Il sanguinamento:
una frequente causa di accesso al Pronto Soccorso
nel follow-up dei pazienti in terapia anticoagulante…

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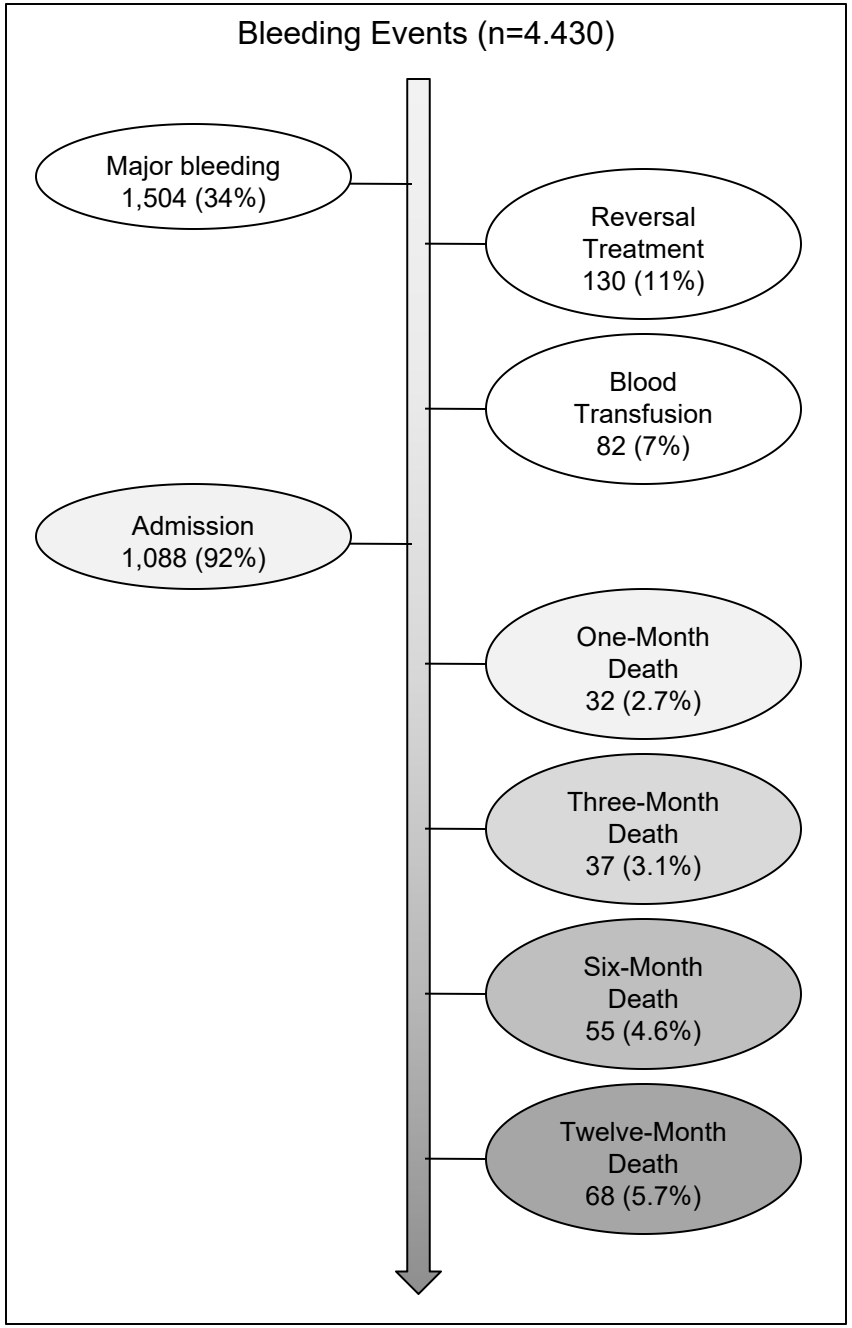
Real-Life Evidence

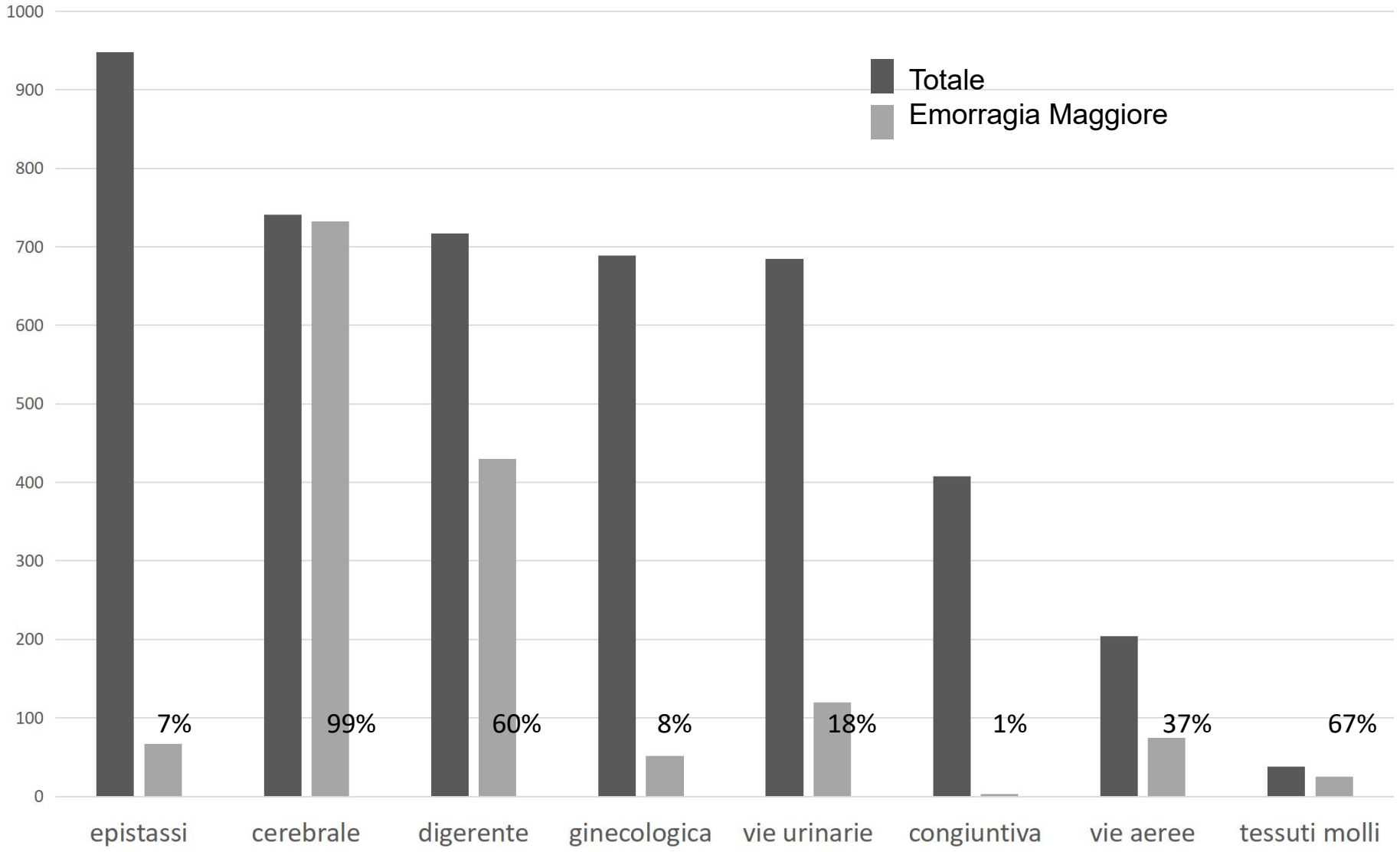
SIMEU Toscana

Bleeding at the Emergency Department

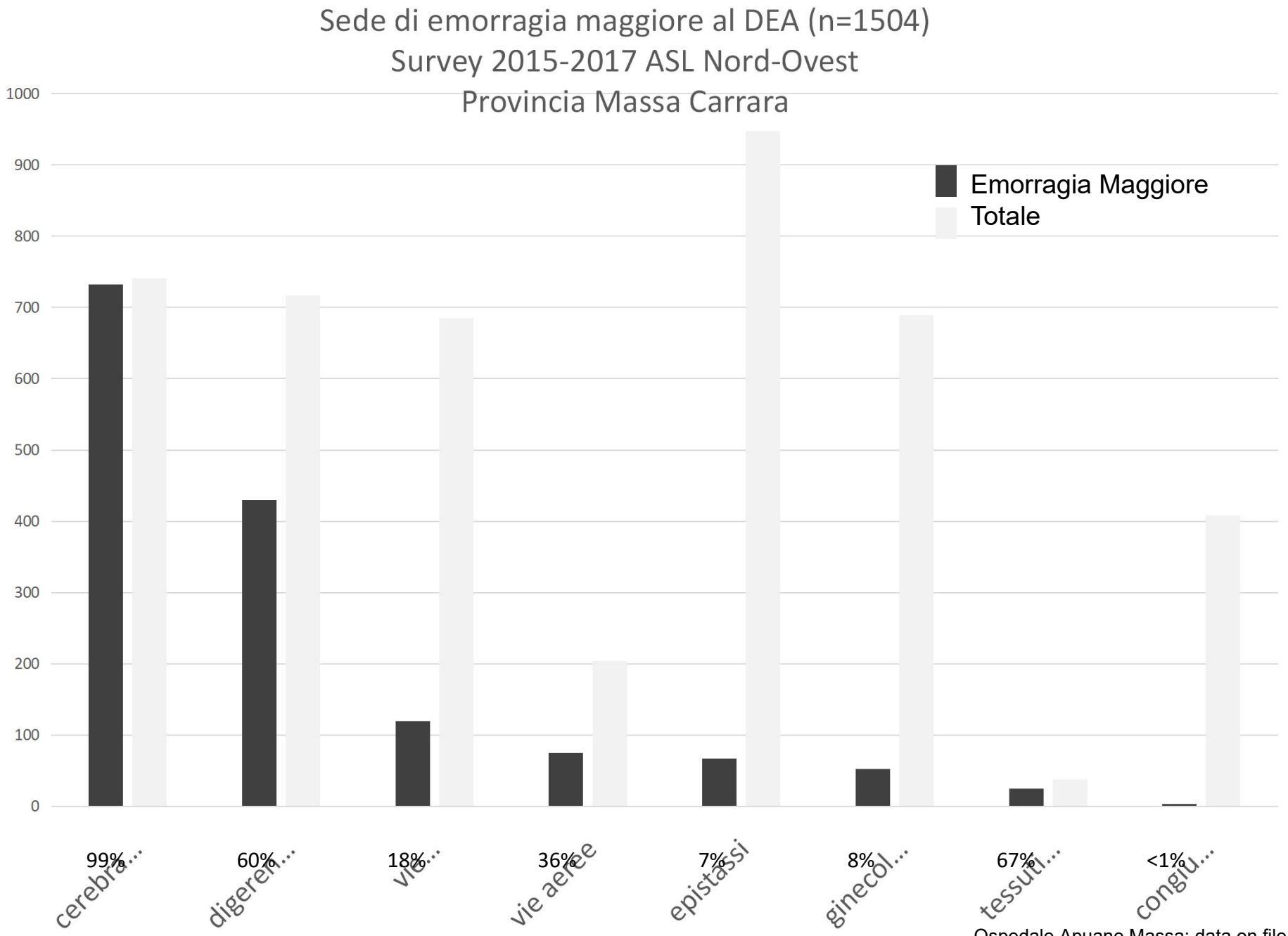
Survey ASL NordOvest SSN Toscana
Apuane Community Hospital, Massa
Catchment area: 250.000 inhabitants
4.430 patients enrolled,
3-year Survey 2015-2017


Bleeding Events (n=4.430)
Major bleeding
1,504 (34%)
Reversal
Treatment
130 (11%)
Blood
Transfusion
82 (7%)
Admission
1,088 (92%)
One-Month
Death
32 (2.7%)
Three-Month
Death
37 (3.1%)
Six-Month
Death
55 (4.6%)
Twelve-Month
Death
68 (5.7%)

Sede di emorragia al DEA (n=4.430)
Survey 2015-2017 ASL Nord-Ovest
Provincia Massa Carrara

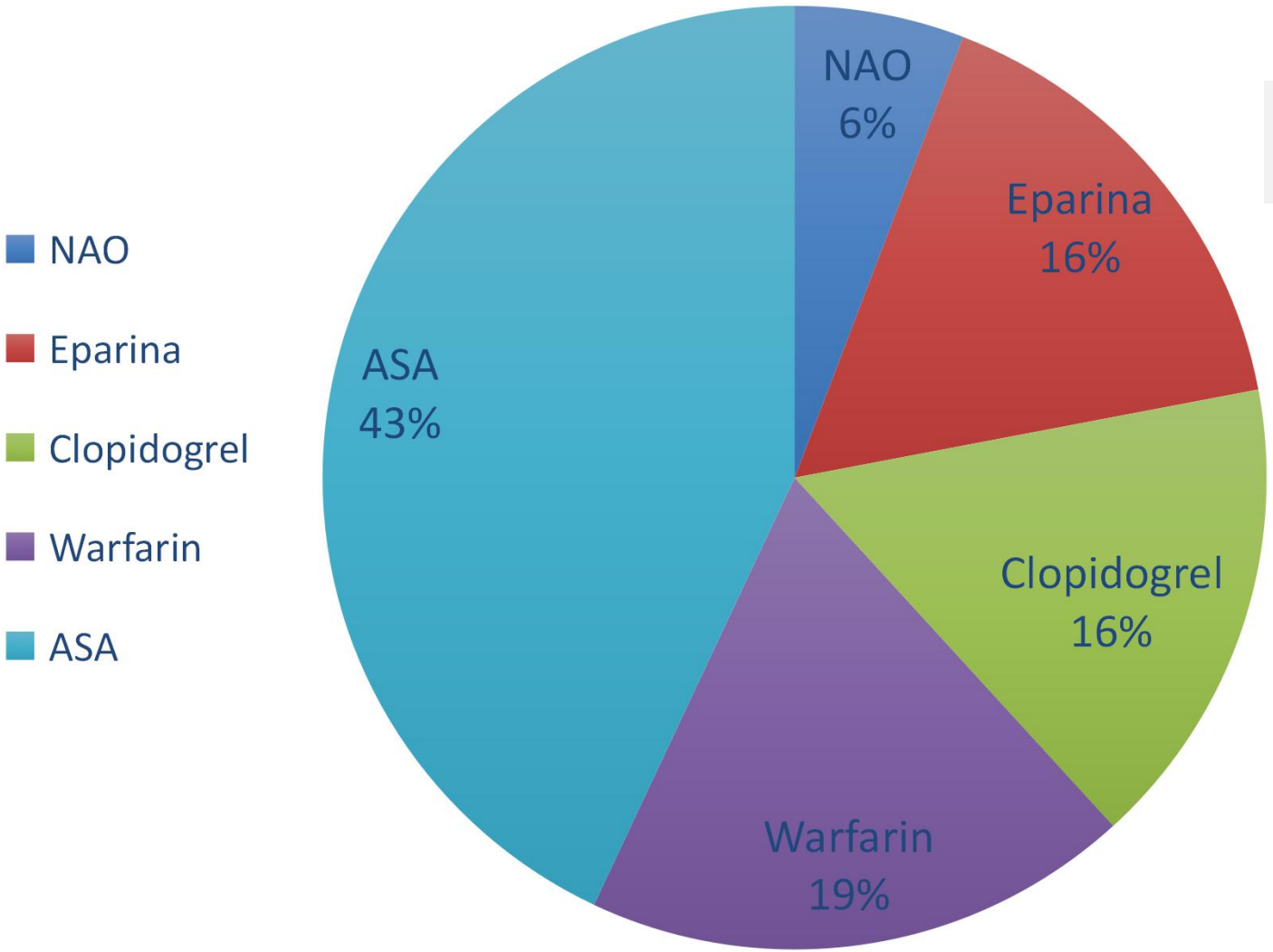


Ospedale Apuane Massa; data on file



Ospedale Apuane Massa; data on file

Emorragia maggiore e terapia antitrombotica



59% antiaggreganti

Ospedale Apuane Massa; data on file

Pazienti in terapia con nuovi anticoagulant orali e sanguinamento al DEA

P value: emorragia maggiore versus minore			
Antiaggreganti	270	32%	p<0.001
Anticoagulanti	1377	91%	p<0.001
P value: anticoagulanti vs antiaggreganti = 0.100			

Ospedale Apuane Massa; data on file

Pazienti in terapia con nuovi anticoagulant orali e sanguinamento al DEA

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P value: anticoagulanti vs antiaggreganti = 0.100			

	Totale Sanguinamenti % di Pz versus catchment area, Massa	Terapia Anticoagulante (catchment area Ospedale Apuane, Massa)
Totale NAO	144 2.6%	5.505
Coumadin Warfarin	433 3.9%	11.046

Ospedale Apuane Massa; data on file

Table 1. Baseline clinical characteristics, comorbidities and ongoing antithrombotics in patients with major bleeding events. (n=1,185). *p* value versus minor bleeding

	Major Bleeding; n=1185(38,9%)	*p* value
Mean Age (year ± s.d.)	74±16	<0.001
Hypertension (n;%)	613 (51,7%)	<0,001
Diabetes Mellitus (n;%)	264 (22,3%)	<0,001
Hypercholesterolemia (n;%)	229 (19,3%)	<0,001
$CHA_2D_2VASC \geq 2$ (n;%)	382 (64,3%)	<0.001
Kidney Disease (n;%)	76 (6,4%)	<0,001
Chronic Obstructive Pulmonary Disease (n;%)	128 (10,8%)	<0,001
Pulmonary Embolism (n;%)	24 (2%)	0,005
Cancer (n;%)	204 (17,2%)	<0,001
Ischemic Vascular Disease (n;%)	329 (27,8%)	<0,001
Anti-coagulants, (n;%)	287(24,2%)	<0,001
Anti-platelets, (n;%)	388 (32,7%)	<0,001

Table 1. Baseline laboratory tests in patients with major bleeding events. (n=1,185). *p* value versus minor bleeding

Patients enrolled; n=3.048 (100%)	Major Bleeding; n=1185(38,9%)	p value
Partial Thrombin Time (n%)	30±9	<0,001
White Blood Cells (n°/°°)	10,1±6,6	<0,001
Fibrinogen (mg/dL)	434±202	0,001
D-Dimer (md/dL)	1734±3055	<0,001
Glucose (mg/dL)	146±61	<0,001
Creatinine (mg/dL)	1,2±0,7	<0,001
Glomerular Filtration Rate (ml/min)	71±26	<0,001

Major bleeding events in the subsets of patients with different anticoagulants treatment strategy (n=577).

Anticoagulation treatment strategy	Patients with ongoing anticoagulation in the catchment area 200,000 inhabitants (n=16.551)	Major Bleeding events according to anticoagulation (n= 577)	Chi square Yates' correction p value
Dabigratan	1.887 (11.4%)	58 (10.1%)	0.374
Rivaroxaban	2.156 (13.0%)	55 (9.5%)	
Apixaban	1.143 (6.91%)	24 (4.2%)	
Edoxaban	319 (1.93%)	7 (1.2%)	
Total DOACs	5.505 (33.3)	144 (25.0%)	<0.0001
Total Warfarin	11.046 (66.7%)	433 (75.0%)	

Al PS il sanguinamento rappresenta una frequente causa di accesso

La terapia
anticoagulante o antiaggregante
aumenta il rischio di sanguinamento

Antithrombotics: Prevention &Treatment Strategy

Atrial Fibrillation

2016 ESC Guidelines for the management of atrial fibrillation (Eur Heart J 2016. doi: 10.1093/eurheartj/ehw210)

Pulmonary embolism

2016 ACCP Guidelines. VT and PE guidelines. Chest 2016
2014 ESC Guidelines. Guidelines for the management of PE. Eur Heart J 2014

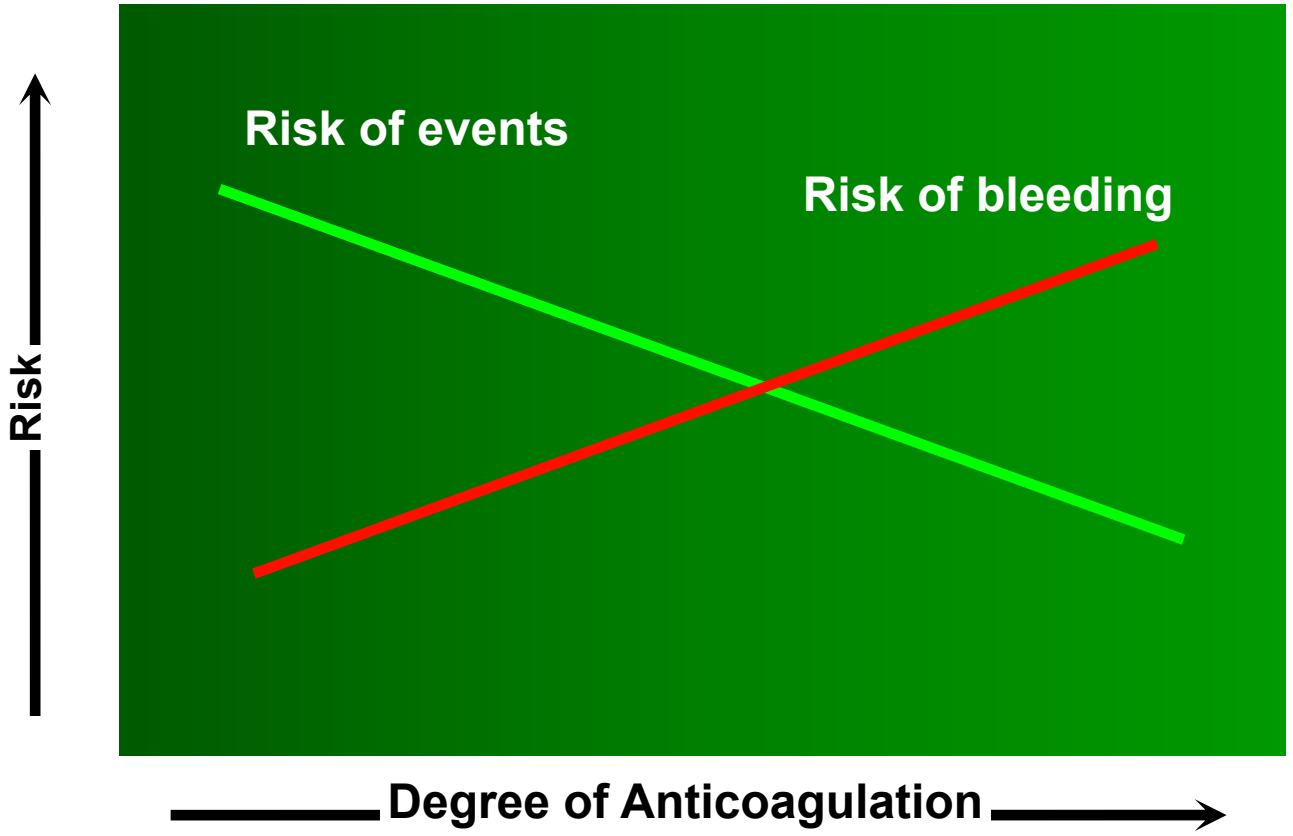
Acute Coronary Syndrome

2012 ESC Guidelines for the management of AMI in patients presenting with STEACS (Eur Heart J 2012).
2015 ESC Guidelines for the management of ACS in patients presenting without STEACS (Eur Heart J 2015).

International Society of Thrombosis and Haemostasis

2005 Definition of major bleeding in clinical investigations… J Thromb Haemost 3(4) 692-4
2011 Standardized bleeding definition for cardiovascular clinical trials Circulation 2011, 123: 2736-47.

Bilancing Events and Bleeding



Hemostasis ⟷ **Thrombosis**

…two sides of the same coin

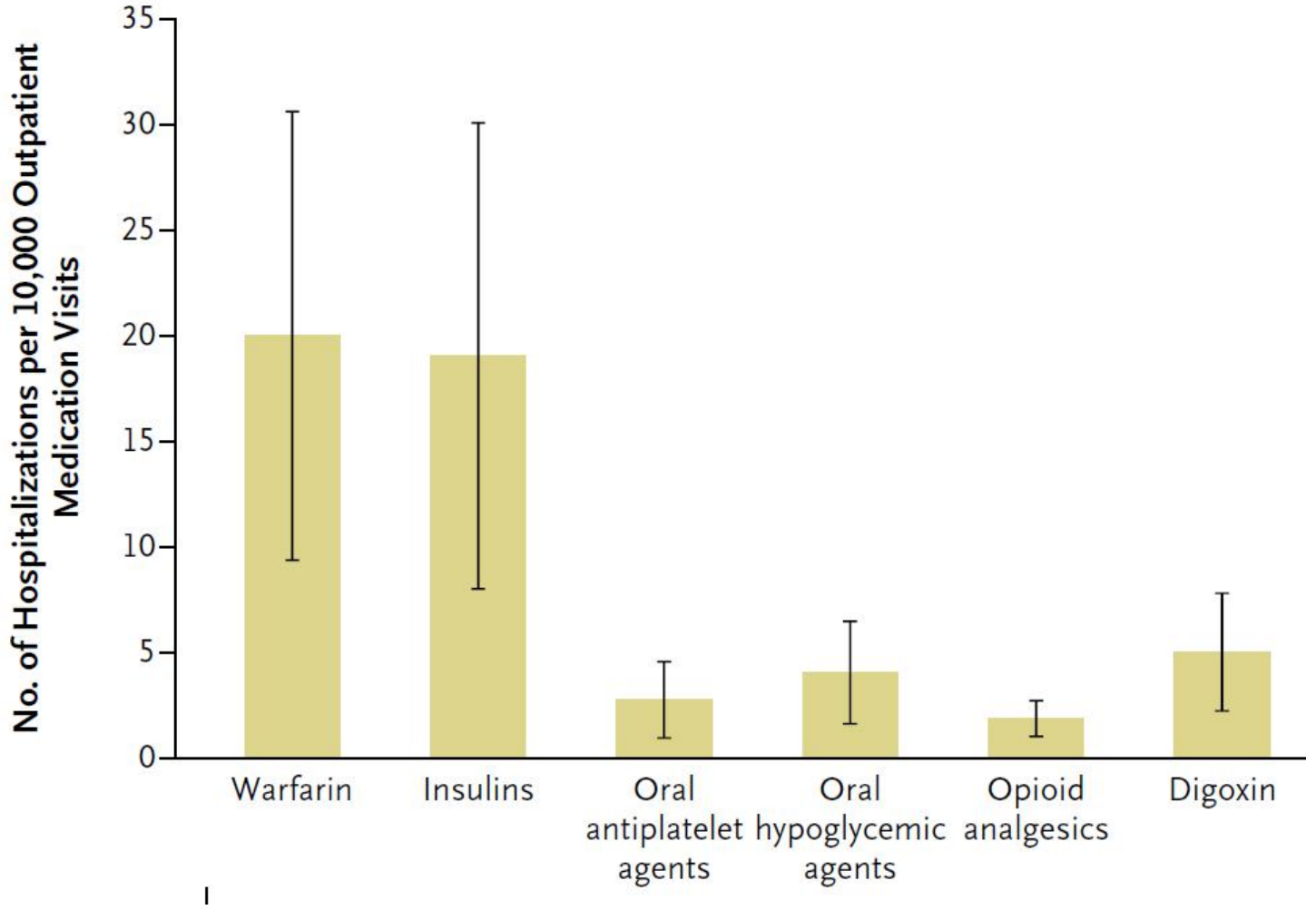
National Surveillance of Emergency Department Visits for Outpatient Drug Events

Warfarin, ASA, Clopi
6.2+2.5+1.6
= 10.3%

Drug	Cases, No.	Annual Estimate, No. (%)
Insulins	1577	55 819 (8.0)
Warfarin	1234	43 401 (6.2)†
Amoxicillin	1022	30 135 (4.3)
Aspirin	473	17 734 (2.5)
Trimethoprim-sulfamethoxazole	447	15 291 (2.2)
Hydrocodone-acetaminophen	420	15 512 (2.2)
Ibuprofen	526	14 852 (2.1)
Acetaminophen	497	12 832 (1.8)
Clopidogrel	241	10 931 (1.6)†
Cephalexin	288	10 620 (1.5)
Penicillin	270	9275 (1.3)
Amoxicillin-clavulanate	274	8959 (1.3)
Azithromycin	255	8794 (1.3)
Levofloxacin	230	8682 (1.2)
Naproxen	245	8634 (1.2)
Phenytoin	238	7937 (1.1)
Oxycodone-acetaminophen	227	7328 (1.0)

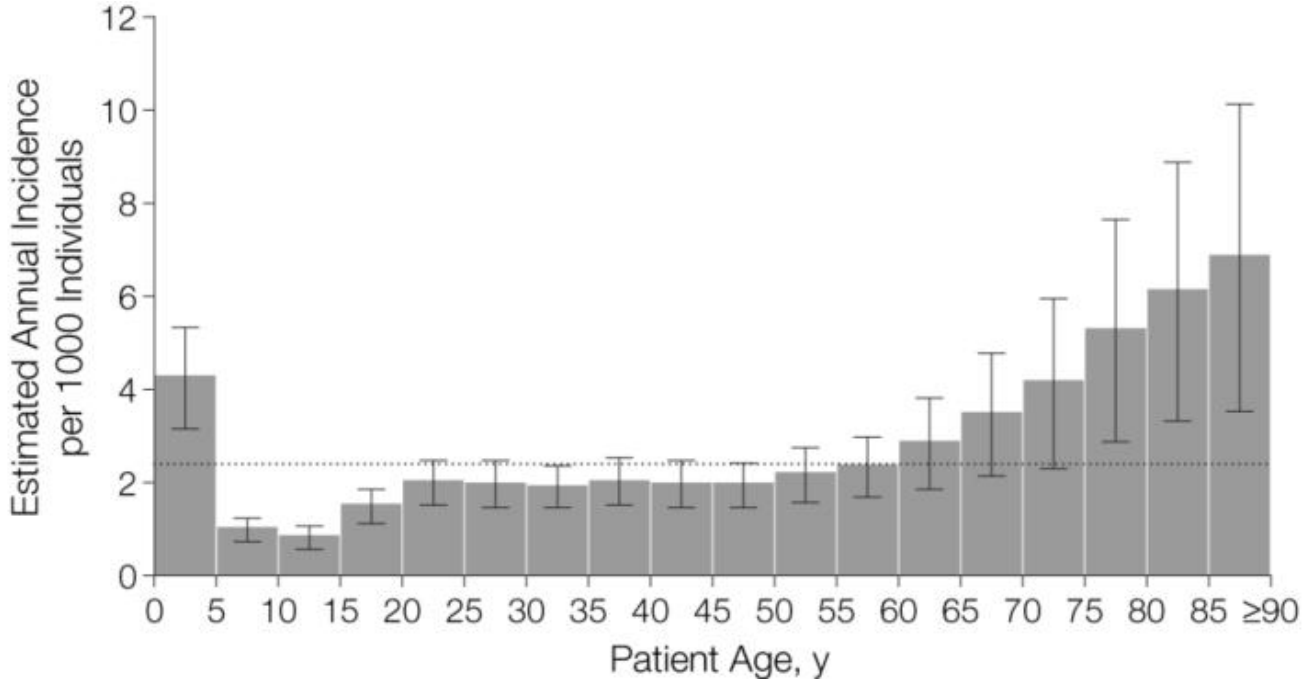
JAMA. 2006;296(15):1858-1866. doi:10.1001/jama.296.15.1858

Emergency hospitalization for adverse drug events



Emergency Hospitalizations for Adverse Drug Events in Older Americans.
Budnitz DS. N Engl J Med 2011; 365: 2002-12

National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events



The estimated annual population rate of adverse drug events (dotted line) is 2.4 per 1000 (95% confidence interval, 1.7-3.0). Error bars represent 95% confidence intervals. Data are from the 2004-2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

JAMA. 2006;296(15):1858-1866. doi:10.1001/jama.296.15.1858

Update on Antithrombotics and Bleeding
Case-Load & Case-Mix in the ED

In Pronto Soccorso

sanguinamento spontaneo-
in terapia antitrombotica-
post traumatico-

Subcommittee of Control of Anticoagulation

International Society on Thrombosis and Haemostasis, 2005

Emorragia Maggiore	Emorragia Life-Threatening
Riduzione Hb ≥ 2 g/dL	Emorragia Fatale
Necessità trasfusione ≥2U GRC	Emorragia intracranica sintomatica
Sanguinamento in sito critico (intracranico, oculare con minus visus, spinale, pericardico, intraarticolare, intramuscolare con sindrome compartimentale, retroperitoneale	Riduzione Hb ≥ 5 g/dL
	Necessità trasfusione ≥4U GRC
	Sanguinamento richiedente supporto inotropo
	Sanguinamento richiedente trattamento chirurgico urgente

2005 Definition of major bleeding in clinical investigations. J Thromb Haemost 3(4) 692-4

Emorragia Maggiore

1) Emorragia fatale

2) Sanguinamenti sintomatici in una delle seguenti sedi critiche:
- -emorragie intracraniche
- -ematoma spinale
- -ematoma intraoculare
- -ematoma retroperitoneale
- -emartro
- -emopericardio
- -emorragia intramuscolare con sindrome compartimentale

3) Emorragie con perdita acuta di ≥2 g/dl di Hb
o necessità trasfusione ≥2 Unità di GRC

4) Sanguinamento richiedente supporto inotropo
Sanguinamento richiedente trattamento chirurgico urgente

2005 Definition of major bleeding in clinical investigations. J Thromb Haemost 3(4) 692-4

Quando :

Osservare
Monitorare
Ricoagulare
Trasfondere

…PS

…Sala

Giovanni di Paolo di Grazia
(Siena, 1398-1482)
Detail of the Beheading of St. John the Baptist,
The Art Institute of Chicago.

-Endoscopia digestiva
-AngioTC per diagnosticare
-Radiologo interventista per trattare

Angiographic Embolization for Gastroduodenal Hemorrhage

Safety, Efficacy, and Predictors of Outcome

George A. Poultsides, MD; Christine J. Kim, MD; Rocco Orlando III, MD; George Peros, MD; Michael J. Hallisey, MD; Paul V. Vignati, MD

Conclusions: Angiographic embolization for gastroduodenal hemorrhage was associated with in-hospital rebleeding in almost half of the patients. Angiographic failure can be predicted if embolization is performed late, following blood transfusion of more than 6 units, or for rehemorrhage from a previously suture-ligated duodenal ulcer.

Arch Surg. 2008;143(5):457-461

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Table 2. Published Series of Angiographic Embolization for Upper Gastrointestinal Tract Bleeding

Source	Patients, No.	Technical Success Rate, %	Primary Clinical Success Rate, %	Empirical (Blind) Embolizations, %	Major Ischemic Complications, %	Mortality, %
Lieberman et al,[11] 1984	32	100	59	16	6	26
Dempsey et al,[12] 1990	34	NA	62	59	0	41
Encarnacion et al,[13] 1992	29	NA	62	NA	0	34
Lang,[14] 1992	57	91	40	NA	16	NA
Walsh et al,[15] 1999	50	92	52	50	2	40
Aina et al,[16] 2001	75	99	76	38	4	35
Schenker et al,[17] 2001	163	95	58	63	1	33
Defreyne et al,[18] 2001	20	95	68	33	5	32
Ljungdahl et al,[19] 2002	18	94	78	28	0	6
Ripoll et al,[20] 2004	31	94	65	NA	3	26
Holme et al,[21] 2006	40	95	65	70	0	25
Our study	57	94	51	39	7	21

Abbreviation: NA, not available.

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Table 1. Univariate and Multivariate Predictors of Embolization Failure

Predictor	Patients, No. (%) (N=57)	Univariate Analysis	Logistic Regression Analysis	
		P Value	OR (95% CI)	*P* Value
Age > 70 y	26 (46)	.32	0.59 (0.13-2.53)	.48
Male	38 (67)	.13	2.53 (0.63-10.08)	.18
Duodenal ulcer after suture ligation	5 (9)	.11	0.24 (0.07-0.78)	.03
Prior coagulopathy	15 (26)	.43	7.27 (0.95-55.51)	.05
Immunosuppression	14 (25)	.40	1.40 (0.17-11.08)	.74
Renal failure at presentation	15 (26)	.06	0.25 (0.03-1.82)	.17
MOSF	15 (26)	.15	0.09 (0.01-1.26)	.07
> 6 U of PRBCs prior to procedure	27 (47)	.02	0.25 (0.06-0.95)	.04
Permanent embolic agents	29 (51)	.73	0.35 (0.07-1.69)	.19
Empirical embolization	22 (39)	.45	1.92 (0.47-7.72)	.35

Abbreviations: CI, confidence interval; MOSF, multiple organ system failure; OR, odds ratio; PRBCs, packed red blood cells.

Cardiovasc Intervent Radiol (2013) 36:608–612
DOI 10.1007/s00270-012-0462-5

CIRSE

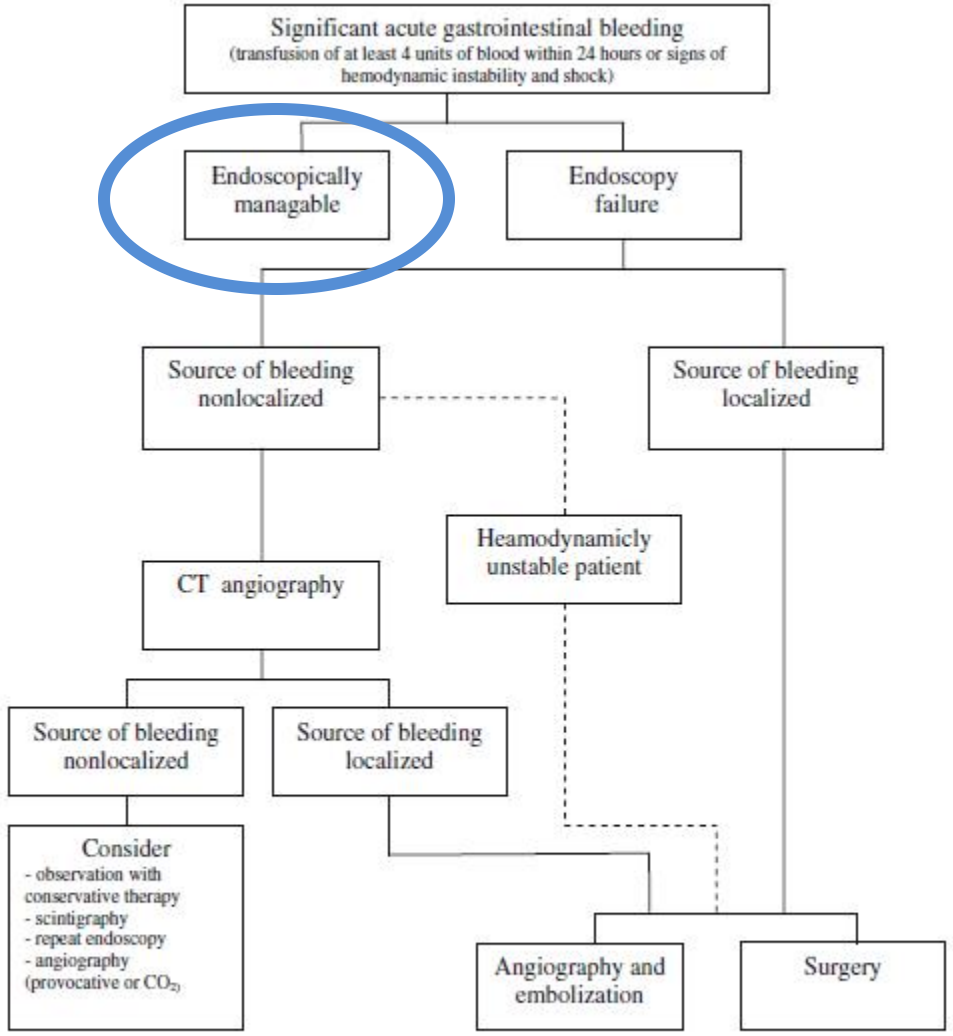
CIRSE STANDARDS OF PRACTICE GUIDELINES

Quality Improvement Guidelines for Transcatheter Embolization for Acute Gastrointestinal Nonvariceal Hemorrhage

Vlastimil Valek · Jakub Husty

Upper GI bleeding	
Technical success	93 %
Clinical success	67 %
Rebleeding rate	33 %
Lower GI bleeding |	
Technical success	95 %
Clinical success	76 %
Rebleeding rate	24 %

Emergency Medicine



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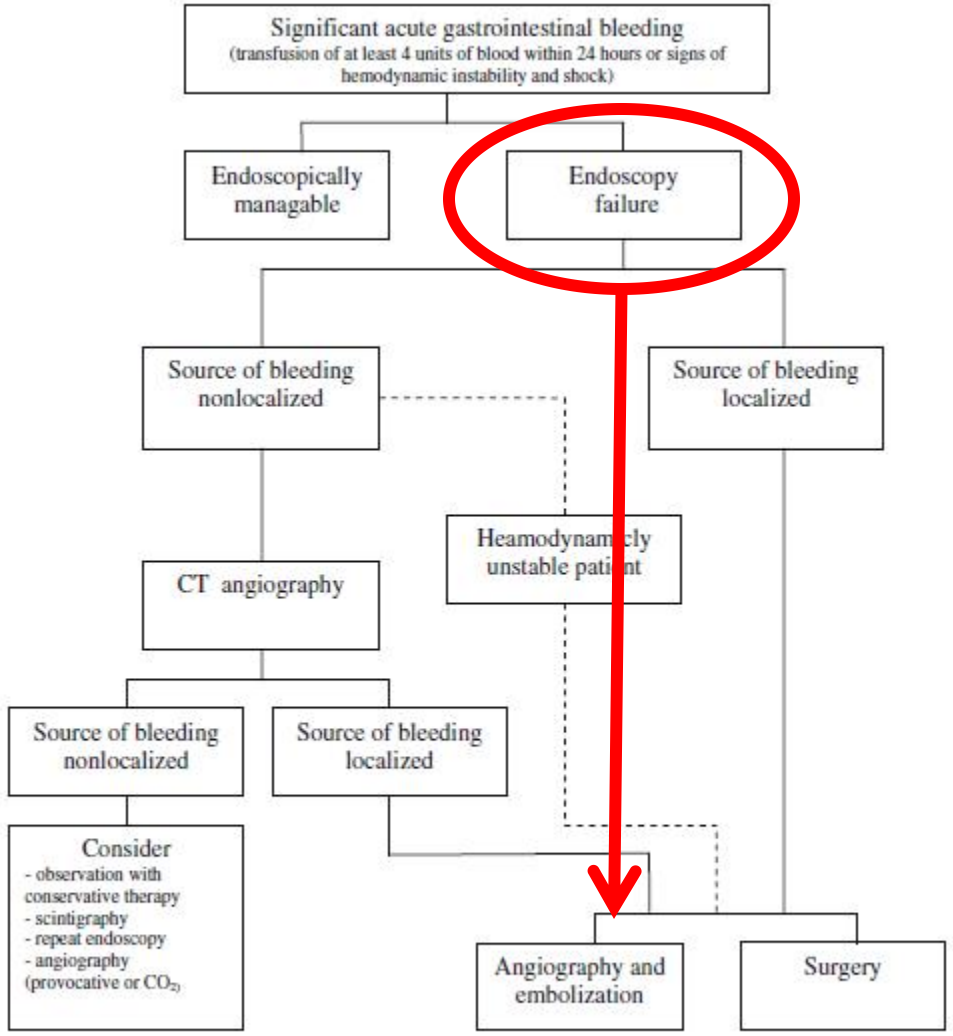
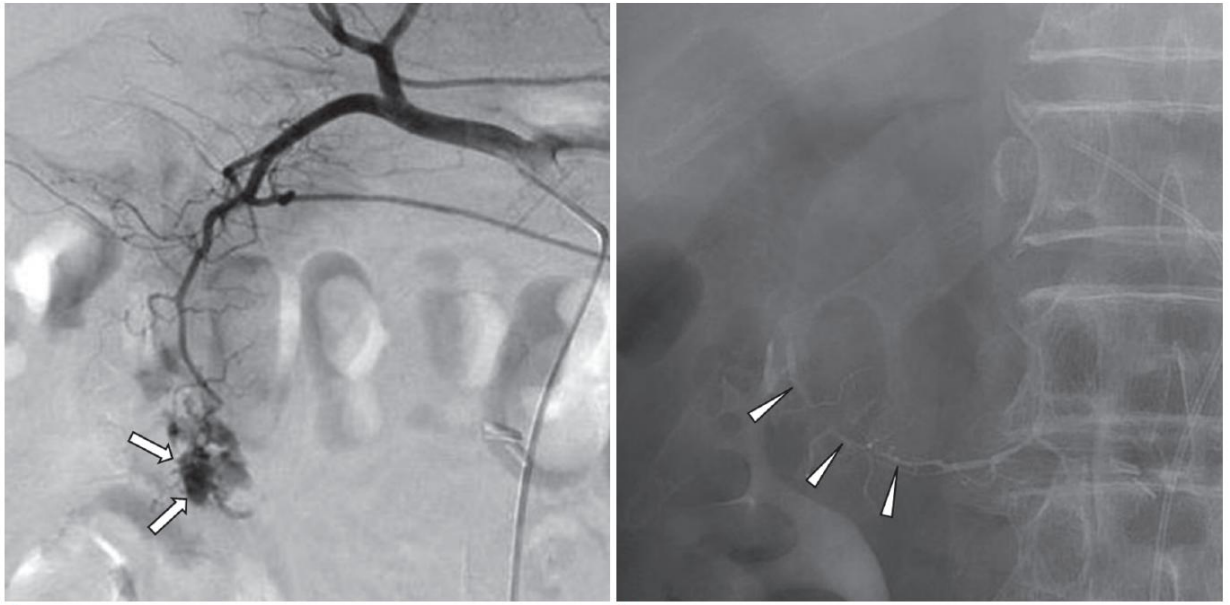
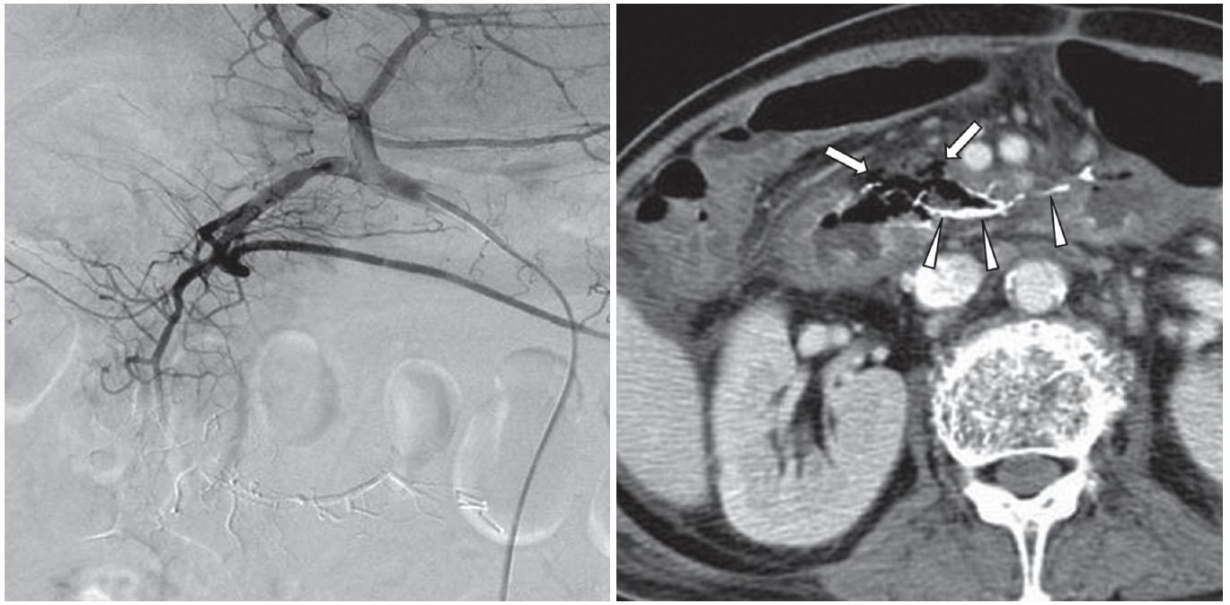




A B



C D

65-year-old man with B-cell lymphoma presented with melena.

A. Celiac angiogram shows contrast extravasation (arrows) from small branches of gastroduodenal artery. **B, C.** Long segmental embolization was done with N-butyl cyanocrylate (NBCA) to prevent back flow from the superior mesenteric artery. Spot radiograph **(B)** and superior mesenteric artery angiogram **(C)** show NBCA cast (arrowheads) without further bleeding. **D.** A computed tomography scan 4 days later showed bowel ischemia and perforation (arrows) with peritonitis surrounding radiopaque embolic material (arrowheads).

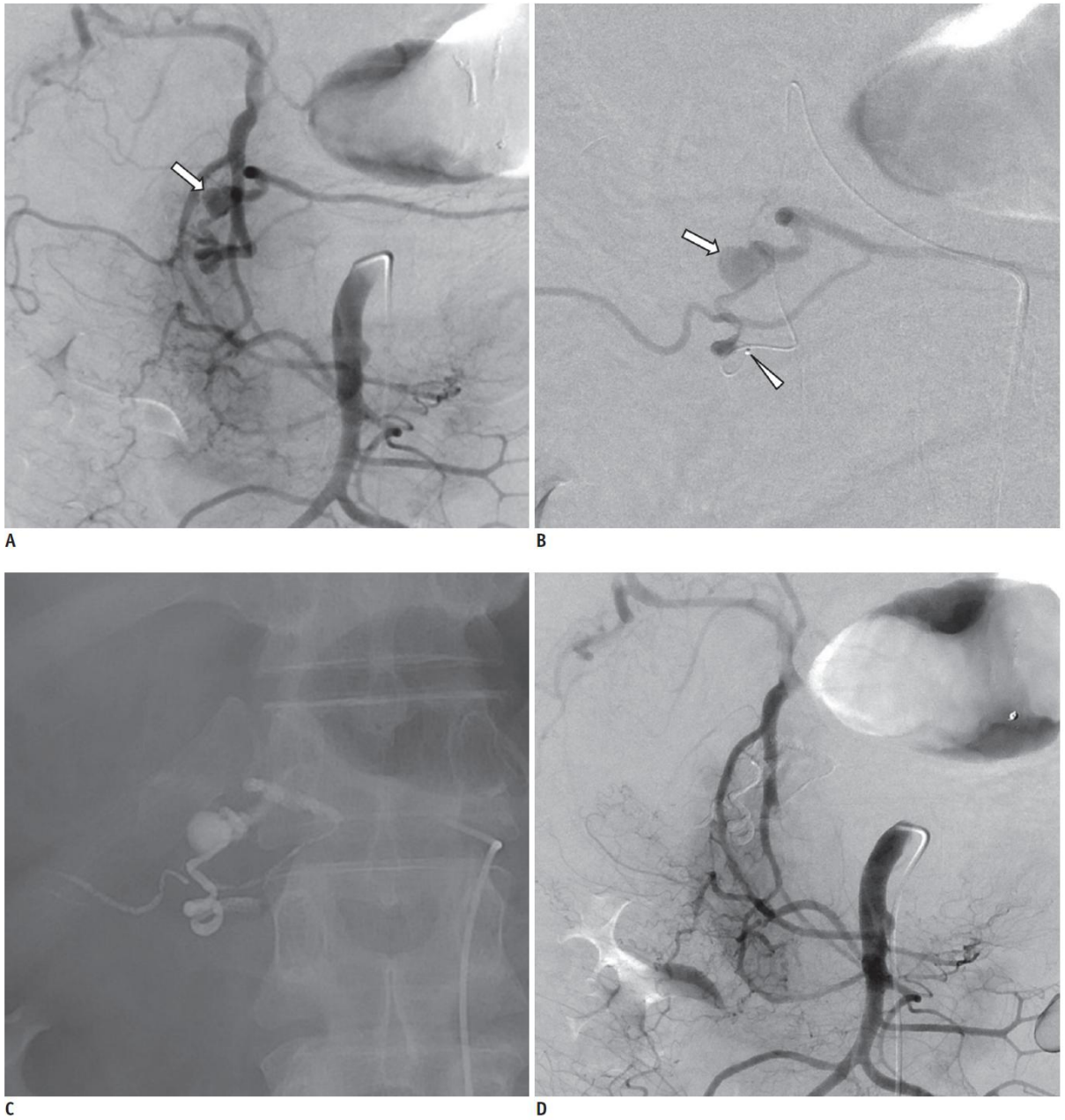


Fig. 3. 54-year-old man with ERCP-induced pancreatitis.
This patient had undergone embolization for bleedings from short gastric and left interior phrenic arteries. **A.** Superior mesenteric artery (SMA) angiogram shows pseudoaneurysm (arrow) at distal gastroduodenal artery. **B.** The tip (arrowhead) of microcatheter was advanced as far as to pseudoaneurysm (arrow), however, could not reach it. **C.** N-butyl cyanocrylate (NBCA) embolization (1 : 3 mixture with lipiodol) was done with NBCA cast covering pseudoaneurysm. **D.** Completion SMA angiogram shows no visualization of pseudoaneurysm. Hematochezia was controlled.

Bronchial Artery Embolization for the Treatment of Hemoptysis in Patients with Cystic Fibrosis

GEORGE M. BRINSON, PEADAR G. NOONE, MATTHEW A. MAURO, MICHAEL R. KNOWLES, JAMES R. YANKASKAS, JEET S. SANDHU, and PAUL F. JAQUES

Division of Pulmonary and Critical Care Medicine and the UNC-CF Center, Department of Medicine, University of North Carolina School of Medicine, and Department of Radiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 157 1998

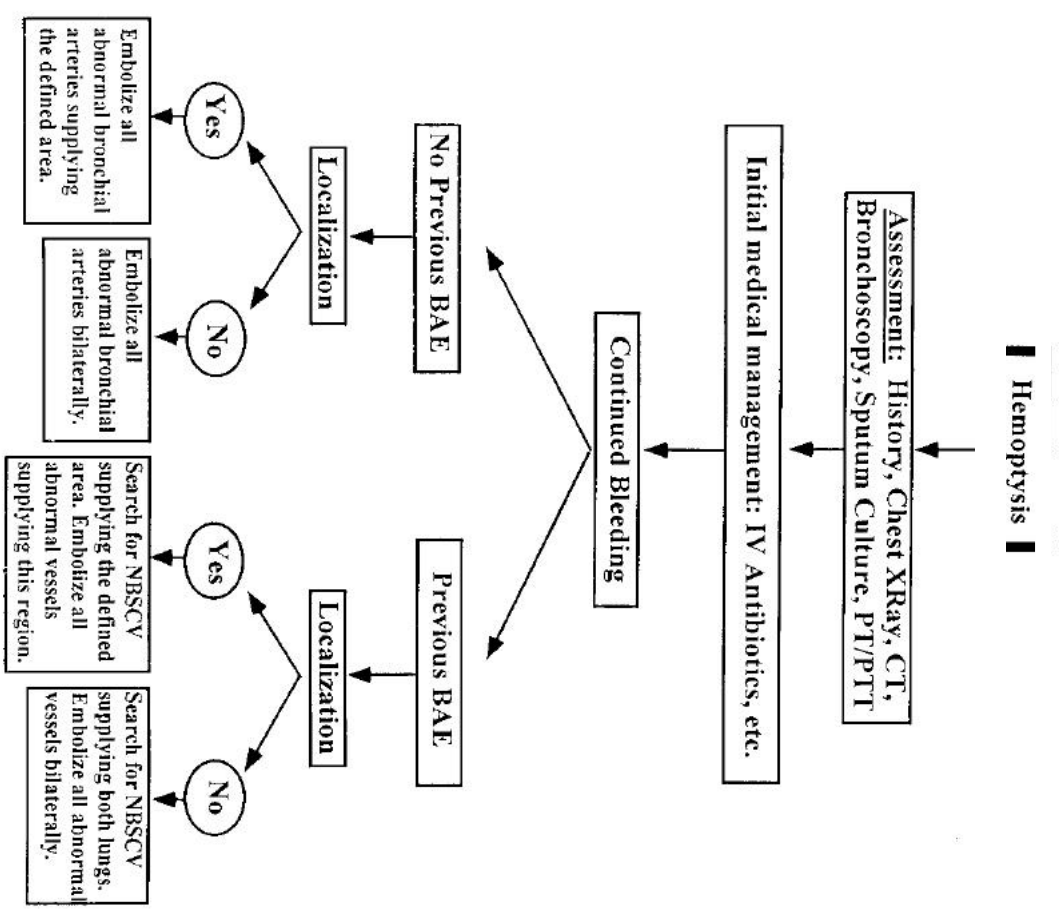


Figure 4. Proposed algorithm for the treatment of hemoptysis in patients with cystic fibrosis.

Bronchial Artery Embolization for the Treatment of Hemoptysis in Patients with Cystic Fibrosis

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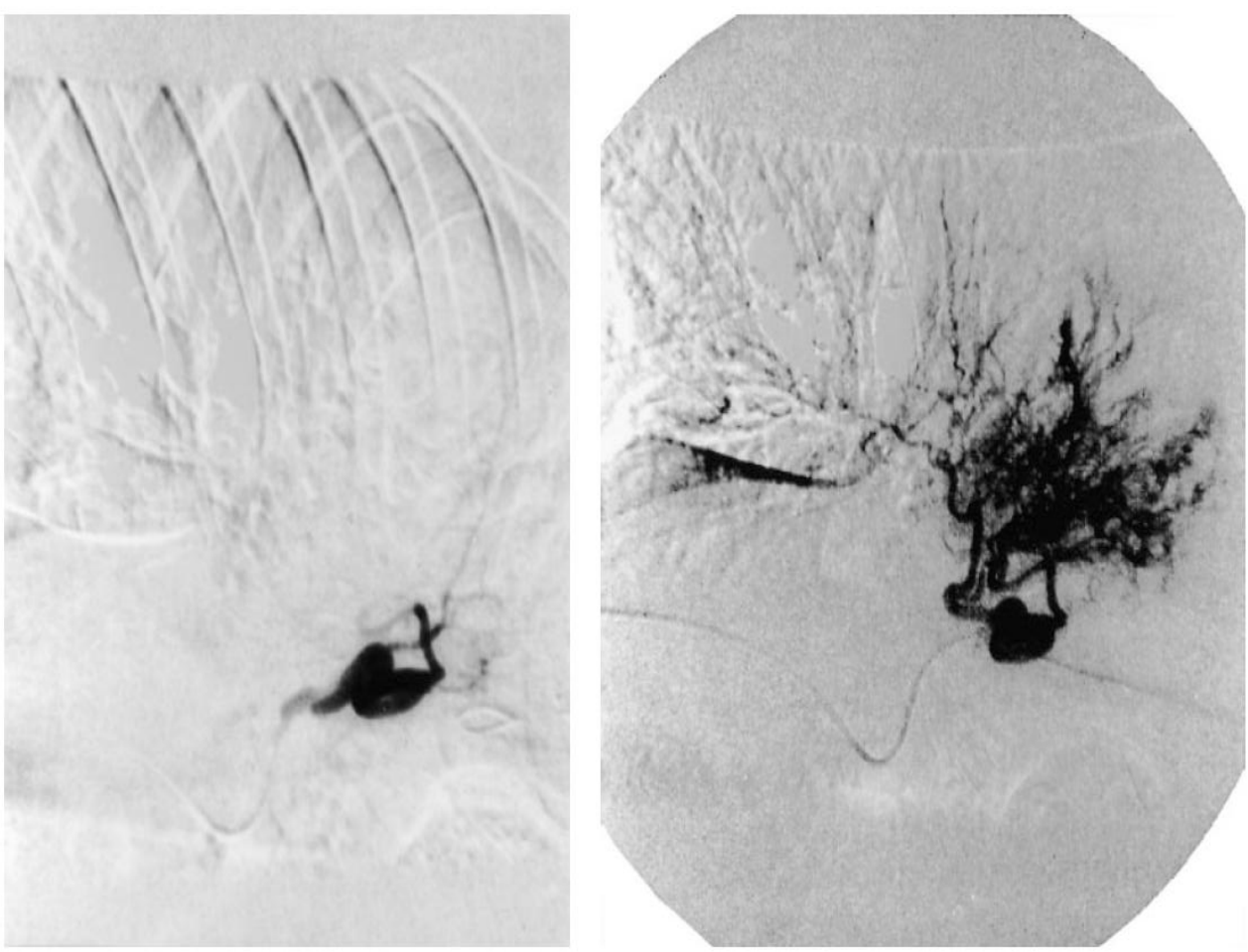


Figure 1. (*Top panel*) Angiogram of a hypertrophied right bronchial artery supplying the right upper lobe. (*Bottom panel*) Angiogram of the same bronchial artery after embolization with polyvinyl alcohol particles.

The Oncologist®

Symptom Management and Supportive Care

Management of Bleeding in Patients with Advanced Cancer

JOSE PEREIRA, TIEN PHAN

Department of Oncology, University of Calgary, Calgary, Alberta, Canada

Table 2. Management of bleeding in patients with advanced cancer: systemic interventions

- Vitamin K (phytonadione)
- Vasopressin/desmopressin
- Somatostatin analogues (octreotide)
- Antifibrinolytic agents
  - —Tranexamic acid
  - —Aminocaproic acid
  - —Aprotinin
- Blood Products
  - —Platelets
  - —Fresh frozen plasma
  - —Coagulation factors
  - —Packed red blood cell

Table 1. Management of bleeding in patients with advanced cancer: local measures

- Nonadherent dressings
- Hemostatic dressings
  - —Absorbable gelatin (sponge)
  - —Microfibrillar collagen
  - —Absorbable collagen sheet
  - —Absorbable collagen sponge
  - —Oxidized cellulose and regenerated cellulose
  - —Fibrin sealants
  - —Alginates
- Hemostatic agents
  - —Epinephrine
  - —Acetone
  - —Thrombin/thromboplastin
  - —Topical cocaine
  - —Prostaglandins E2 and F2
  - —Silver nitrate
  - —Formalin
  - —Aluminum astringents
  - —Sucralfate
- Radiotherapy
- Surgery
  - —Vessel ligation
  - —Tissue resection
- Endoscopy
- Interventional radiology
  - —Transcutaneous arterial embolization
  - —Transcutaneous arterial balloons

Embolization in Trauma

- Angiography supplanted by CT

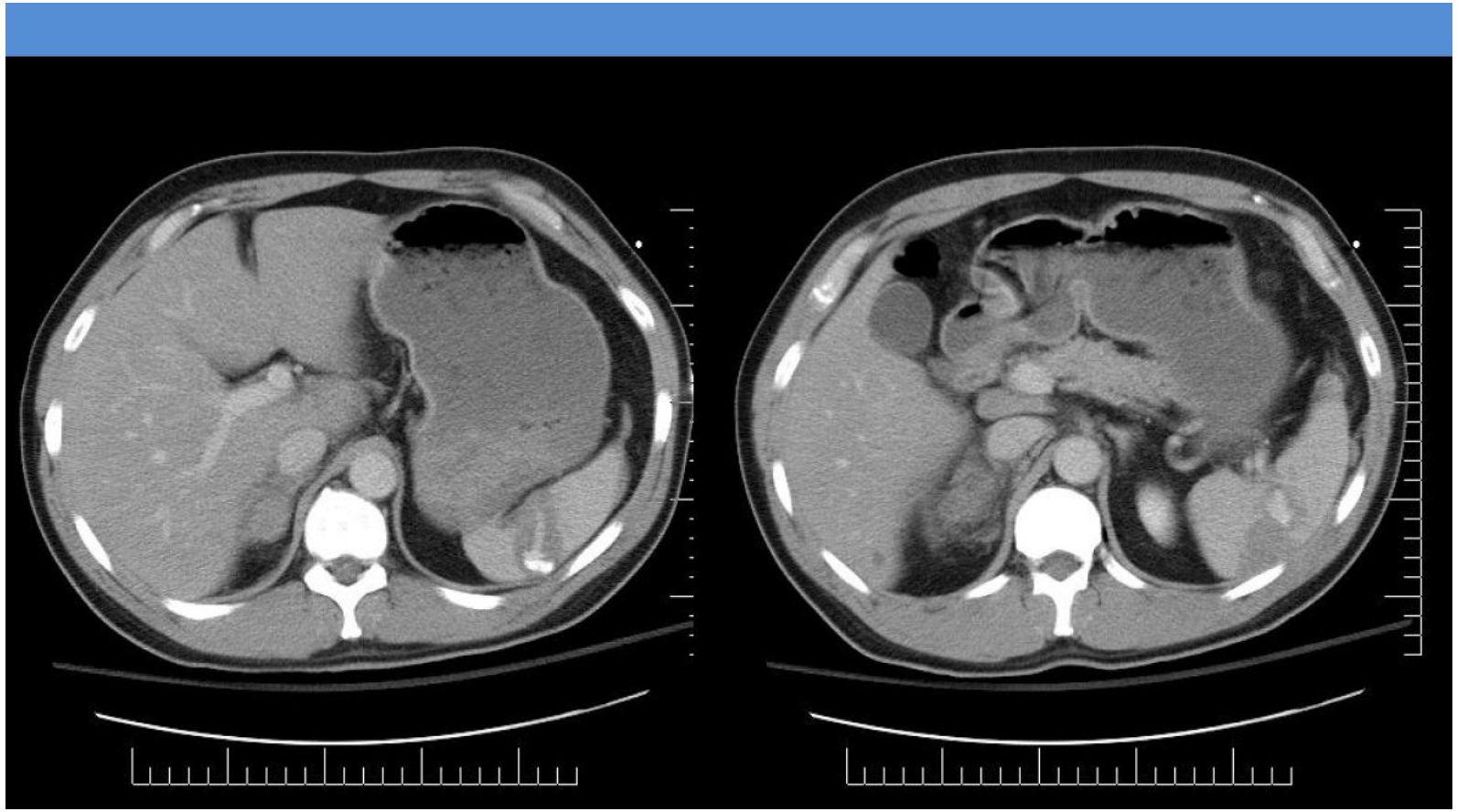
- Liver and Spleen susceptible to blunt and penetrating trauma embolization feasible (liver dual blood supply, spleen rich collateral network)

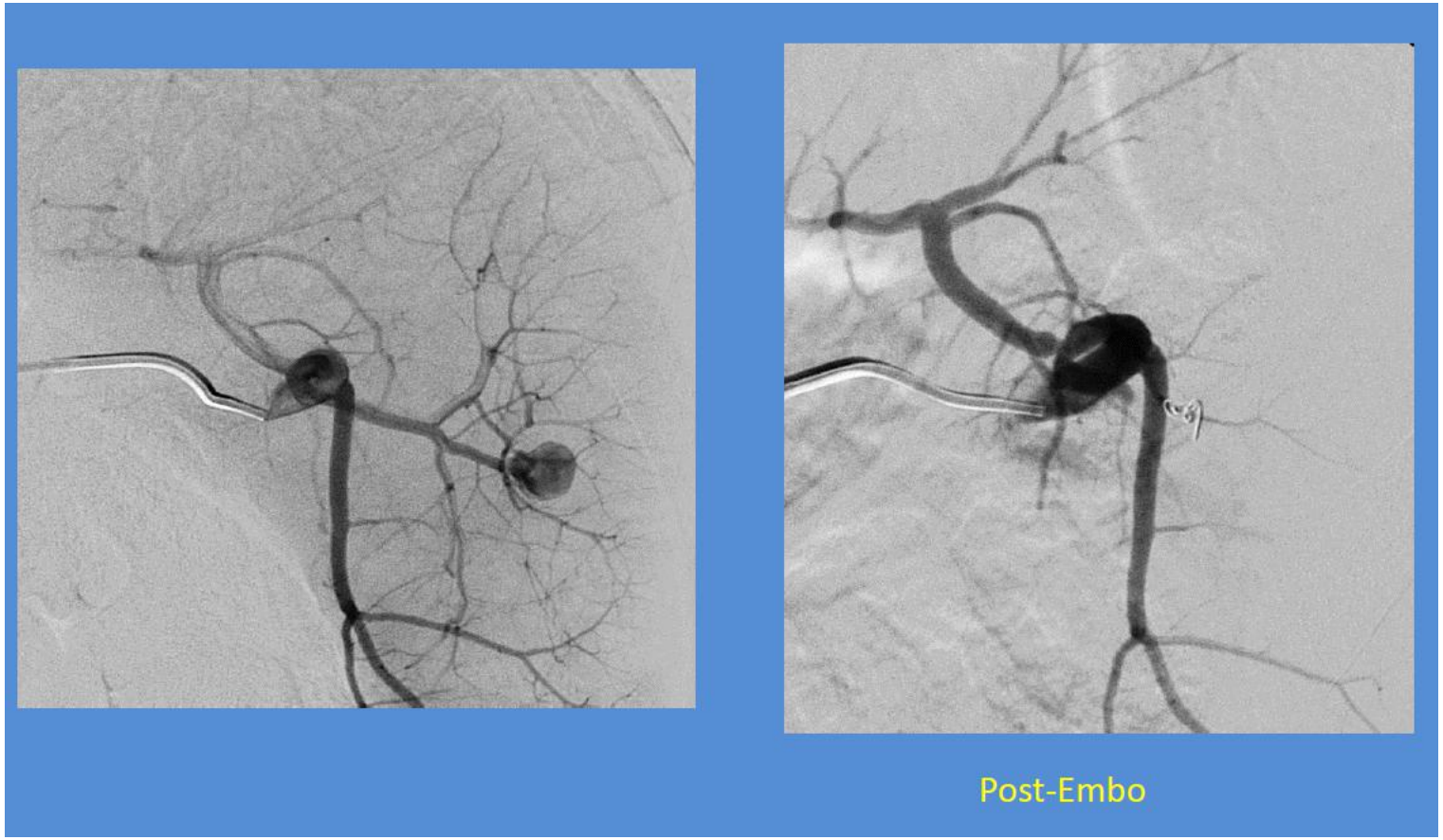
Splenic Laceration

Sclafani et al reported an 84% salvage rate

Shanmuganathan et al reported a 94% salvage rate

…using splenic embolization





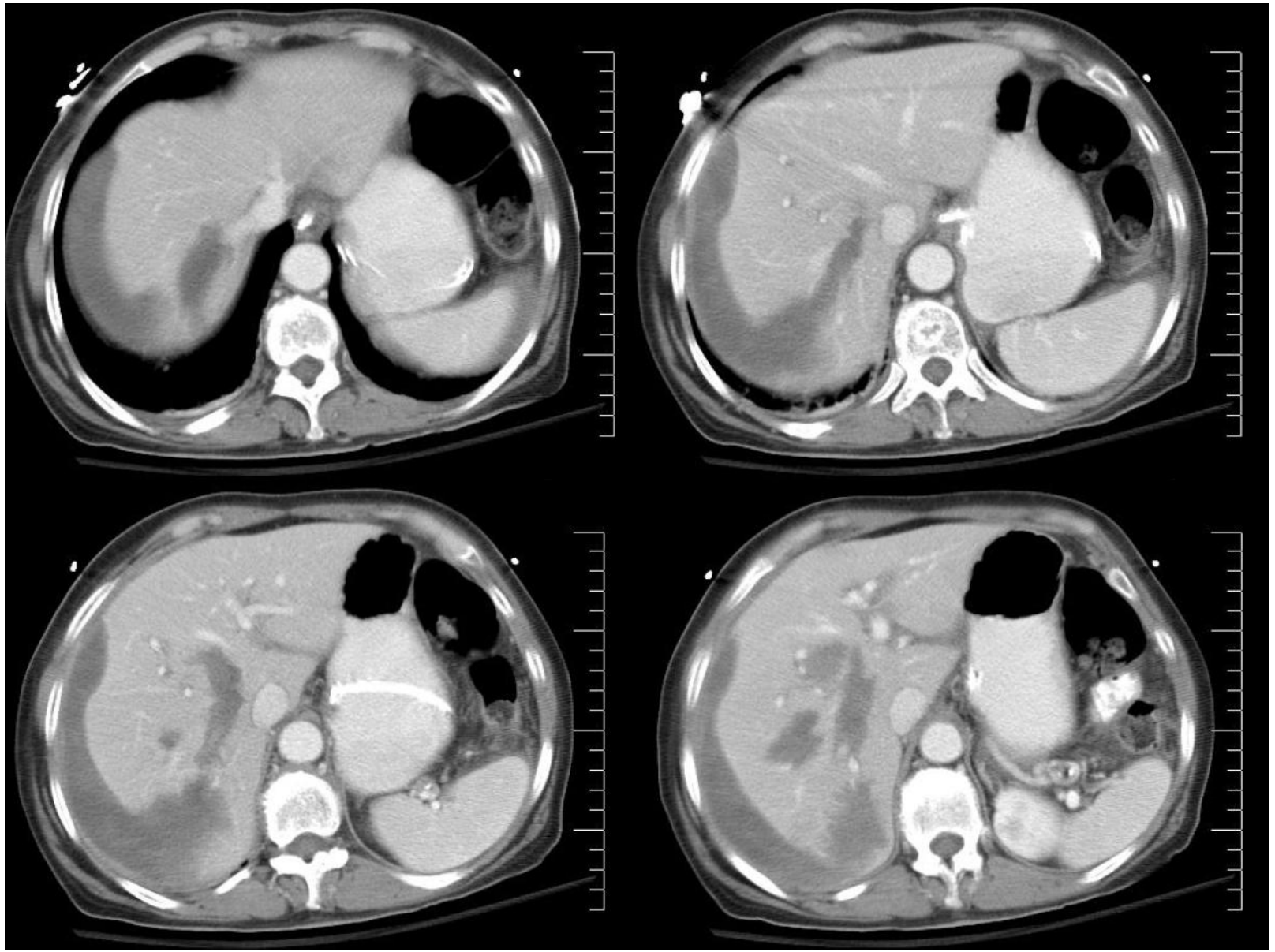
Post-Embo

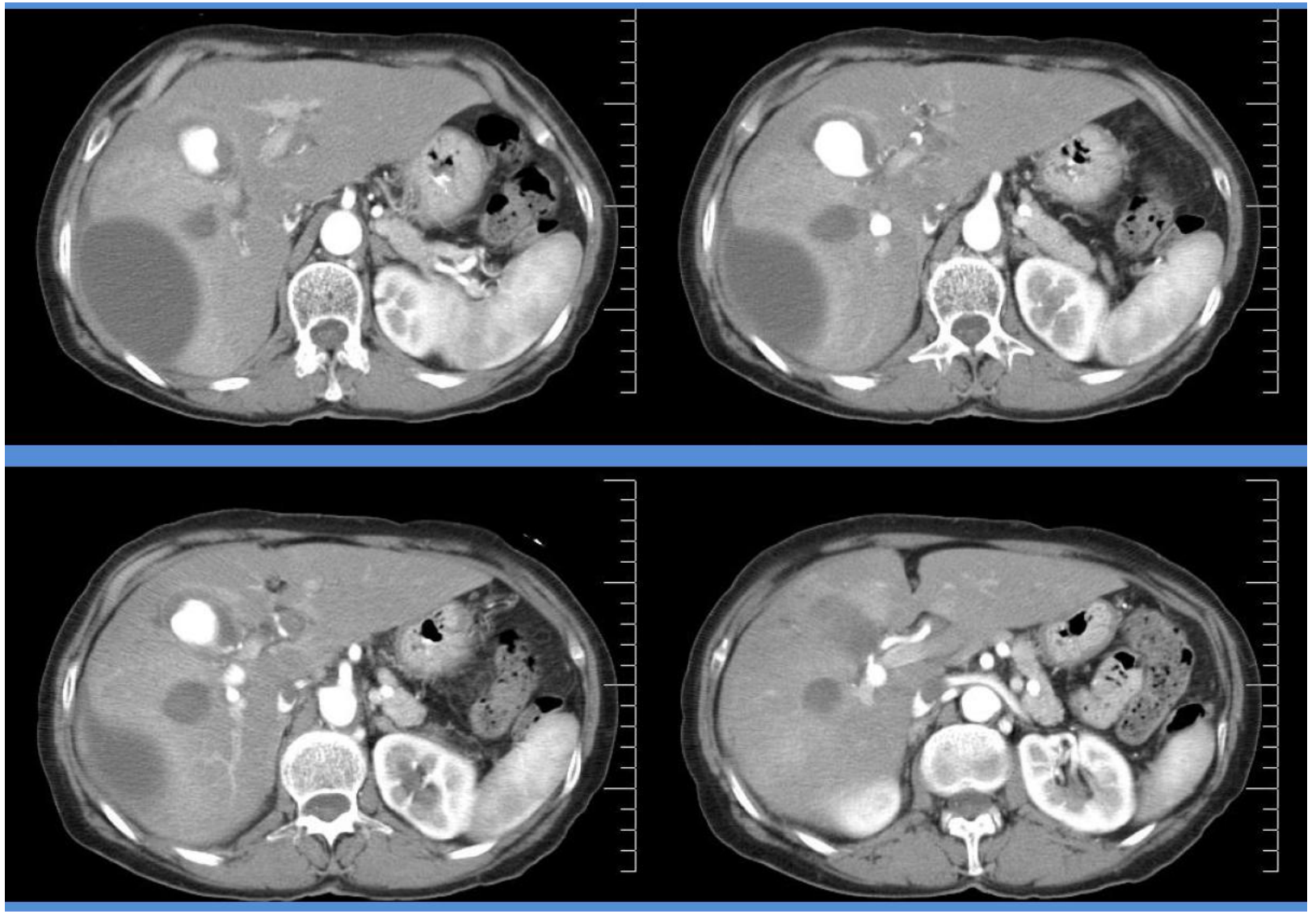
Embolization in Trauma

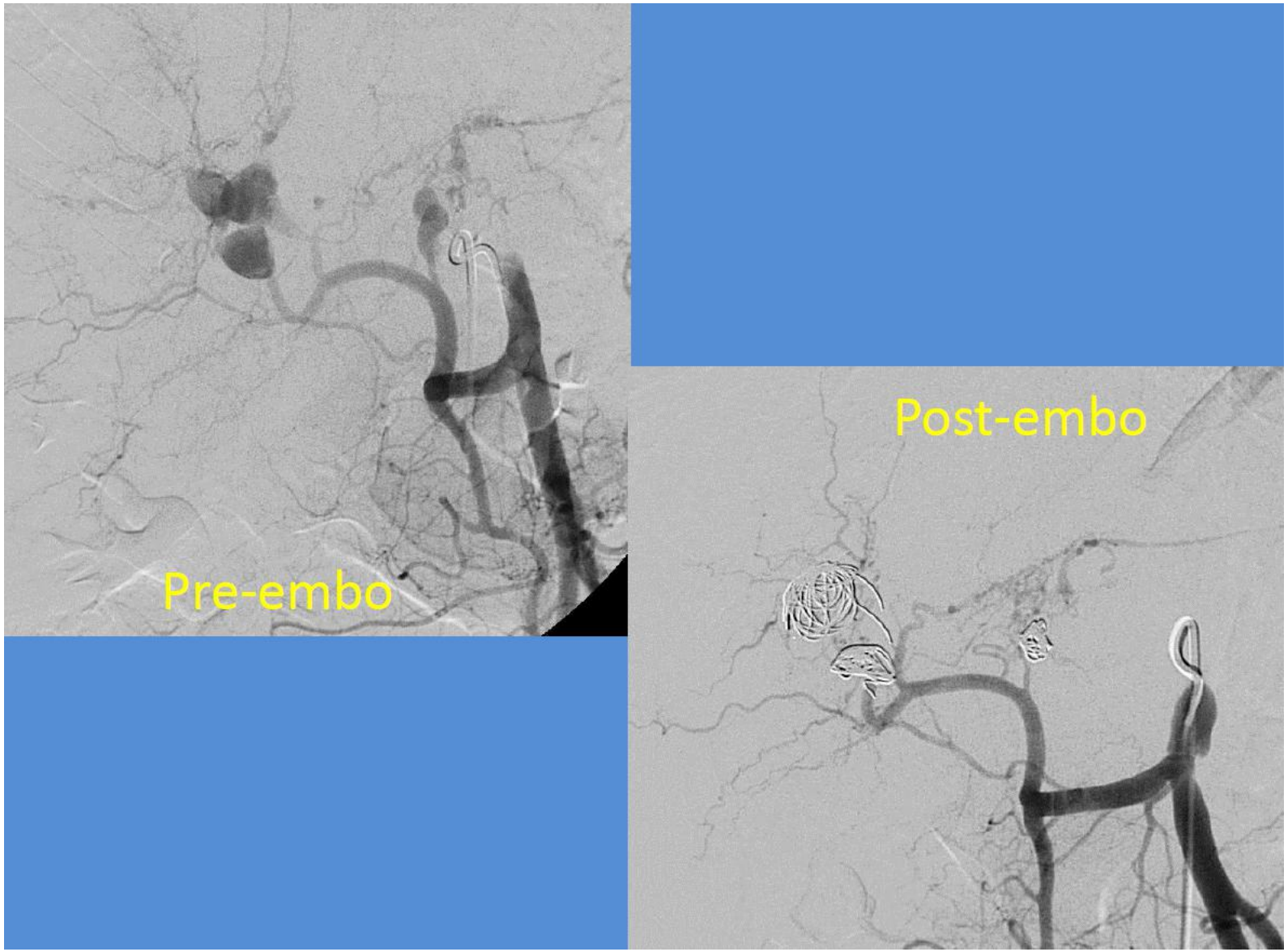
- Angiography supplanted by CT

- Liver and Spleen susceptible to blunt and penetrating trauma embolization feasible (liver dual blood supply, spleen rich collateral network)

Liver Laceration






Pre-embo
Post-embo

Peripheral vascular trauma

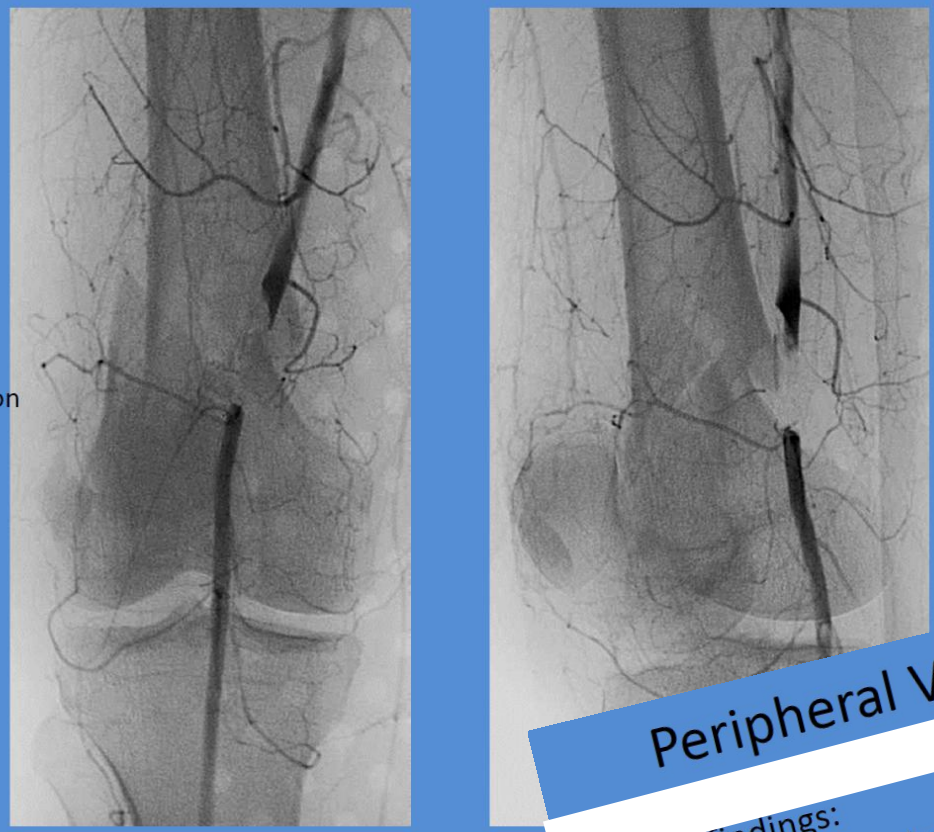
Anterior tibial artery transection with occlusion and extravasation

Peripheral Vascular Trauma

- Indications for angiography:
  - Pulse deficit
  - Ischemia
  - Expanding hematoma
  - Pulsatile bleeding
  - Bruit/thrill
  - Isolated neurologic deficit

Peripheral vascular trauma

Distal femur fracture with popliteal artery transection

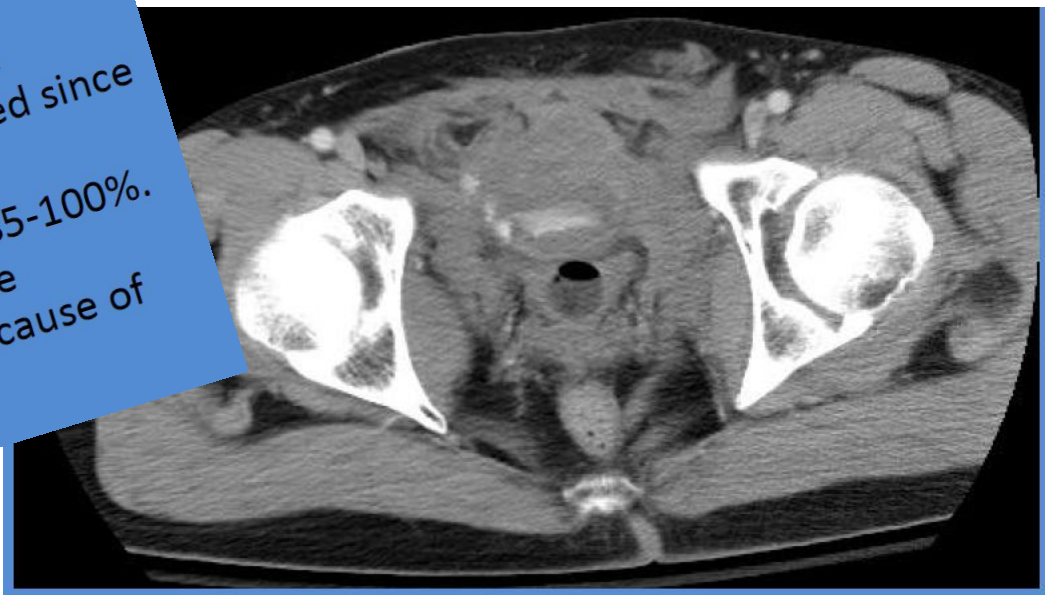


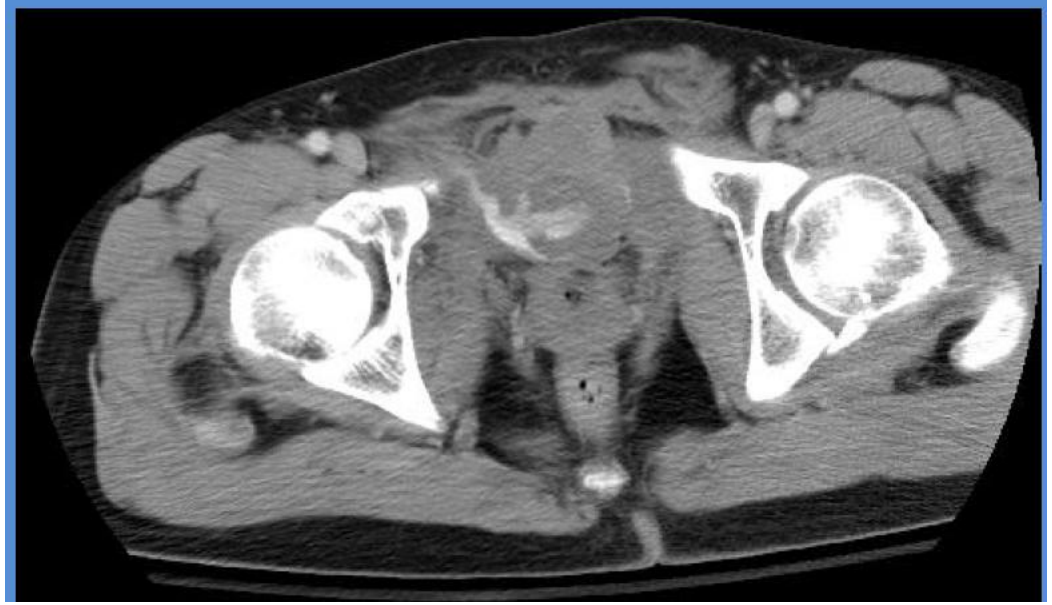
Peripheral Vascular Trauma

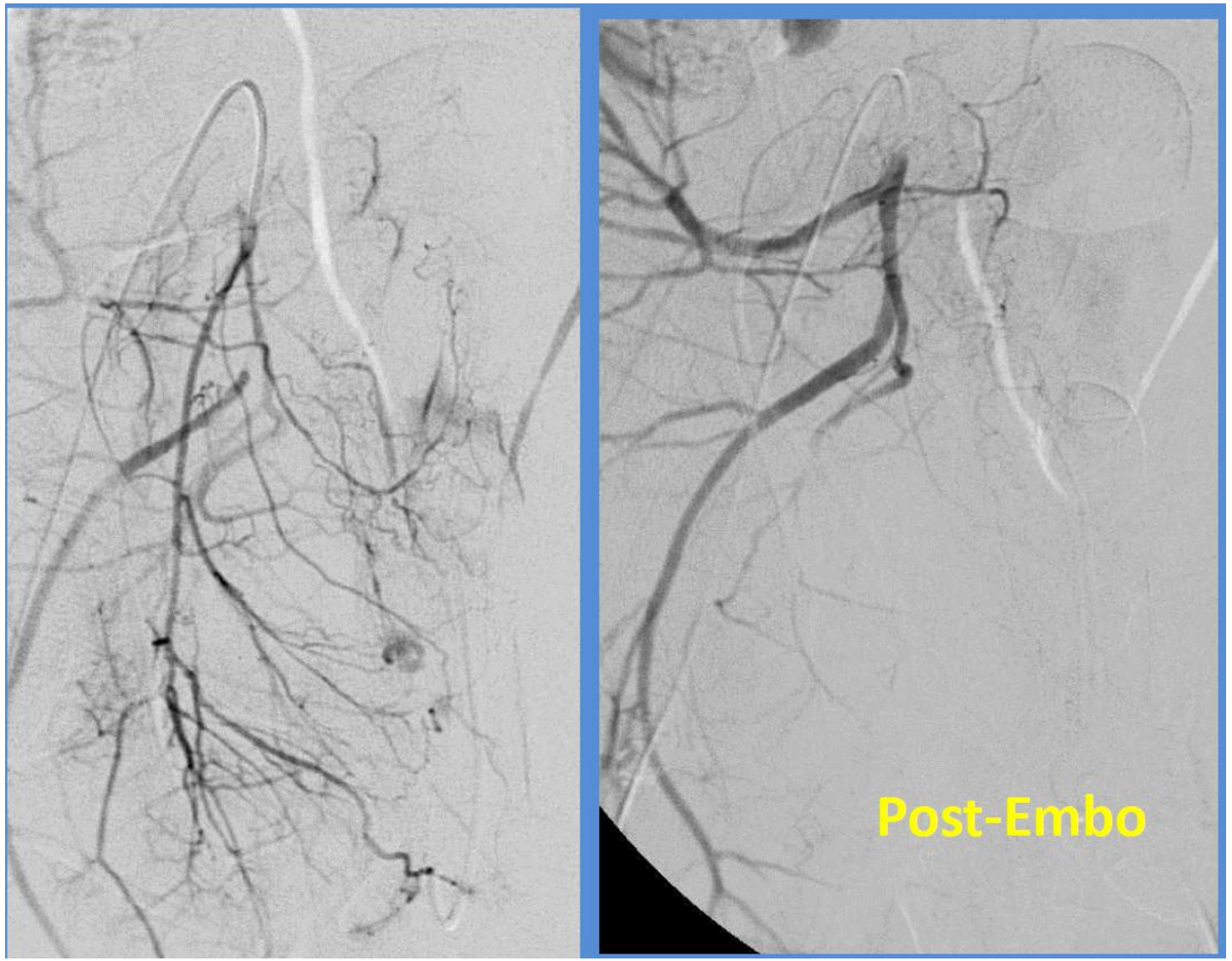
- Angio findings:
  - Extrinsic compression/displacement (hematoma)
  - Dissection/intimal flap
  - Intramural hematoma
  - Laceration (partial/complete)
  - Occlusion
  - Thrombosis
  - Extravasation
  - Pseudoaneurysm
  - Spasm
  - AV fistula

Pelvic Embolization

- Percutaneous transcatheter embolization has been shown to be safe and efficacious when used to treat pelvic hemorrhage
- Endovascular management of hemorrhage following pelvic fracture has been described since the 1970s
- success rate of stopping hemorrhage is 85-100%. (despite high technical success rates, the mortality rate is approximately 50% because of concomitant injuries)



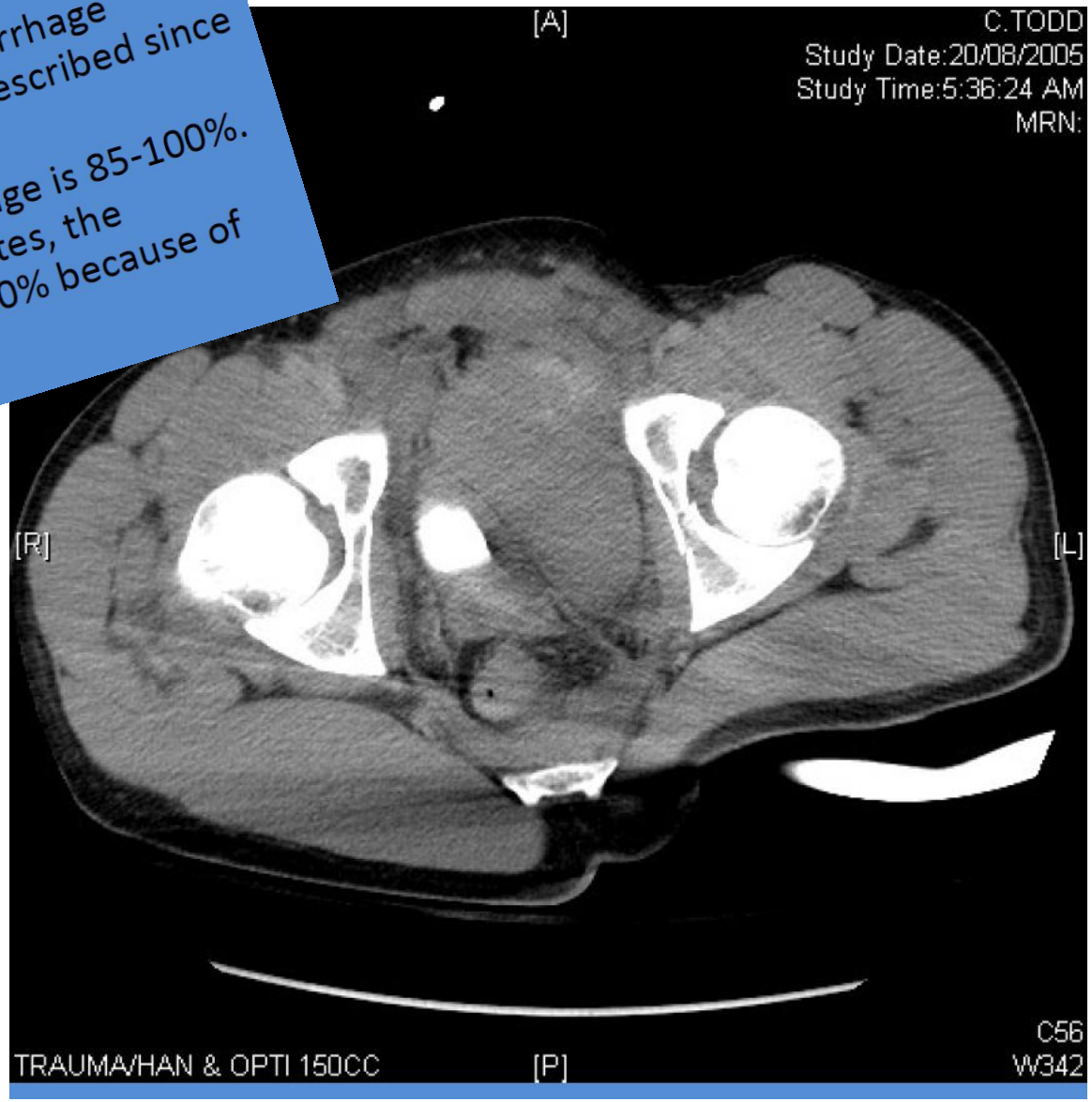


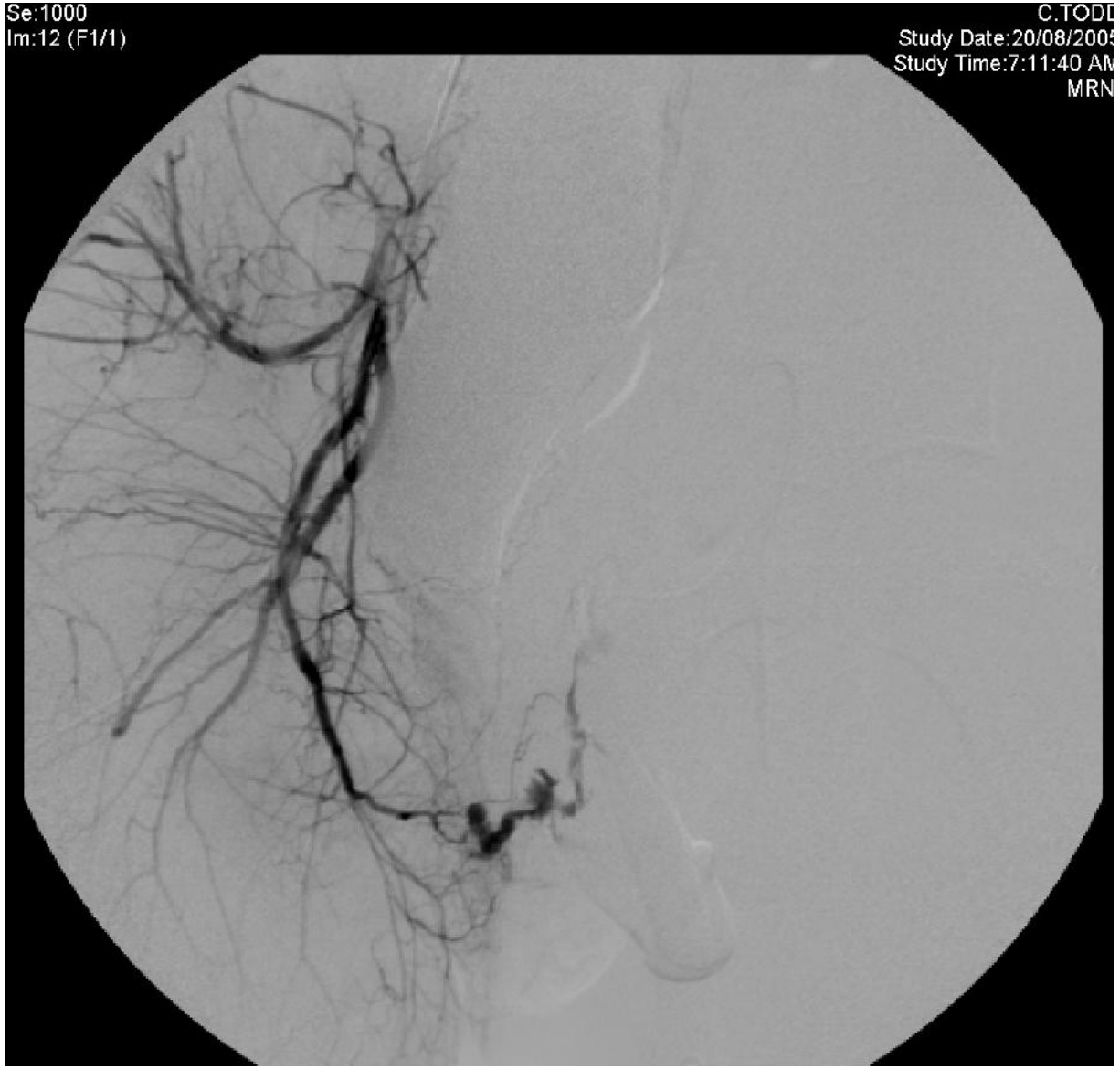

Post-Embo

Pelvic Embolization

- Percutaneous transcatheter embolization has been shown to be safe and efficacious when used to treat pelvic hemorrhage
- Endovascular management of hemorrhage following pelvic fracture has been described since the 1970s
- success rate of stopping hemorrhage is 85-100%. (despite high technical success rates, the mortality rate is approximately 50% because of concomitant injuries)

Motorcycle accident male 28 years old

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Im:12 (F1/1)
C.TODD
Study Date:20/08/200
Study Time:7:11:40 AM
MRN


Se:1000
Im:13 (F1/1)
C.TODD
Study Date:20/08/200
Study Time:7:11:40 AM
MRN


Se:1000
m:17 (F1/1)
Study Date:20/08/2005
Study Time:7:11:40 AM
MRN


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m:21 (F1/1)
C.TODD
Study Date:20/08/2005
Study Time:7:11:40 AM
MRN:
C635

Interventi di Radiologia Interventistica
Ospedale Apuane, Massa-Carrara, ASL Nordovest, Toscana
(censiti sistema OrmaWEB) anni 2015-2017

Radiologia Interventistica	2015	2016	2017
Interventi “elettivi”	10	9	13
Interventi “urgenti”	25	17	23
Totale	35	26	36

Ospedale Apuane , dati on file

Interventi di Radiologia Interventistica
Ospedale Apuane, Massa-Carrara, ASL Nordovest, Toscana
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Interventi “elettivi”	10	9	13
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Totale			

Radiologia Interventistica	2015	2016	2017
Interventi “per trauma”	8	19	32
Interventi “non trauma”	3	7	4
Totale	11	26	36

Ospedale Apuane , dati on file

Interventi di Radiologia Interventistica
Ospedale Apuane, Massa-Carrara, ASL Nordovest, Toscana
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Totale			

Radiologia Interventistica	2015	2016	2017
Interventi “per trauma”	8	19	32

Radiologia Interventistica	2015	2016	2017
Interventi “per sanguinamento di organi o frattura ossea”	1	4	9
Interventi “per sanguinamento in distretti”	5	15	23
Totale	6	19	32

Ospedale Apuane , dati on file

Interventi di Radiologia Interventistica
Ospedale Apuane, Massa-Carrara, ASL Nordovest, Toscana
(censiti sistema OrmaWEB) anni 2015-2017

Radiologia Interventistica	2015	2016	2017

Radiologia Interventistica	2015	2016	2017
Non-Trauma, Distretto:	1	1 ematoma pelvi 1 K vescica 4 aneurisma aa (arti ed addome) 1 angiodisplasia stomaco-duodeno	1 K vescica 1 aneurisma aa splenica 1 emorragia retto 1 K addome
Trauma, Distretto:	5	2 pancreas 1 milza 1 rene 15 addome-bacino	1 pancreas 1 fegato 3 milza 3 rene 1 anca-coscia 23 addome-bacino
Totale	6	26	36

Real-Life Evidence

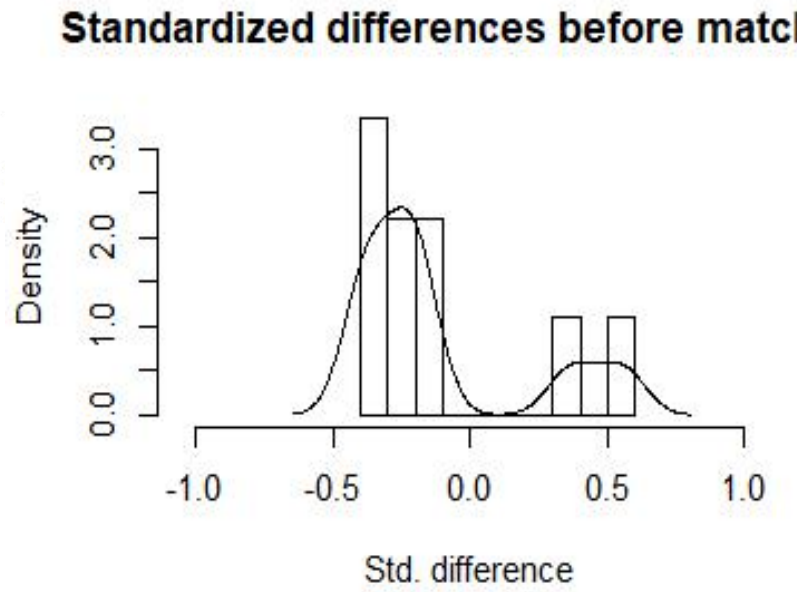
SIMEU Toscana

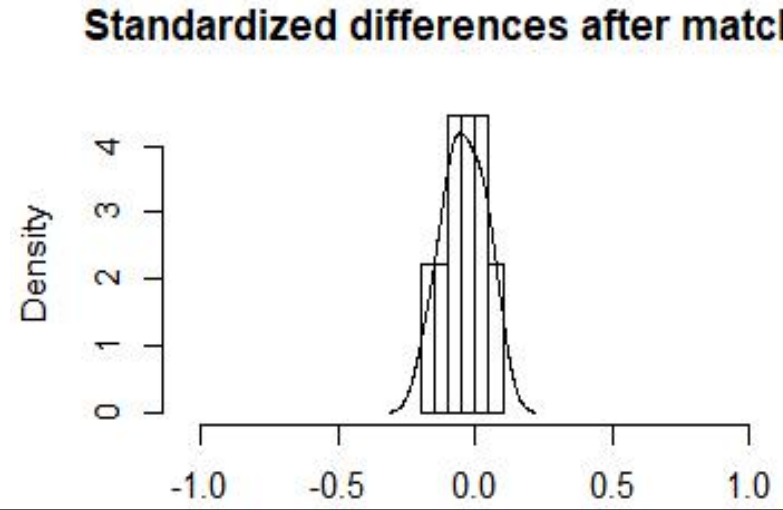
Bleeding at the Emergency Department

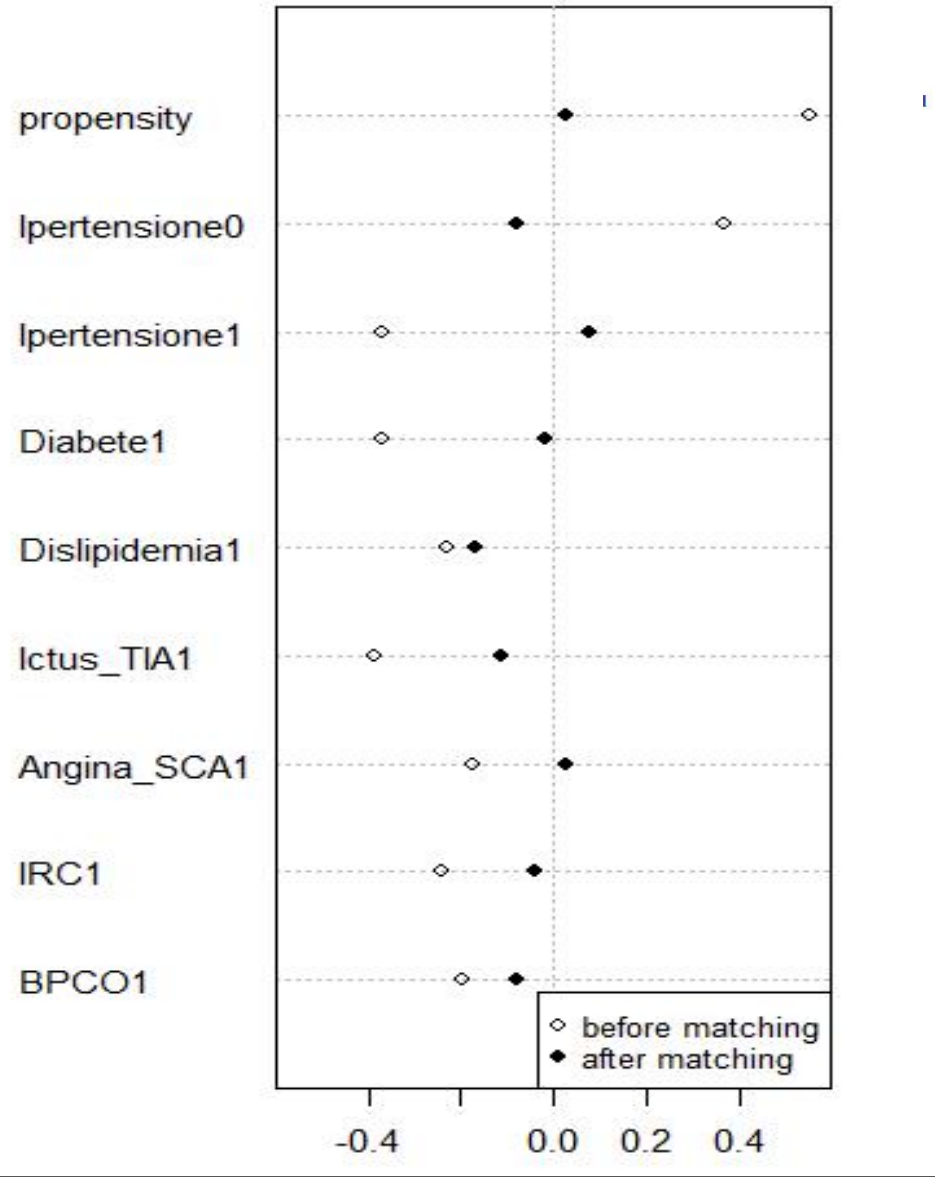
Survey ASL NordOvest SSN Toscana
Apuane Community Hospital, Massa
Catchment area: 250.000 inhabitants
4.430 patients enrolled,
3-year Survey 2015-2017

Contents lists available at ScienceDirect

American Journal of Emergency Medicine







Contents lists available at ScienceDirect

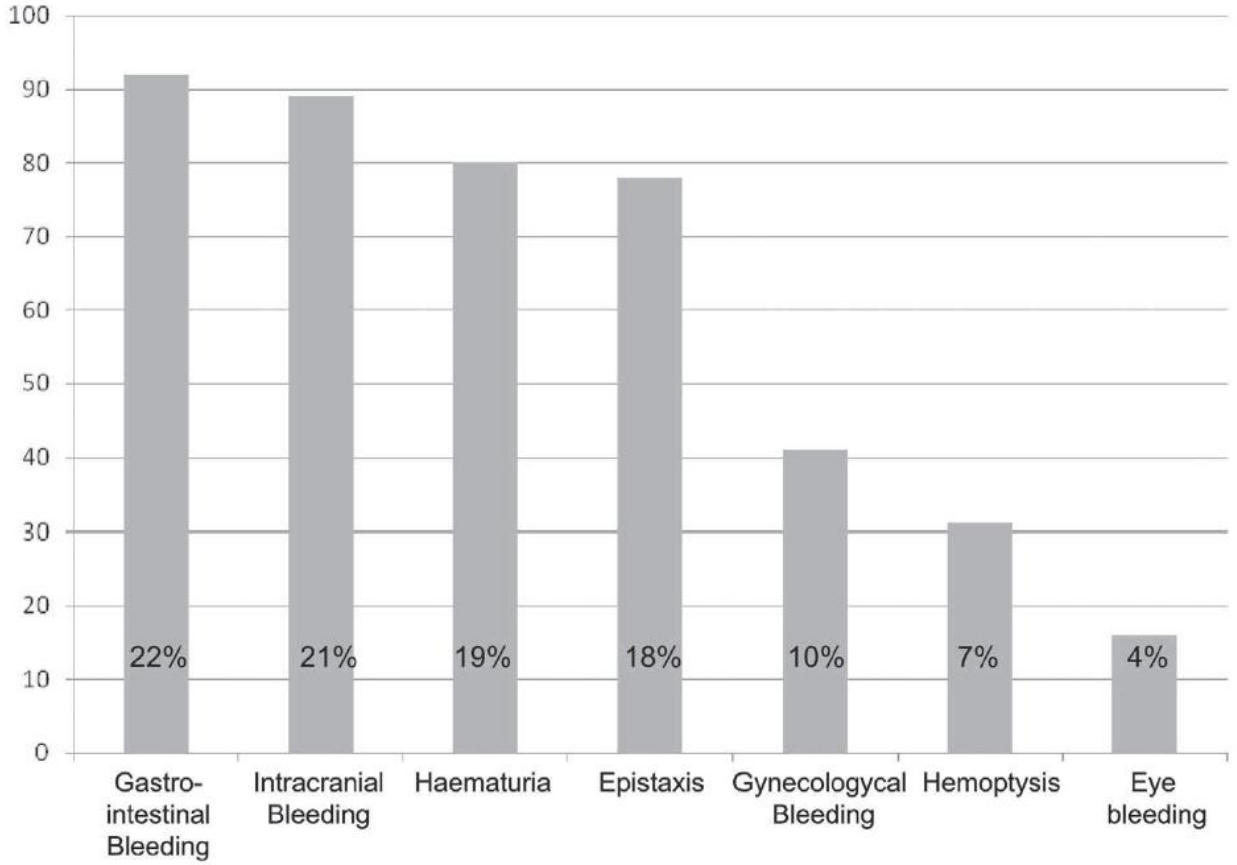
American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Short and long-term mortality of patients presenting with bleeding events to the Emergency Department

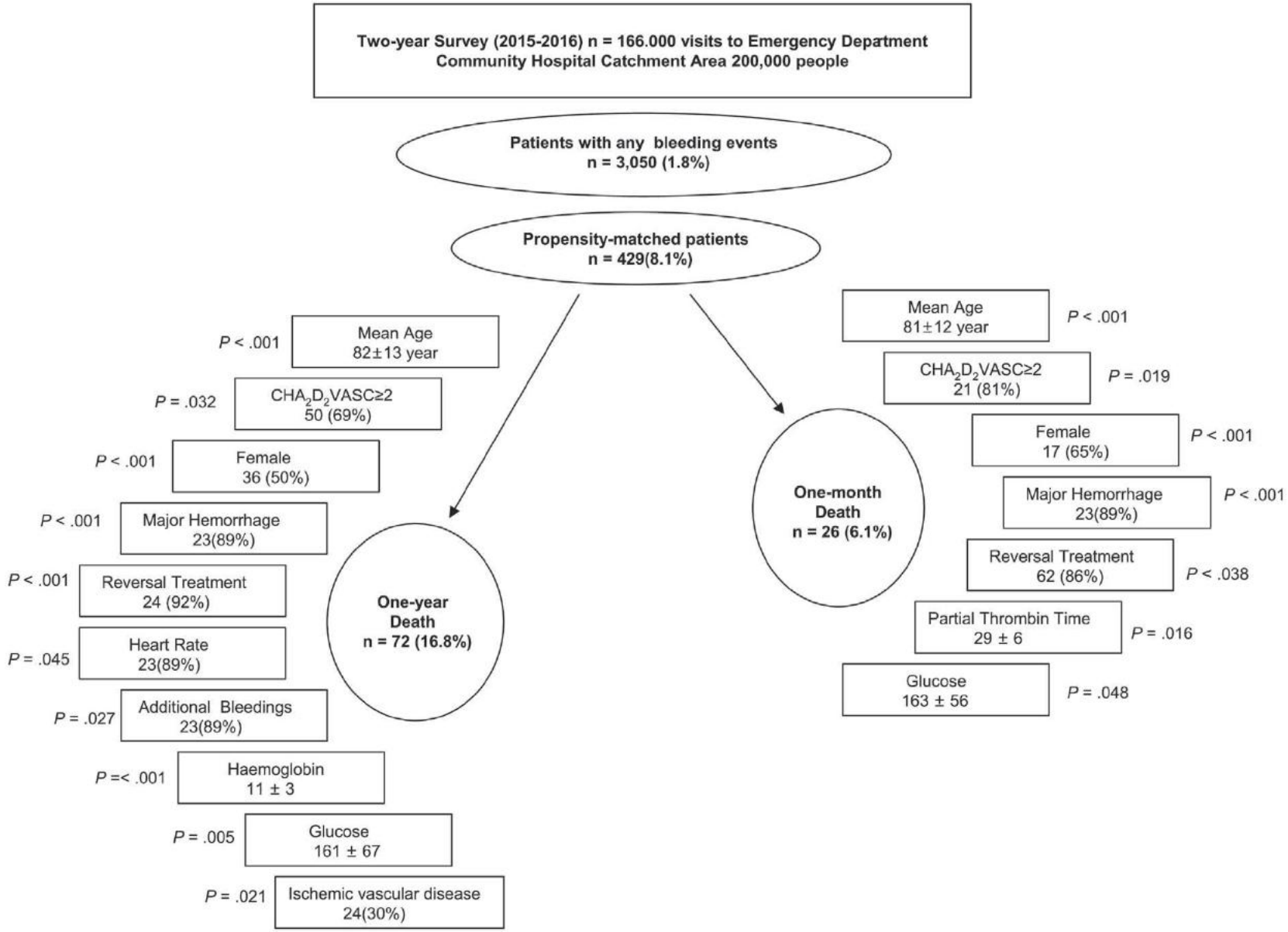
Alberto Conti, MD [a,*], Noemi Renzi, MD [a], Daniele Molesti, MD [a], Simone Bianchi, MD [a], Irene Bogazzi, MD [a], Giada Bongini, MD [a], Giuseppe Pepe, MD [b], Fabiana Frosini, MD [b], Alessio Bertini, MD [c], Massimo Santini, MD [d]

[a] North-West District Tuscany HealthCare, Apuane General Hospital, Emergency Department, Massa-Carrara, Italy
[b] North-West District Tuscany HealthCare, Versilia and San Luca General Hospital, Emergency Department, Viareggio-Lucca, Italy
[c] North-West District, Tuscany HealthCare, Spedali Riuniti Livorno, Emergency Department, Livorno, Italy
[d] North-West District Tuscany HealthCare, Cisanello General Hospital and University of Pisa, Emergency Department, Pisa, Italy



. Patients enrolled in the study and stratified according to the different site of bleeding (n = 429).

Conti A. Am J Emerg Med 2017



The chart of time to clinical evaluation, management, short- and long-term death in patients presenting with any bleeding events and enrolled in the study (n = 4

Conti A. Am J Emerg Med 2017

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Independent predictors of short-term (one-month) and long-term (one-year) death in the cohort of patients presenting to the Emergency Department with any bleeding event and submitted to propensity score matching (n = 429).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Independent predictors of one-month death						
Major bleeding	27.4	8.05–93.5	<0.001	26.09	51.0–123.5	<0.001
Female gender	0.13	0.06–0.31	<0.001	6.46	2.34–17.8	<0.001
White blood cells	1.11	1.03–1.19	0.005	1.16	1.03–1.30	0.011
Age	1.05	1.01–1.08	0.010			
Glucose	1.01	1.00.-1.01	0.048			
$CHA_2D_2VASC \geq 2$	0.31	0.11–1.12	0.027			
Independent predictors of one-year death						
Major bleeding	10.1	5.76–17.9	<0.001	7.07	3.29–15.2	<0.001
Age	1.07	1.04–1.09	<0.001	1.09	1.04–1.32	<0.001
Female gender	4.76	2.78–8.14	<0.001	2.30	1.03–5.13	0.043
White blood cells	1.06	1.01–1.12	0.030			
$CHA_2D_2VASC \geq 2$	0.52	0.29–0.94	<0.001			

Conti A. Am J Emerg Med 2017

Contents lists available at ScienceDirect

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Short and long-term mortality of patients presenting with bleeding events to the Emergency Department☆,☆☆

Alberto Conti, MD [a,*], Noemi Renzi, MD [a], Daniele Molesti, MD [a], Simone Bianchi, MD [a], Irene Bogazzi, MD [a], Giada Bongini, MD [a], Giuseppe Pepe, MD [b], Fabiana Frosini, MD [b], Alessio Bertini, MD [c], Massimo Santini, MD [d]

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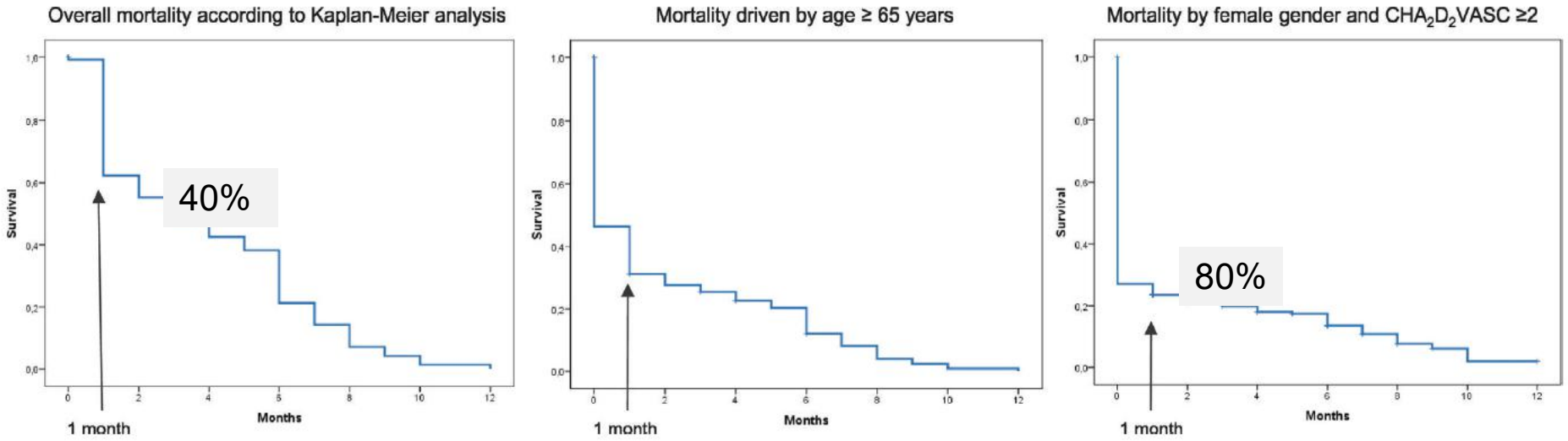
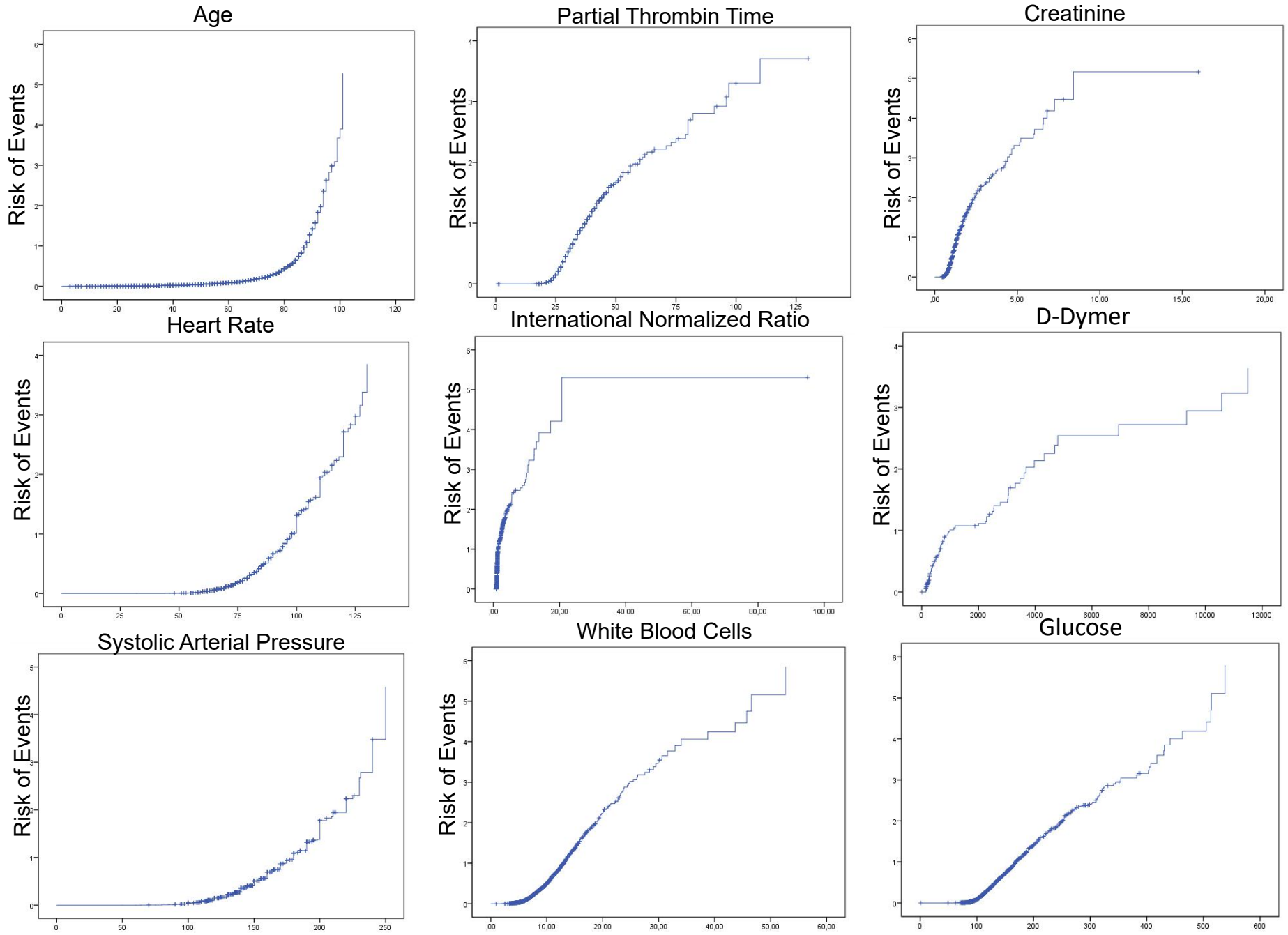


. Mortality in the cohort of patients presenting with any bleeding events according to Kaplan-Meier analysis (n = 429).

Results: Out of 166,000 visits to the Emergency Department, 3.050 patients (1.8%) were enrolled and eventually 429 were analyzed after propensity. Overall, anticoagulants or antiplatelets were given to 234(54%). Major bleed-

Conti A. Am J Emerg Med 2017

Figure 3.


Age
Risk of Events
Partial Thrombin Time
Risk of Events
Creatinine
Risk of Events
Heart Rate
Risk of Events
International Normalized Ratio
Risk of Events
D-Dymer
Risk of Events
Systolic Arterial Pressure
Risk of Events
White Blood Cells
Risk of Events
Glucose

ORIGINAL ARTICLE

Role of Hypertension and Other Clinical Variables in Prognostication of Patients Presenting to the Emergency Department With Major Bleeding Events

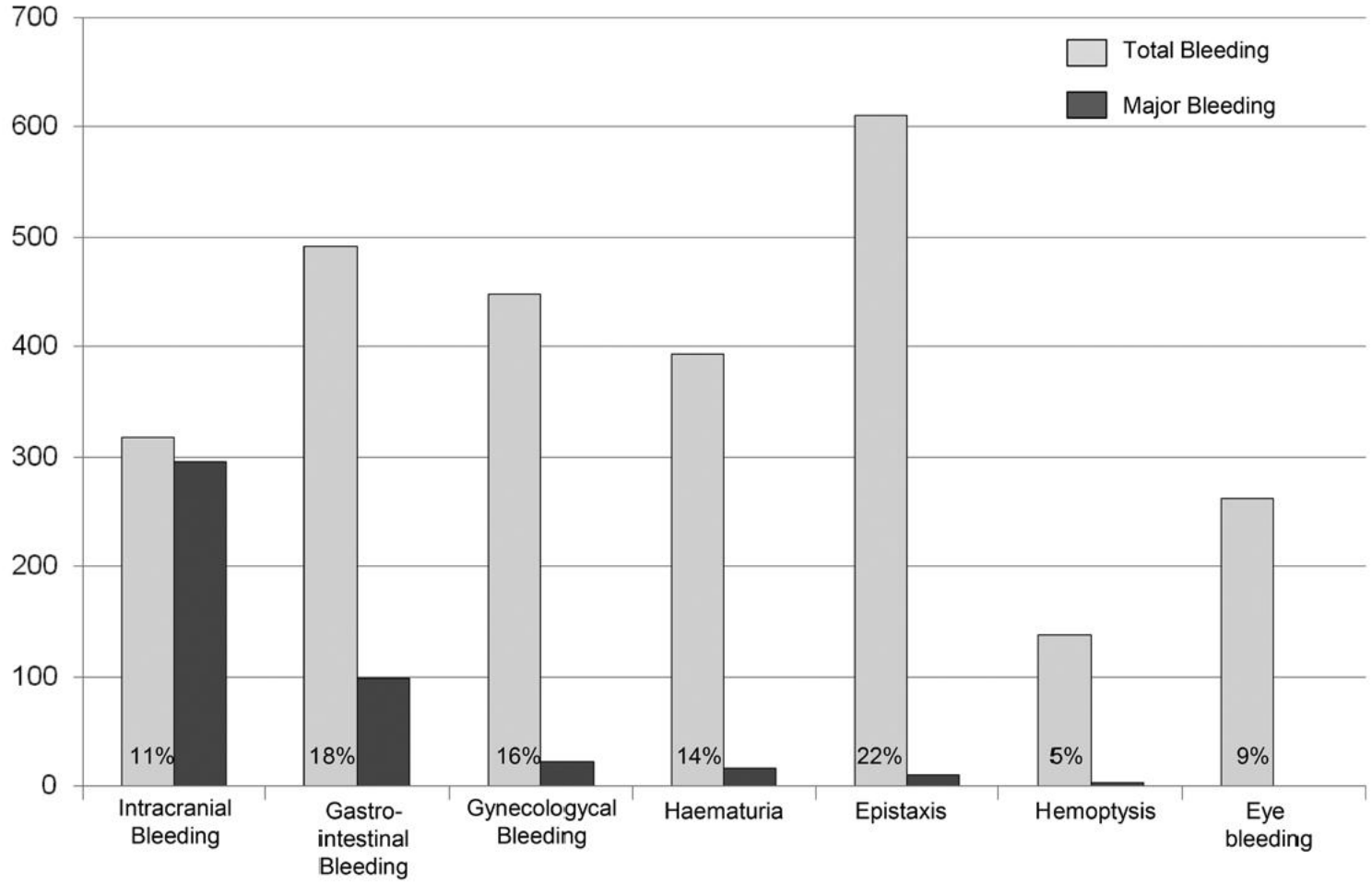
Alberto Conti, MD, Daniele Molesti, MD,* Simone Bianchi, MD,* Stefania Catarzi, MD,* Mariuccia Mazzucchelli, MD,* Antonella Covelli, MD,* Andrea Tognarelli, MD,* Mafalda Ester Perrotta, MD,* Alessandro Pampana, MD,† Giovanni Orlandi, MD,‡ Iginio Dell'Amico, MD,§ Alberto Baratta, MD,¶ Giuseppe Arena, MD,‖ and Tito Torri, MD***

Results: Enrolled patients were 2,792 (mean age, 65.6 ± 19.9 years) during 2-year survey including 166,000 visits, of 200,000 inhabitants catchment area; 8,239 patients received warfarin and 3,797 DOACs. Hypertension account for 1,077 (39%) patients; major bleeding for 474 (17%); death for 29 (1%), and 72 (3%) on 1-month and 1-year, respectively. Hypertension, age, glucose, cancer, ischemic vascular disease, and CHA2D2VASc score were more likely to link with major bleeding. On multivariate analysis, only age (odds ratio [OR], 1.02; $P < 0.001$), CHA_2D_2VASc score ≥ 2 (OR, 2.14; $P = 0.001$), and glucose (OR, 1.01; $P = 0.005$) were predictors of major bleeding. Kaplan–Meier analysis demonstrated patients with hypertension as compared with patients without showed 60% versus 20% death on 1-month ($P < 0.001$). Warfarin compared with DOACs was more likely to present with major bleeding (0.7% versus 0.2%; OR, 2.8; $P = 0.005$). Receiver operator characteristics analysis showed high value (0.61) of age and glucose over creatinine and systolic arterial pressure (P = NS).

Conclusions: Four in 10 patients with major bleeding showed hypertension; of these 8 in 10 will die within 1 month. Warfarin compared with DOACs was more likely to present with major bleeding.

Conti A et al Crit Path Cardiol 2018 (in press)

Role of Hypertension and Other Clinical Variables in Prognostication of Patients Presenting to the Emergency Department With Major Bleeding Events



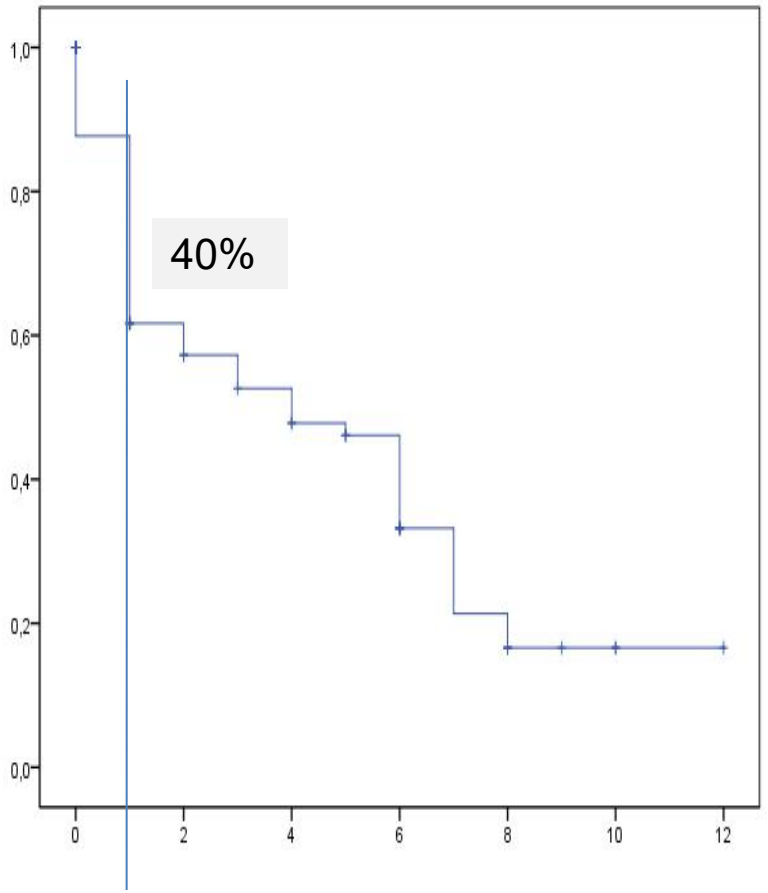
Patients enrolled in the study and stratified according to the different site of any bleeding (n = 2.792) and major bleeding events (n = 474).

Conti A et al Crit Path Cardiol 2018 (in press)

ORIGINAL ARTICLE

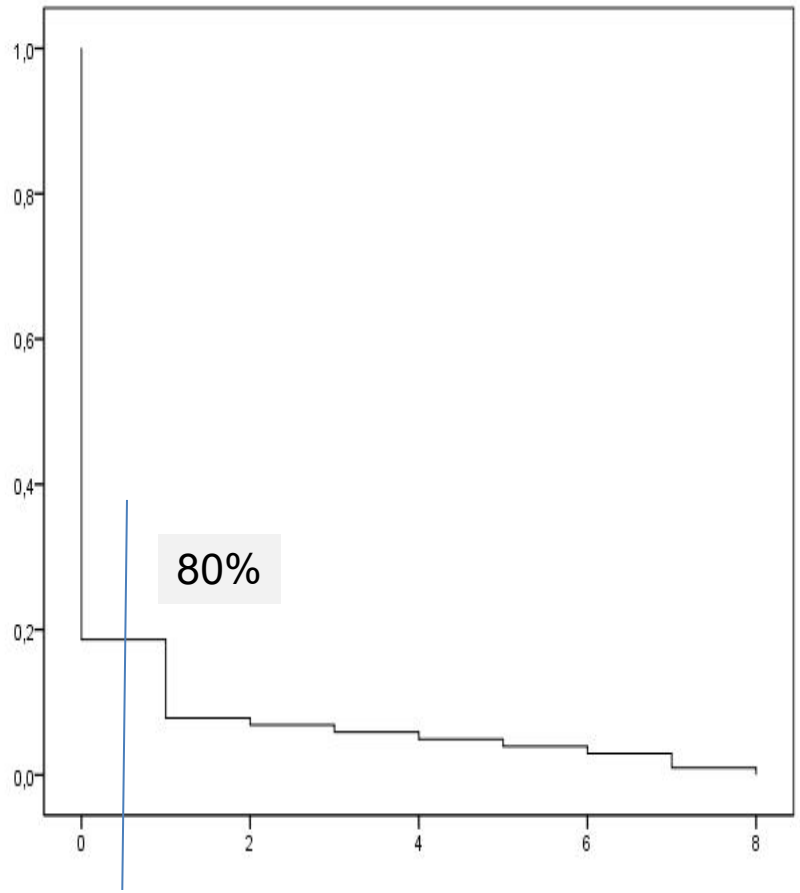
Role of Hypertension and Other Clinical Variables in Prognostication of Patients Presenting to the Emergency Department With Major Bleeding Events

Major Bleeding



One-month death

Major Bleeding and Hypertension



One-month death

Conti A et al Crit Path Cardiol 2018 (in press)

Role of Hypertension and Other Clinical Variables in Prognostication of Patients Presenting to the Emergency Department With Major Bleeding Events

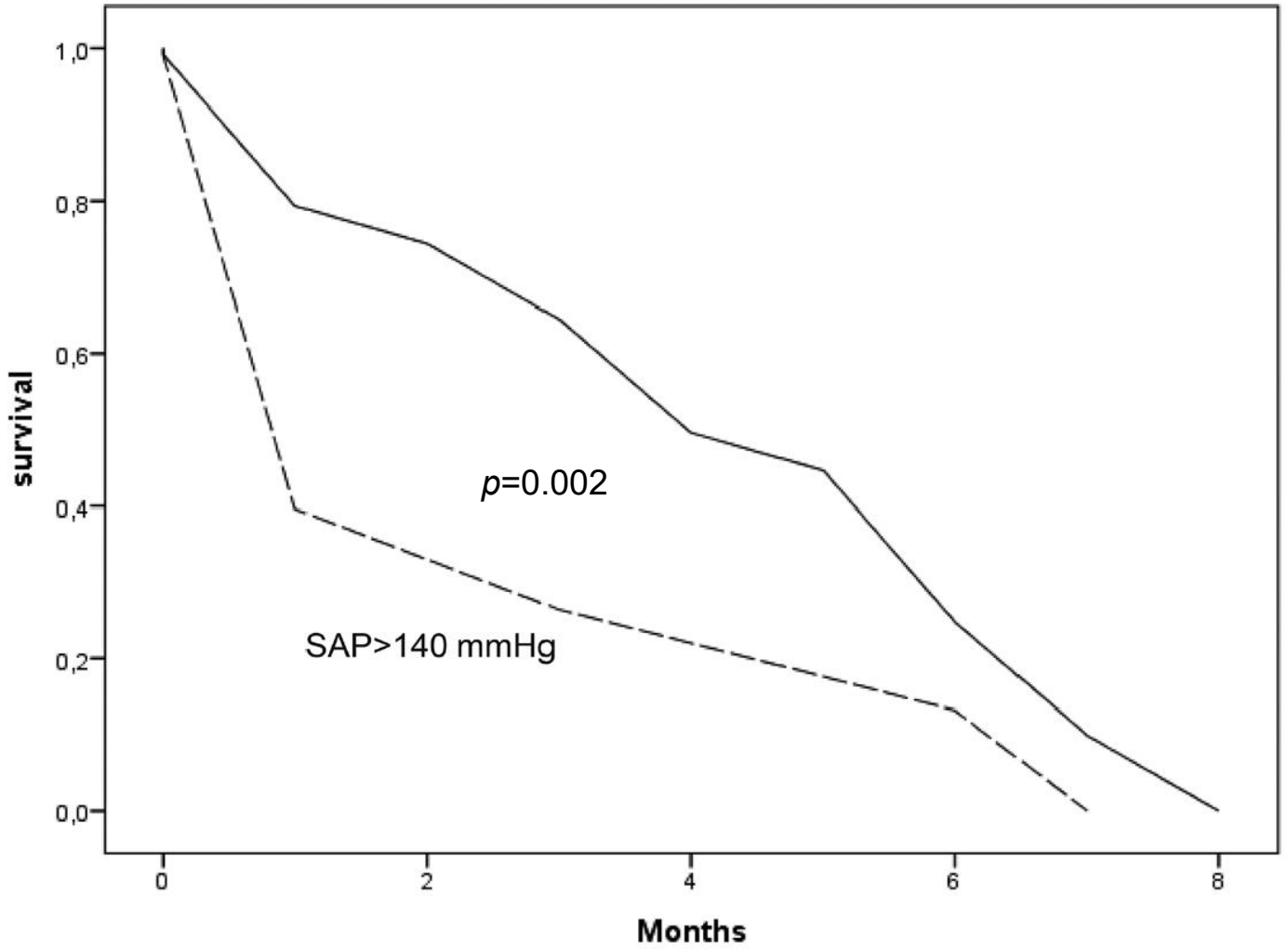


FIGURE 4. Survival curves of patients with major bleeding or major bleeding associated with hypertension according to Ka r analysis (n = 474). Continuous black line, patients presenting with systolic arterial pressure lower or equal to 140 mm Hg; dotted black line, patients presenting with systolic arterial pressure higher than 140 mm Hg, $P = 0.022$.

Conti A et al Crit Path Cardiol 2018 (in press)

Prevenzione e trattamento del sanguinamento…

In ambito cardiologico…

Milestones in Thrombosis Prevention

(ACS Management)

Anti-Thrombin Rx

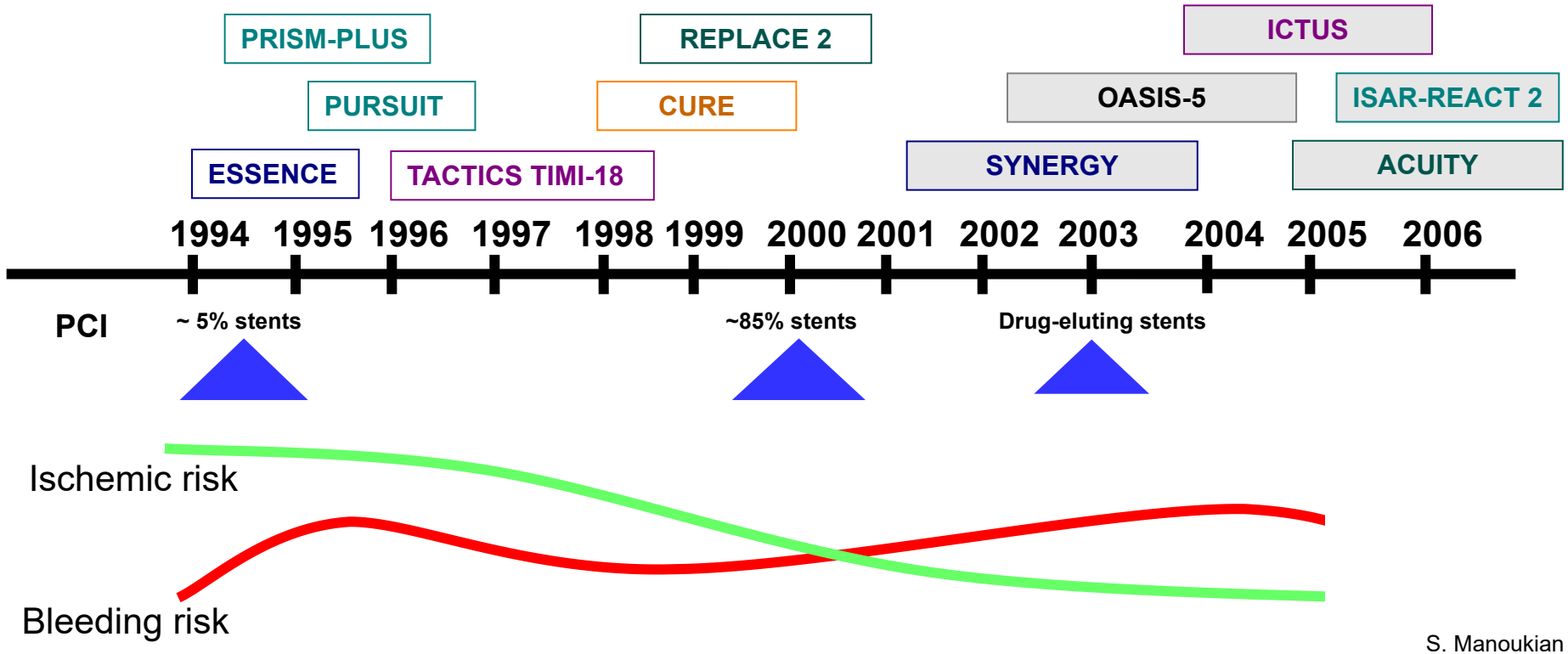
Heparin LMWH Bivalirudin Fondaparinux

Anti-Platelet Rx

Aspirin **GP IIb/IIIa blockers** **Clopidogrel**

Treatment Strategy

Conservative **Early invasive**



S. Manoukian

Measures to minimize bleeding while on dual antiplatelet therapy

ESC European Society of Cardiology

Recommendations	Class	Level
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75–100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Milestones in Thrombosis Prevention

(ACS Management)

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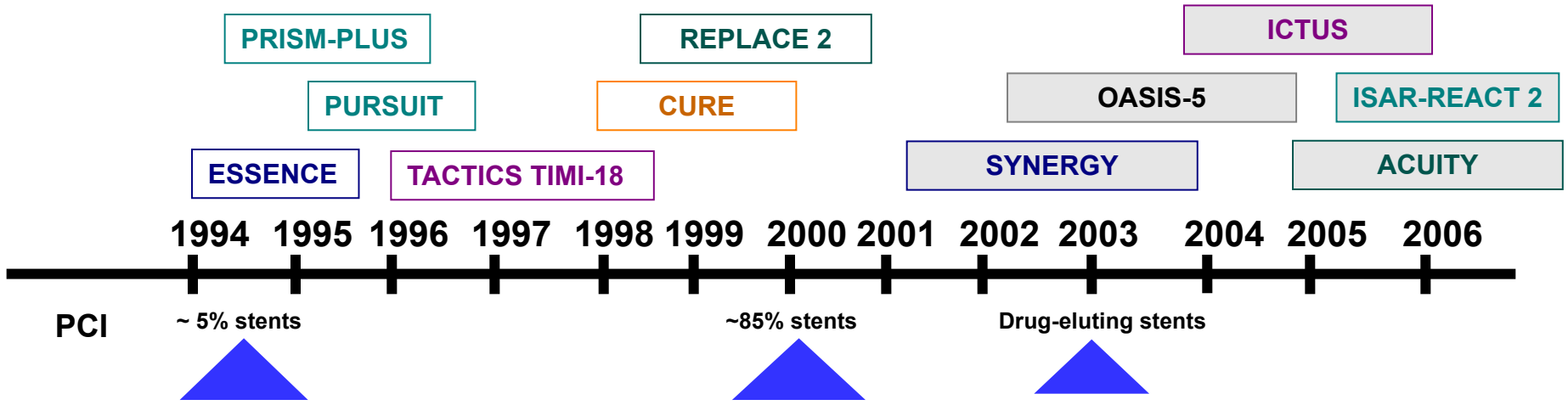
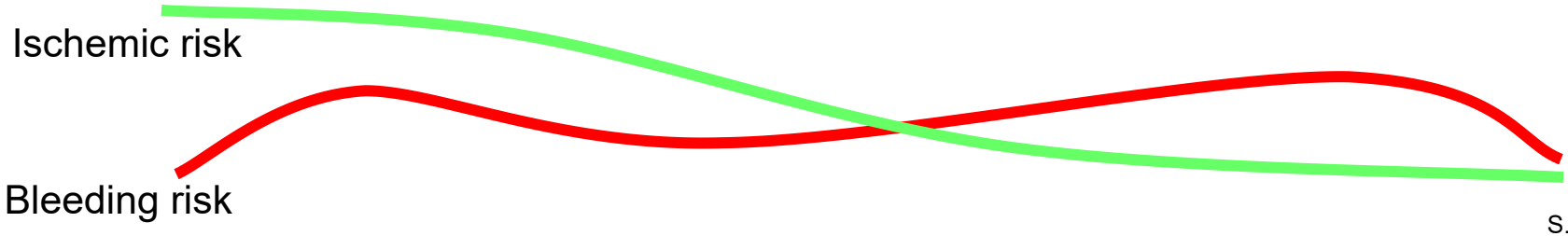


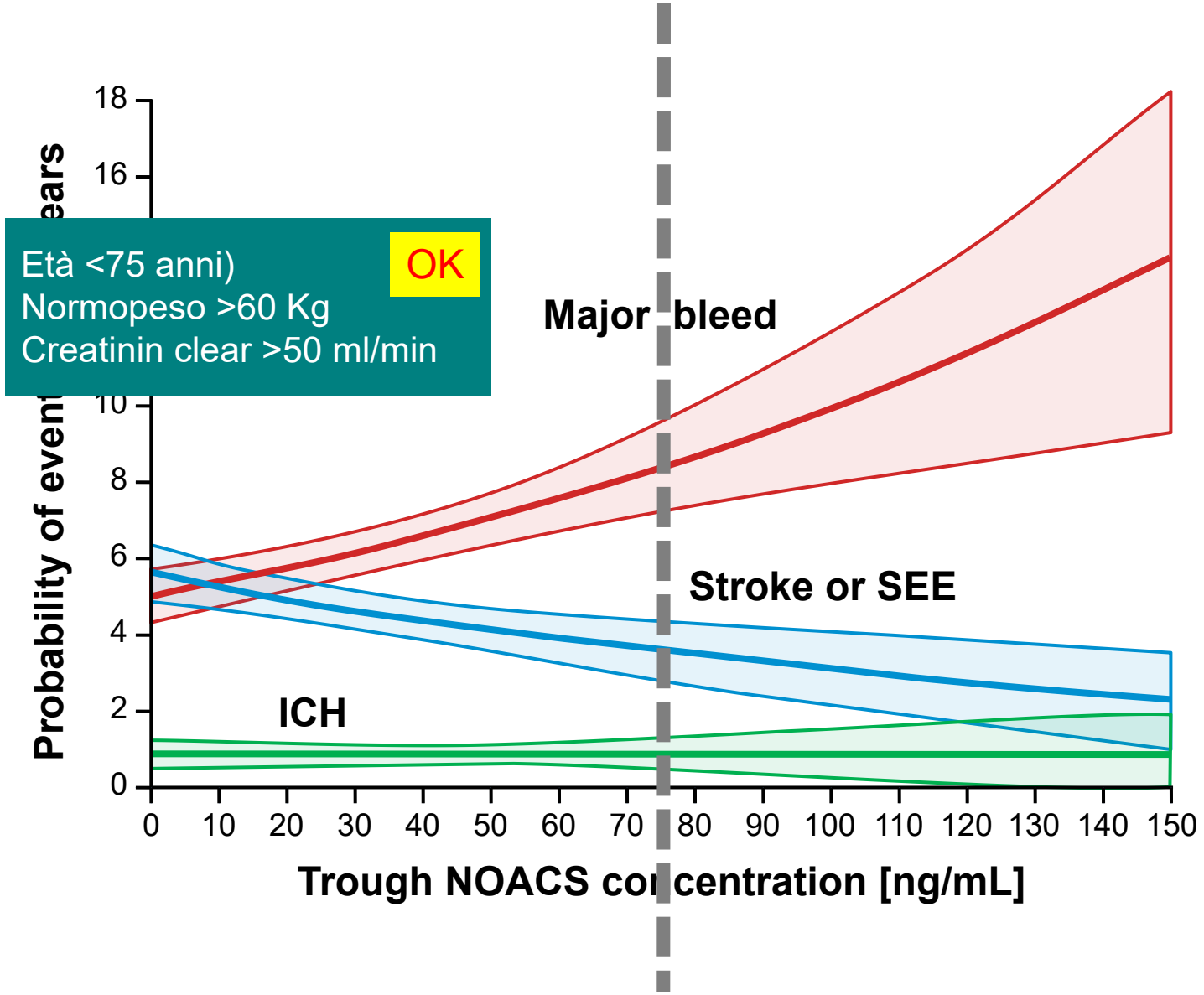


S. Manoukian

Prevenzione e trattamento del sanguinamento…

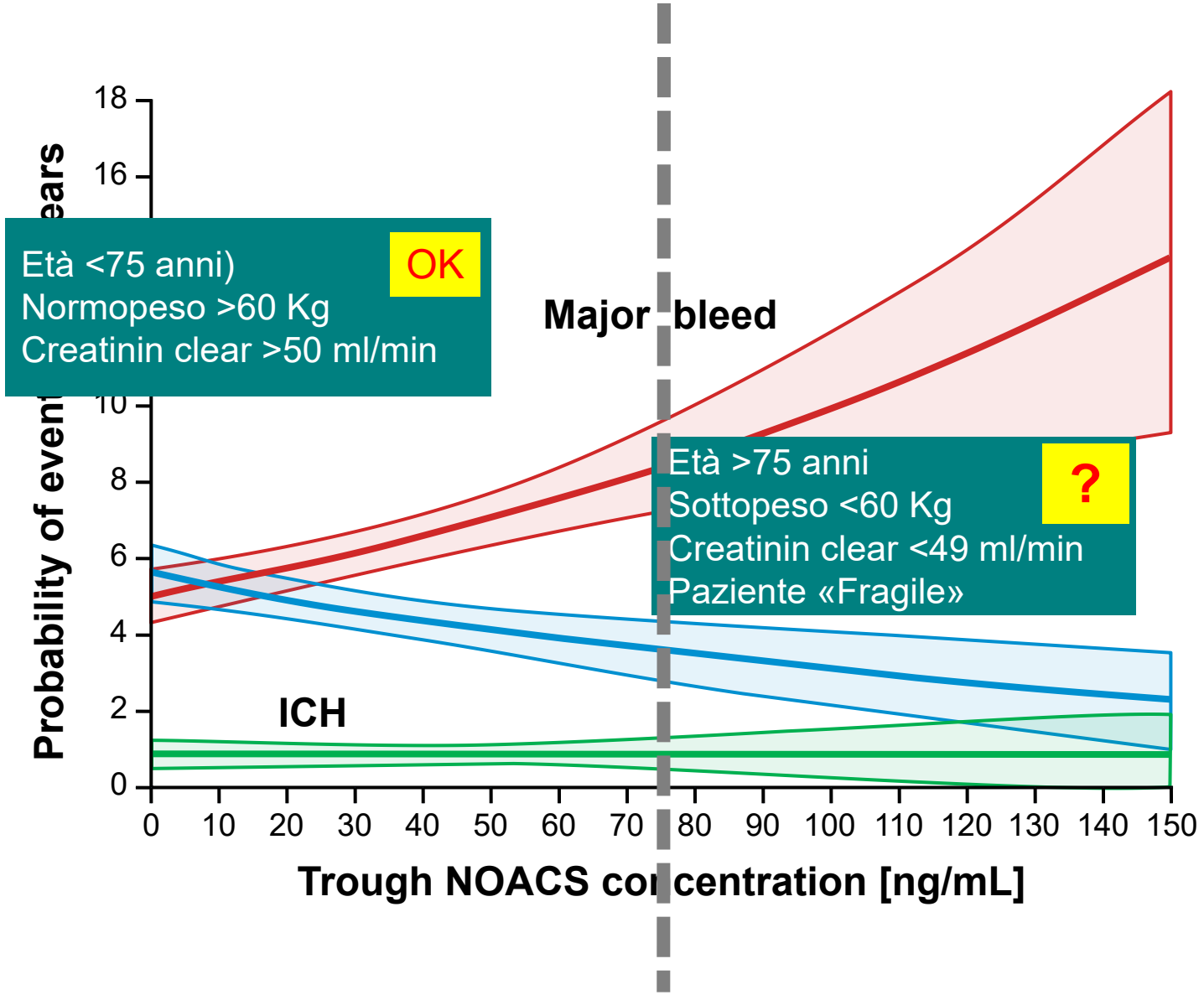
In ambito neurologico…

NOACS: trough concentration and outcomes



Ruff CT, et al. *presented ESC 2014*

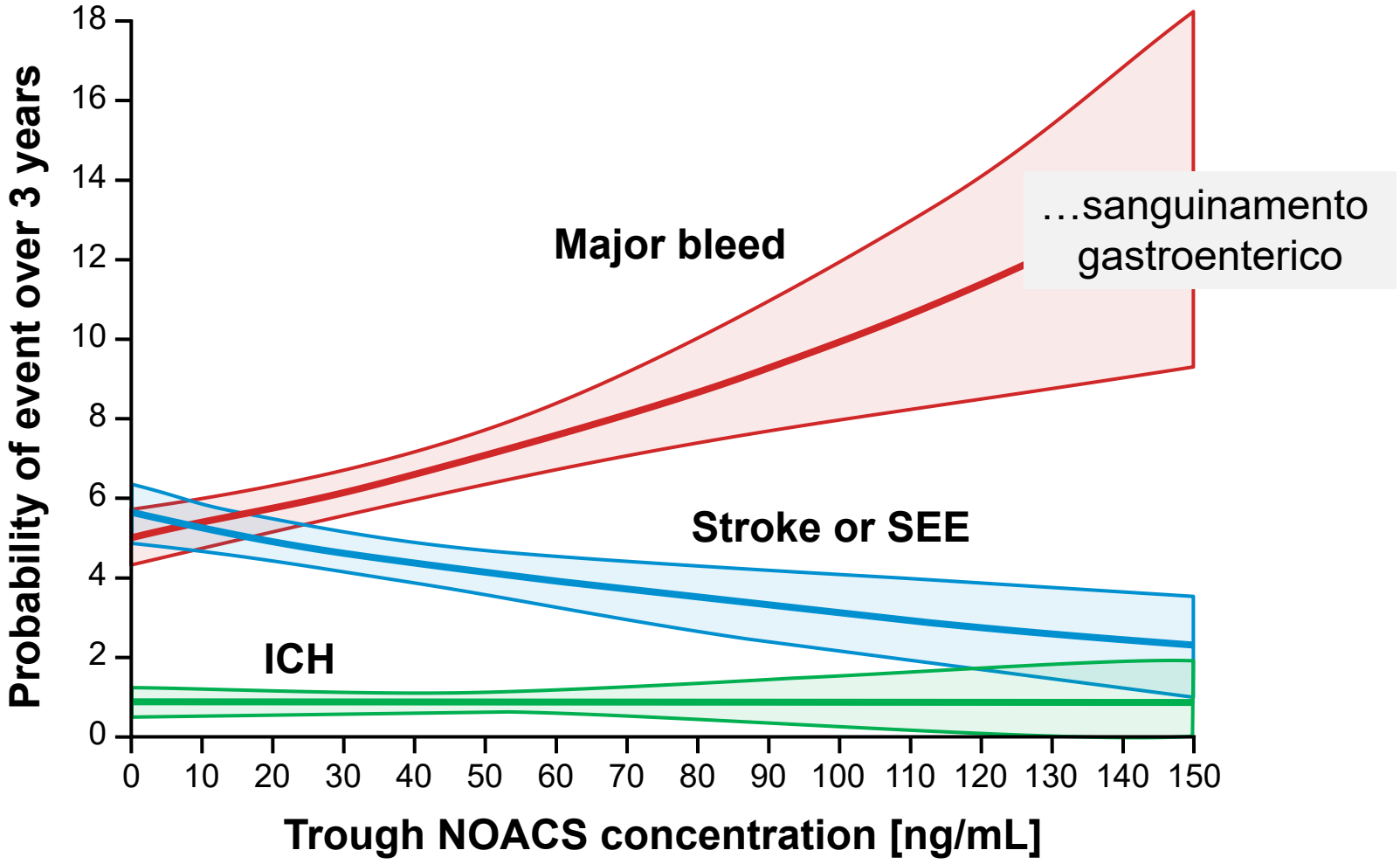
NOACS: trough concentration and outcomes



Ruff CT, et al. *presented ESC 2014*

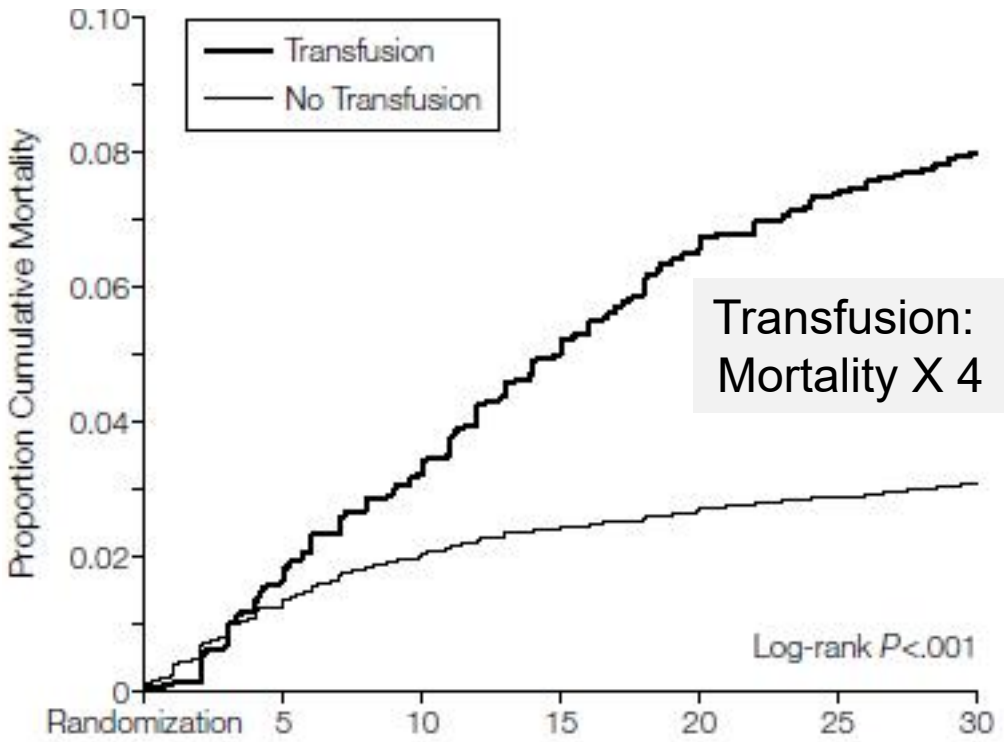
Anti-coagulation trough concentration and outcomes with DOACs treatment strategy

(Stroke Prevention)



Ruff CT, et al. *presented ESC 2014*

If Bleeding Kills…Blood Transfusion Do Not Save Lives!



Transfusion: Mortality X 4

24000 pts with ACS analyzed from GUSTO IIb, PURSUIT and PRAGON.

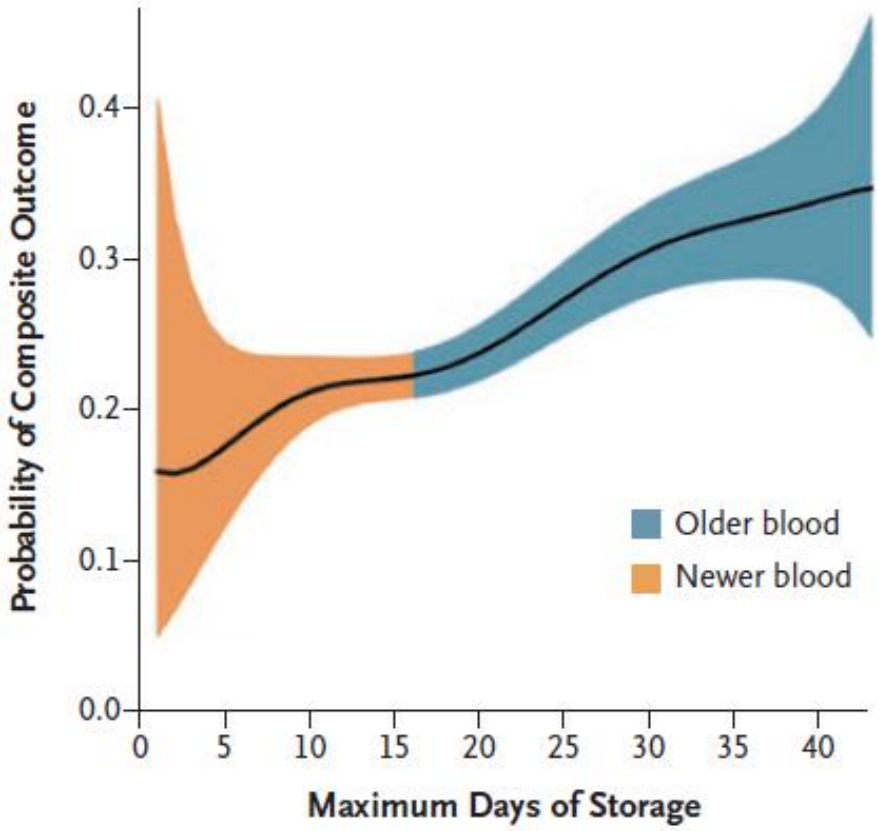
10% underwent transfusion.

Transfusion was associated with HR of 3.94 [CI 3.26-4.75] of death.

-**Blood Transfusion**: only to emodynamic stabilization

Rao et al. JAMA. 2004;292:1555-1562

Blood transfusion do not save lives!



- Red cell transfusion in post-CABG and valve pts was studied.
- 3000 pts were given old blood (> 2 weeks) and 3000 pts were given new blood (< 2 weeks).
- At 1 year, mortality was significantly less in pts given new blood (7.4% vs 11%, $p < 0.001$).

Koch et al. N Engl J Med 2008;358:1229-39.

Prevenzione e trattamento del sanguinamento…

In ambito gastroenterologico…

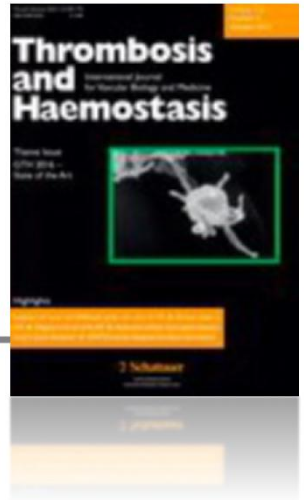
Scegliere l’anticoagulazione con minor rischio di sanguinamento gastroenterico

Guidelines for reversal of anticoagulants

New Guidelines for Reversal Anticoagulants in Intraparenchymal Hemorrhage

Anticoagulation Services (https://depts.washington.edu/anticoag/home) **February 2016**

-Warfarin
-Heparin
-Fondaparinux
-Bivaluridin
-DOACs



Anticoagulation Education Task Force White Paper

Managing reversal of direct oral anticoagulants in emergency situations

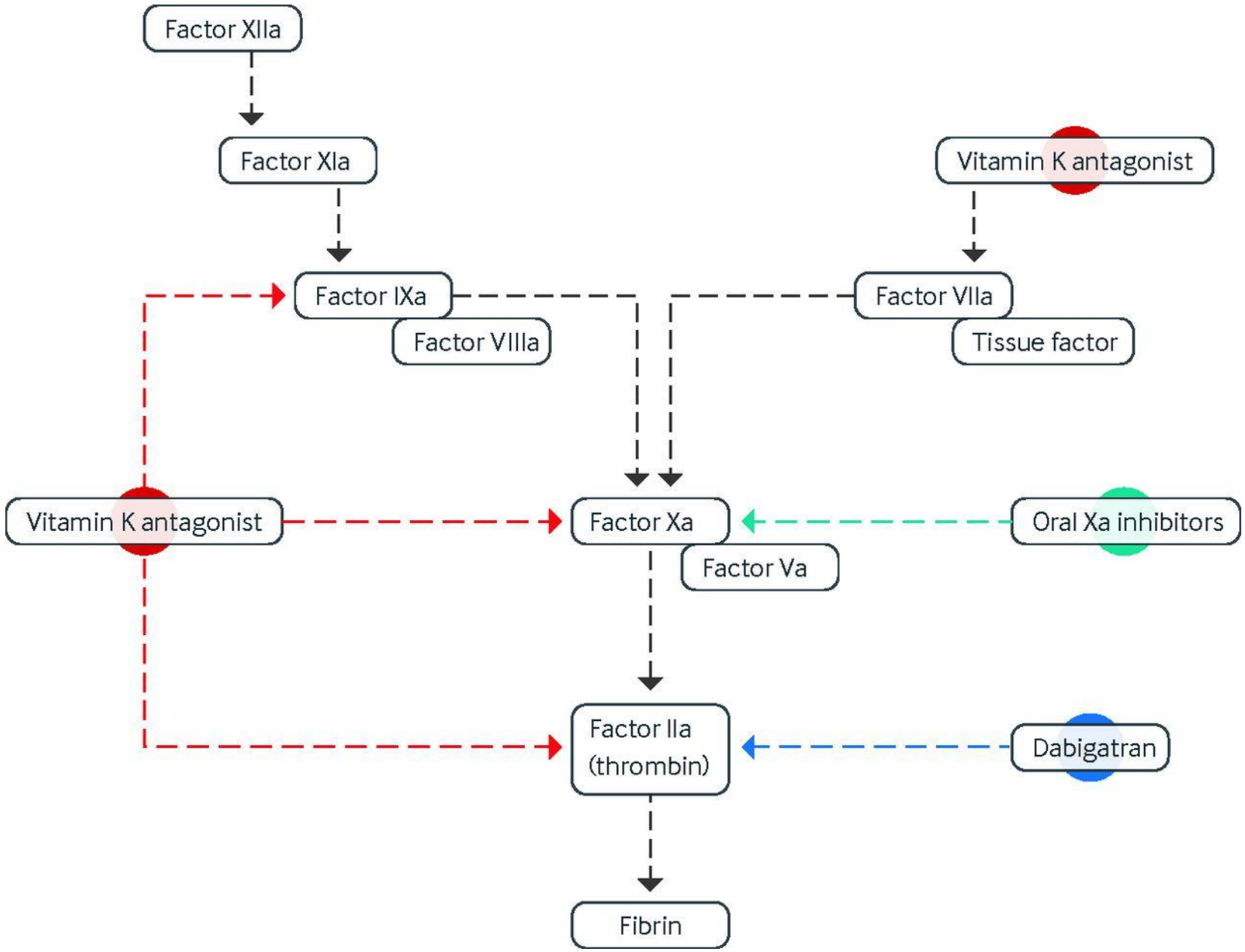
Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

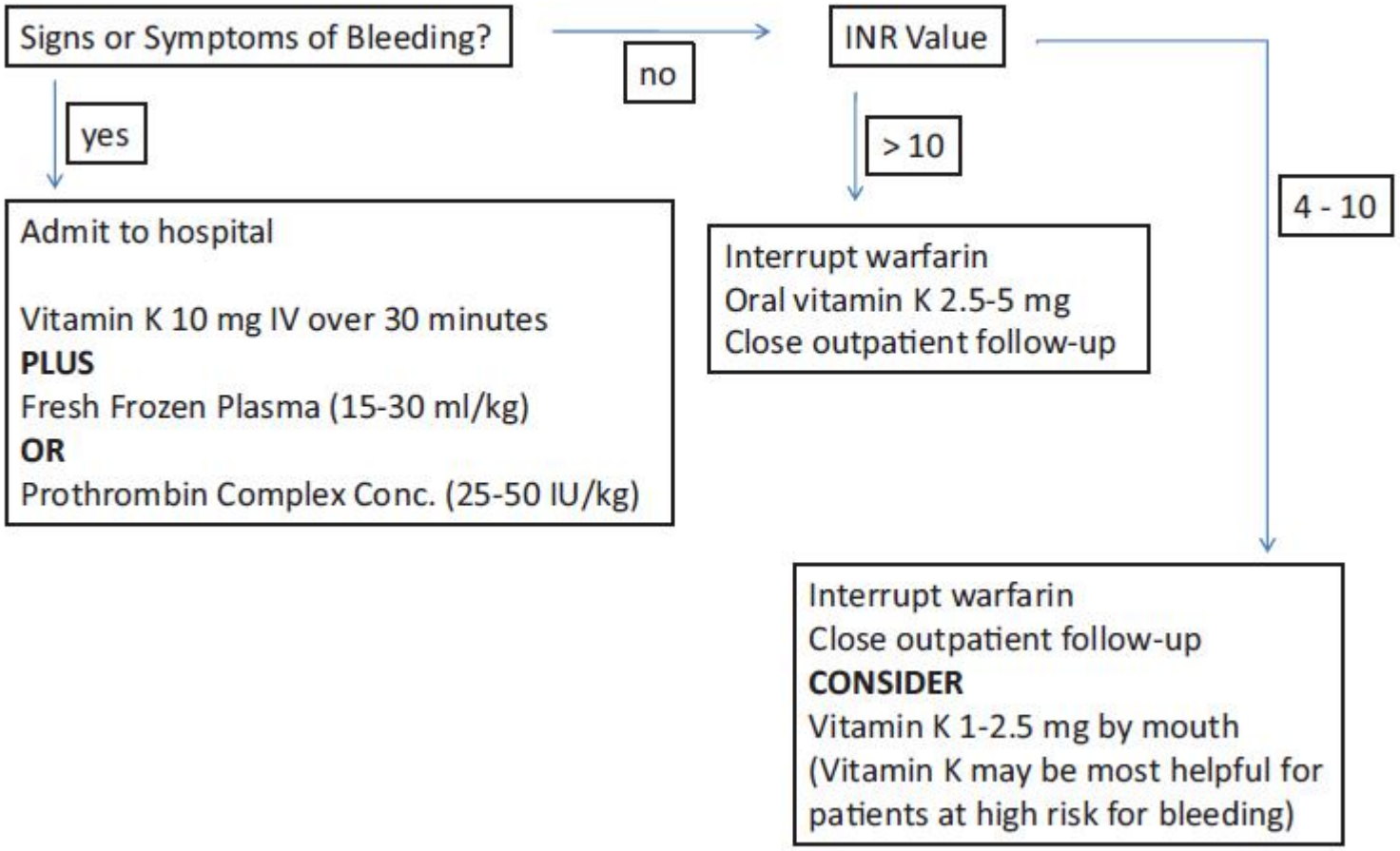
[1]University of Insubria, Varese, Italy; [2]Academic Medical Centre, Amsterdam, The Netherlands; [3]Department of Immunohematology & Transfusion Medicine and the Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, Italy; [4]Department of Neurology, Heidelberg University, Heidelberg, Germany; [5]Centre for Heart Rhythm Disorders, University of Adelaide, Royal Adelaide Hospital, South Australian Health & Medical Research Institute, Adelaide, Australia; [6]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [7]Arrhythmia Alliance and AF Association, Hampshire, UK; [8]Arrhythmia Research Unit, Universitario La Paz , Madrid, Spain; [9]General Hospital Cuprija, Cuprija, Serbia; [10]International Medical Services and Emergency Medicine, Vithas-Xanit International Hospital, Benalmadena, Malaga, Spain; [11]Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; [12]Stroke Alliance For Europe (SAFE), London, UK; [13]First Cardiology Clinic, Hippokration Hospital, University of Athens, Greece; [14]University of Leuven, Leuven, Belgium; [15]Division of Cardiovascular Sciences, St George's University of London, London, UK; [16]ICMS, Imperial College, London, UK

Thrombosis and Haemostasis, 2016

Coaugulation cascade



Management of a warfarin-treated patient whose INR exceeds 4. A suggested algorithm



Garcia DA, Crowther MA. Circulation 2012; 125:2944-2947.

Product for bleeding management of a warfarin-treated patient

Product	Time to Effect (After Administration)	Duration of Effect	Evidence of Efficacy for Warfarin Revesal	Risk of Thrombosis
Oral vitamin K	24 h	Days	++++	NS
Intravenous vitamin K	8–12 h	Days	++++	NS
Fresh frozen plasma	Immediate	12–24 h	++	NS
PCC	Immediate	12–24 h	+++	+ (Higher with activated PCC)
Recombinant factor VIIa	Immediate	2–6 h	+	++

Garcia DA, Crowther MA. Circulation 2012; 125:2944-2947.

Guidelines for reversal of anticoagulants

NAMES		STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
Warfarin *(Coumadin)*		

INR	CLINICAL SCENARIO	MANAGEMENT
< 4.5	No bleeding	• Hold warfarin until INR in therapeutic range
	Rapid reversal required	• Hold warfarin • Consider vitamin K 2.5mg oral
4.5-10	No bleeding	• Hold warfarin until INR in therapeutic range • Consider vitamin K 2.5mg oral
	Rapid reversal required	• Hold warfarin • Give vitamin K 2.5mg oral or 1mg IV infusion *(IV administration of vitamin K has faster onset of action)*
>10	No bleeding	• Hold warfarin until INR in therapeutic range • Give vitamin K 2.5mg oral or 1-2mg IV infusion over 30 minutes, and repeat q24h as needed *(IV administration of vitamin K has faster onset of action)*
	Rapid reversal required	• Hold warfarin • Give vitamin K 1-2mg IV infusion over 30 minutes, and repeat q6-24h as needed
Any INR	Serious or life-threatening bleeding	• Hold warfarin • Give vitamin K 10mg IV infusion over 30 minutes • Give 4 units FFP/plasma • *OR consider 4-factor PCC (Kcentra)* *(preferred for life-threatening bleeding)* *INR 1.5 – 3.9: 25 units/kg (maximum 2500 units)* *INR 4.0 – 6.0: 35 units/kg (maximum 3500 units)* *INR > 6.0: 50 units/kg (maximum 5000 units)*

NEW Guidelines for Reversal of Anticoagulants in Intraparenchymal Hemorrhage
Anticoagulation Services (https://depts.washington.edu/anticoag/home) **February 2016**

Reverse dell'anticoagulazione da VKA

Trattamenti SPECIFICI da adottare in caso di emorragia maggiore a rischio di vita o perdita di organo/funzione in corso di Warfarin

- Sospendere la TAO in corso
- Determinare INR
- Somministrare Vit.K (10mg/100 SF lentamente) efficacia max in 24h
- Concentrati di complesso protrombinico

se INR <2	20 U/Kg
se INR 2-4	30 U/Kg
se INR >4	40 U/Kg
se **INR >6**	**50 U/Kg**

Controllare INR dopo 15' dall'infusione e se >1,5 ripetere lo schema di terapia partendo dal valore di INR per ripetere lo schema

- Infondere Plasma (15 mL/Kg)
- Trasfusione di piastrine se < 60000

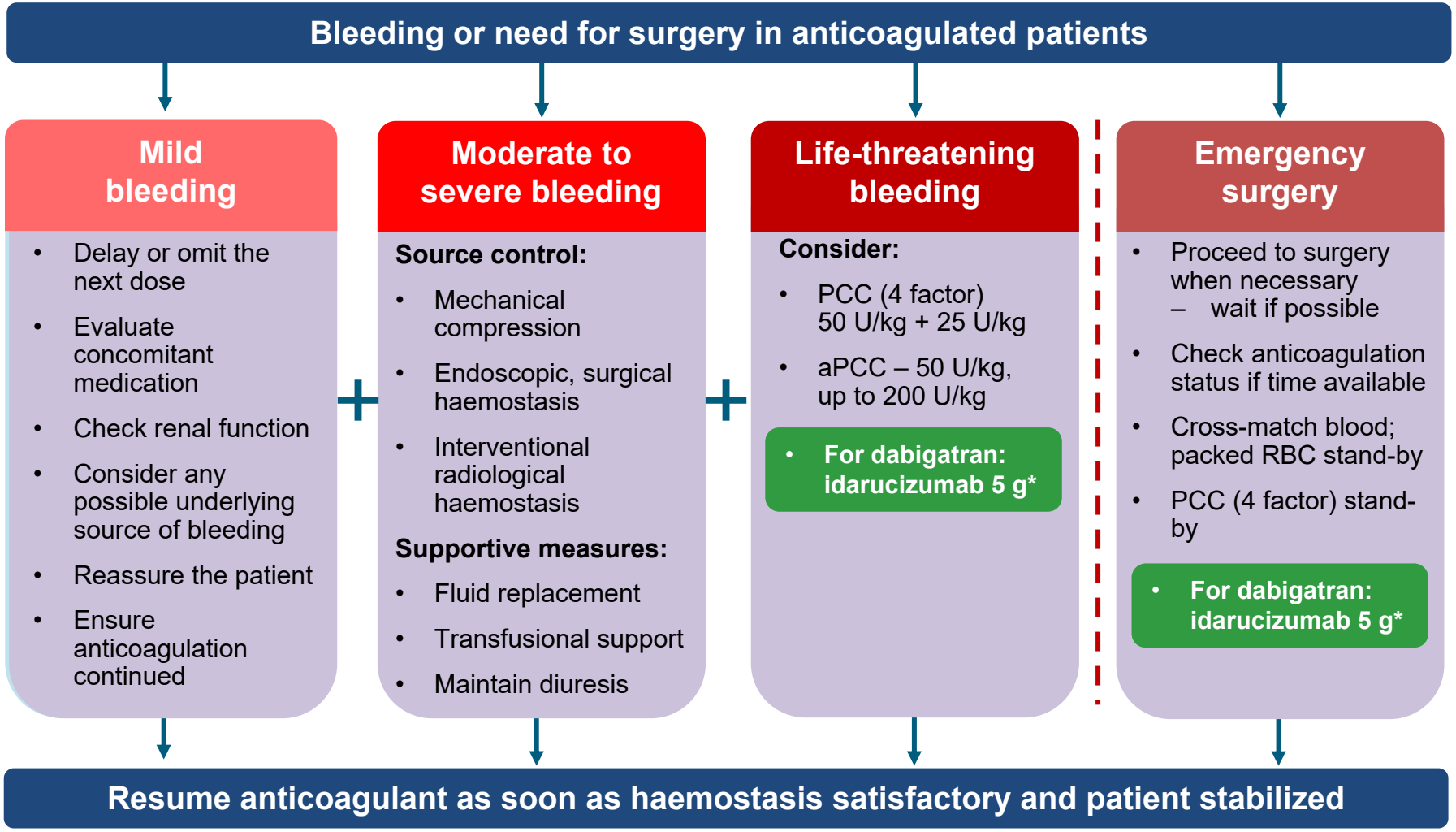
LG

FCSA 2014

Guidelines for reversal of anticoagulants

NAMES	ELIMINATION HALF-LIFE	REMOVED BY HD	STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
apixaban *(Eliquis)*	8-15 hours (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity assay (UWMedicine: apixaban assay [APIXN1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
dabigatran *(Pradaxa)*	14-17 hours (up to 34 hrs in severe renal impairment)	~ 65%	• Drug activity can be assessed with aPTT and/or plasma-diluted thrombin time (UWMedicine: dabigatran assay [DABIG]) • If ingested within 2 hours, administer activated charcoal • *For life-threatening bleeding or emergency surgery, consider idarucizumab (Praxbind) 5gm IV* **NOTE:** idarucizumab will likely correct aPTT and plasma-diluted thrombin time but the correlation of lab results with improved outcomes is not established **NOTE**: Plasma dabigatran concentrations can increase more than 12-24 hours after idarucizumab, likely due to re-distribution from the extravascular compartment. **NOTE**: The risks and benefits of repeat idarucizumab administration are not known.
Edoxaban (Savaysa)	10-14 hours (longer in renal impairment)	~ 25%	• There is no assay for edoxaban at this time. • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
Rivaroxaban *(Xarelto)*	Healthy: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity (UWMedicine: rivaroxaban assay [RIVAR1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown

Idarucizumab is recommended to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding



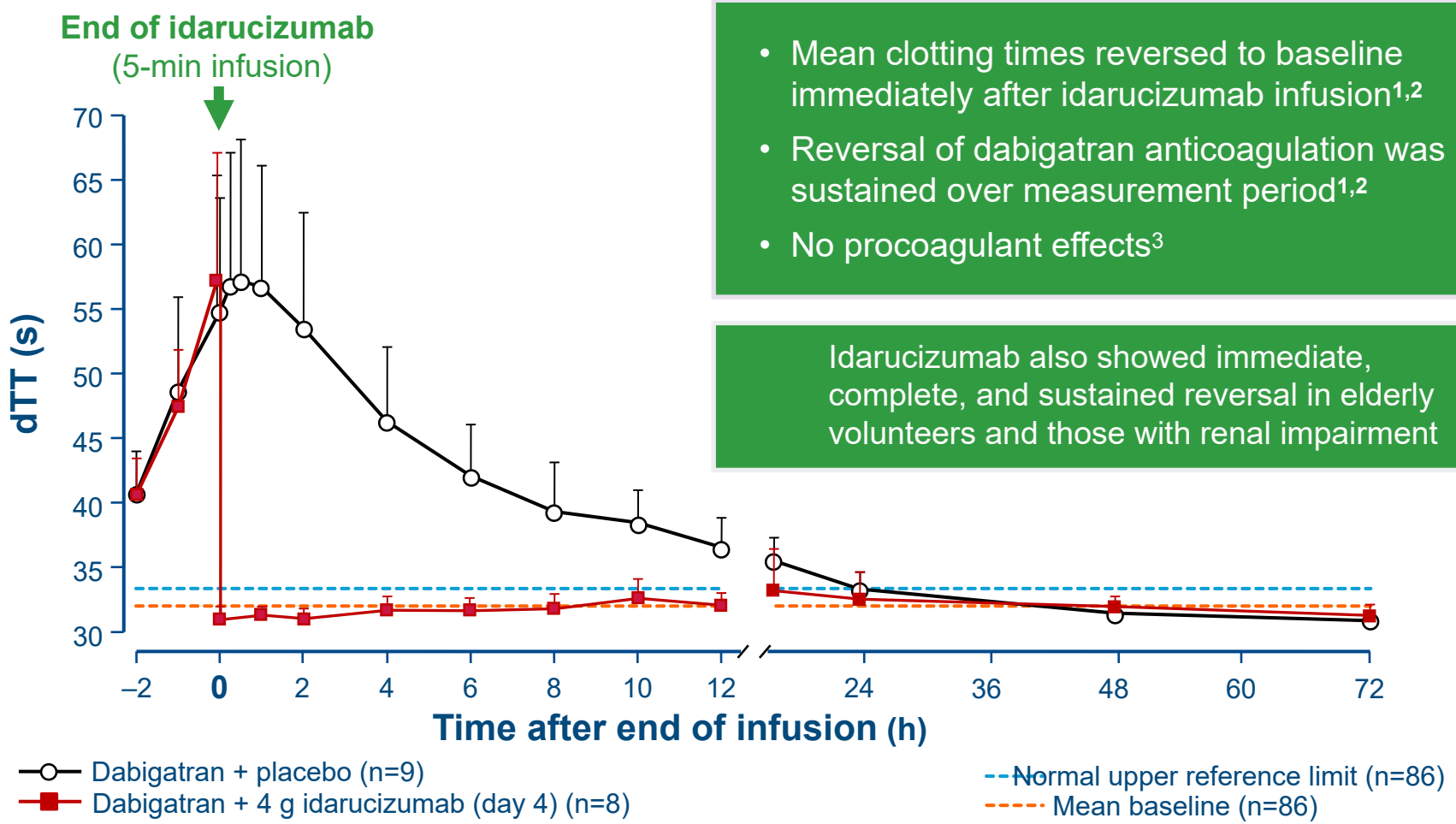
*Idarucizumab is the preferred treatment to reverse dabigatran; PCC, prothrombin complex concentrate; RBC, red blood cell; Anticoagulation Education Task Force White Paper: Ageno W et al. Thromb Haemost 2016

NOAC reversal agents are in development

NOAC reversal agent	Target	Mechanism of action
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]
Andexanet alfa (PRT064445)[1]	FXa inhibitors	Recombinant modified FXa: competitive affinity for direct FXa inhibitors[3]
Ciraparantag (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[4]

FXa, activated Factor X

1. Greinacher et al. Thromb Haemost 2015; 2. Schiele et al. Blood 2013; 3. Lu et al. Nat Med 2013;
4. Ansell et al. N Engl J Med 2014



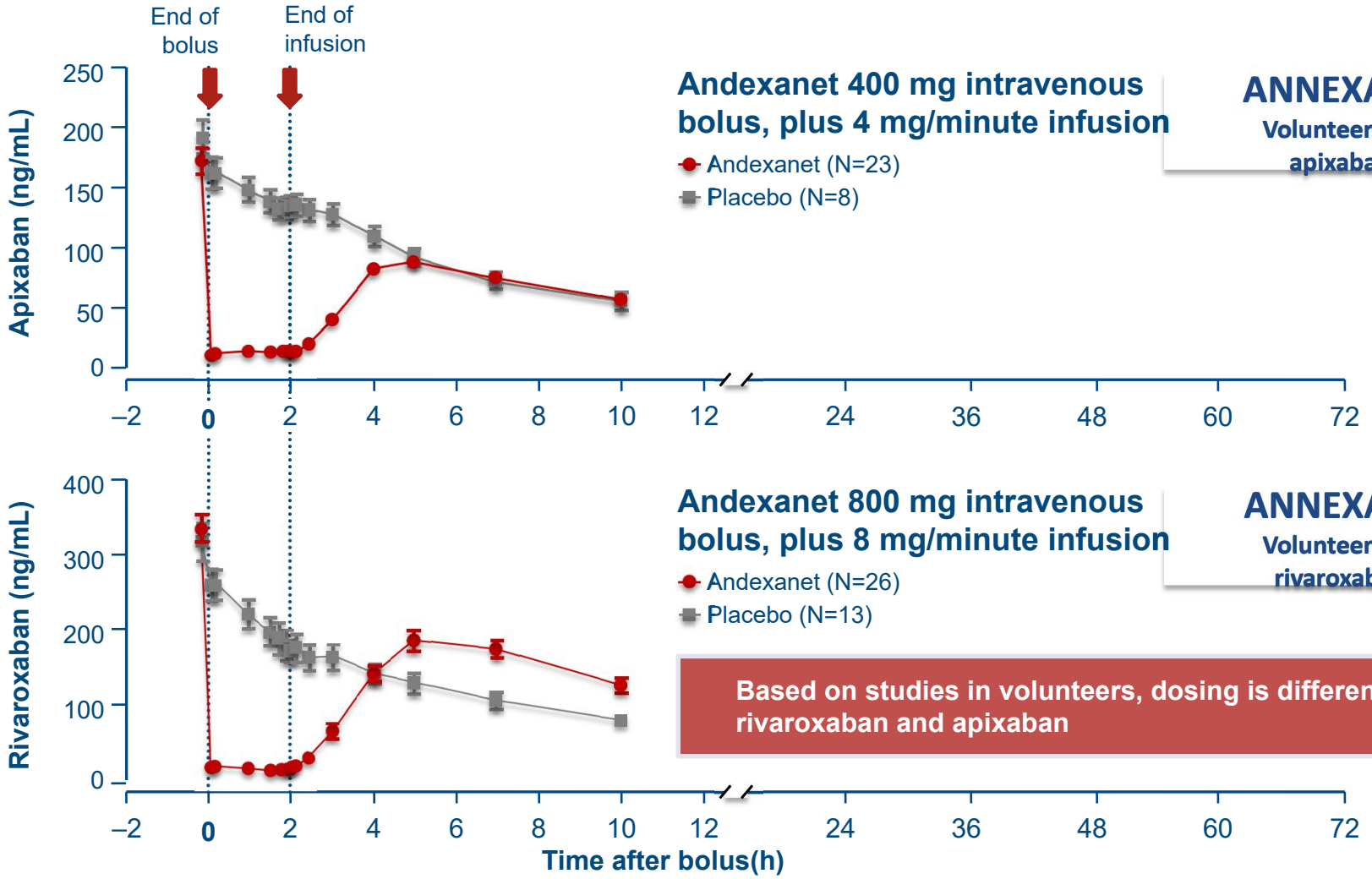
- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

Andexanet alfa

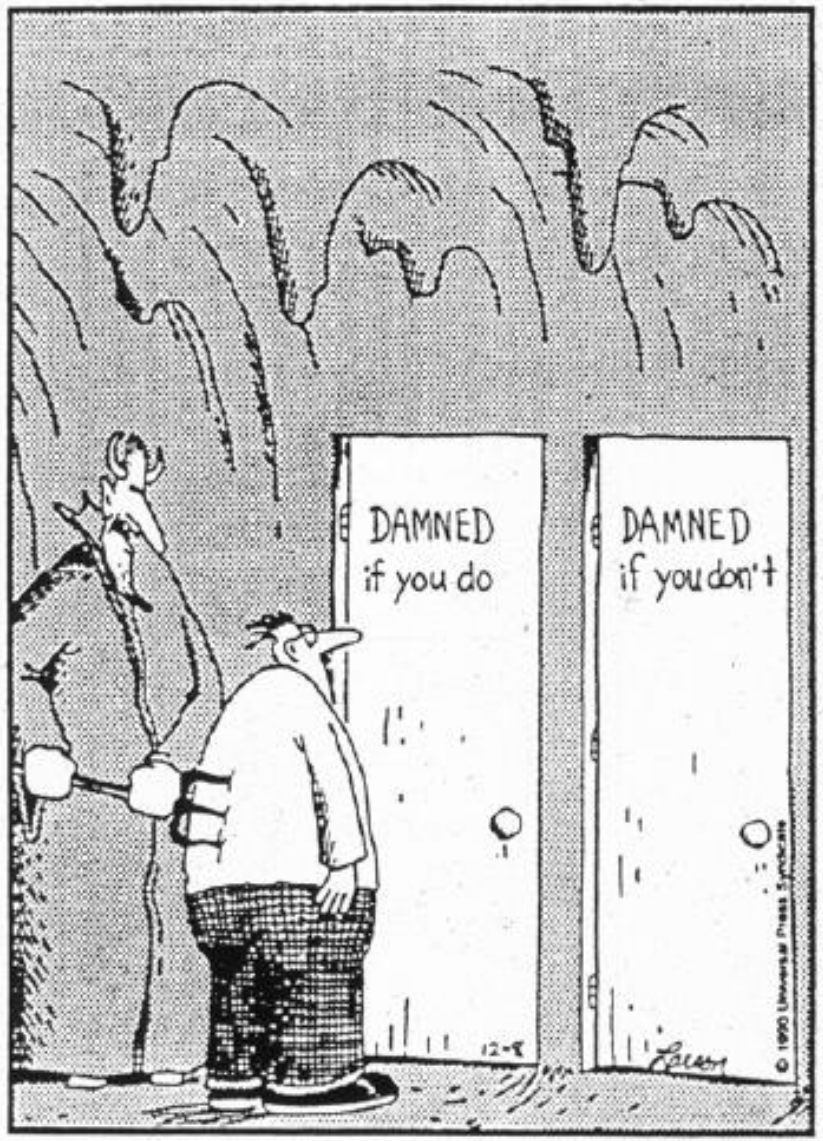
In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



Based on studies in volunteers, dosing is different for rivaroxaban and apixaban

1. Siegal DM et al. N Engl J Med 2015

Anyway at the end of our work and strengths…in the ED



…via ringrazio per l’attenzione

Regione Toscana