

IL PAZIENTE FRAGILE IN CARDIOLOGIA

Torino
Sabato 11 maggio 2019

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Ospedale San Giovanni Bosco



RESPONSABILI SCIENTIFICI

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ASL Città di Torino Ospedale San Giovanni Bosco

I nuovi anticoagulanti orali: Update 2019

Fabrizio UGO

**Ospedale San Giovanni Bosco
Torino**

FRAGILITA'– ASSENZA DI DEFINIZIONE

Quasi tutti i Geriatri sono d'accordo nel dire che il paziente “fragile” si riconosce ad una prima occhiata anche se quasi nessuno è in grado di fornirne una descrizione adeguata.

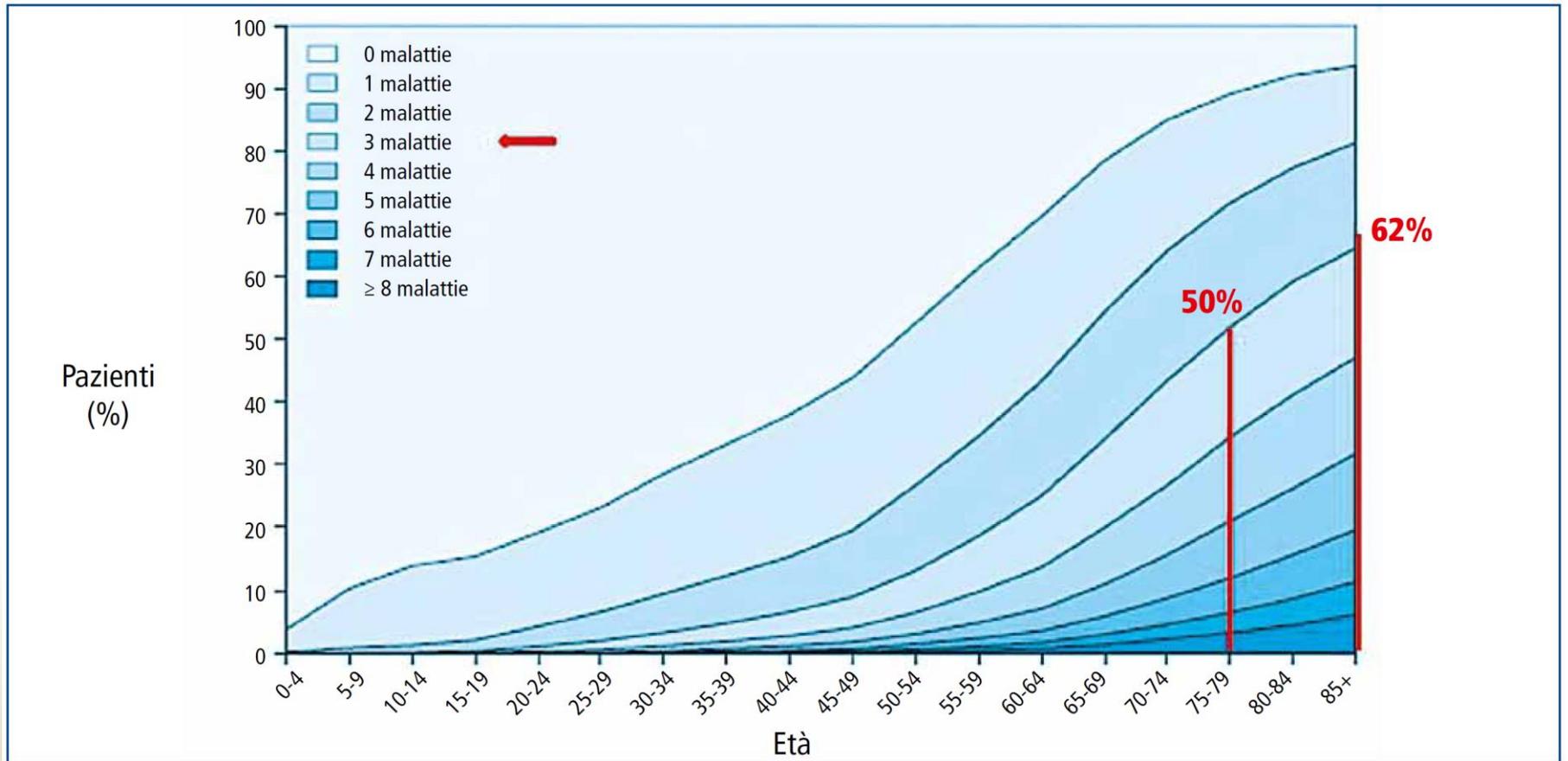
**L. FERRUCCI et Al
AIP, 2002; SIGG 2002**

Fragilità?

FRAGILITA' ≠ ETA'



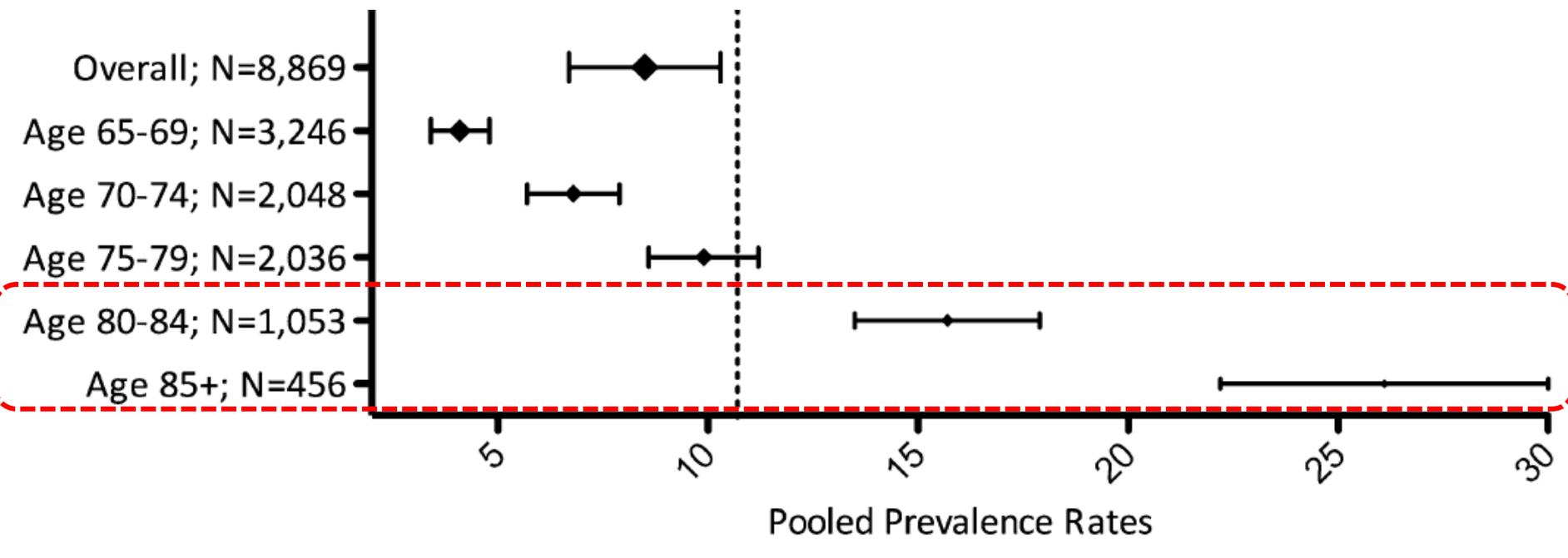
Multi morbidità nella popolazione anziana



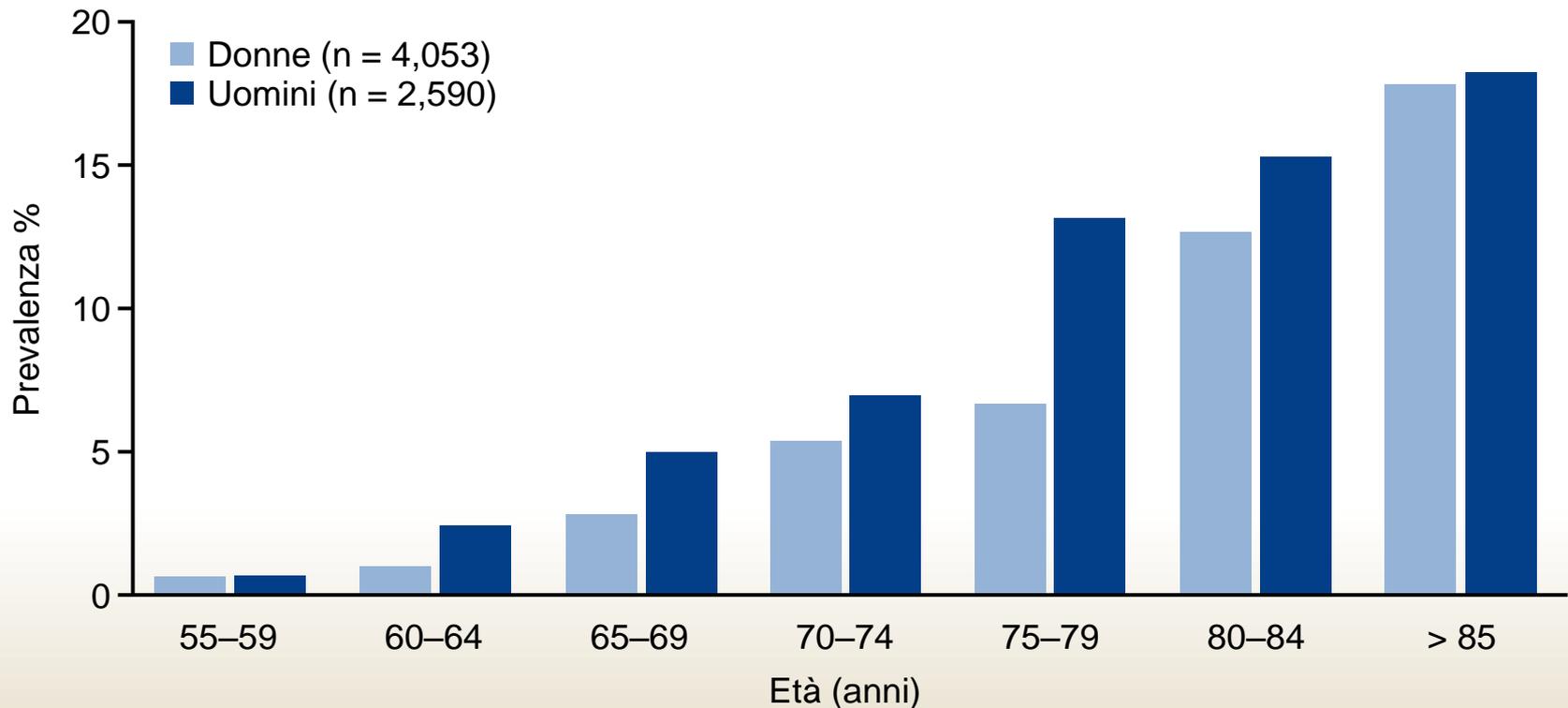


Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review

Prevalence of frailty: Frailty Index or Fried Frailty Index



Fibrillazione atriale: prevalenza ed età in Europa





**...Sono i pazienti che
avremmo trattato con**



Nel Paziente anziano con FA



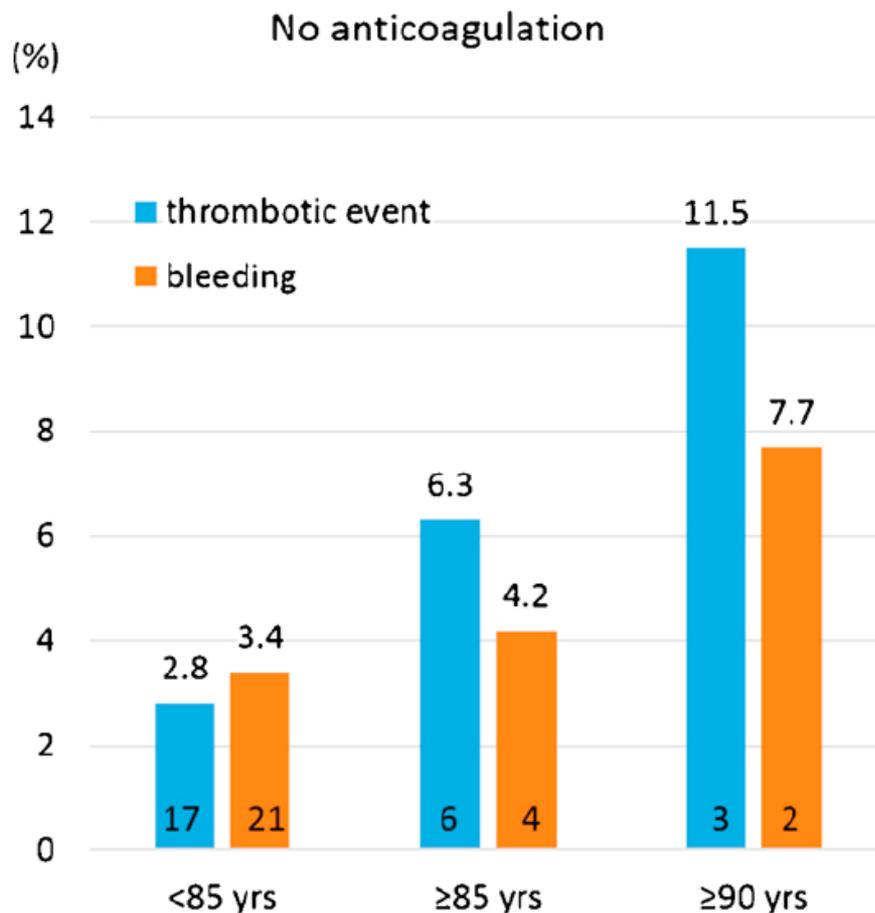
**Non protegge dagli
eventi Embolici /
Ischemici**

**Fa sanguinare
come un NAO**

Rischio trombotico e rischio di sanguinamento nell'anziano

PREvention of thromboembolic events –
European Registry in Atrial Fibrillation
(PREFER in AF)

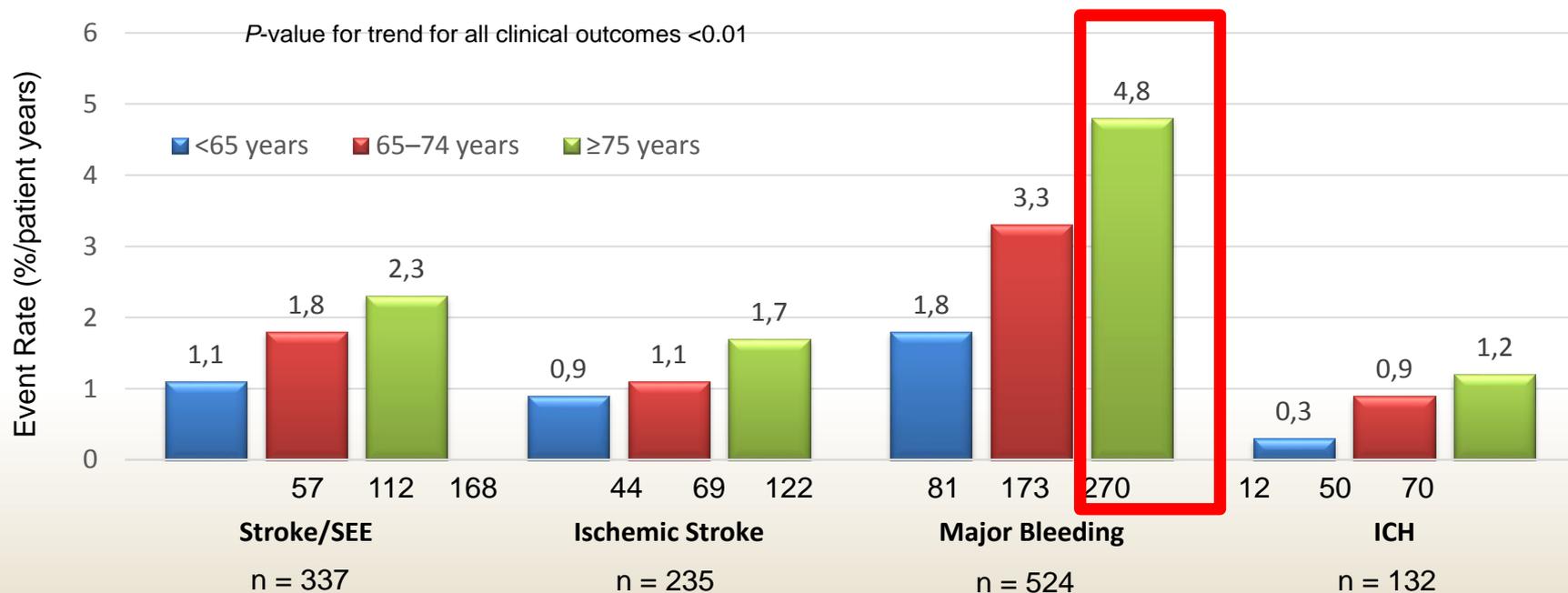
**Nel paziente anziano non
trattato con anticoagulanti,
il rischio trombotico
supera quello emorragico**



Effetto dell'età sugli outcome clinici nei pazienti in Warfarin

Adjusted HR (95% CI)

Comparison	Stroke/SEE	Ischemic Stroke	Major Bleeding	ICH
65–74 vs <65 years	1.45 (1.04–2.00)	1.13 (0.77–1.67)	1.83 (1.40–2.39)	3.30 (1.72–6.31)
≥75 vs <65 years	1.83 (1.32–2.54)	1.81 (1.24–2.63)	2.68 (2.04–3.52)	3.77 (1.94–7.30)



PAZIENTI ANZIANI

RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE-AF-TIMI 48



(72±9)



(40%)
(17%)



73 (65-78)



(44%)
(4.6%)



70 (63-76)



(31%)
(13%)

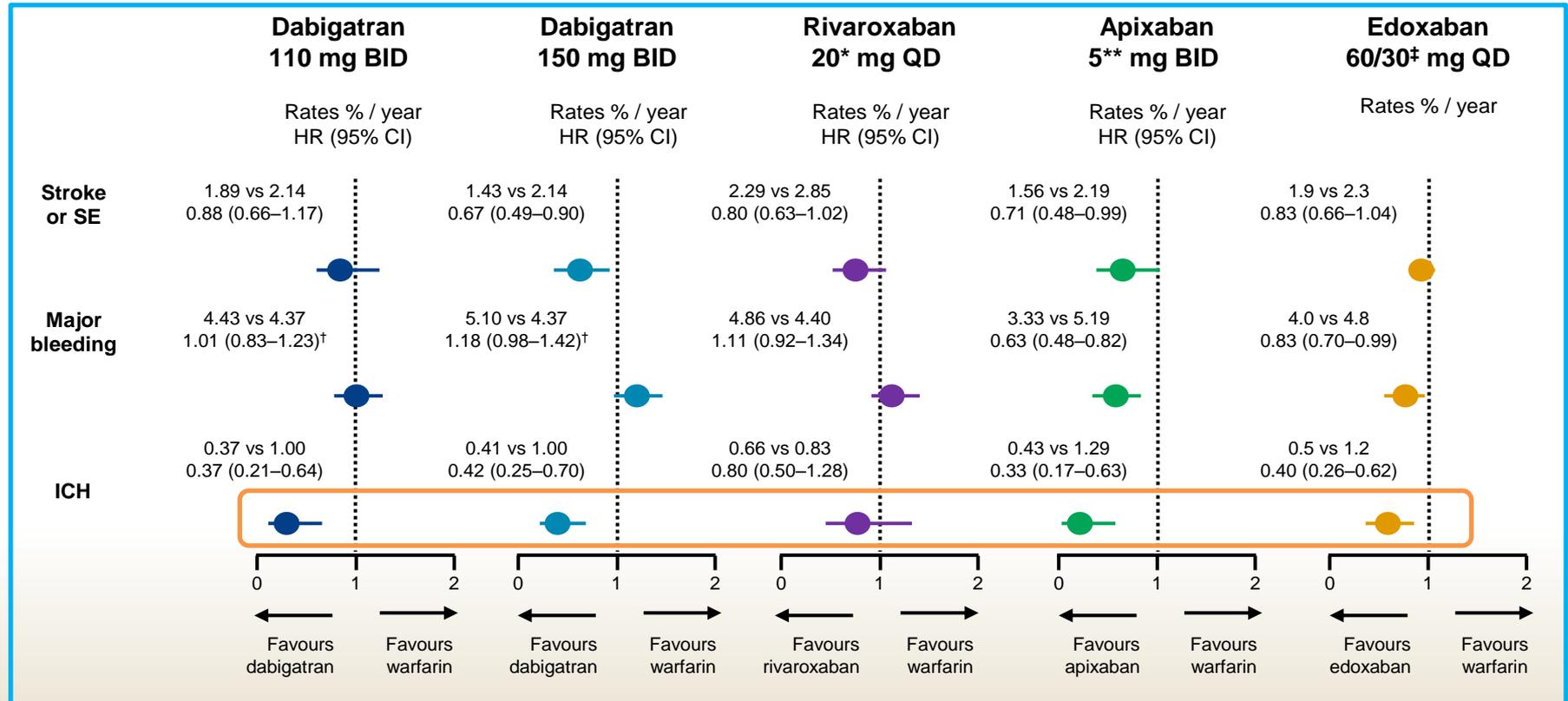


72 (64-78)



(40.1%)
(17%)
(4.2%)

Efficacia e sicurezza dei NOACs vs Warfarin nei pazienti ≥ 75 anni



*Reduced to 15 mg if CrCl 30–49 mL/min

**Reduced to 2.5 mg twice-daily if at least two of the following criteria were present: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl

†P<0.001 vs warfarin

‡Reduced dose as per the SmPC

BID, twice daily; ICH, intracranial haemorrhage; QD, once daily

Modified from Capranzano P, et al. Expert Rev Cardiovasc Ther 2013;11:959–73;

Kato ET, et al. J Am Heart Assoc 2016;5:e003432

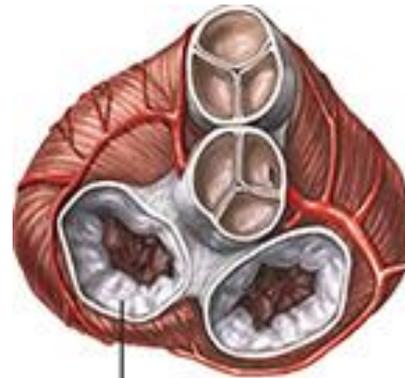
DOACs 2019: update

- Fibrillazione atriale e valvole
- Triplice trattamento antitrombotico post PCI
- Insufficienza renale – calcifilassi – pazienti in dialisi
- Pazienti a rischio di cadute
- Politerapia
- Demenza ed Aderenza alla terapia

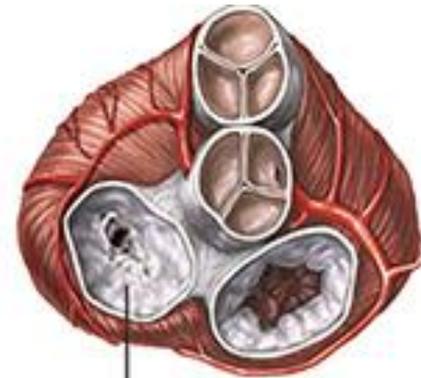
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Indicazioni e controindicazioni dei DOACs



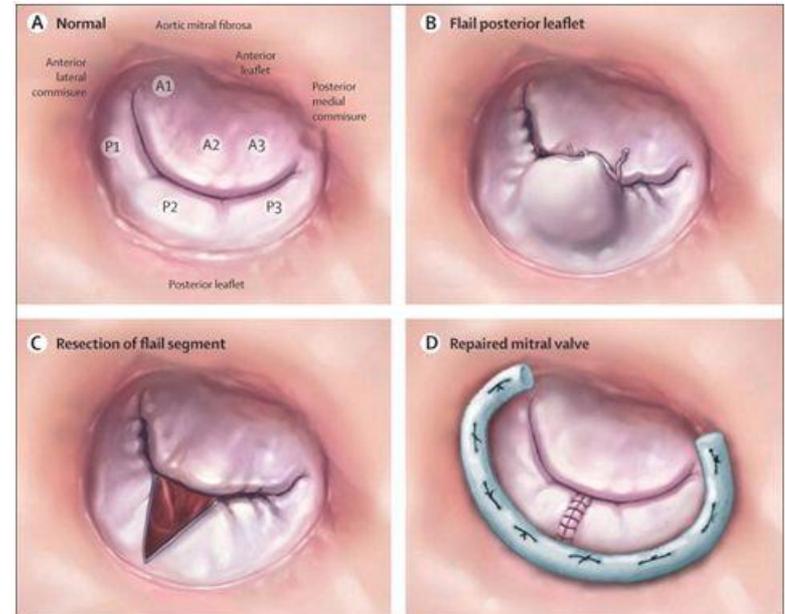
Normal
mitral valve



Rheumatic mitral valve
(with stenosis)

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated

Indicazioni e controindicazioni dei DOACs

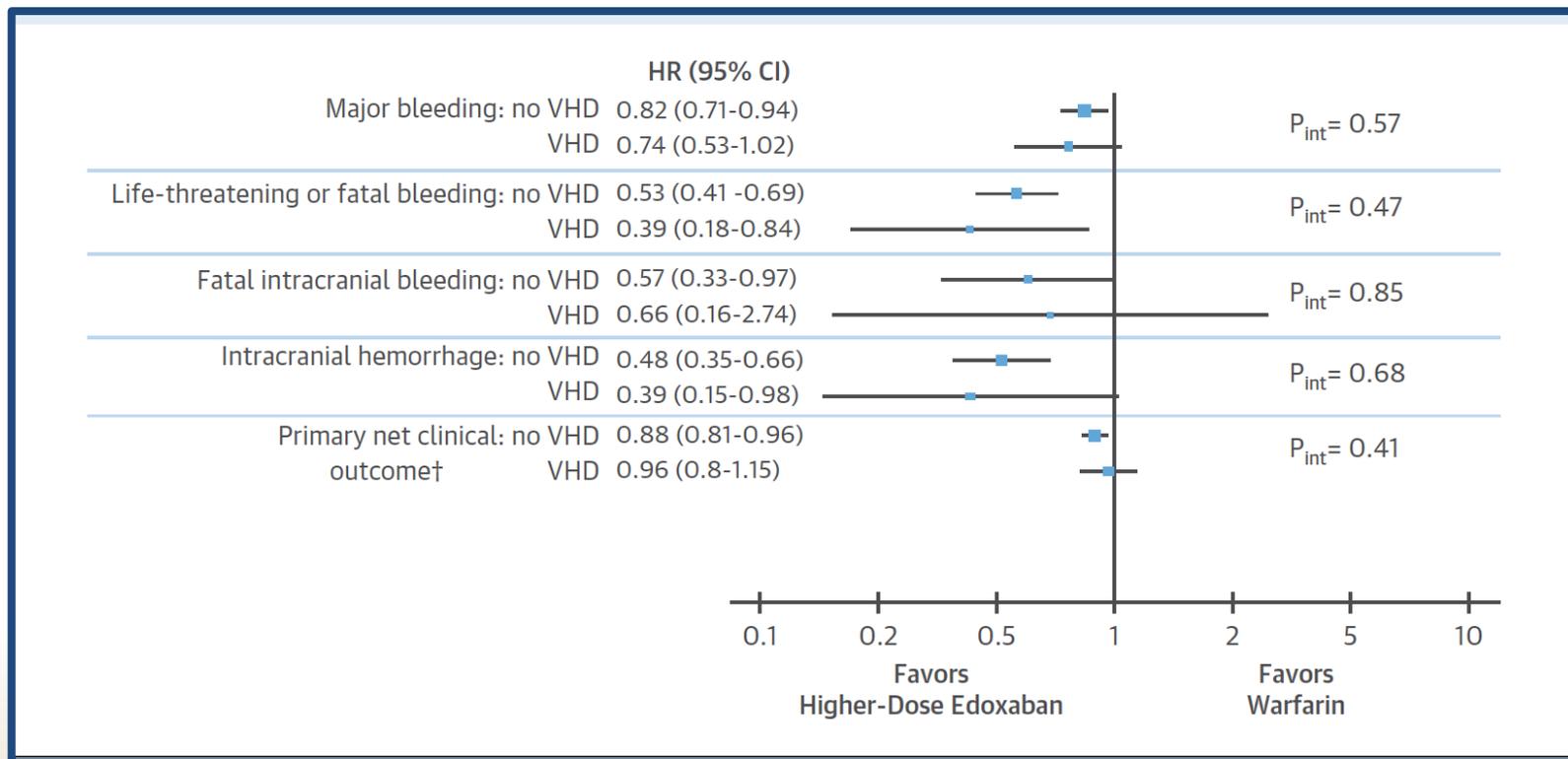


<p>Bioprosthetic valve (after > 3 months post operatively)</p>	<p>Not advised if for rheumatic mitral stenosis</p> <p>Acceptable if for degenerative mitral regurgitation or in the aortic position</p>
<p>Mitral valve repair (after > 3 months post operatively)</p>	<p>Some patients included in some NOAC trials</p>

RESEARCH LETTER

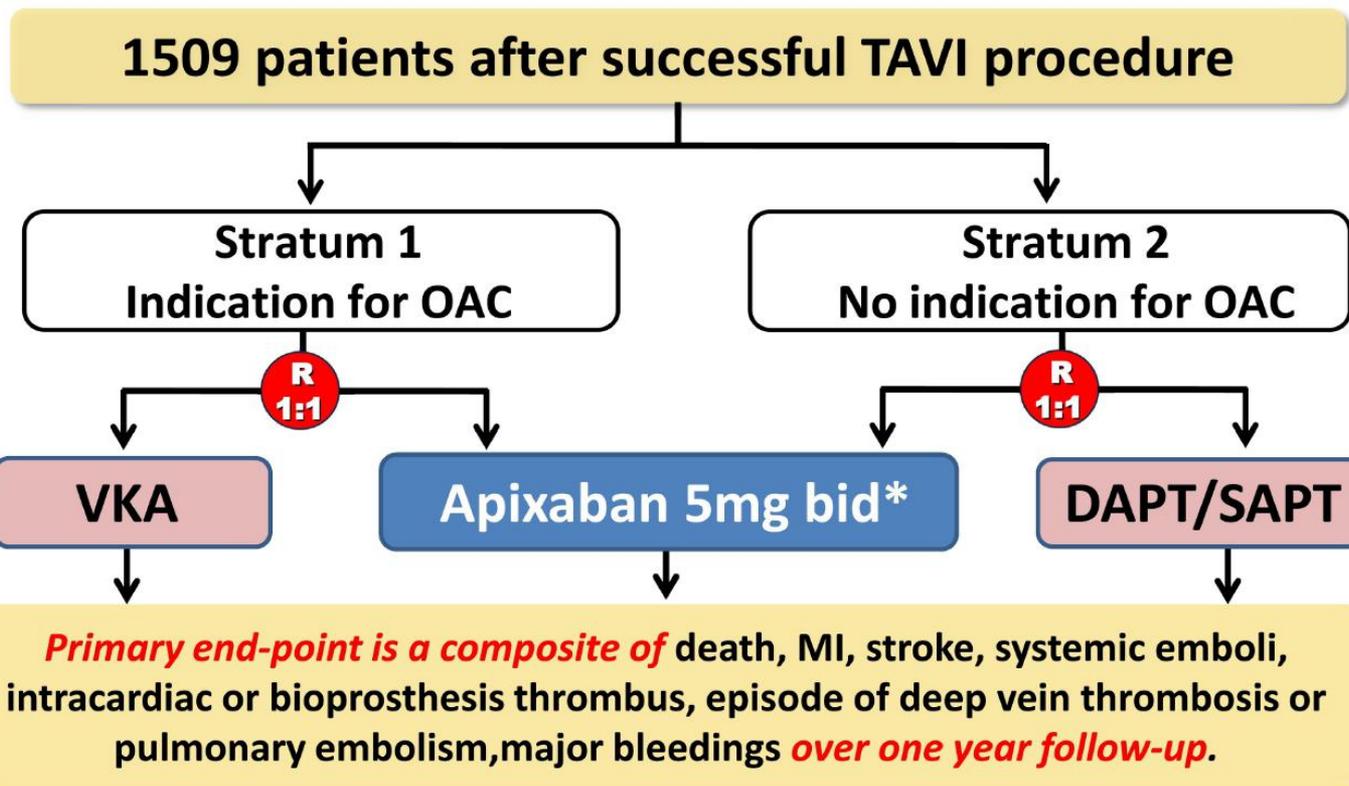
Edoxaban for the Prevention of Thromboembolism in Patients With Atrial Fibrillation and Bioprosthetic Valves

EDOxabAN vs WARfARIN IN AF VHD vs non VHD



- **nessuna differenza di EFFICACY** tra Edoxaban e Warfarin in VHD-AF
- **SAFETY: minore incidenza di sanguinamenti**

ATLANTIS: Study design



*2.5mg bid if :

- creatinine clearance 15-29mL/min
- two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133μMol)
- Concomitant oral antiplatelet therapy



Experimental arm



Standard of care

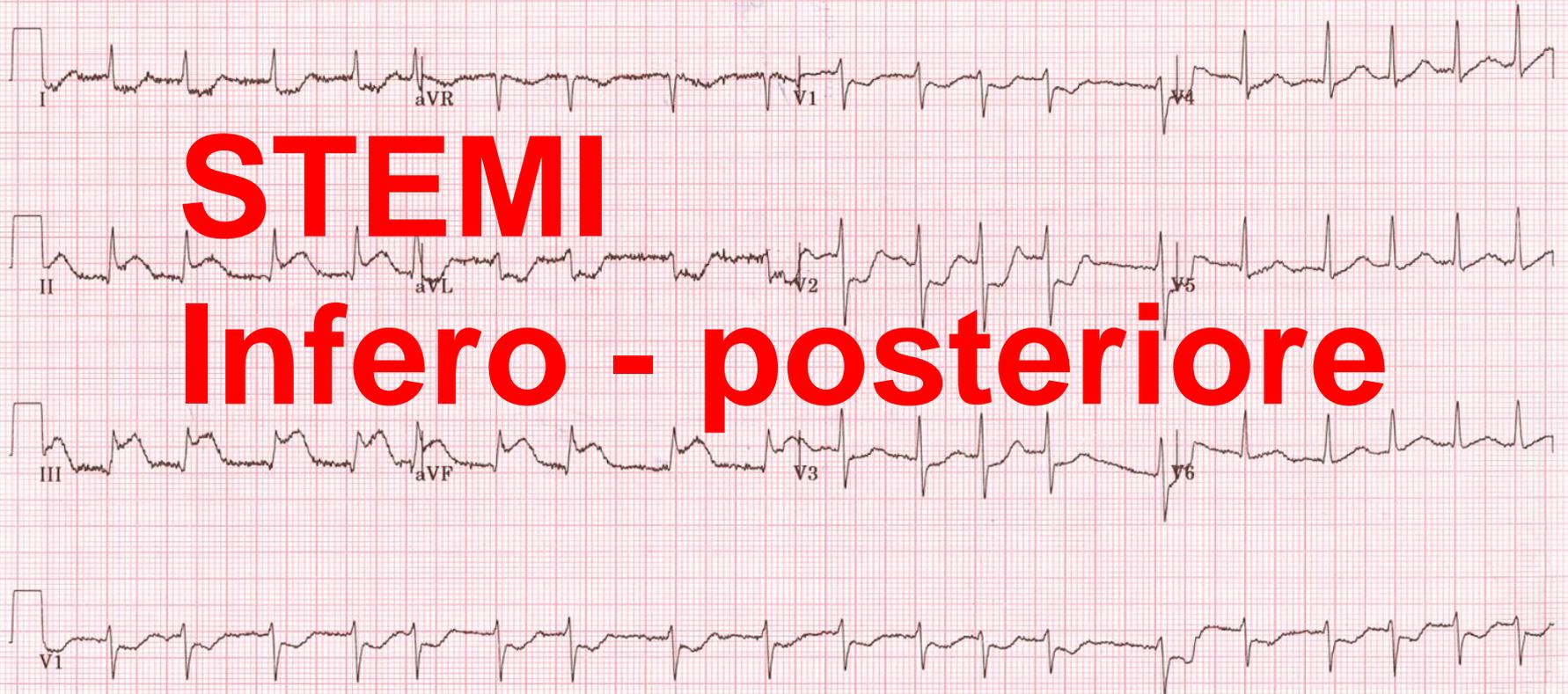
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Caso Clinico: ECG del pronto soccorso

Uomo di 85aa

Confermato da:



STEMI
Infero - posteriore

100Hz 25.0mm/s 10.0mm/mV

4 x 2,5s + 1 der. ritmo

MAC5K 006A

12SL™ v233

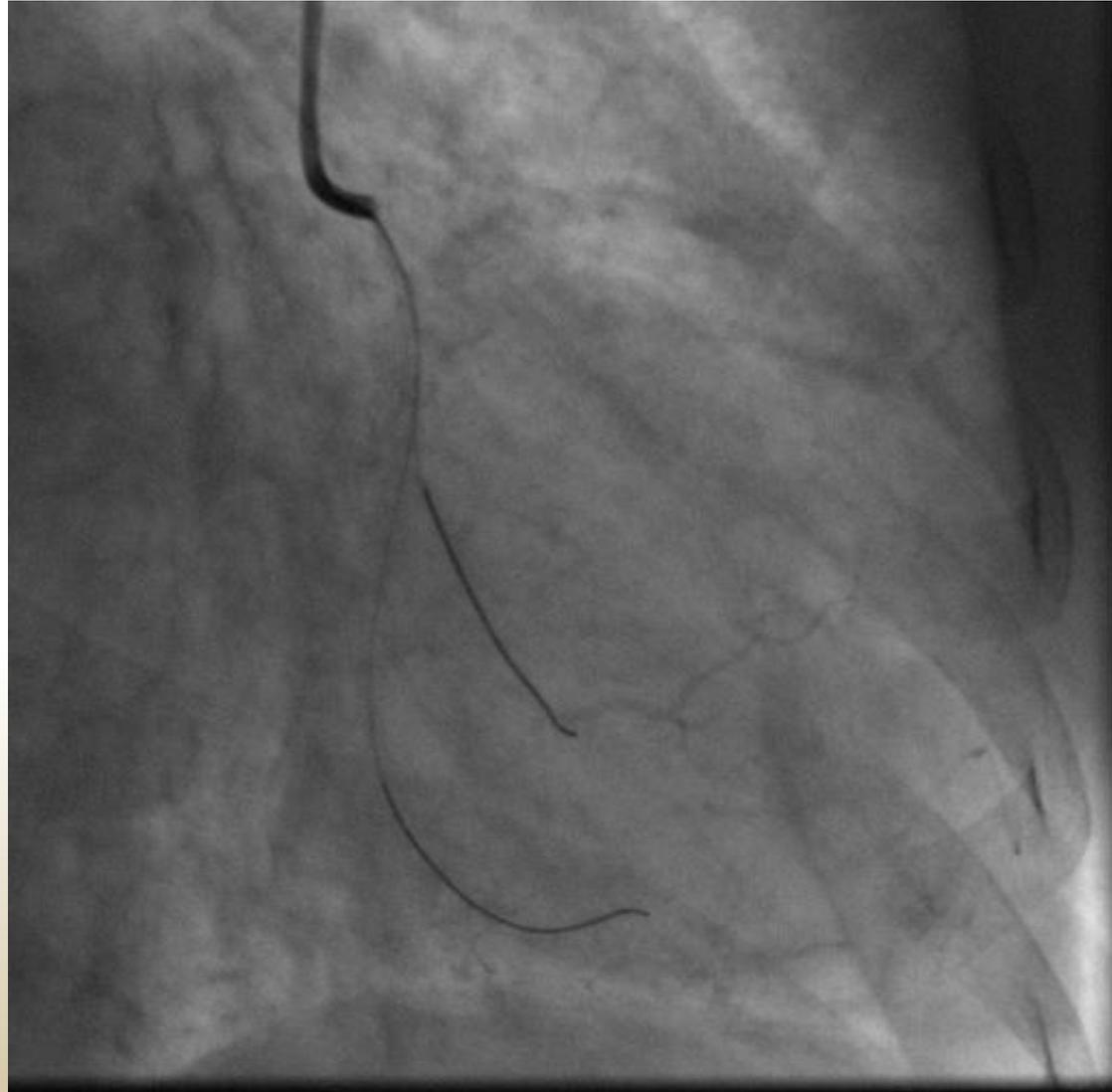
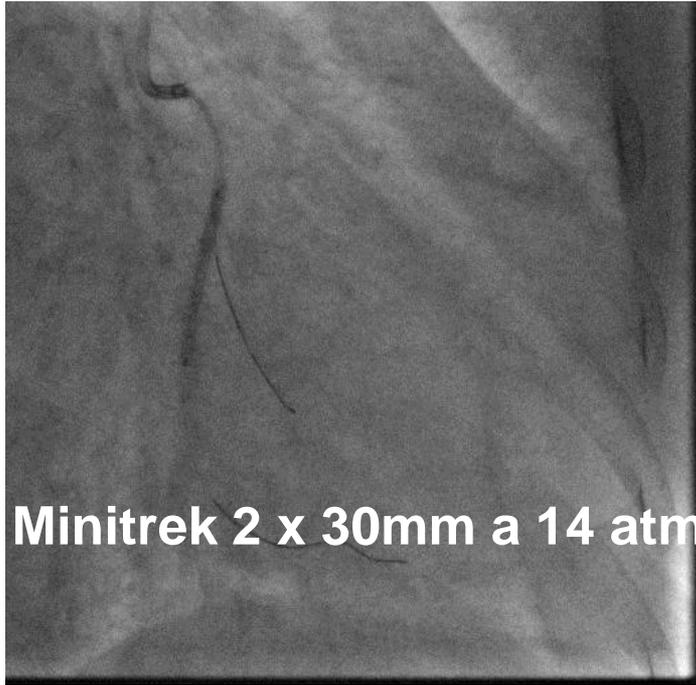
Coronarografia



Coronarografia

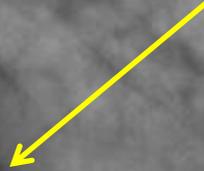


Angioplastica su ramo Circonflesso

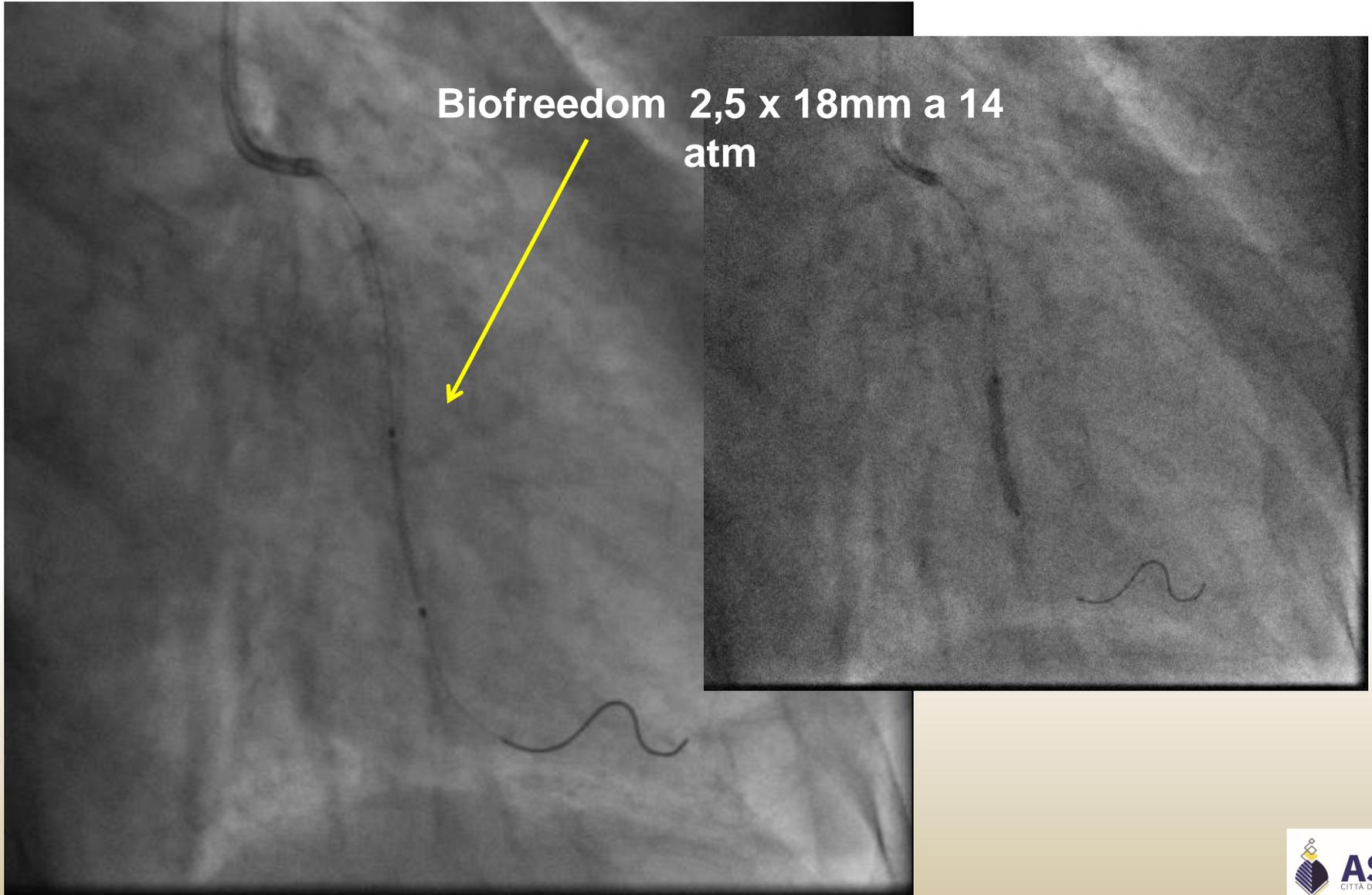


Angioplastica su ramo Circonflesso

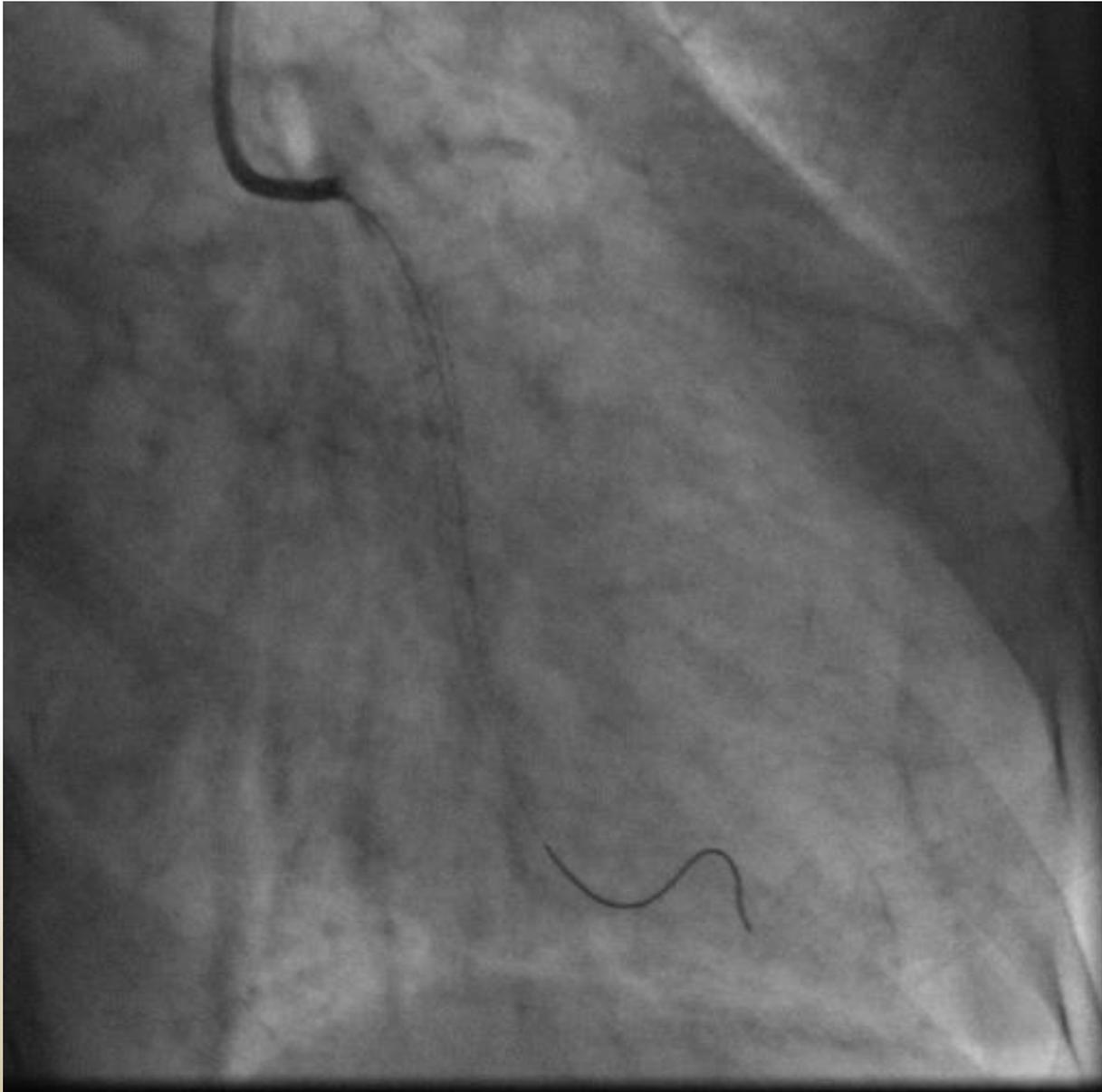
Biofreedom 2,5 x 36mm a 14 atm



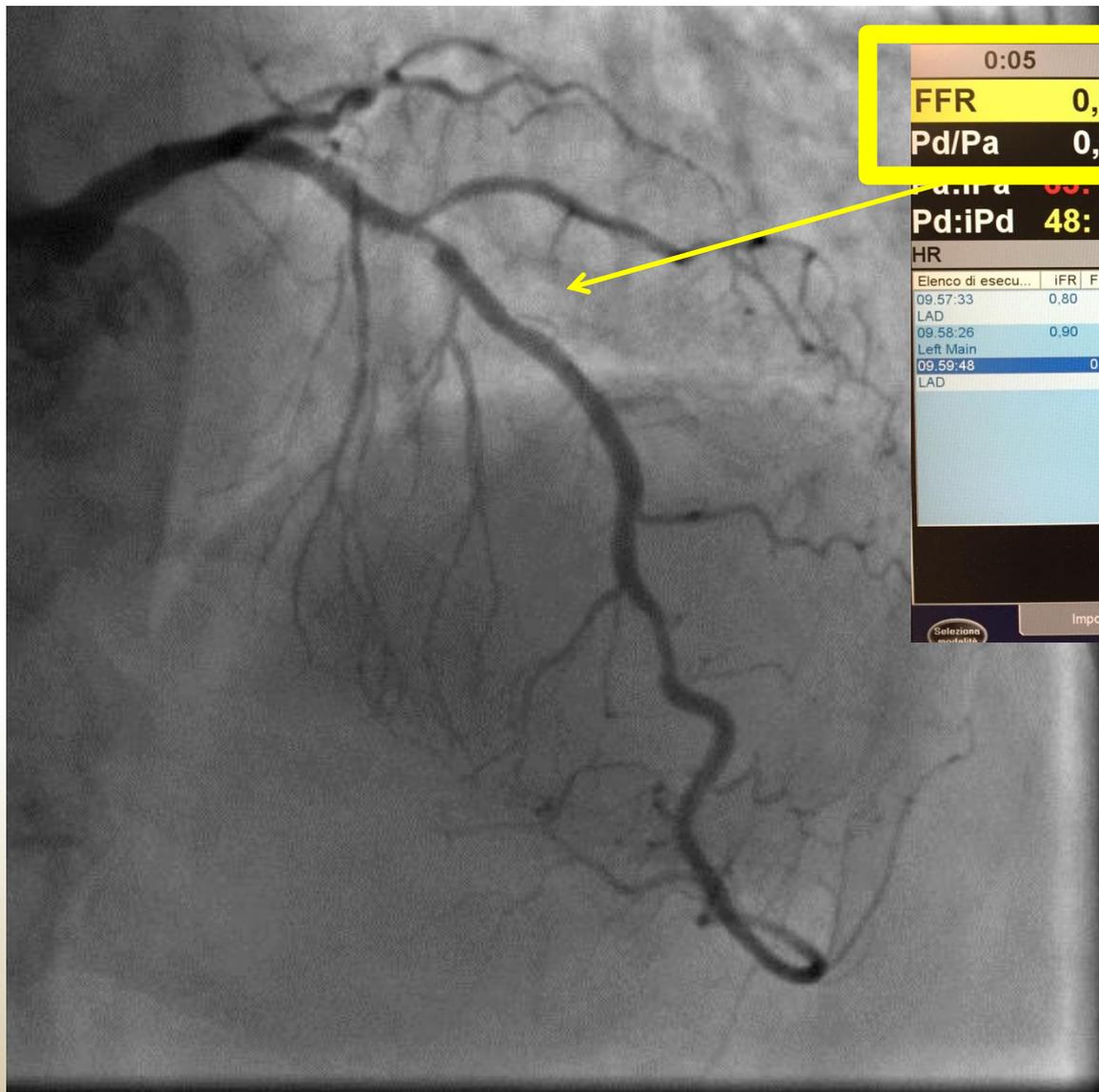
Angioplastica su ramo Circonflesso



Angioplastica su ramo Circonflesso



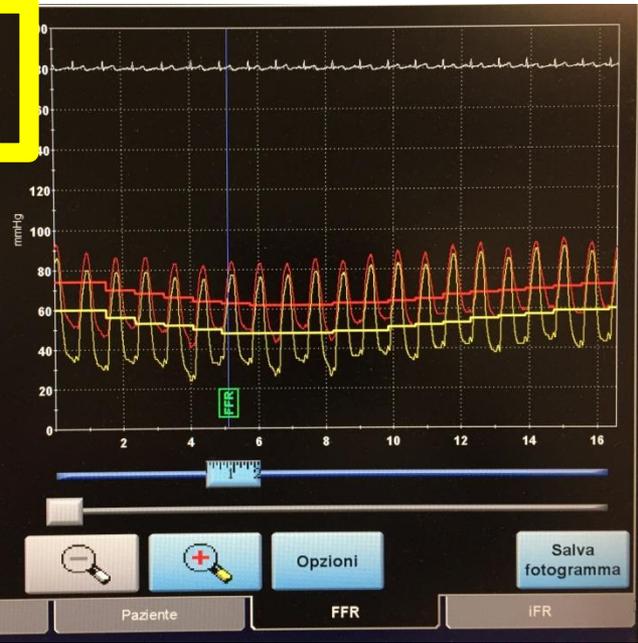
Valutazione IVA con FFR



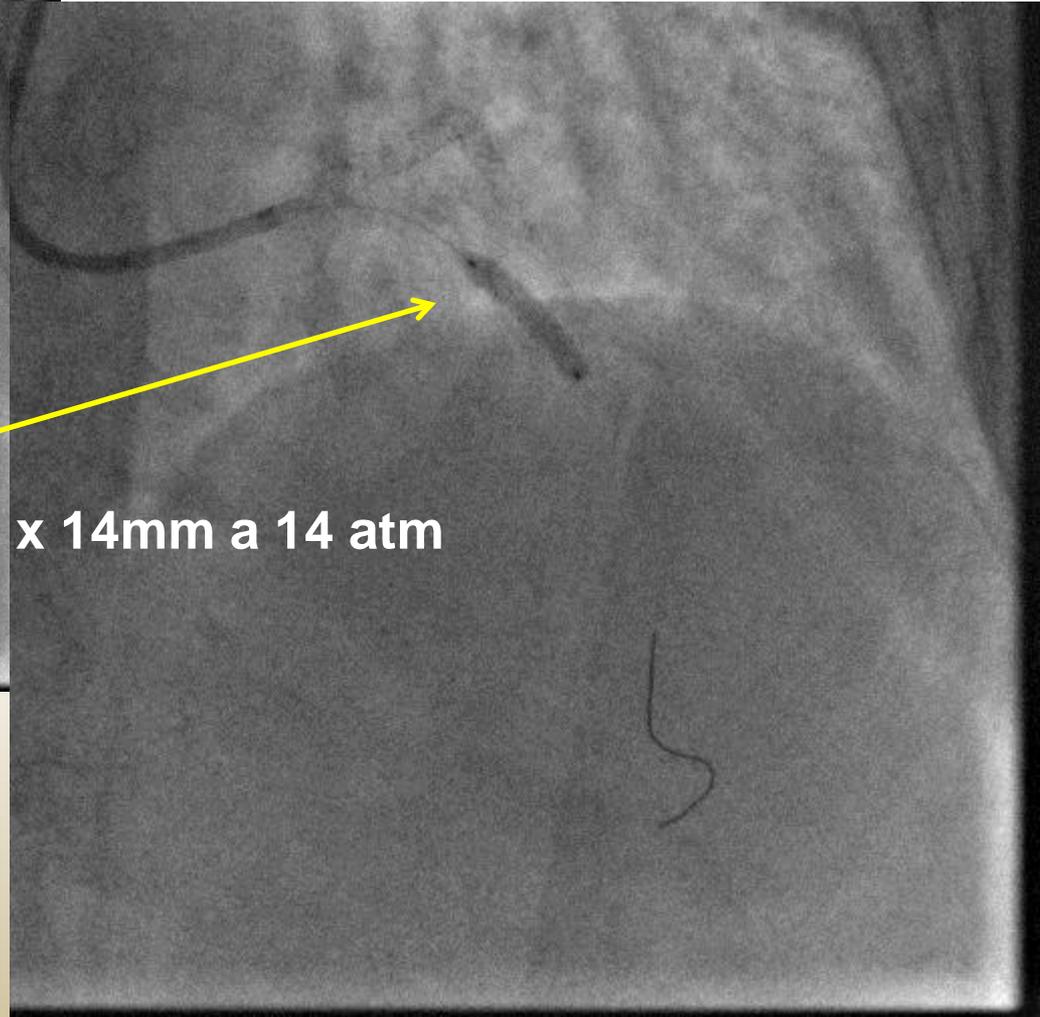
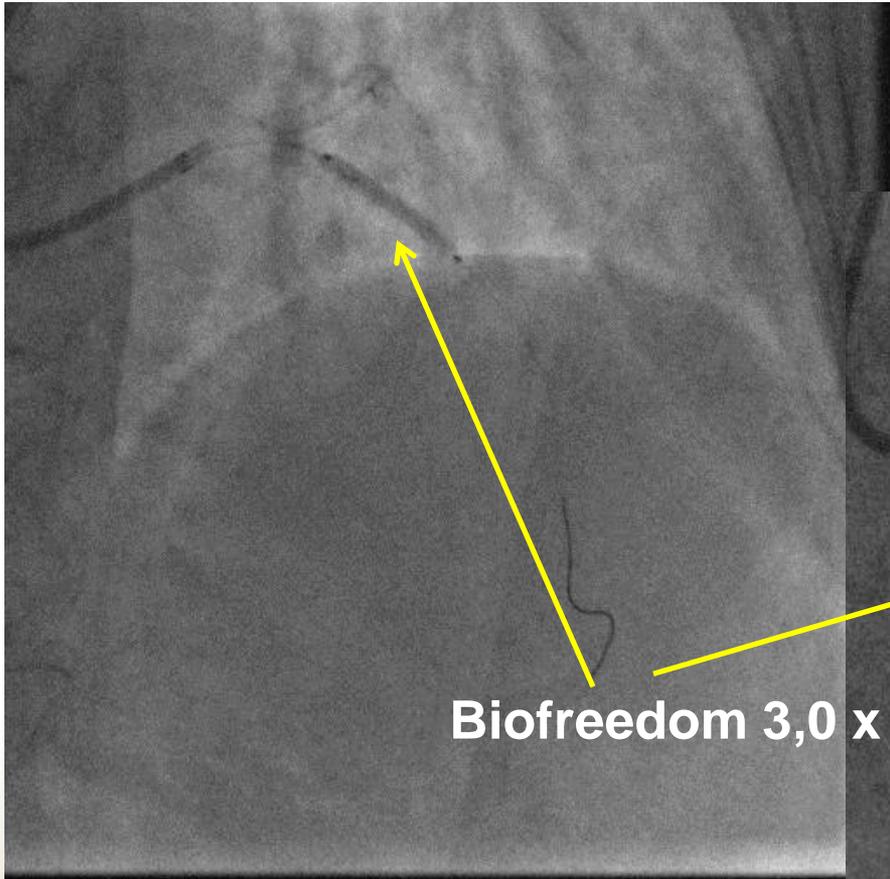
0:05
FFR 0,76
Pd/Pa 0,76

Pd:Pa 85:77
Pd:iPd 48:68
HR 71

Elenco di esecu...	IFR	FFR
09:57:33	0,80	
LAD		
09:58:26	0,90	
Left Main		
09:59:48	0,76	
LAD		

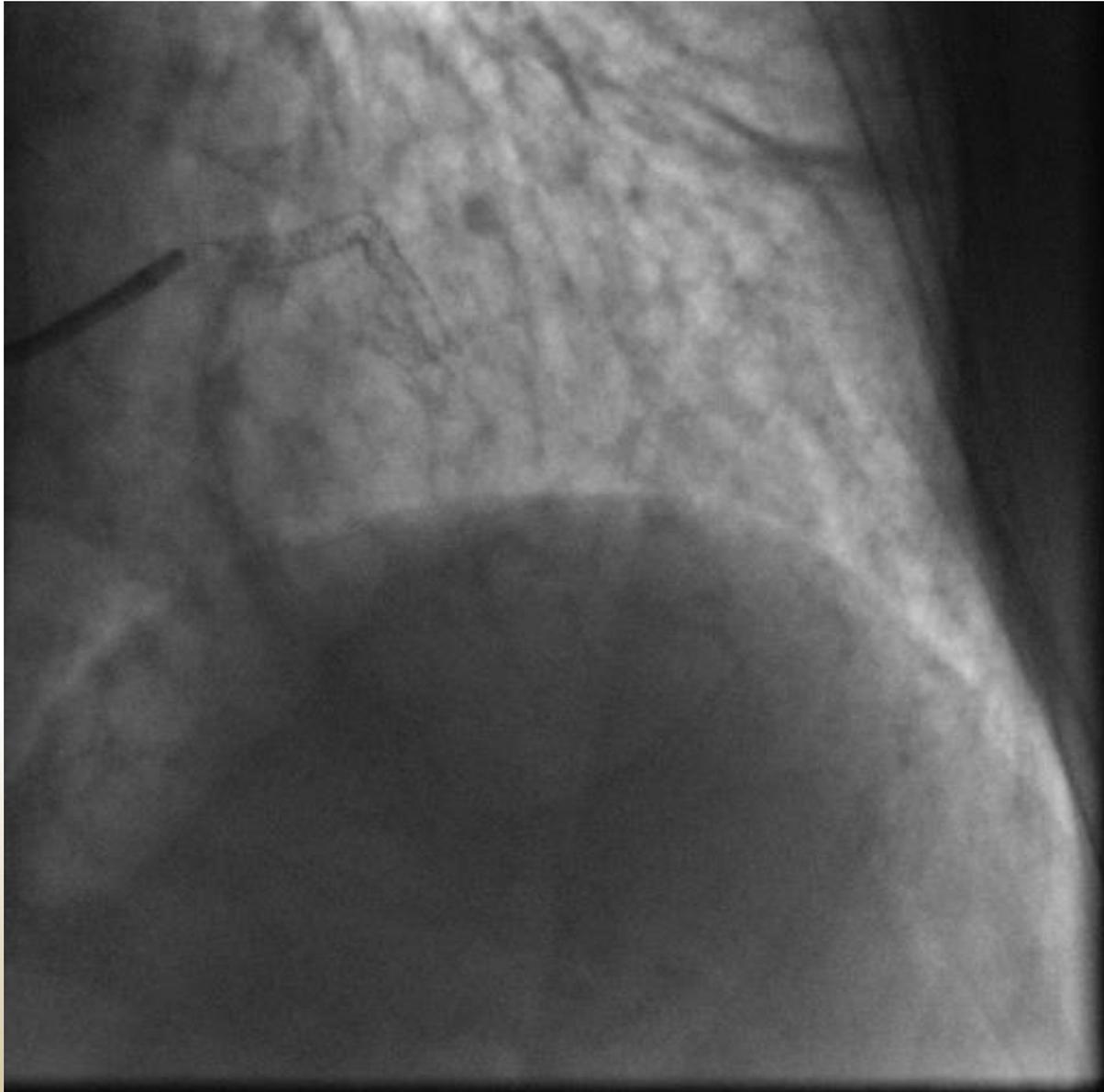


Angioplastica su IVA

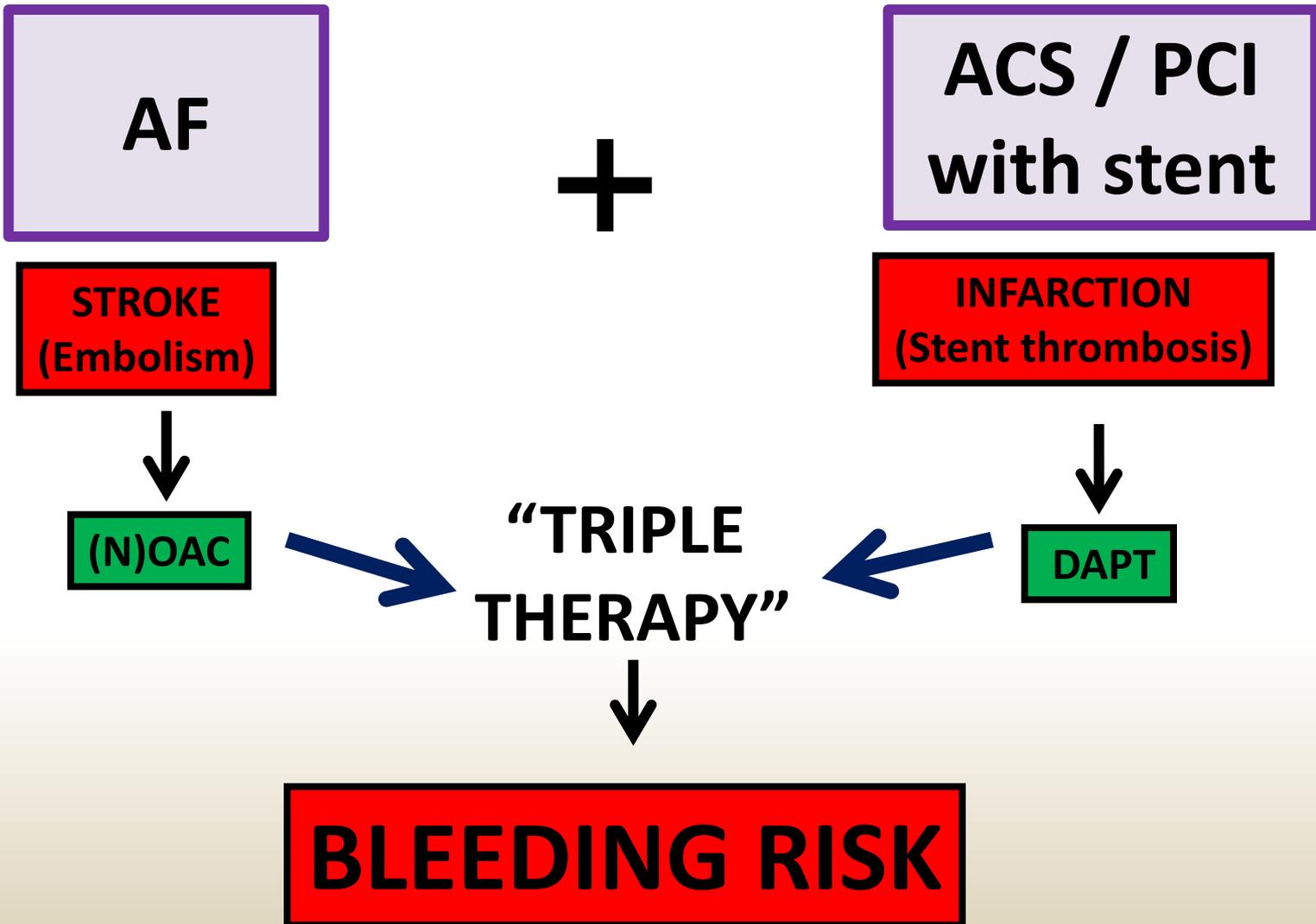


Biofreedom 3,0 x 14mm a 14 atm

Risultato finale 1

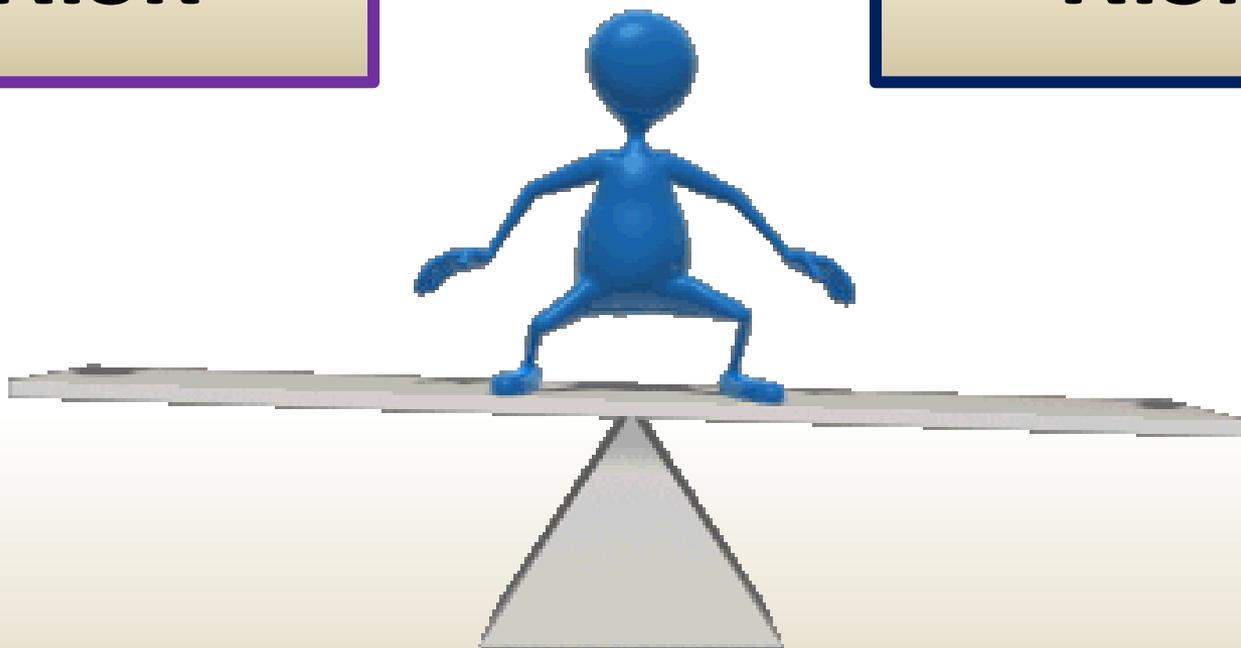


THE PROBLEM



**ISCHEMIC
Risk**

**BLEEDING
Risk**



Patients with an indication for oral anticoagulation undergoing PCI¹

Concerns about ischaemic risk² prevailing

Concerns about bleeding risk³ prevailing

Time from treatment initiation

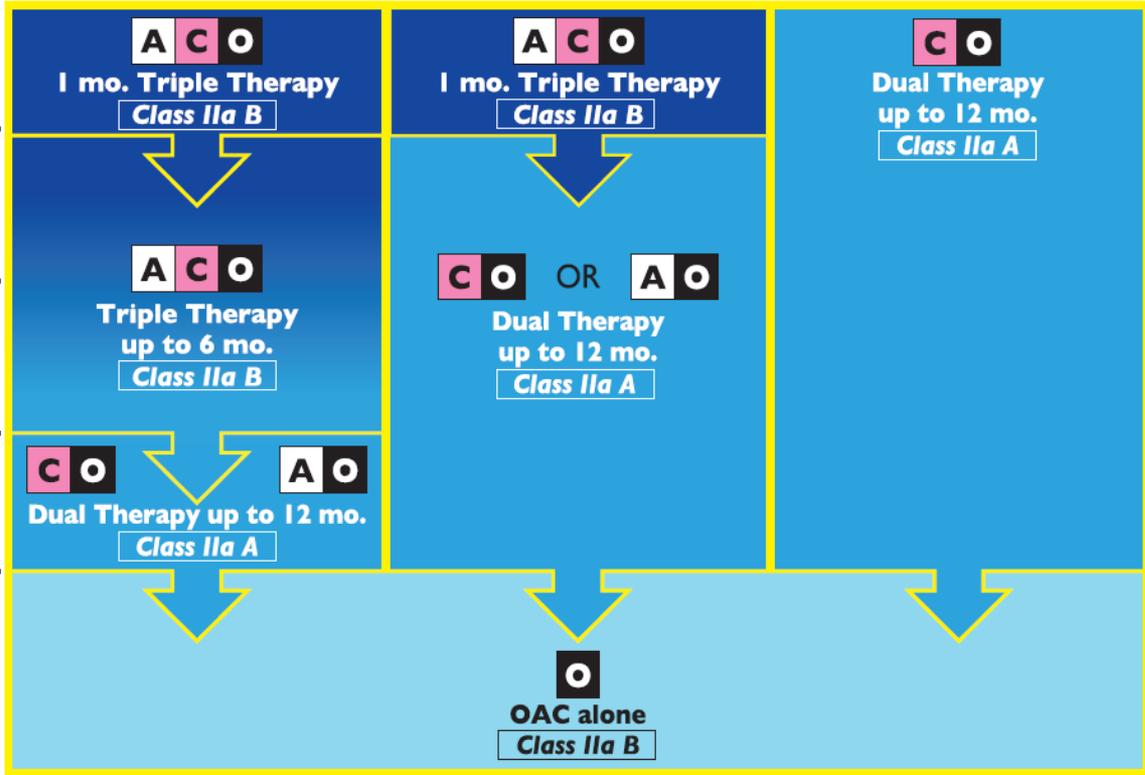
1 mo.

3 mo.

6 mo.

12 mo.

Beyond 12 mo.



A = Aspirin **C** = Clopidogrel **O** = Oral anticoagulation

DOACs 2019: update

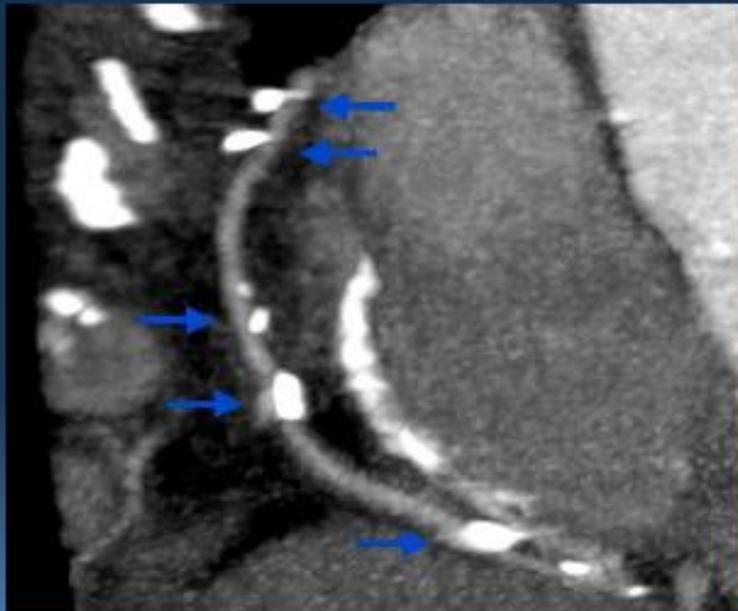
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WARFARIN IN CKD PATIENTS

Calcific uremic arteriopathy occurs in 1–4% of dialysis patients and portends a poor prognosis (45% mortality at 12 months).

Vitamin K antagonists affect the synthesis and function of the matrix Gla protein, which is a potent inhibitor of tissue calcification.

In dialysis patients, warfarin has been linked to calcific uraemic arteriopathy (calciphylaxis) as well as aortic valve calcification.



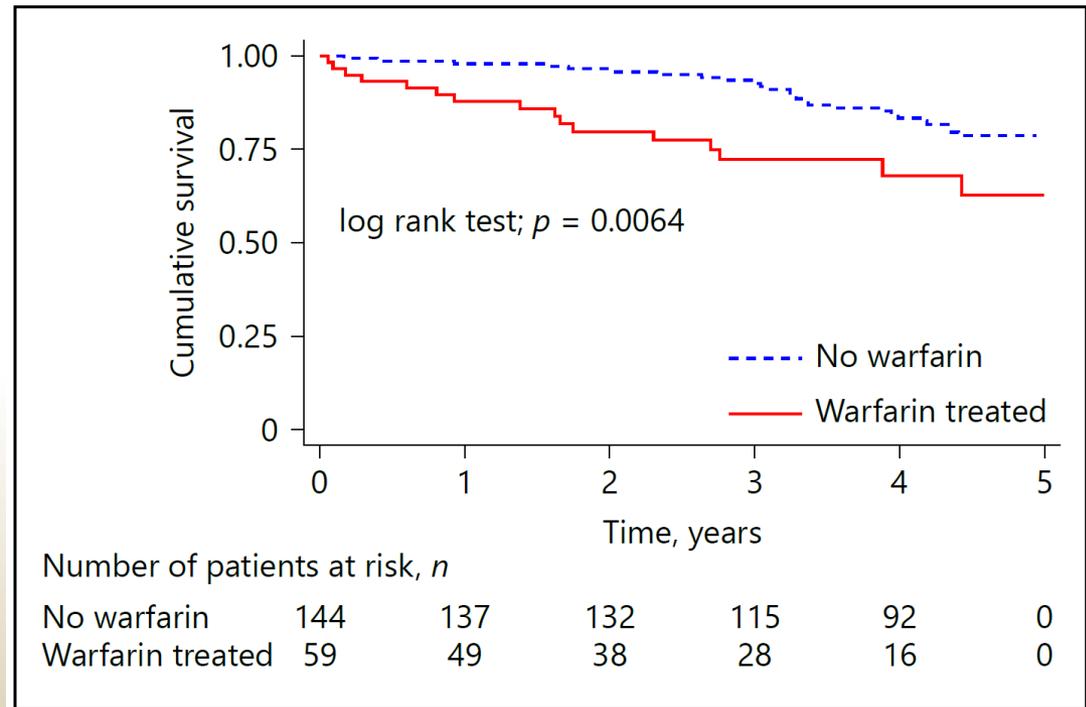
Warfarin Use and Increased Mortality in End-Stage Renal Disease

A retrospective matched cohort study,
Follow-up 5.8 years

AMONG WARFARIN USERS:

Significant bleeding (incident rate ratio, IRR 3.57 with 95% CI 1.51–8.45; $p < 0.01$)

Myocardial infarction (IRR 4.20 with 95% CI 1.78–9.91; $p < 0.01$)



Dose reduction for patient characteristics in NOAC studies

RE-LY¹

- None

ROCKET-AF²

- 20→15 mg QD for:
 - Creatinine clearance <30–49 mL/min

ARISTOTLE³

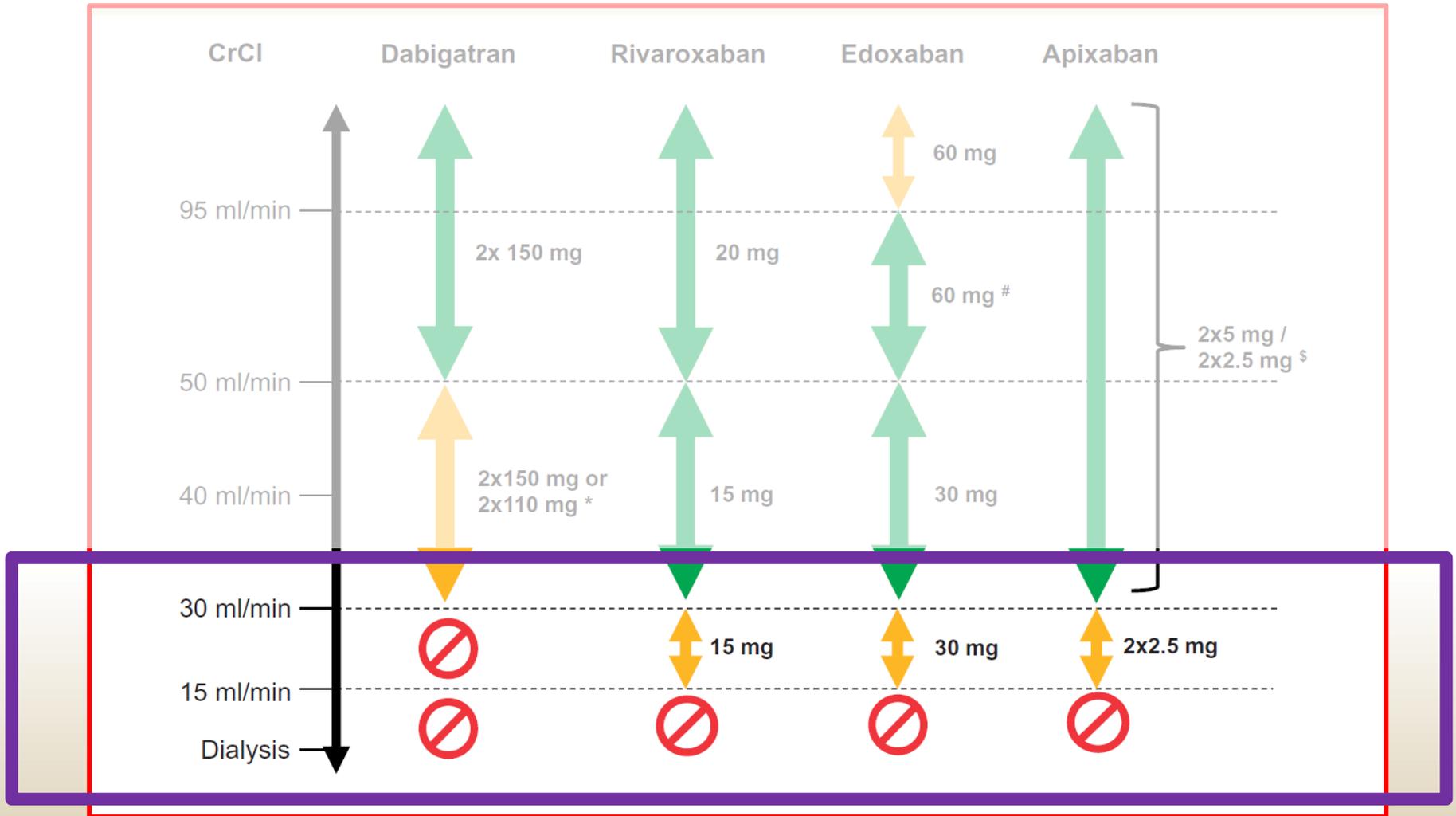
- 5→2.5 mg BID for ANY TWO of:
 - Age ≥80 years
 - body weight ≤60 kg
 - Serum creatinine ≥1.5 mg/dL

ENGAGE-AF⁴

- 60→30 mg QD for:
 - Creatinine clearance 30–50 mL/min
 - body weight ≤60 kg
 - Use of quinidine, verapamil or dronedarone

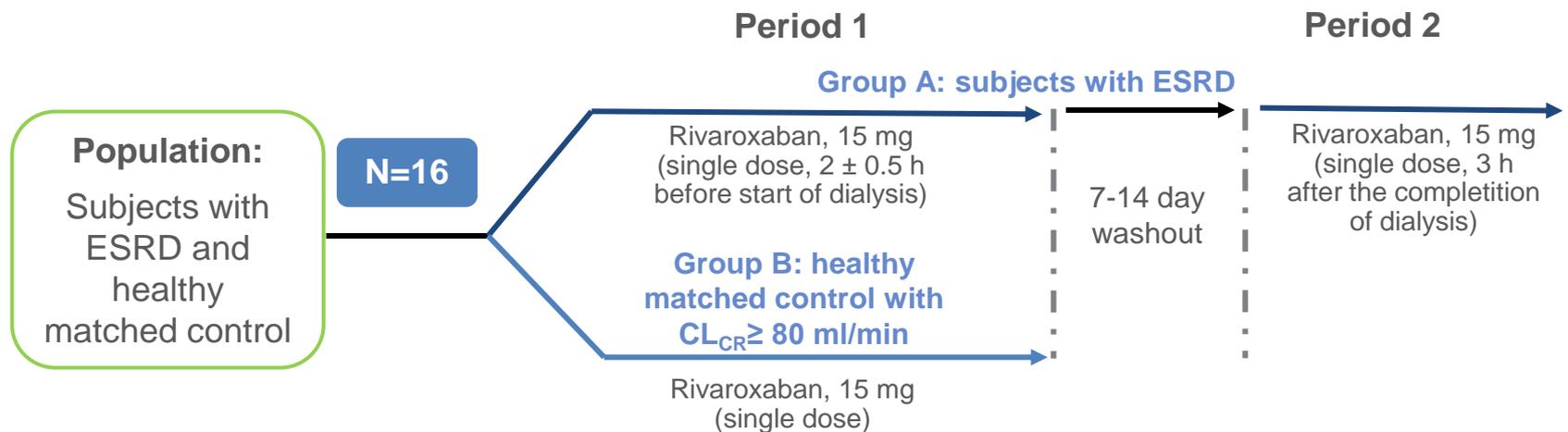
BID=twice daily; QD=once daily

Use of DOACs according to renal function



PK, PD and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis

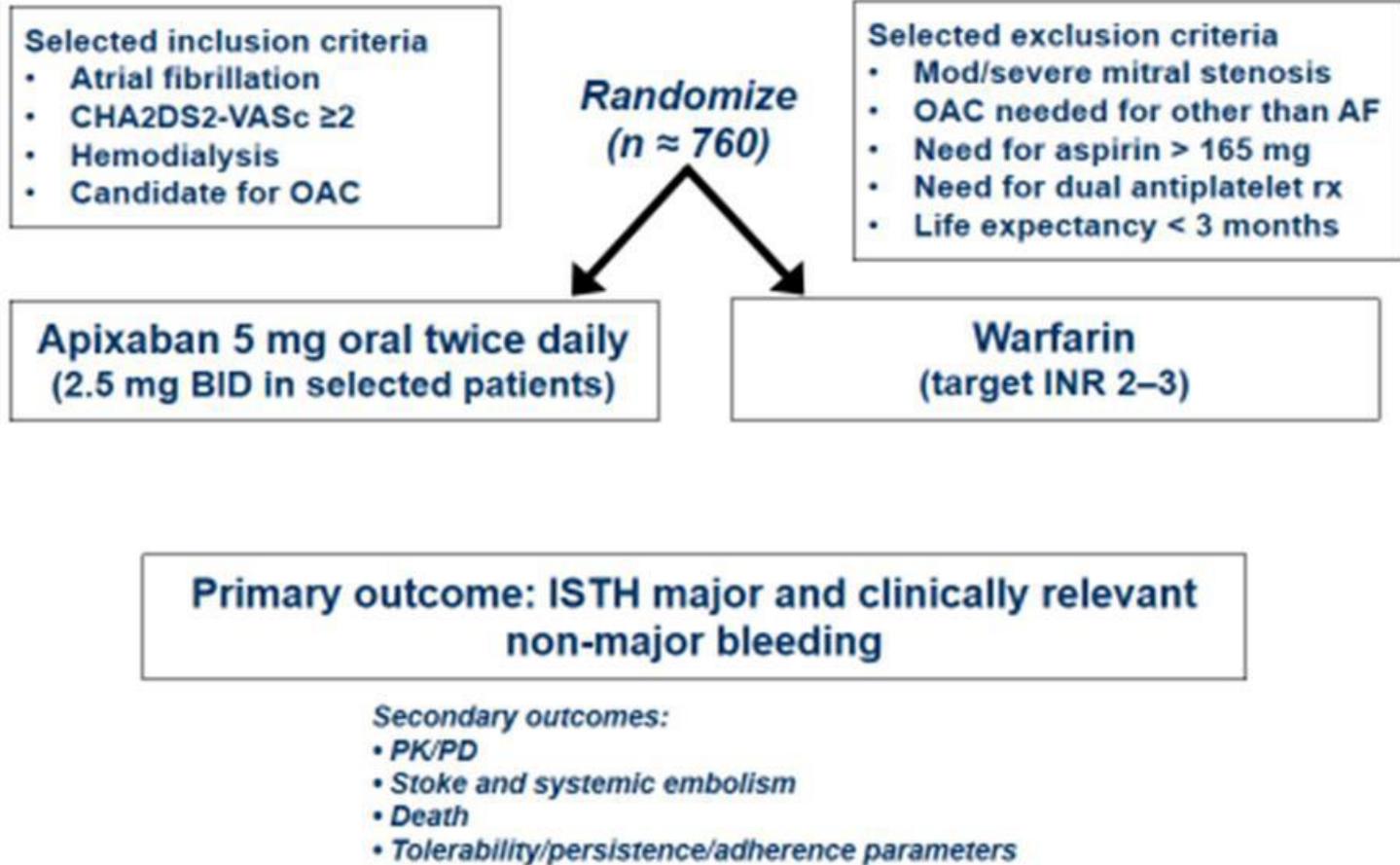
Objective: (1) to characterize the single-dose PK and PD of rivaroxaban administered as a 15-mg dose, both once before and once after dialysis, in subjects with ESRD, and (2) to compare this PK and PD profile in subjects with ESRD to that in healthy control subjects with $CL_{CR} \geq 80$ ml/min



Results:

- rivaroxaban plasma AUC increased by 56% administered post-dialysis. This reflects an approximate 35% decrease in overall clearance due to ESRD;
- rivaroxaban administration prior to a 4-hour hemodialysis session resulted in only a 5% lowering of plasma AUC as compared to the AUC with post-dialysis dosing, indicating that dialysis has a minimal impact on the PK of rivaroxaban;
- No bleeding events occurred during the study

RENAL-AF Trial: Study Overview



Sponsor: Christopher Granger, Duke University Medical Center

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- Politerapia
- Demenza ed Aderenza alla terapia

Incidence of Intracranial Hemorrhage and Outcomes After Ground-level Falls in Geriatric Trauma Patients Taking Preinjury Anticoagulants and Antiplatelet Agents

SUBHASH REDDY, M.B.B.S.,† ROHIT SHARMA, M.D.,* JONATHAN GROTTTS, M.A.,* LISA FERRIGNO, M.D.,*
STEPHEN KAMINSKI, M.D.*

*From *Santa Barbara Cottage Hospital, Santa Barbara, California; and the †Cleveland Clinic, Cleveland, Ohio*

TABLE 1. *Patient Baseline Characteristics and Outcomes by Anticoagulant Type*

	Warfarin (n = 218)	Clopidogrel (n = 95)	Aspirin (n = 249)	Overall (n = 562)	P Value†
Age (years)	84.3 (6.8)	81.6 (8.1)	83.3 (8.2)	83.4 (7.7)	0.005
Male	102 (46.8%)	51 (53.7%)	110 (44.2%)	263 (46.8%)	0.298
History of hypertension	164 (75.2%)	70 (73.7%)	168 (67.5%)	402 (71.5%)	0.158
Glasgow Coma Scale	14.6 (1.6)	14.6 (1.7)	14.6 (1.3)	14.6 (1.5)	0.886
Loss of consciousness	22 (10.1%)	15 (15.8%)	47 (18.9%)	84 (14.9%)	0.025
Abbreviated Injury Score for head	1.4 (1.3)	1.7 (1.3)	1.4 (1.3)	1.5 (1.3)	0.118
Injury Severity Score	5.6 (5.4)	6.4 (5.5)	6.4 (6.1)	6.1 (5.7)	0.257
Intracranial hemorrhage	27 (12.4%)	19 (20.0%)	40 (16.1%)	86 (15.3%)	0.210
Subdural hemorrhage	17 (7.8%)	11 (11.6%)	27 (10.8%)	55 (10.0%)	0.433
Epidural hemorrhage	0	1 (1.1%)	0	1 (0.2%)	0.168
Subarachnoid hemorrhage	7 (3.2%)	6 (6.3%)	18 (7.2%)	31 (5.5%)	0.136
Skull fracture	5 (2.3%)	4 (4.2%)	13 (5.2%)	22 (3.9%)	0.243
Craniotomy	3 (1.4%)	2 (2.1%)	2 (0.8%)	7 (1.2%)	0.620
Complication*	10 (4.6%)	1 (1.1%)	7 (2.8%)	18 (3.2%)	0.199
Hospital length of stay	2.6 (2.0)	2.8 (2.2)	2.3 (2.5)	2.5 (2.3)	0.473
Intensive care unit length of stay	0.3 (1)	0.6 (1.3)	0.6 (1.9)	0.5 (1.5)	0.177
Mortality	5 (2.3%)	3 (3.2%)	5 (2.0%)	13 (2.3%)	0.828

Rischio cadute

I pazienti con CHADS2 score ≥ 2 beneficiavano della terapia anticoagulante a prescindere che fosse stato considerato il rischio di caduta.

Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. Am J Med 2005; 118:612–617.

È stato stimato che un paziente con rischio annuale di stroke del 5% dovrebbe cadere 295 volte in un anno perché il rischio di sanguinamenti maggiori per una caduta possa superare il beneficio del warfarin.

Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med 1999; 159:677–685

Nei pazienti con storia di frequenti **cadute**, i **benefici** della terapia anticoagulante **superano i rischi di sanguinamento**, è imperativo inserire nel percorso terapeutico **correttivi** dei **fattori modificabili** che li espongono alle cadute

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Farmaci che interferiscono con i NOACs suddivisi per meccanismo d'azione

Substrati P-gp

Atorvastatina

Ciclosporina

Digossina

Loperamide

Indinavir, nelfinavir, ritonavir

Chinidina

Desametasone, idrocortisone

Vinblastina, vincristina

Daunorubicina, doxorubicina, etoposide

Inibitori P-gp

Amlodarone

Ceftriaxone, claritromicina, eritromicina

Ciclosporina, tacrolimus

Diltiazem

Dipiridamolo, propranololo

Idrocortisone

Ketoconazolo, itraconazolo

Nicardipina, nifedipina

Chinina, chinidina

Ritonavir, sequinavir, nelfinavir

Tamoxifene

Verapamil

Induttori P-gp

Rifampicina, cotrimazolo

Fentoina, fenobarbital

Erba di S. Giovanni

Tabella 1. Interazioni fra warfarin e antiinfettivi

Interazione con effetto di potenziamento (rischio di sanguinamento)

<i>Altamente probabile</i>	<i>Probabile</i>	<i>Possibile</i>	<i>Altamente improbabile</i>
Ciprofloxacina	Amoxiclavulanico	Amoxicillina	Cefamandolo
Cotrimossazolo	Azitromicina	Cloramfenicolo	Cafazolina
Eritromicina	Claritromicina	Gatifloxacina	Sulfisossazolo

Tabella 2. Interazioni fra warfarin e farmaci cardiovascolari

Interazione con effetto di potenziamento (rischio di sanguinamento)

<i>Altamente probabile</i>	<i>Probabile</i>	<i>Possibile</i>	<i>Altamente improbabile</i>
Amiodarone	Aspirina	Amiodarone (tossicosi)	Bezafibrato

Tabella 3. Interazioni immunologiche

Interazione con...

Altamente probabile

Fenilbutazone

Piroxicam

Interazione con effetto di inibizione (rischio di trombosi)

Mesalamina	Azatioprina	Sulfasalazina
------------	-------------	---------------

* a seconda degli studi

Barbiturici Clordiazepossido Propofol

Carbamazepina

* se è presente anche una patologia epatica; ** bifasica con inibizione tardiva.

Il Warfarin è nella Top Ten dei farmaci con più interazioni...

... Ed è secondo solo ai chemioterapici..

Warfarin – interazioni col cibo



HIGH	MODERATE	LOW
Broccoli (cooked)	Abalone	Alfalfa
Brussel sprouts	Asparagus	Beans (green)
Cabbage (raw)	Avocado	Breads, cereal
Canola oil	Beans (snap)	Capscicum
Endive (raw)	Cabbage (cooked)	Carrot
Kale	Cheese (blue)	Cauliflower
Lettuce (gourmet)	Margarine	Celergy
Liver	Olive oil	Cheese (cheddar), milk
Parsley	Peas	Chickpeas (cooked)
Silver beet (cooked)	Pickle, dill	Corn (sweet, kernels, cooked)
Soybean oil	Red cabbage	Eggs and butter
Spinach		Lettuce (iceberg)
		Mushrooms
		Potatoes
		Pumpkin
		Rice
		Sunflower and sesame oil
		Sweet potato

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Demenza e FA

Cardiovascular Health Study

5150 pz

FA: 552

NO FA :4598

10%

Declino cognitivo più precoce e più rapido

- La demenza è un fattore di rischio indipendente di prognosi peggiore ed è presente nel 10% degli over 65aa e nel 40% degli over 80aa
- Il declino cognitivo è peggiore nei pazienti anziani affetti da insufficienza cardiaca e fibrillazione atriale

Demenza

Il beneficio della terapia anticoagulante è netto.

Sono esclusi dal trattamento anticoagulante pazienti in cui non è presente un **care giver** in grado di assicurare l'aderenza alla terapia

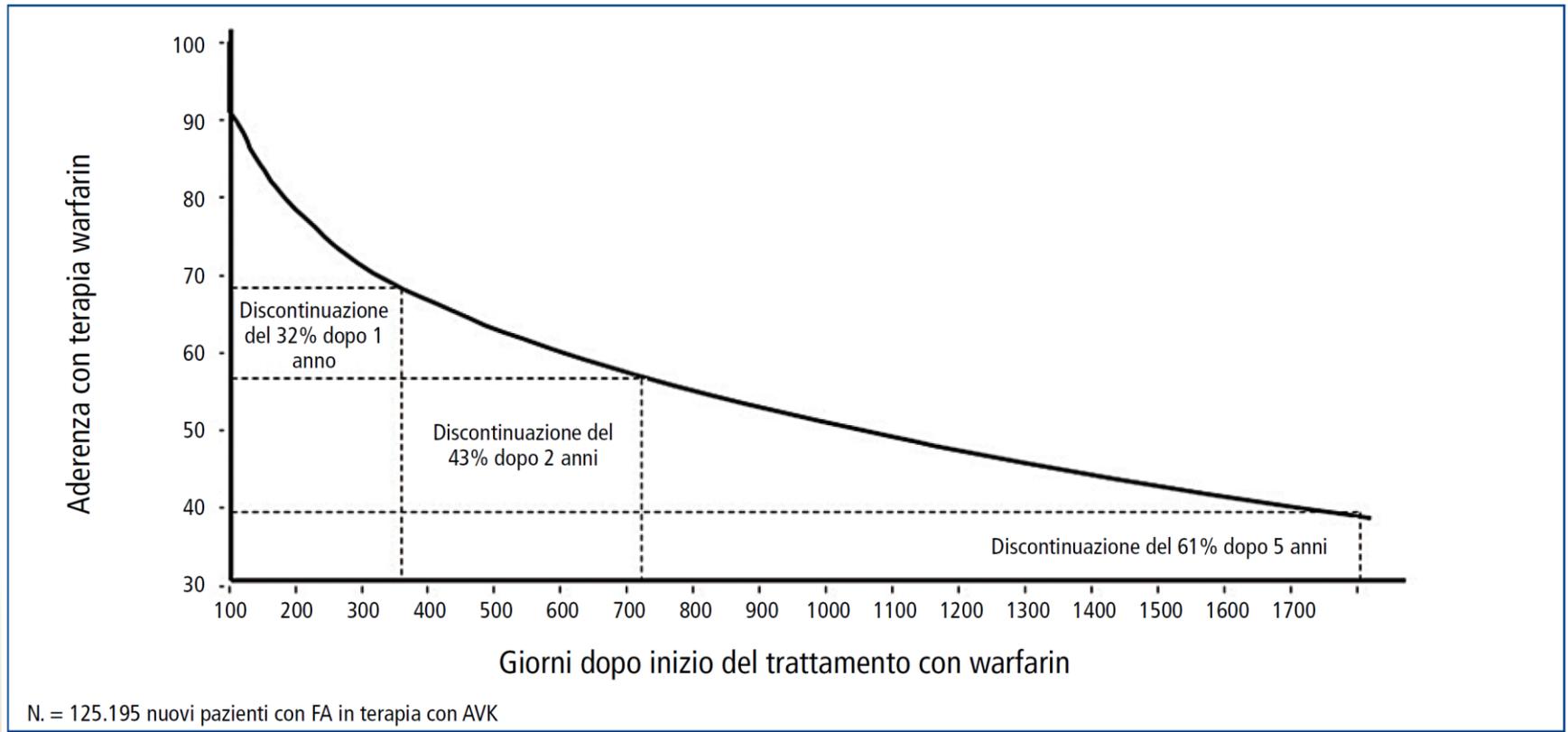
Checklist during follow-up contacts

	Interval	Comments
1. Adherence	Each visit	<ul style="list-style-type: none"> ● Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence ● Re-educate on importance of strict intake schedule ● Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring⁵¹; special education session; . . .)
2. Thromboembolism	Each visit	<ul style="list-style-type: none"> ● Systemic circulation (TIA, stroke, peripheral) ● Pulmonary circulation
3. Bleeding	Each visit	<ul style="list-style-type: none"> ● 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation ● Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	<ul style="list-style-type: none"> ● Prescription drugs; over-the-counter drugs (Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants section). ● Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥75 years (especially if on dabigatran) or frail (see chapter 2)
	x-monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	<ul style="list-style-type: none"> ● As recommended by current guidelines³ ● Particularly: uncontrolled hypertension (systolic >160 mmHg), medication predisposing for bleeding (e.g. aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether <ol style="list-style-type: none"> a. The chosen NOAC is the best for the patient b. The chosen dose is correct

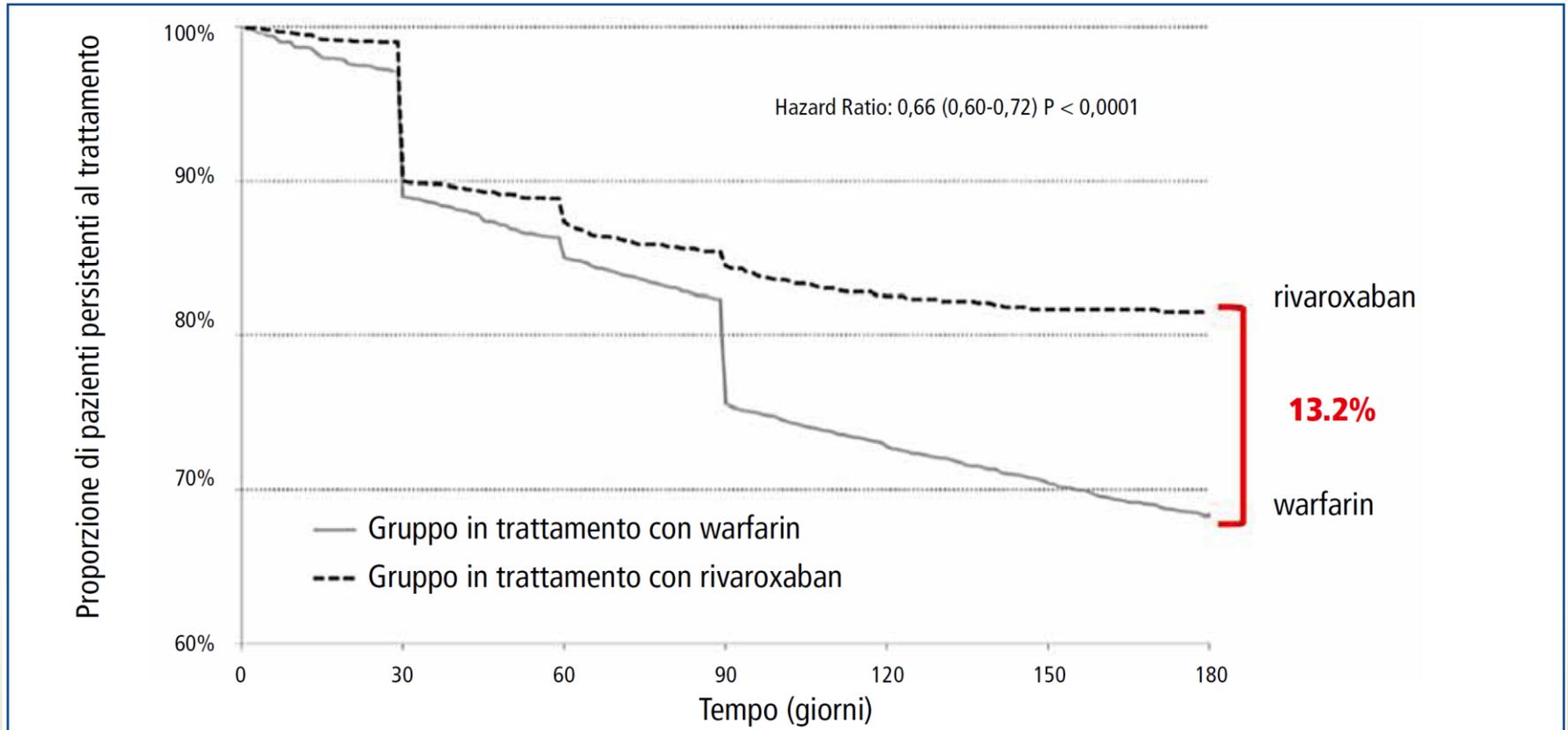
Geriatrics Working Group AIFA 2014

- 1 anziano su 2 oltre i 65 aa assume dai 5 ai 9 farmaci/die
- Il 60% degli >65enni manifesta scarsa aderenza alla terapia per malattie croniche (depressione, ipertensione, diabete e osteoporosi)

Aderenza alla terapia con AVK in real-life



Aderenza al trattamento anticoagulante a 6 mesi





la Terapia Anticoagulante della FA deve prevedere una valutazione multidimensionale del paziente attraverso un approccio integrato fra specialisti e medico di medicina generale



Il paziente e l'eventuale caregiver devono essere coinvolti nelle scelte terapeutiche

Recommended follow-up
(see EHRA at www.NOACforAF.eu for information & practical advice)

Check each visit:

1. Adherence (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling:

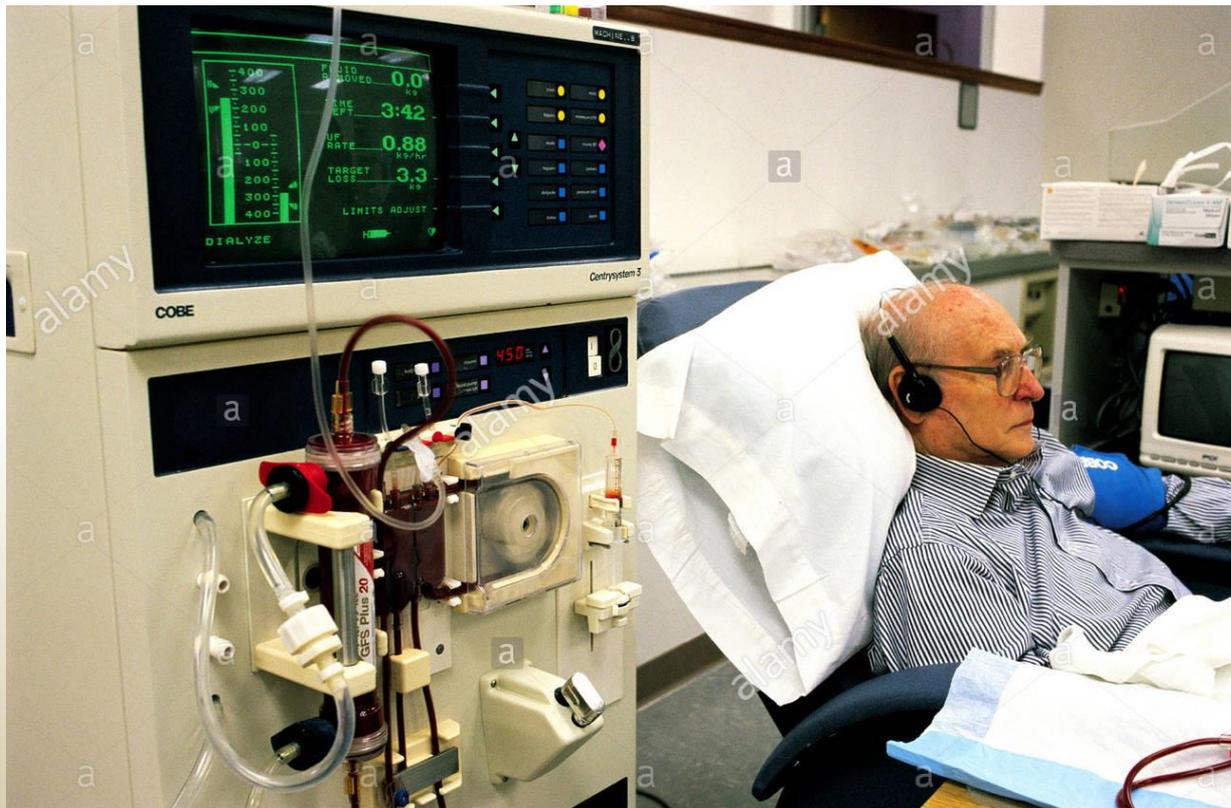
- monitoring of anticoagulation level is not required!
- yearly: Hb, renal and liver function
- if >75-80 y (especially if dabigatran or edoxaban), or frail: 6-monthly renal function
- if CrCl ≤ 60 ml/min:
 recheck interval in months = CrCl / 10
- if intercurrent condition that may have impact:
 renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Il monitoraggio clinico deve essere personalizzato in base al profilo clinico del singolo paziente

Personal Take home message

- I DOACs oggi, nei pazienti anziani, fragili e con comorbidità differenti ed affetti da FA rappresentano sempre di più la prima scelta nel trattamento anticoagulante



Grazie.....

