as aPTT, INR, platelet counts, and ECT; TT; or appropriate factor Xa activity

- **ISO-SPREAD luglio 2016**

La letteratura suggerisce la possibilità di prendere in considerazione la trombolisi ev in pazienti trattati con farmaci anticoagulanti orali diretti con verosimile effetto sub-terapeutico, evidenziato dalla storia clinica (dose ed intervallo temporale dall'ultima assunzione, funzionalità renale) e da test specifici e standardizzati (tempo di Trombina, Tempi di Ecarina o Hemoclot per il dabigatran, anti-Xa per il rivaroxaban e l'apixaban)

- **Actilyse – scheda tecnica**

L'uso di Actilyse può essere preso in considerazione qualora il dosaggio o il tempo intercorso dall'ultima assunzione di un trattamento anticoagulante renda improbabile la conferma dell'efficacia residua di quest'ultimo con appropriato/i test dell'attività anticoagulante per il/i prodotto/i interessato/i, non mostrando attività clinica rilevante sul sistema della coagulazione (ad es. INR ≤ 1,3 per gli antagonisti della vitamina K o altro/i test rilevante/i per altri anticoagulanti orali entro il rispettivo limite superiore di normalità).

Thrombolysis after idarucizumab

	Pt	Time from last dose to admission	NIHSS	Test coag	Idarucizumab	Onset-to-needle	Outcome
1	F, 67 yrs	4 hrs (150x2)	10	TT=130"	5 gr	??	Unchanged; No ICH
2	M, 76 yrs	3.5 hrs (110x2)	11	TT=218" aPTT=73"	5 gr	??	NIHSS=1
3	F, 75 yrs	?? (110x2)	7	Dabi conc = 90ng/ml TT = 150" (14-21) PTT & INR normali	According to protocol	120 min	NIHSS=18 (ischemic lesion, no ICH)
4	M, 75 yrs	9.5 hrs (110x2)	5	TT=66.8" INR & PTT normale	5 gr	??	NIHSS=0
5	F, 76 yrs	9 hrs (110x2)	11 → 8	ND	5 gr	170 min	NIHSS=1 (small ischemic lesion; no ICH)
6	M, 68 yrs	45 min (110x2)	3	aPTT & INR normali Dabi conc=34.1 lg/L	5 gr	110 min	NIHSS=3

1. Schafer N. et al. J Stroke & Cerebr Dis. 2016;25(8):126
2. Berrouschot J. et al. Stroke. 2016;47(7)
3. Kafke W. et al. Case Rep Neurol 2016;8:140–144
4. Gawen A. et al. J Med Case Rep. 2016 Sep 29;10(1):269
5. Schulz JG. J Neurol Sci 2016;370:44
6. Mutzenbach JS et al. Ann Clin & Translat Neurol 2016; 3(11): 889–892

r-tPA somministrato immediatamente dopo la fine infusione di Idarucizumab senza attendere esito test coagulazione di controllo. Nessun evento trombotico riportato.

International Journal of Stroke
WSO

Thrombolysis and thrombectomy in patients treated with dabigatran with acute ischemic stroke: Expert opinion

International Journal of Stroke
2017, Vol. 12(1) 9–12

DOI: 10.1177/1747493016669849
wso.sagepub.com
SAGE

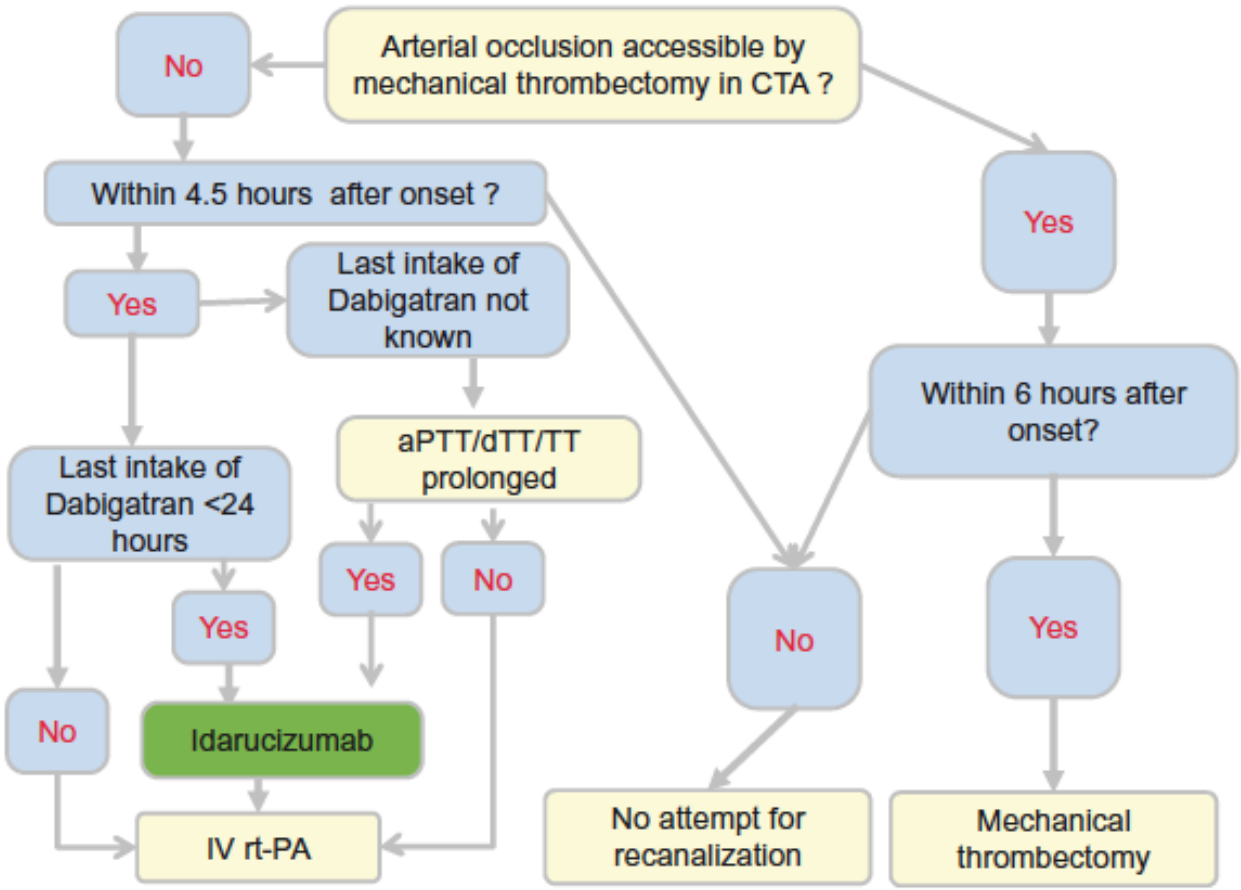
HC Diener[1], R Bernstein[2,3], K Butcher[4], B Campbell[5], G Cloud[6], A Davalos[7], S Davis[8], JM Ferro[9], M Grond[10], D Krieger[11,12], G Ntaios[13], A Slowik[14] and E Touzé[15]

Alteplase[13]	Idarucizumab[11]
4.4 Special warnings and precautions for use Patients receiving oral anticoagulant treatment: The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (e.g. INR $\leq$ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).	Indications and usage Praxbind is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed: For emergency surgery/urgent procedures[a] In life-threatening or uncontrolled bleeding

[a]Urgent procedures: any urgent procedure that cannot be postponed, any diagnostic, therapeutic, interventional or pharmacological intervention (such as thrombolysis), and where rapid removal of an anticoagulatory effect of dabigatran is required, may be considered. In the RE-VERSE AD trial (group B), no clinical restrictions were prespecified.[11,14]

The use of idarucizumab followed by rt-PA is covered by the label of both drugs.

Figure 1. Flow diagram for thrombolysis or thrombectomy inpatients treated with Dabigatran



aPPT, activated partial thromboplastin time; CTA, computerized tomography angiography; dTT, diluted thrombin time; IV, intravenous; rt-PA, recombinant tissue plasminogen activator

When to stop or resume anticoagulation?

ISO - SPREAD 2015 - In caso di ictus ischemico attribuibile a FANV, il trattamento anticoagulante orale va iniziato o ripreso prima possibile. La scelta del timing si basa sulla gravità clinica dell'ictus, sulla estensione e sulle caratteristiche della lesione cerebrale all'imaging, sul calcolo individuale del rischio tromboembolico ed emorragico. Nel caso di TIA il trattamento può essere ripreso subito

1–3–6–12 day rule

The optimal time at which to start/restart anticoagulation after a stroke should take into account the individual patient's risk factors for hemorrhagic transformation of the acute brain infarct, such as infarct size. Although pertinent clinical data regarding the timing of the reinstitution of anticoagulation are missing, some advocate as a rule of thumb, the 1–3–6–12 day rule, with reinstitution of anticoagulation in patients with a transient ischemic attack (TIA) after one-day, with small, nondisabling infarct after three-days, and with a moderate stroke after six-days; while large infarcts involving large parts of the arterial territory should not be treated before two (or even three) weeks have elapsed (Europace (2013) 15 (5): 625-651).

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

- 1037 consecutive patients with acute ischemic stroke and known or newly diagnosed AF without contraindications anticoagulation were included in the study (59 from Asia). Of these, 1029 patients were included in the analysis.
- Study outcomes were (1) recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolisms; (2) symptomatic cerebral bleedings and major extracerebral bleeding at 90 days.
- The primary outcome was the composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding.

		Outcome event	hemorrhagic	ischemic
AC	766	11.7%	5.4%	6.4%
LMWH	113			
DOAC	93			
AVK	284			
LMWH+AVK	276			
AP	231	14.4%	3.8%	10.6%
NONE	32			
p		*0.22*	*0.31*	*0.023*
TOT		**12.6%**	**5.0%**	**7.6%**

Best timing for initiating anticoagulation treatment for secondary stroke prevention is 4-14 days

At unadjusted analysis the lowest risk of primary outcome in pts treated with oral AC was 5-10 days; in particular the risk of ischemic event was stable up to day 15, while the risk of bleeding was lowest between 5-10 days.

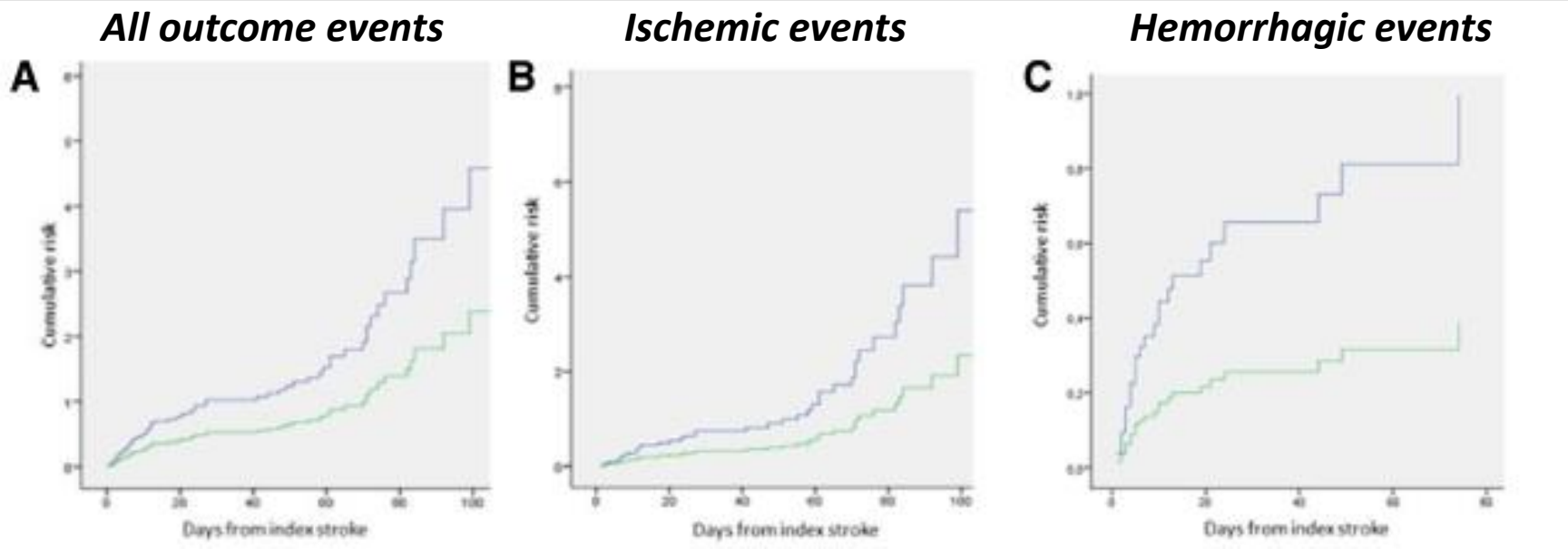


Figure 2. A, All outcome events in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. Hazard Ratio (HR)=0.53 (0.30–0.93), *P*=0.025. **B**, Ischemic outcome events (stroke, transient ischemic attack, systemic embolism) in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. HR=0.43 (0.19–0.97), *P*=0.043. **C**, Symptomatic cerebral bleedings in patients treated with anticoagulants between days 4 and 14, compared with the other treated patients. HR=0.39 (0.12–1.19), *P*=0.09. Green, anticoagulation between 4 and 14 days from stroke onset; blue, other treated patients (treatment before 4 or after 14 days).

Paciaroni M et al. Stroke 2015;46:2175-2182

Outline

Hemorrhagic event in anticoagulated patients

if and when to resume anticoagulation

The balance of expected benefit

Risk of thromboembolic events if anticoagulation is not resumed

a)NVAF (CHA_2DS_2VASc)

b)Valvular disorders

c)Valve prosthesis

d)Cardiomyoptahy

e)…..

Risk of recurrent ICH if anticoagulation is resumed

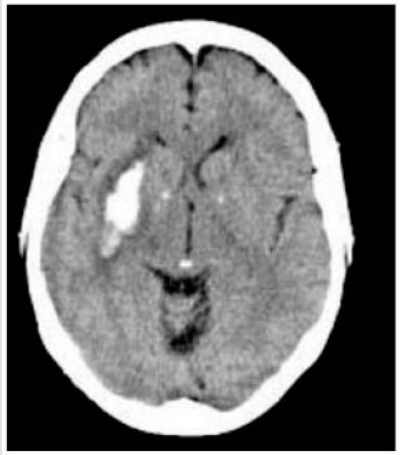
a)Index event

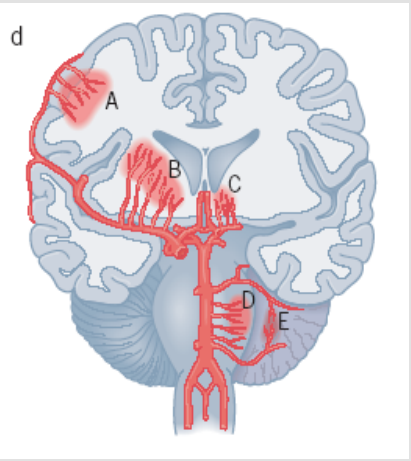
b)Patients risk factors

c)MRI findings

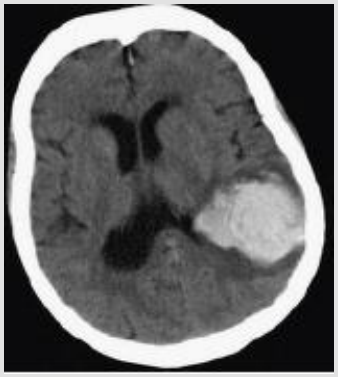
ICH - Risk of rebleeding

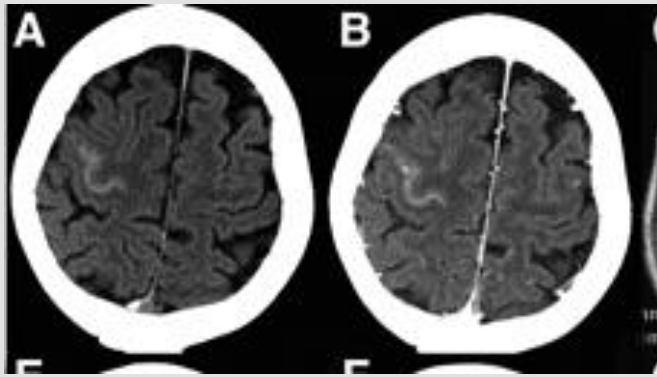
Deep hemorrhage
Small vessel disease





Lobar hemorrhage /
cerebral convexity subaracnoid hemorrhage
Cerebral amyloid angiopathy





	1-year risk	2-year risk	
DEEP	2.1%	4%	Viswanathan A et al.Neurology 2006; 66: 206.
LOBAR	15%	22%	Eckman MH et al. Stroke 2003; 34: 1710.

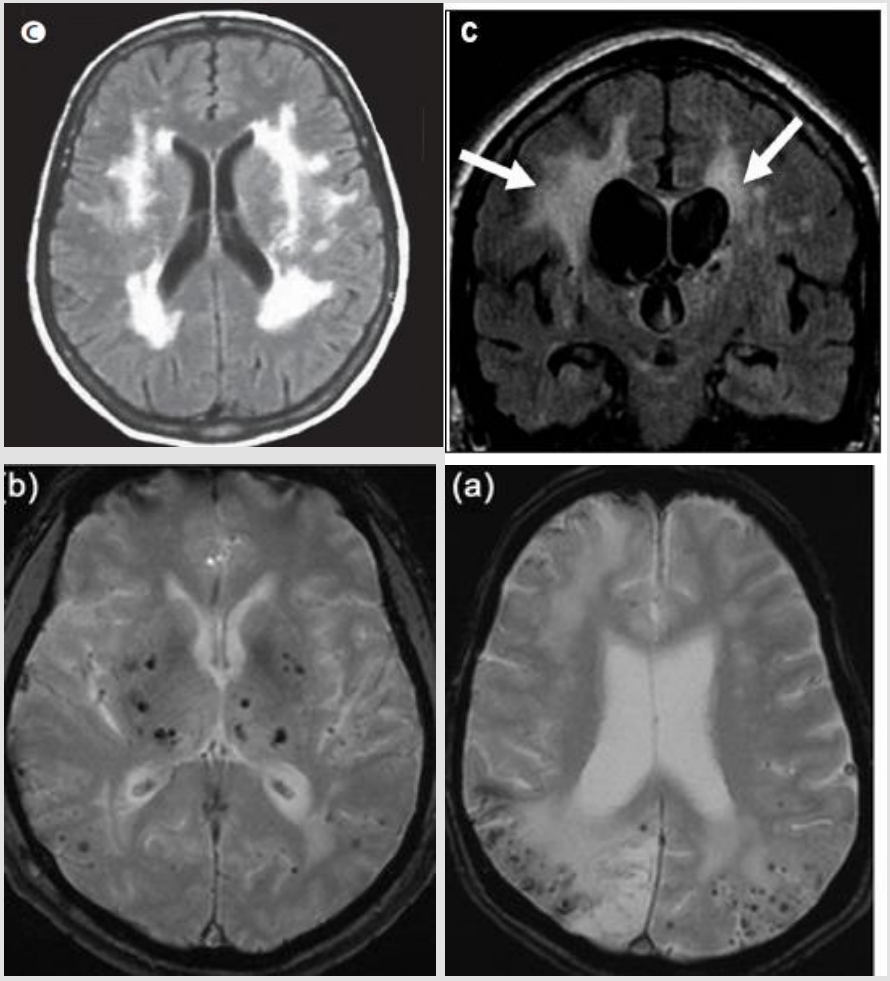
Patients risk factors of recurrent ICH after resuming TAO

- Possibile, but studies underpowered
  - Male sex
  - Hypertension
  - Prosthetic valves
  - Renal failure
  - Previous ischemic stroke
  - Cancer
  - Spontaneous events

- Recognized factors for TAO-related ICH
  - Age
  - Intensity of anticoagulation
- Recognized factors for TAO-related ICH in NVAF
  - Hypertension
  - Prior stroke
  - Prior embolism
  - Prior majior bleeding
- In other clinical settings (VTE, prosthetic valve)????

RISK SCORES NOT FOCUSED ON ICH

MRI findings



Leukoaraiosis in the setting of anticoagulation

has been demonstrated an independent risk factor for warfarin-related ICH in survivors of ischemic stroke, including those in the commonly employed range of anticoagulation

Smith E., et al.. Neurology. 2002;59:193-7

was not found independently associated with the incidence of OAC-ICH after adjustment for the presence of microhemorrhages

Lee SH et al. Neurology. 2009;72(2):171–176

Microbleeds

Conflicting results

Whang Z et al Stroke 2014

OAT & ICH & risk of rebleeding

Canadian Stroke Network Registry: one-year mortality rate in patients who resumed warfarin therapy was not higher than that in those who did not restart warfarin (48% and 61%, respectively). ICH expansion or re-bleeding was recorded in 15% of patients in both groups.

Yung D et al.. Can J Cardiol 2012; 28: 33-39.

719 consecutive pts with OAC-ICH → 177 (24%) resumed OAC (68% mechanical valves and 19% AF). Treatment resumption pts had: Lower incidence of ischemic events (5.2% vs 15%; $p<0.001$); Non-significant increase of bleedings (8.1% vs 6.6%); Reduced 5-year mortality (8.5% vs 18%), ischemic stroke (3.5 vs 7.6), ICH (3.6% vs 5.1%)

1752 AF pts surviving OAC-ICH, anticoagulant resumption pts had: Lower CE events and all cause mortality (13.6 vs 27.3%); Similar ICH (8.0% vs 8.6%); Lower rate of thrombosis (12.3 vs 3.7%; $p=0.092$); Lower all-cause mortality.

Nielsen PB et al. Circulation 132(2015):517-525

160 pts surving OAC-ICH, Anticoagulant resumption was associated with: higher incidence of ICH (7,6% vs 3.7%, $p=0.497$)

Witt DM et al Thromb Res 136 (2015):1040-1044

But….

Retrospective studies

Non randomized

Majority of pts with mechanical valve prothesis

All with warfarin

Not reported location of ICH

Can Patients Be Anticoagulated After Intracerebral Hemorrhage?

A Decision Analysis

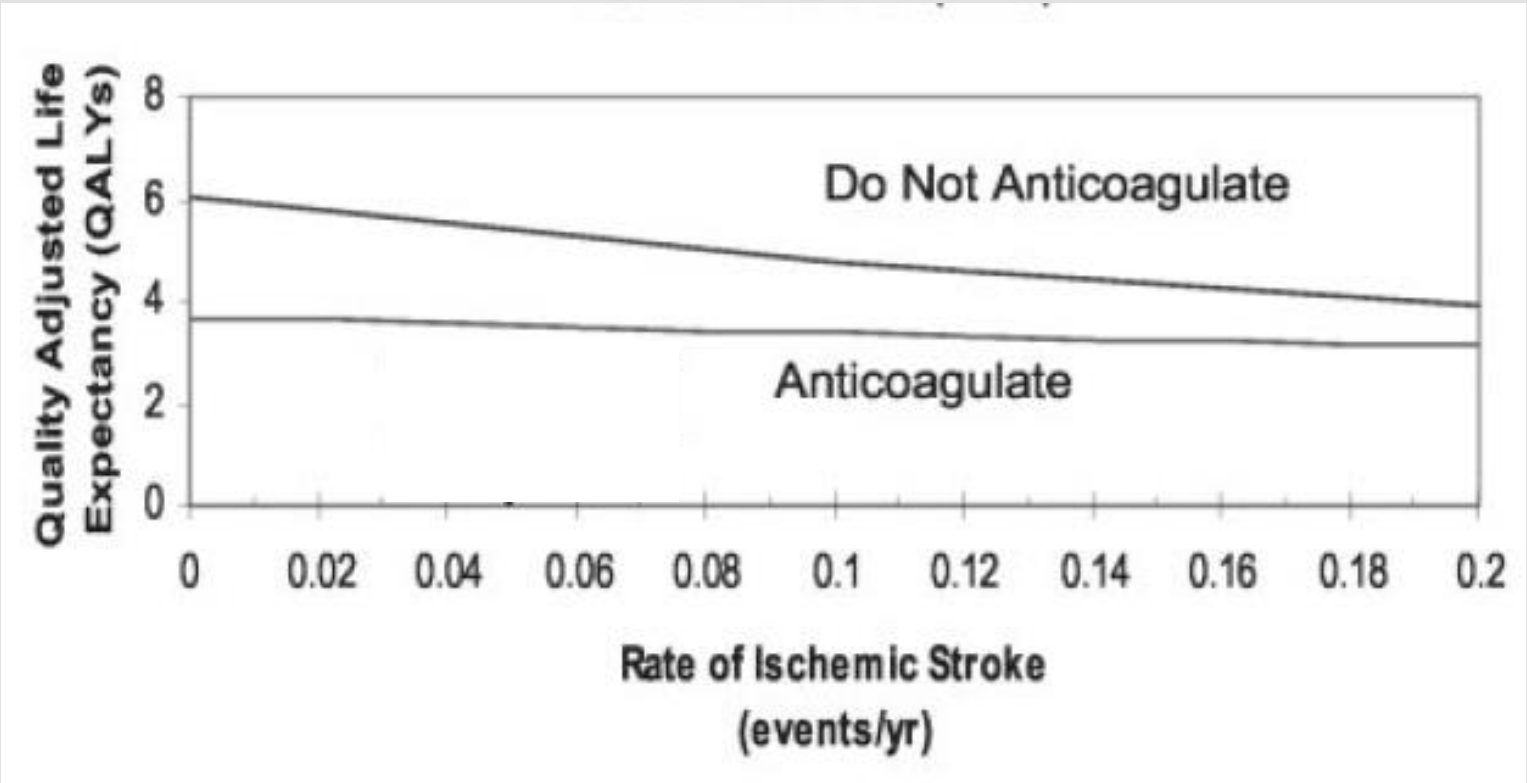
Methods—We used a Markov state transition decision model stratified by location of hemorrhage (lobar or deep hemispheric). Effectiveness was measured in quality-adjusted life years (QALYs). Data sources included English language literature identified through MEDLINE searches and bibliographies from selected articles, along with empirical data from our own institution. The base case focused on a 69-year-old man with a history of ICH and newly diagnosed nonvalvular atrial fibrillation.

TABLE 1. Data Required in the Analysis: Probabilities, Rates, and Quality of Life

Parameter	Value			
Rate of thromboembolism (untreated)	0.045/y[1,38]			
Efficacy of treatment				
With warfarin	0.68[1]			
With aspirin	0.21[38]			
Rate of thromboembolism (treated)	0.014/y			
Probable outcome from thromboembolic event				
Death	0.27[1]			
Permanent sequelae	0.44[1,37]			
With severe disability	0.29[1,11,18]			
With mild disability	0.7[1,11,18]			
Good recovery	0.29			
Location of hemorrhage	Recurrent Lobar ICH	Recurrent Deep ICH	Extracranial	Subdural Hematoma
Rate of bleeding (untreated)	0.15/y[12,13]	0.021/y[13]	0.006/y[24]	0.00025/y[1,39]
Probable outcome from bleeding event (without warfarin)*				
Death	0.190	0.207	0.15	0.20[38]
Severe long-term disability GOS=3†	0.428	0.436		0.07‡
Mild long-term disability GOS=4†	0.196	0.187		0.40‡
Good recovery GOS=5†	0.185	0.170		0.17‡
Relative risk of bleeding on anticoagulants	2.0	2.0	2.4	4.0[1,39]
Rate of bleeding on anticoagulants	0.30	0.04	0.014/y[24]	0.001/y[1]
Relative risk of bleeding on aspirin			1.08[24]	2.0[38]
Rate of bleeding on aspirin			0.0065/y[24]	0.0005/y[38]
Probable outcome from bleeding event (on warfarin)				
Death	0.379	0.405	0.15	0.20[38]
Severe long-term disability GOS=3†	0.429	0.420		0.09[38]
Mild long-term disability GOS=4†	0.111	0.103		0.50[38]
Good recovery GOS=5†	0.080	0.073		0.20[38]
			Quality of Life	
Long-term morbidities (Q values)				
Well			1.0	
Well while receiving anticoagulants			0.99[38]	
Severe long-term disability			0.11[38]	
Mild long-term disability			0.76[38]	
Dead			0.0	
Short-term morbidities in patients with resolution				
Extracranial bleeding event§			0.84	
ICH‖			0.79	
Thromboembolic event¶			0.79	
			Age-Adjusted Annual Excess Mortality	
Annual excess mortality after				
ICH with long-term disability			0.06[22]	
Ischemic stroke with long-term disability			0.06[22]	

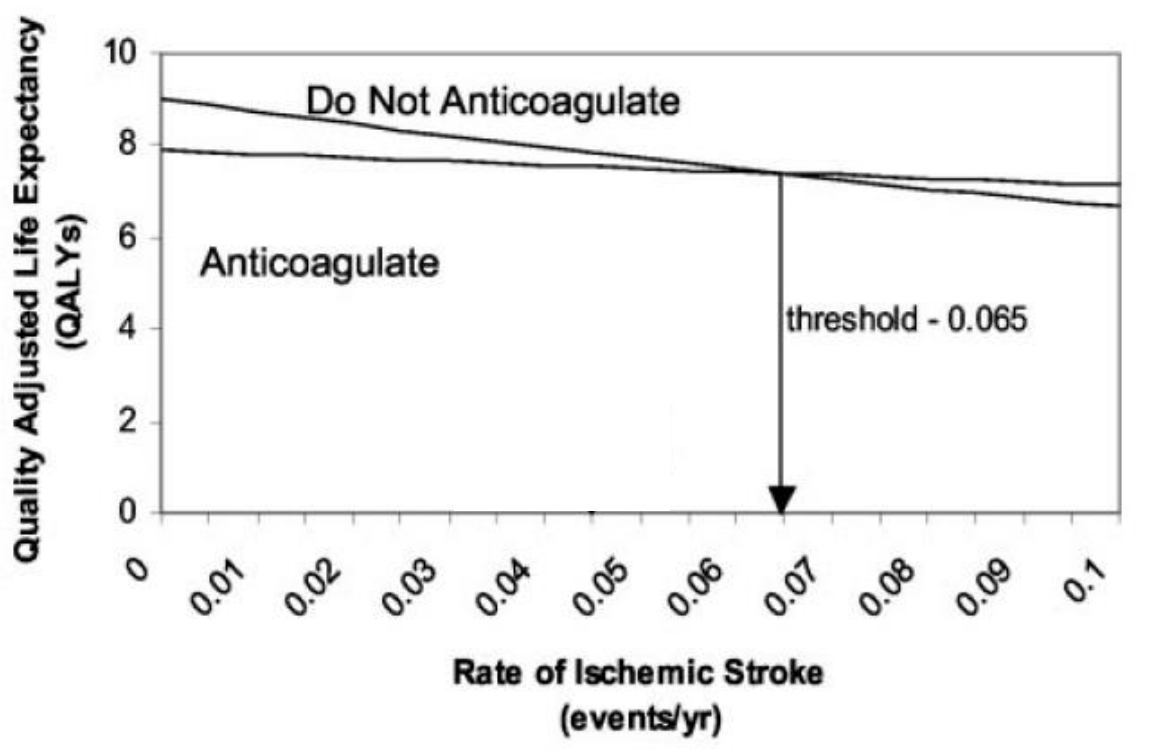
Eckman MH et al. Stroke. 2003;34:1710-1716

Lobar hemorrhage



Eckman et al. Stroke 2003

Deep hemorrhage



CHADS-Vasc	score rate (% year)
1	1.3
2	2.2
3	3.2
4	4.0
5	**6.7**
6	9.8
>6	>10

Eckman et al. Stroke 2003

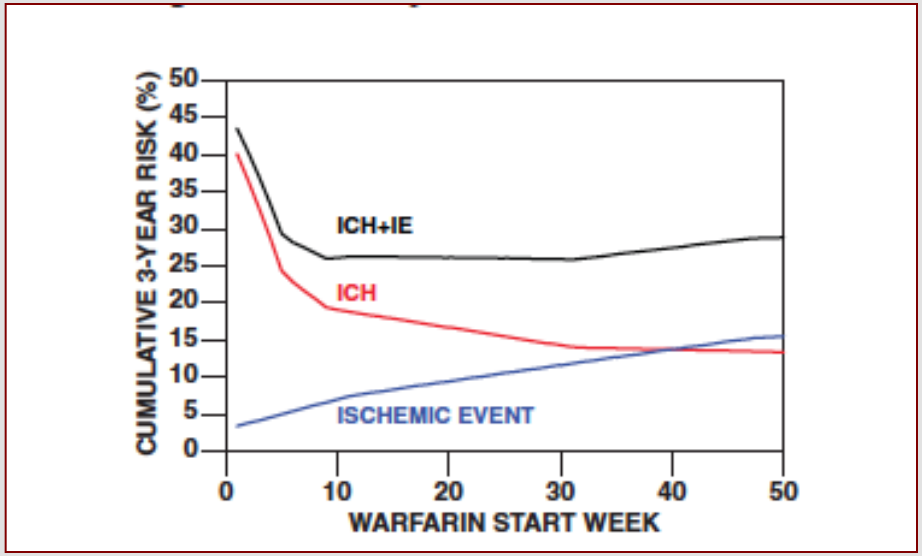
Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

2869 consecutive patients with ICH over 6 years at 3 tertiary centers. (2 in Sweden and 1 in Canada → 234 pts with VKA-associated intracerebral, subarachnoid, or subdural haemorrhages: recurrent ICH occurred in 14% of patients who resumed warfarin therapy and in 8% of those who did not. The risk of recurrent ICH on warfarin has been reported to be >5-fold higher in lobar compared with deep ICHs.

We calculated the daily risk of intracranial hemorrhage or ischemic stroke with and without resumption of warfarin; we focused on patients who survived the first week and had cardiac indication for anticoagulation or previous stroke. Using a Cox model, we estimated rates for these 2 adverse events in relation to different time points of resumed anticoagulation. The combined risk of either a new intracranial hemorrhage or an ischemic stroke was calculated for a range of warfarin resumption times.

			With Cardiac Indication*	
Characteristic	Total Patients	First-Week Survivors	Warfarin Resumed	Warfarin Not Resumed
n	234	177	45	87
Age, median (IQR)	76 (67–81)	75 (65–80)	70 (63–77)	78 (70.5–72)†
Male sex, n (%)	142 (61)	112 (63)	31 (69)	56 (64)
Indication for anticoagulation, n (%)‡				
Atrial fibrillation	135 (58)	102 (58)	22 (49)	79 (91)
Risk score $CHADS_2=0$	1 (1)	1 (1)	0 (0)	1 (1)
Risk score $CHADS_2=1$	23 (17)	20 (20)	6 (27)	14 (18)
Risk score $CHADS_2=2$	44 (33)	34 (33)	6 (27)	28 (35)
Risk score $CHADS_2=3$	23 (17)	18 (18)	4 (18)	13 (16)
Risk score $CHADS_2=4$	25 (19)	19 (19)	4 (18)	15 (19)
Risk score $CHADS_2=5$	14 (11)	7 (7)	2 (9)	5 (6)
Risk score $CHADS_2=6$	1 (1)	1 (1)	0 (0)	1 (1)
Unknown	4 (3)	2 (2)	0 (0)	2 (3)
Venous thromboembolism	37 (16)	30 (17)	0 (0)	0 (0)
Mechanical aortic valve	24 (10)	19 (11)	15 (33)	4 (5)
Mechanical mitral valve	11 (5)	9 (5)	7 (16)	2 (2)
Other	27 (11)	17 (10)	1 (2)	2 (2)

Majeed A et al. Stroke 2010; 41: 2860-2866.



The optimal timing for resumption of warfarin therapy appears to be between 10 and 30 days from TAO-ICH

Grazie per l’attenzione

Sistema Socio Sanitario
Regione Lombardia
ASST Cremona

Take home messages

- *Pensare alla possibilità che il paziente assuma un DOAC*
  - Accurata anamnesi farmacologica
  - *Pazienti identificabili*
- *Implementare adeguata diagnostica laboratorio*
  - *TT, ECT, emoclot x dabigatran;*
  - *Attività anti-Xa x rivaroxaban e apixaban*
  - *Attività anti-IIa calibrata x dabigatran e anti-Xa calibrata per rivaroxaban e apixaban*
- *L'assunzione di DOAC non è una controindicazione assoluta alla trombolisi*
  - Ora ultima assunzione
  - Collaborazione con il laboratorio
- In corso di terapia con dabigatran
  - Idarucizumab
- *Esistono strategie alternative*