

Lixiana's Good Point from Patient Cases

Scientific Session (Daiichi-Sankyo & Daewoong)

June 24th, 2023

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ENABLING
FUTURE MEDICINE



CASE (1)

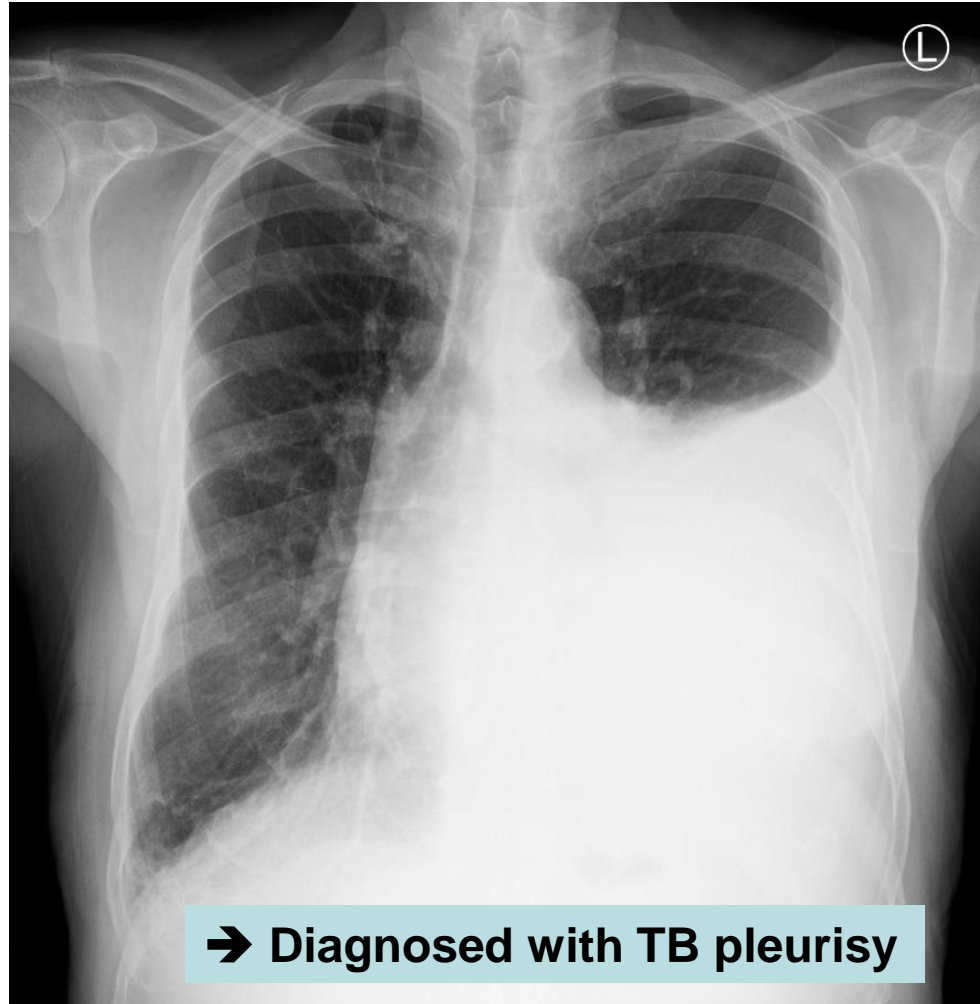
- 80-year-old male, 176 cm / 75 kg
- Dyspnea
- Past history
 - DM (-), HTN (+)
 - Stroke or TIA (-), vascular disease (-)
 - s/p RFCA for PeAF (2011.2.15) → recurrence

CASE (1)

- **TFT: normal**
- **Cr = 0.96, CrCl = 65 mL/min**
- **NT-proBNP = 373 pg/mL**
- **TTE:**
 - **LA diameter 51 mm**
 - **LVEF 57.5%**
 - **No valvular heart disease**

- **CHA₂DS₂-VASc=3, HAS-BLED=1**
- **Dabigatran 110mg bid**

- Chest PA



● Consultation

진료의뢰 내역

순번	내원 구분	상태	의뢰정보					회신정보			
			의뢰과	의뢰의	의뢰일자	요청구분	회신요청	희망과	희망의	센터	회신의
1	O	최종회신	PU		2020-03-31			CA	심재민		심재민

TB pleurisy로 TB medi 드시는 분으로 TB medi 중에 Rifodex와 CA medi 중에

pradaxa가 1등급 severe 나와서 Rifodex는 대체 약이 없고 꼭 드셔야 하는

약이라 pradaxa대체 가능 약이 있는지 상의 위해 진료 의뢰드립니다.

감사합니다.

Drug-Drug Interactions

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction	No data yet	No effect	No effect
Ticagrelor (see also page 49)	P-gp inhibition	+24 to 65% (give loading dose 2h after dabigatran)	No data - carefully monitor	No data - carefully monitor	No data - carefully monitor
Antibiotics					
Clarithromycin; Erythromycin	P-gp inhibition and strong CYP3A4 inhibition	Clarithromycin: +19% AUC; +15% Cmax	Clarithromycin: +60% AUC; +30% Cmax	Erythromycin: +85% AUC; +68% Cmax (dose reduction to 30 mg once daily by label)	Clarithromycin: +50% AUC; +40% Cmax Erythromycin: +30% AUC; +30% Cmax
Rifampicin	P-gp/ BCRP and CYP3A4 induction	minus 66% AUC; minus 67% Cmax	minus 54% AUC; minus 42% Cmax	minus 35% AUC, (but with compensatory increase of active metabolites)	minus 50% AUC; minus 22% Cmax

CASE 1

- Dabigatran → Edoxaban 60mg qd, no stroke/SE
- Tb medication: HREZ 2 month, HRE 4 months

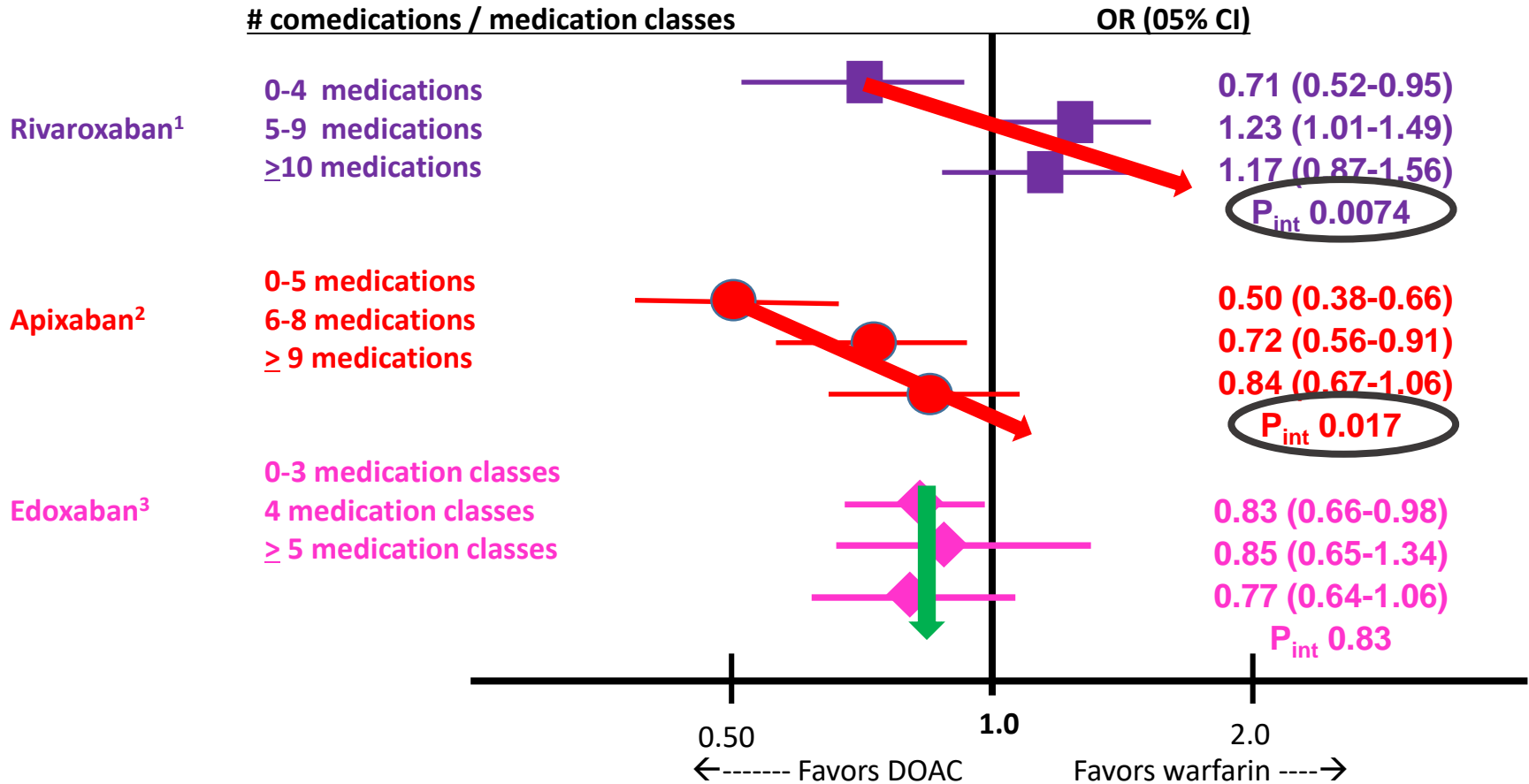


PK/PD of 4 NOACs in NVAF

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa(thrombin)	Xa	Xa	Xa
Dosing	BID	QD	BID	QD
Bioavailability	7%	80%*	66%	62%
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp
Hrs to Cmax	2	2-4	1-3	1-2
Protein binding	35%	>90%	87%	55%
Vol of distribution, L	50-70	50	21	107
CYP metabolism	None	32%	15%	<4%
Renal elimination	80%	66% [†]	27%	50%
Half-life	12-14h	9-13h	8-15h	10-14h

*Nearly 100% if taken with food †Approximately half of which is excreted unchanged in the urine
 CYP=cytochrome P450; NR = not reported; P-gp = p-glycoprotein; BCRP = breast cancer resistance protein

Polypharmacy and Major Bleeding



1. Piccini JP, *Circ* 2016;133:352-60
 2. Chang SH, *JAMA* 2017;318:1250-9
 3. Nicolau AM, *EHI CVP* 2020;6:167-75

Which NOAC Will You Use?

Patients

- 78-year-old female
- 150cm, 48kg
- Cr 0.9mg/dL, CrCl 39mL/min

Appropriate NOAC Dose

● Rivaroxaban 15mg qd

● Apixaban 5mg bid

● Edoxaban 30mg qd

CASE (2)

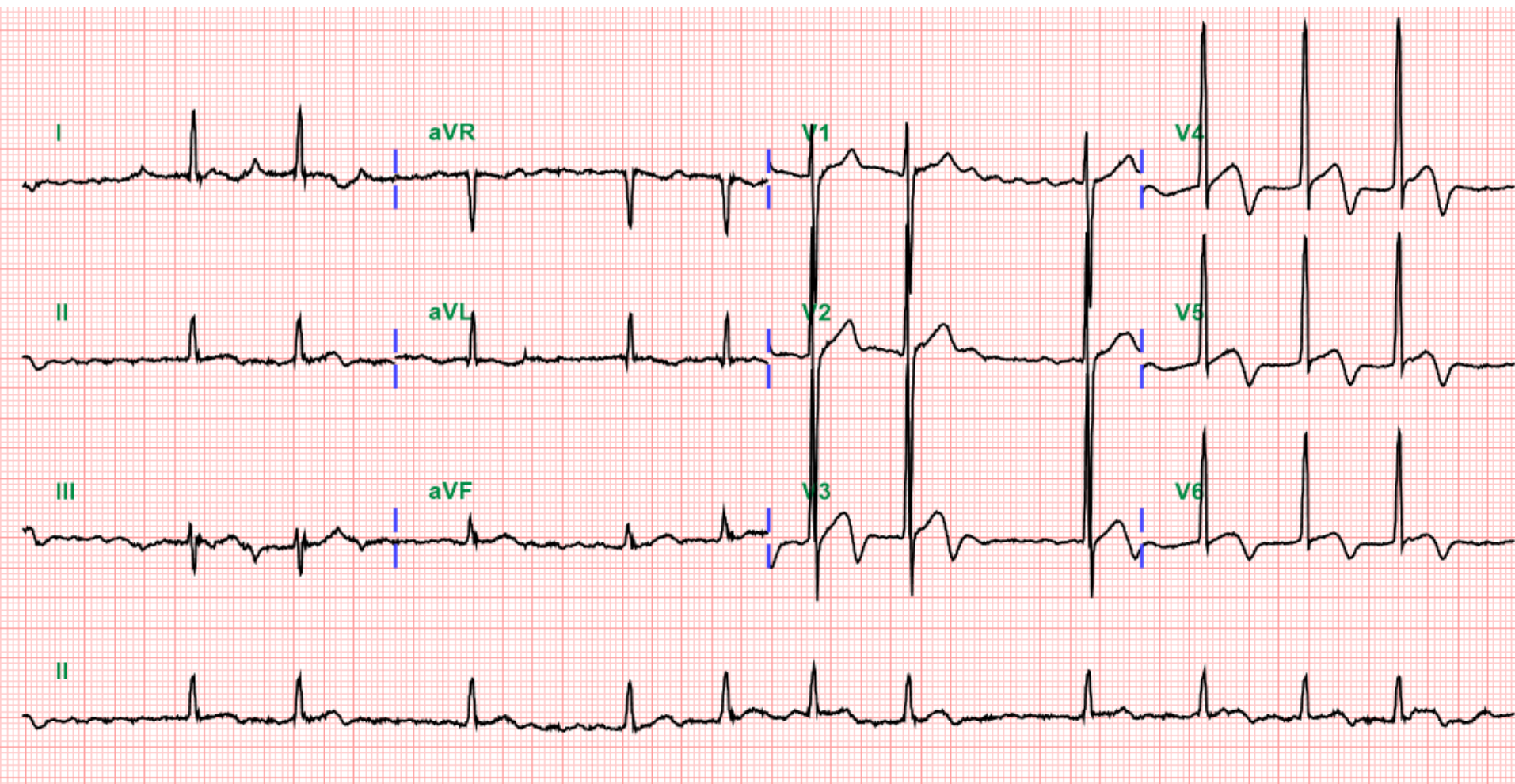
- 80-year-old female, 150 cm / 53 kg
- DOE, Palpitation
- Past history
 - Diagnosed with AF and AHCMP in 2014
 - HTN (+), DM (+), CHF (+)
 - Stroke/TIA (-), vascular disease (-)
 - s/p DCCV in 2015 → recurrence

CASE (2)

- **TFT: normal**
- **Cr = 0.85, CrCl = 44 mL/min**
- **NT-proBNP = 2,406 pg/mL**
- **TTE:**
 - **LA diameter 50.3 mm**
 - **LVEF 62.5%**
 - **Mild MR, Mild to mod TR**

● **CHA₂DS₂-VASc=6, HAS-BLED=1**

● 12 lead ECG



● Chest PA



- **Clinical course**

- Jul. 2015, rivaroxaban 20mg qd (61kg, CrCl = 60)
- Jun. 2017, 발치 후 출혈로 응급실 내원.
- Nov. 2017, 코피로 rivaroxaban 일시 중단.
- 2018, 멍이 잘 든다. (58kg, CrCl = 52)
 - ➔ rivaroxaban 15mg
- 2022, 눈 출혈 자주, 멍 계속 (53kg, CrCl = 44)
 - ➔ edoxaban 30mg

● Follow up

2023.03.21 | 81세 공통재진2

■ 주관적 소견

약 바꾸고 출혈 한번도 없었다.

EHRA I

■ 객관적소견

* 활력징후
수축기혈압/이완기혈압 : 117/69mmHg, 맥박 : 67회/분

■ 검사소견

ECG: AF, 49
HbA1c 6.3
NTproBNP: 2406

■ 진단명

Permanent atrial fibrillation
Hypertrophic cardiomyopathy
Diabetes mellitus (DM)
Hypertension
LA 50, EF 62.5, mild to mod TR, 2015.1.13
창등

■ 진료계획

6m later

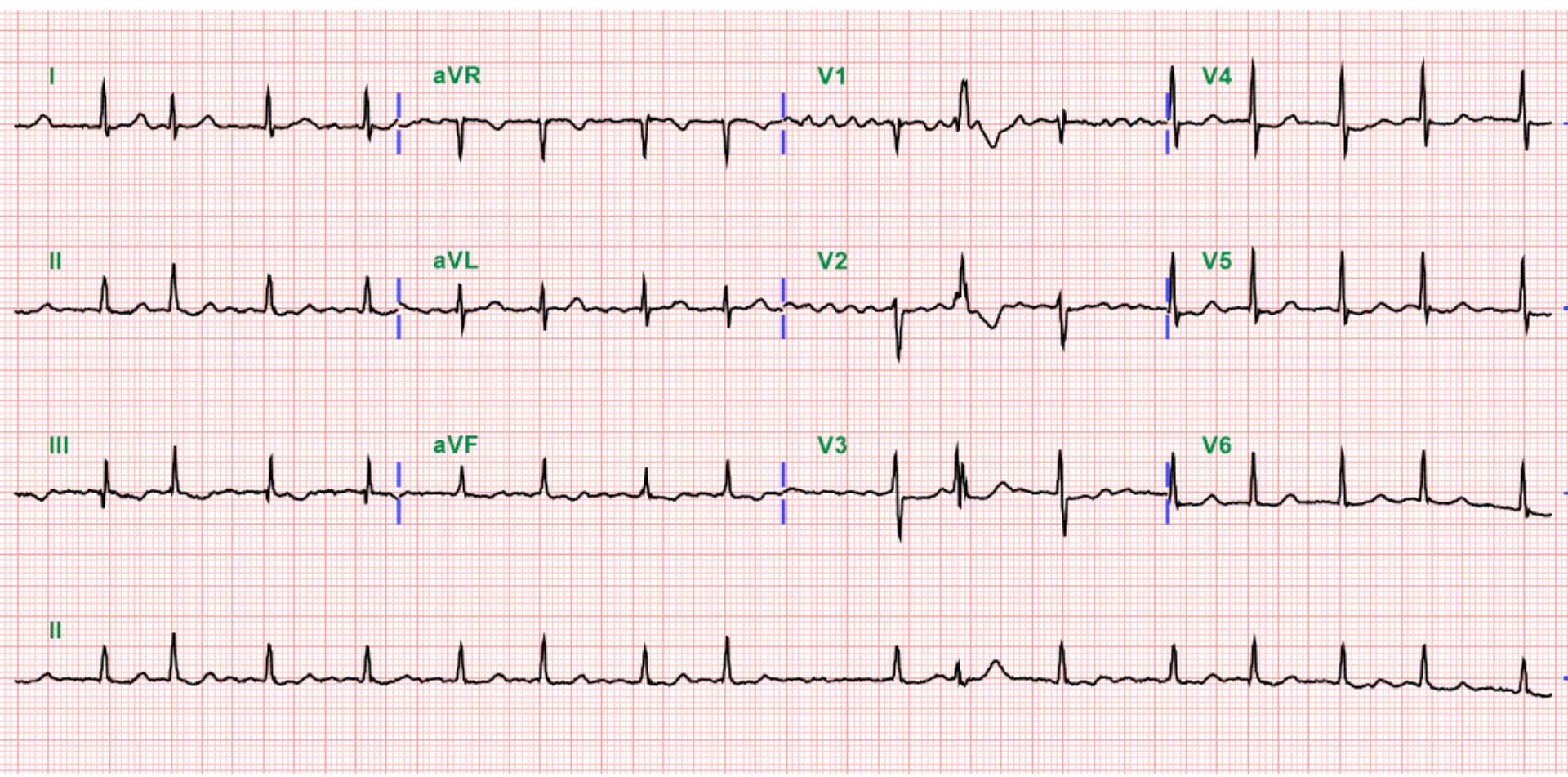
CASE (3)

- 76-year-old female, 150 cm / 62kg
- SOB, chest discomfort
- Past history
 - DM (-), HTN (+)
 - Stroke or TIA (-), vascular disease (-)

CASE (3)

- **TFT: normal**
- **Cr = 0.77, CrCl = 60 mL/min**
- **NT-proBNP = 952 pg/mL**
- **TTE:**
 - **LA diameter 40.2 mm**
 - **LVEF 57.5%**
 - **No valvular heart disease**

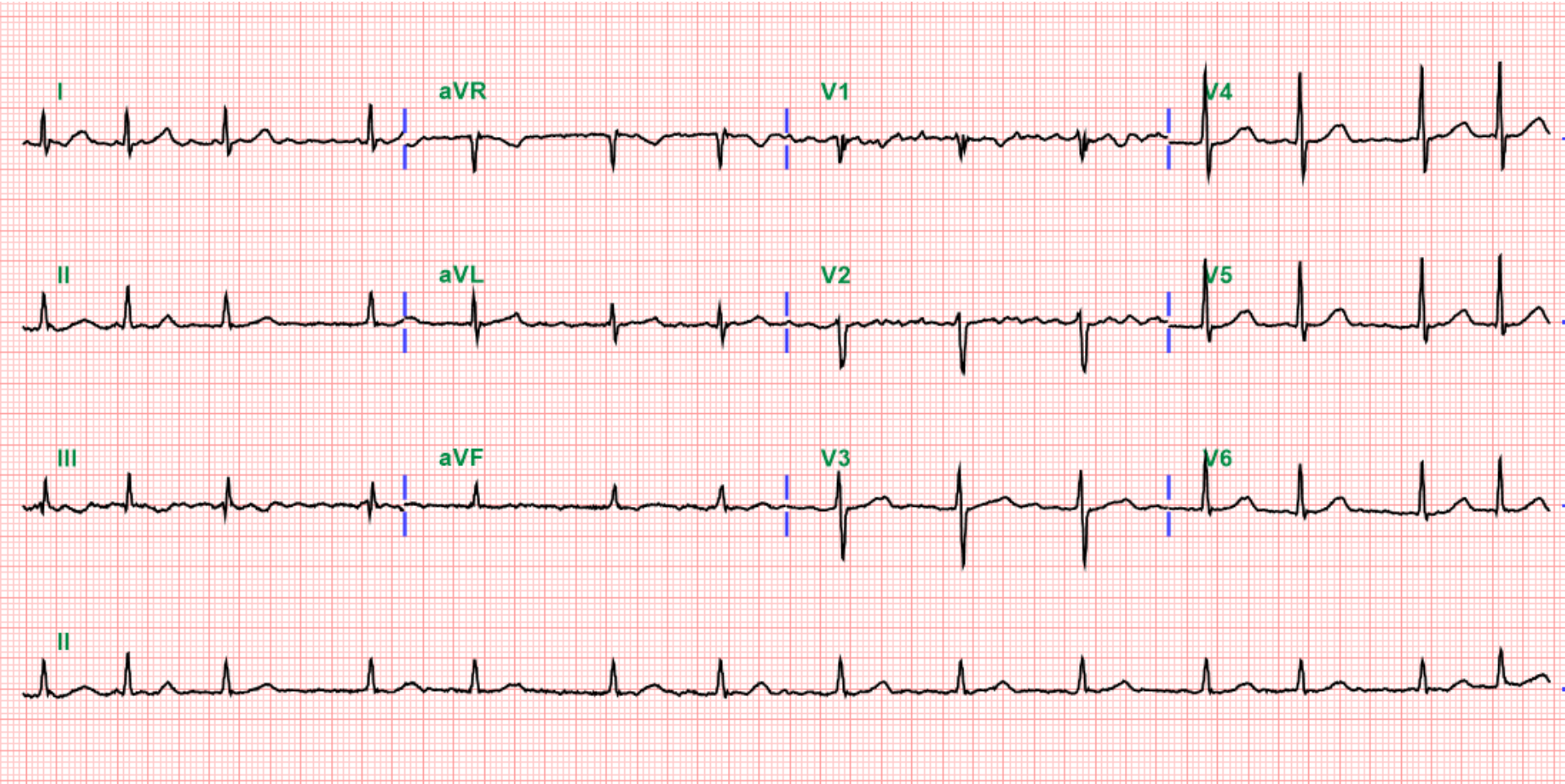
● 12 lead ECG



● DCCV under edoxaban 30mg, no thrombus on TEE



- 1 month later, chest discomfort → apixban 2.5mg bid



● DCCV under apixabn 2.5mg bid without TEE

ID: Patient 1528 2020-09-24 08:47:09 HR = 73bpm RR = 10br/min SpO2 = 99% PI = 1.9% NIBP = 186/93(124)mmHg 2020-09-24 08:38:07

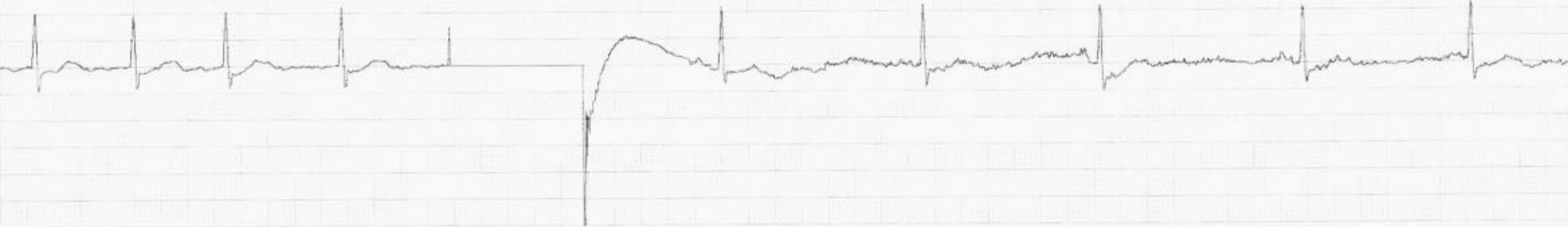
Monitor
1.0 cm/mV

1) pre-CV ECG: AF

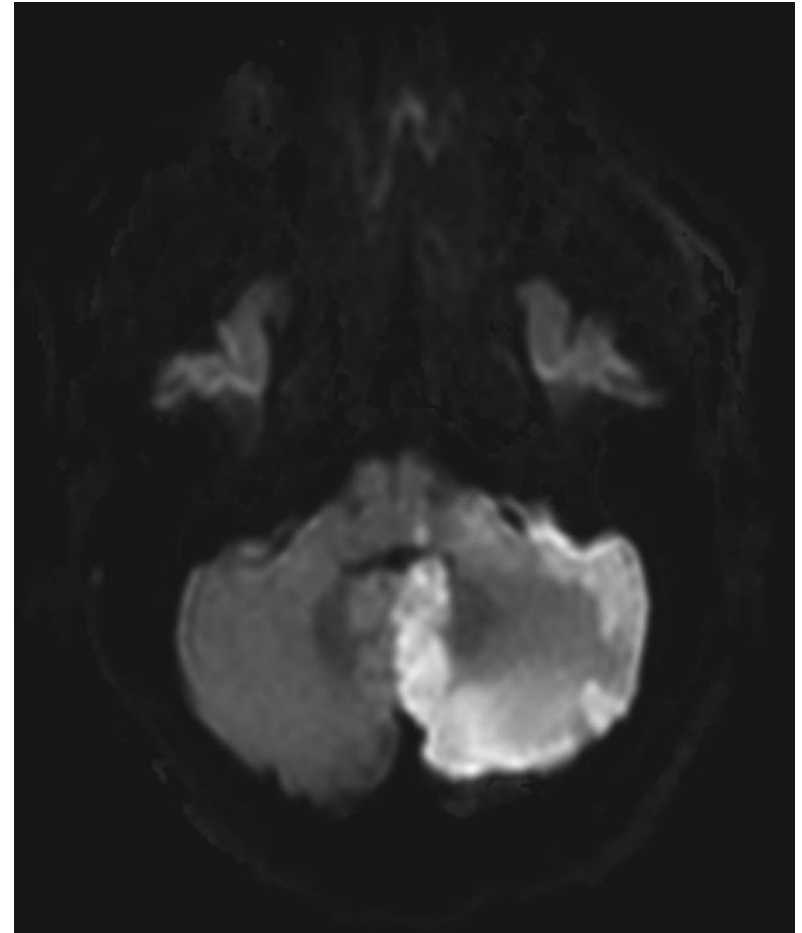
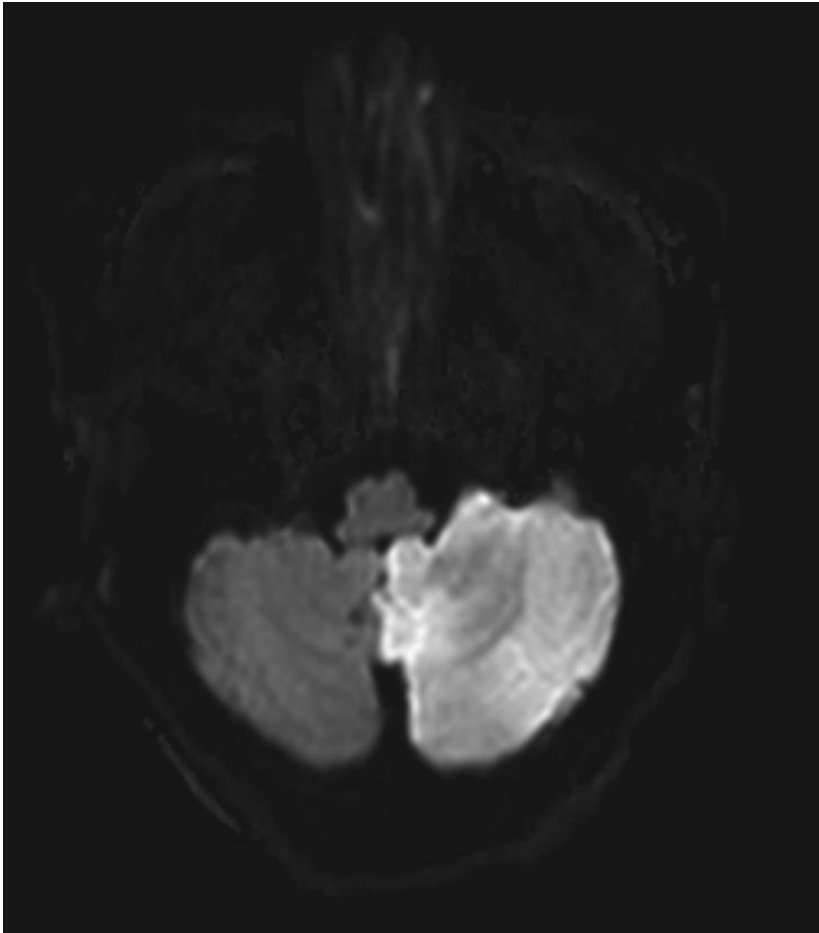


Del = 249J TTI = 73 Ω HR = 76bpm RR = ???br/min SpO2 = 100% PI = 2.0% NIBP = 175/123(141)mmHg 2020-09-24 08:49:20

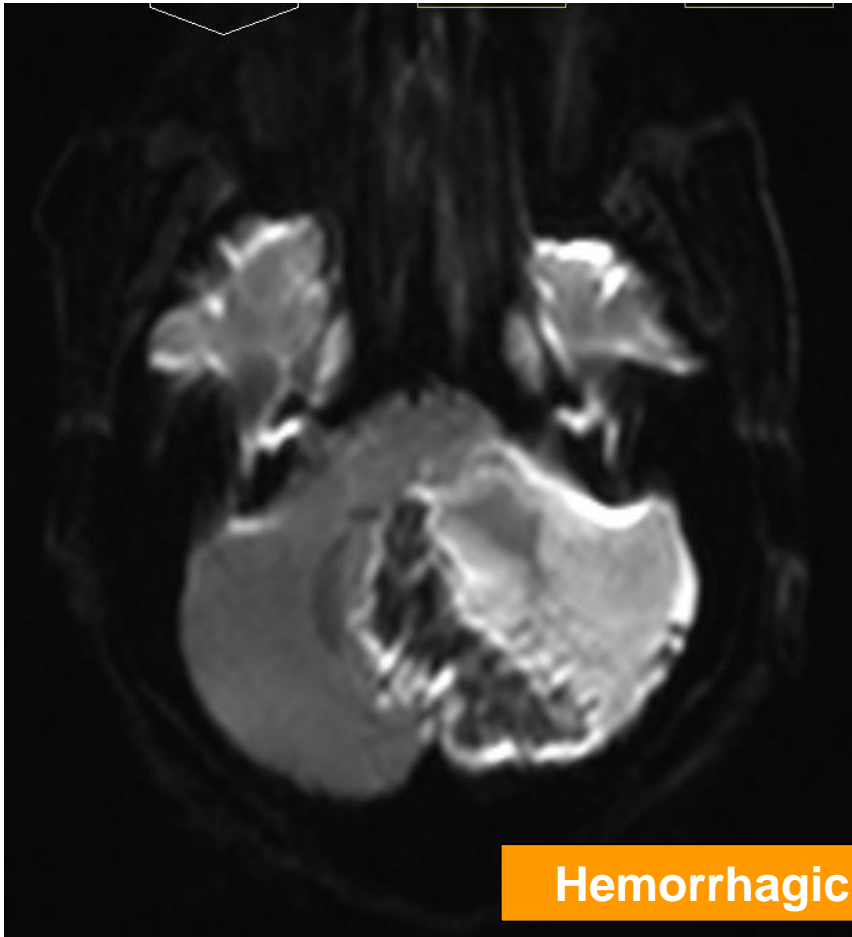
2) #1 200J shock → Success, Sinus brady cardra



- 2 days later



- Next day



Hemorrhagic transformation

Efficacy & Safety According to NOAC Dose

- **Efficacy** when under-dosed:
 - **Edoxaban 30mg > Apixaban 2.5mg**
- **Safety** when standard or under-dosed:
 - **Edoxaban 15mg > Apixaban 2.5mg ≈ Edoxaban 30mg**

CASE (4)

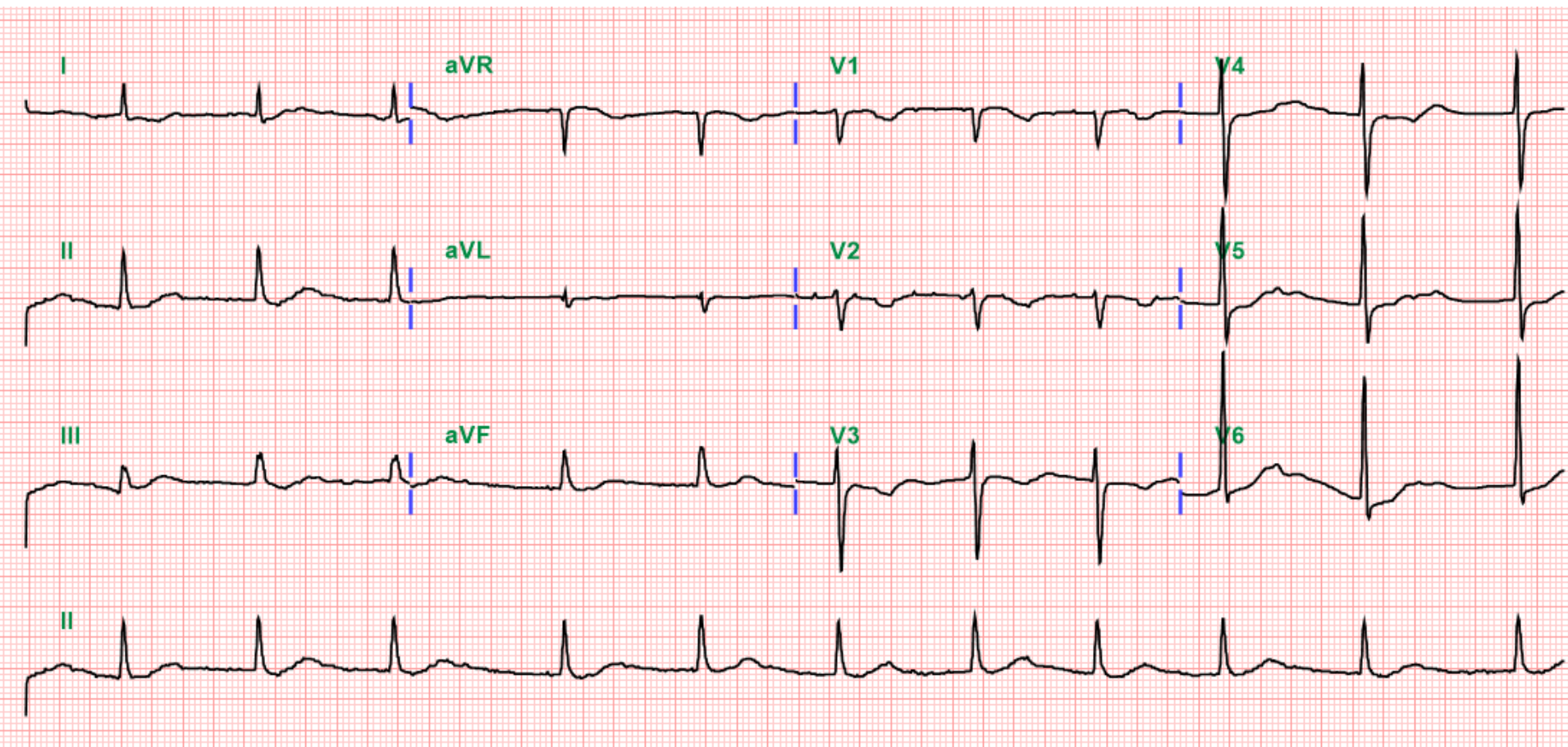
- **84-year-old female, 142 cm / 45 kg**
- **Pain and swelling in Lt. upper limb**
- **Past history**
 - **Diagnosed with AF in 1992**
 - **On warfarin since 2002 with TTR \geq 70%**
 - **DM (-), HTN (+), CHF (+)**
 - **Stroke or TIA (-), vascular disease (-)**
 - **L1 compression fracture → prn NSAIDs**

CASE (4)

- TFT: normal
- Cr = 0.76, CrCl = 39 mL/min
- Hb 6.7 g/dL
- TTE:
 - LA diameter 63.5 mm
 - LVEF 57.5%
 - Mod MR, Mild TR

● CHA₂DS₂-VASc=5, HAS-BLED=2

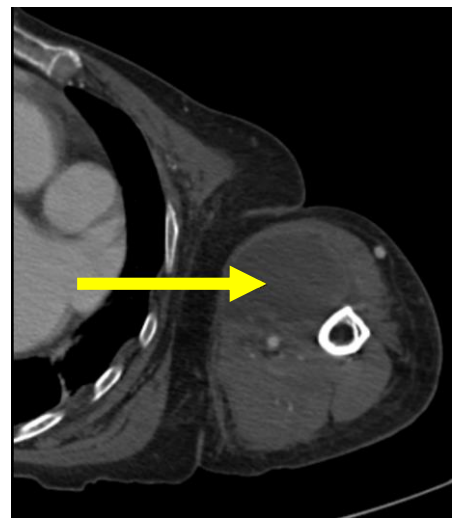
● 12 lead ECG



● Chest AP



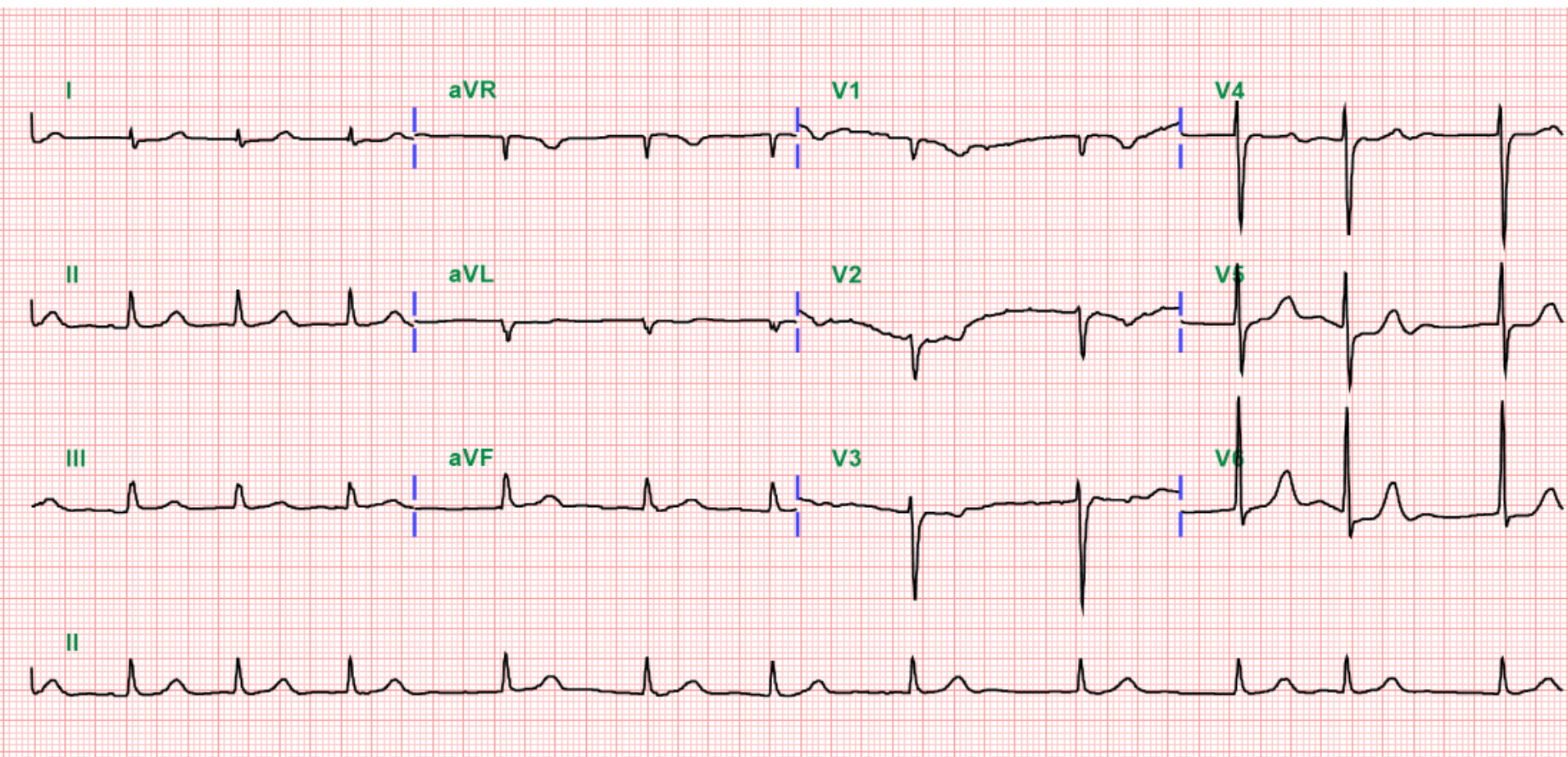
● Upper arm CT, INR 13.2



- **Hospital course**

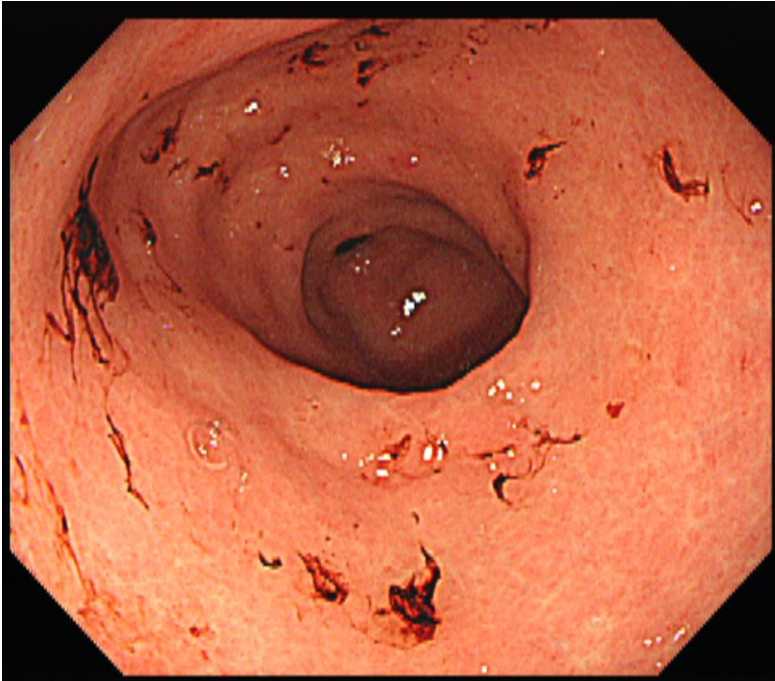
- **Vit K, FFP, Transfusion**
- **Hb 6.7 g/dL → 7.8 g/dL**
- **Apixaban 2.5mg bid**
 - ➔ **Aggravated swelling, R/O compartment synd, Hb 6.6 g/dL**
 - ➔ **Transfusion, no more anticoagulation**
- **Hb 9.9 g/dL, improved pain and swelling**
- **Discharged after 2 weeks**

- 3 wks later, ER visit d/t chest pain & dyspnea, melena

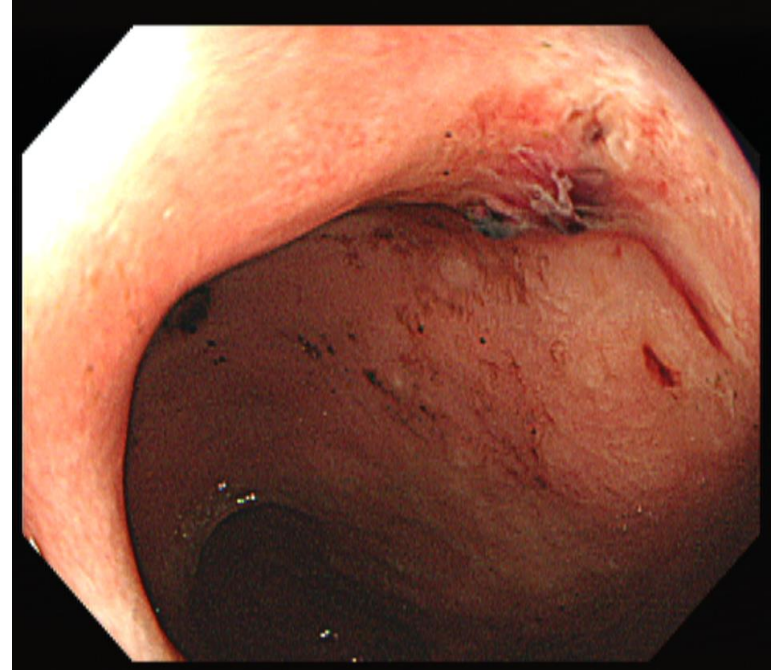


Hb **8.7** g/dL, CK-MB 11.3 → **42.8** ng/mL, TnT 0.45 → **1.65** ng/mL

- EGD and sigmoidoscopy

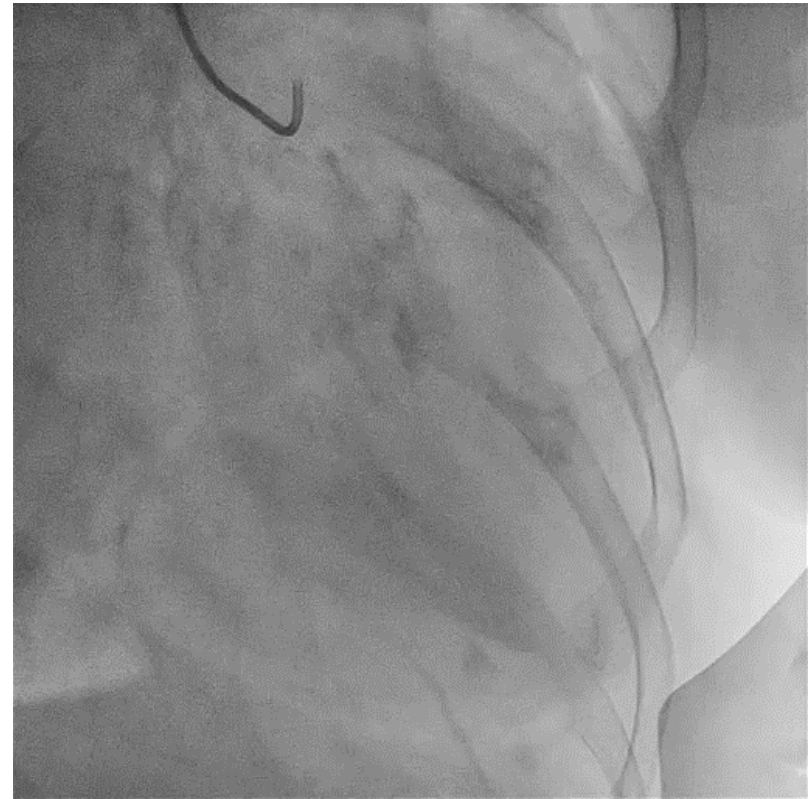
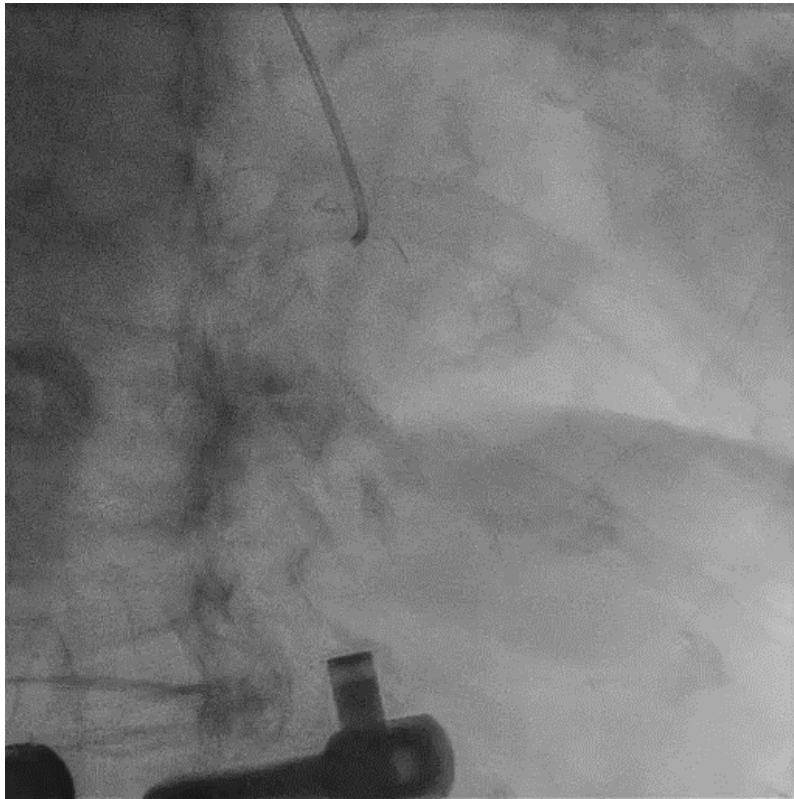


Several erosions with hematin on antrum



Shallow ulcer, proctitis from AV 15cm

- CAG



LCx far distal total occlusion due to thromboembolism

- **Hospital course**

- **Clexane 20mg bid**
- **CK-MB 42.8 ng/mL → 1.88 ng/mL**
- **Edoxaban 15mg qd**
- **Hb 8.7 g/dL → 10.3 g/dL**
- **Discharged after 1 week**
- **Uneventful so far, FU Hb 10.2 g/dL**

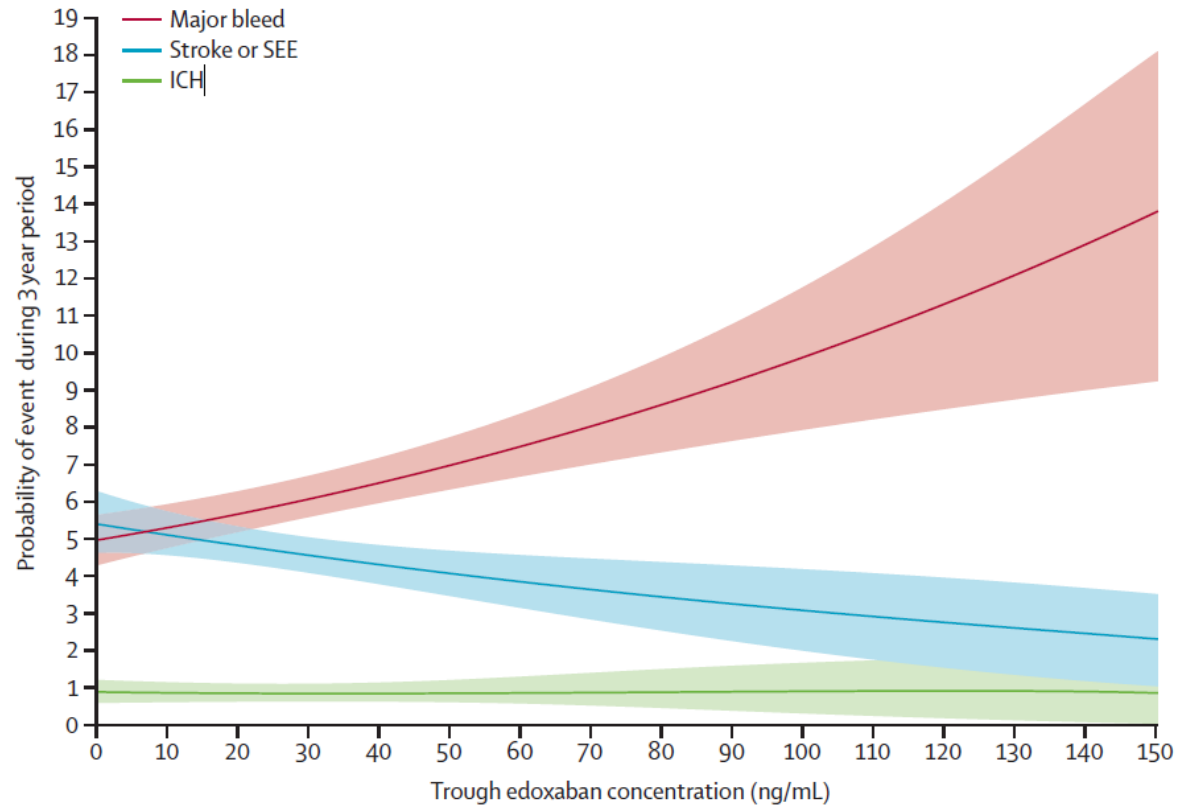
Practical Considerations Using NOACs in Elderly

- **Renal function**
- **Bleeding history**
- **Frailty**
- **Cognitive function (adherence)**
- **Risk of falling**
- **Polypharmacy**
- **Multiple comorbidities**

Edoxaban Concentration and Outcomes

- An analysis of data from the ENGAGE AF-TIMI 48 trial

Probability of clinical outcomes versus edoxaban concentration



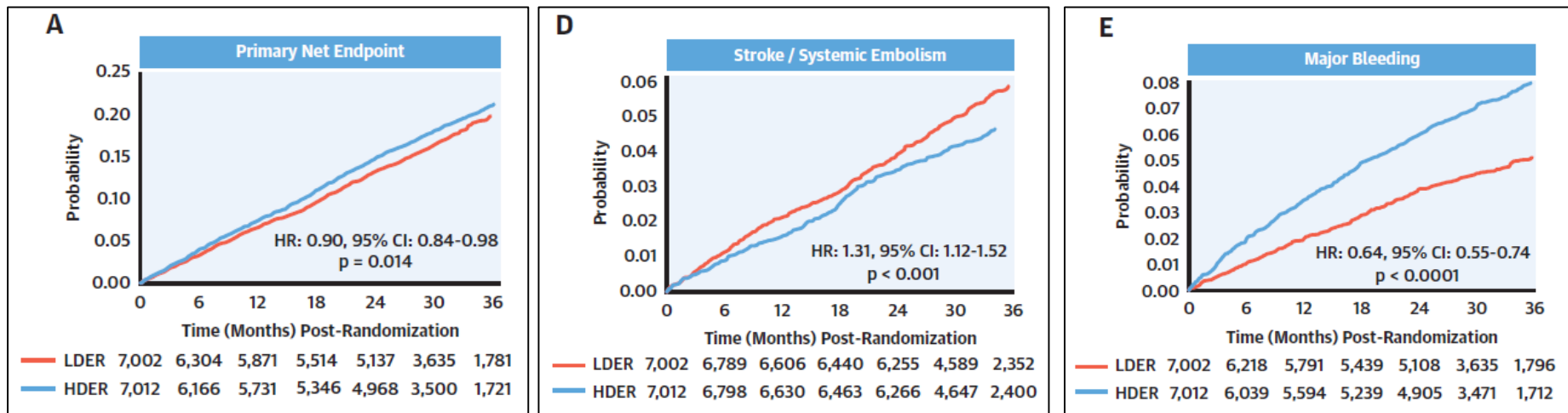
Ruff CT, et al. *Lancet*. 2015 Jun 6;385(9984):2288-95.



LDER versus HDER in ENGAGE AF Trial

- A pre-specified analysis of the ENGAGE AF-TIMI 48 trial
- Comparison of the net clinical outcome (NCO) of LDER versus HDER
- **Primary net endpoint: stroke/systemic embolism, major bleeding, death**

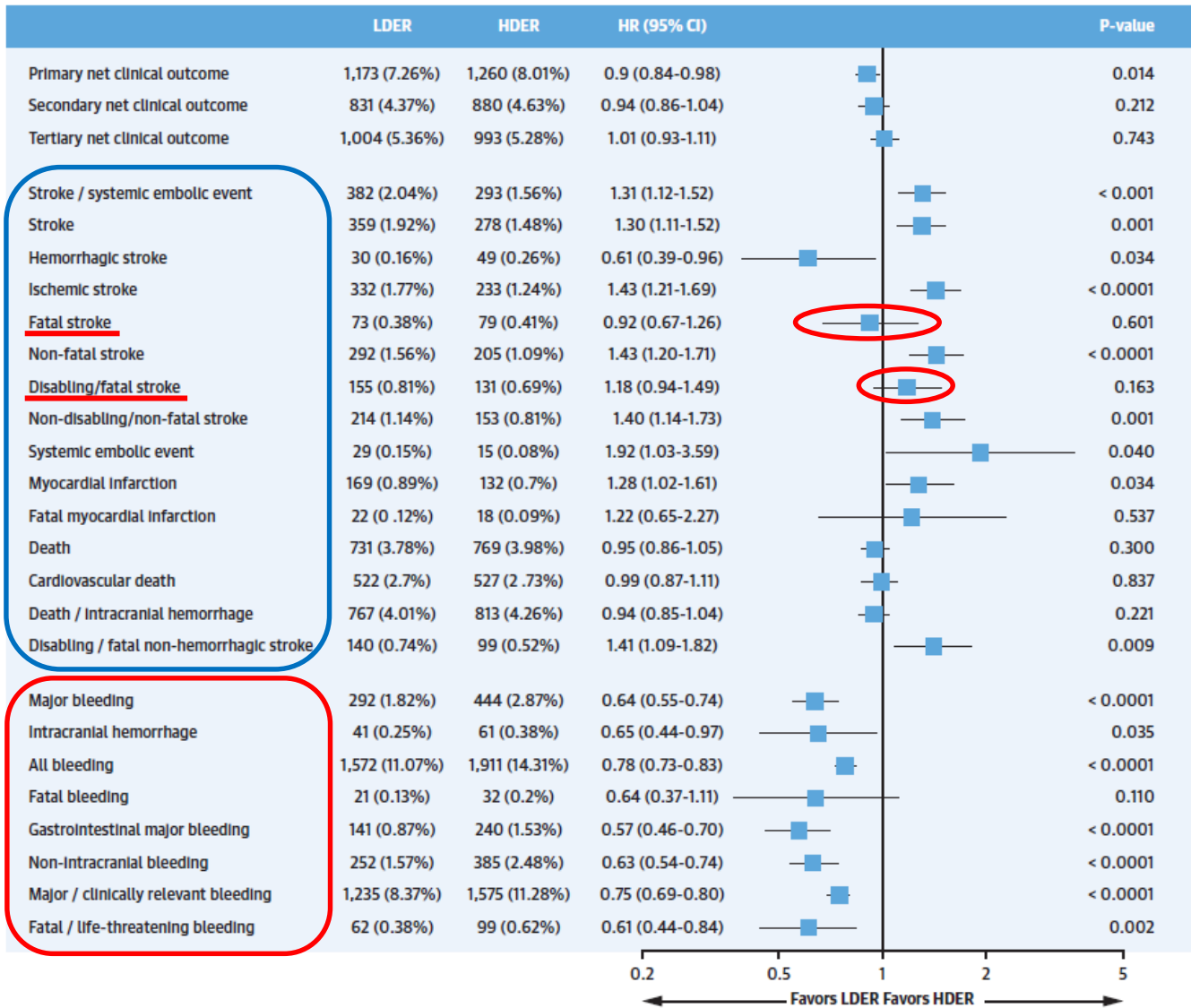
Outcomes on LDER vs. HDER in the ENGAGE AF-TIMI 48 Trial



Steffel J, et al. *J Am Coll Cardiol.* 2021 Mar 9;77(9):1197-1207.



LDER versus HDER in ENGAGE AF Trial



Efficacy

Safety

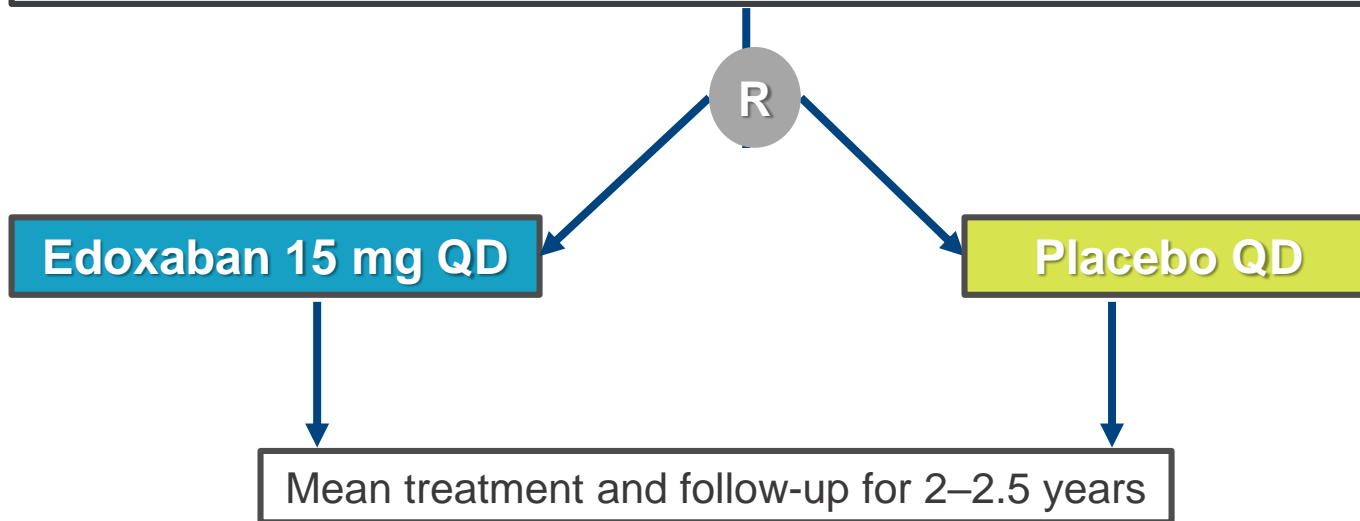


ELDERCARE-AF

A phase 3, randomized, double-blind, placebo-controlled, event-driven, multicenter trial

**Patients ≥ 80 years with CHADS₂ score ≥ 2
Ineligible for standard OAC therapy at approved doses for ≥ 1 of
the following reasons:**

- Low CrCl (15–30 mL/minute)
- Low body weight (≤ 45 kg)
- History of bleeding from critical organs or areas, or GI bleeding
- Concomitant use of NSAIDs or antiplatelet therapy



Okumura K, et al. *N Engl J Med.* 2020 Oct 29;383(18):1735-1745.



ELDERCARE-AF

Baseline Characteristics

	N = 984
Age, year	86.6 ± 4.2
Body weight, kg	50.6 ± 11.0
CrCl, mL/min	36.3 ± 14.4
CHADS ₂ score	3.1 ± 1.1
HAS-BLED score	2.3 ± 0.9
Frailty assessment ^{1,2,a} , n (%)	
Robust or pre-frail score 0–2	542 (55.1)
Frail (score ≥3)	402 (40.9)
History of OAC therapy, n (%)	423 (43.0)
Warfarin	243 (24.7)
Direct OACs	251 (25.5)
Unknown	3 (0.3)

Reasons for ineligibility for SD OAC

	Edoxaban 15 mg (n = 492)	Placebo (n = 492)
Severe renal impairment	198 (40.2)	205 (41.7)
History of bleeding	110 (22.4)	112 (22.8)
Intracranial	41 (8.3)	39 (7.9)
Gastrointestinal	61 (12.4)	66 (13.4)
Other	9 (1.8)	12 (2.4)
Low body weight (≤45kg)	188 (38.2)	186 (37.8)
Continuous use of NSAIDs	149 (30.3)	168 (34.1)
Use of an antiplatelet drug	260 (52.8)	269 (54.7)
Aspirin	134 (27.2)	157 (31.9)
Clopidogrel	71 (14.4)	63 (12.8)
Other	56 (11.4)	51 (10.4)

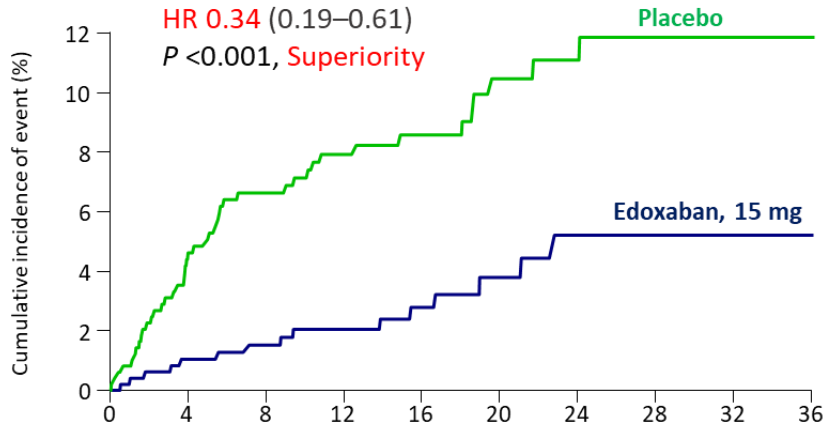
Okumura K, et al. *N Engl J Med.* 2020 Oct 29;383(18):1735-1745.



ELDERCARE-AF

Stroke/Systemic Embolism

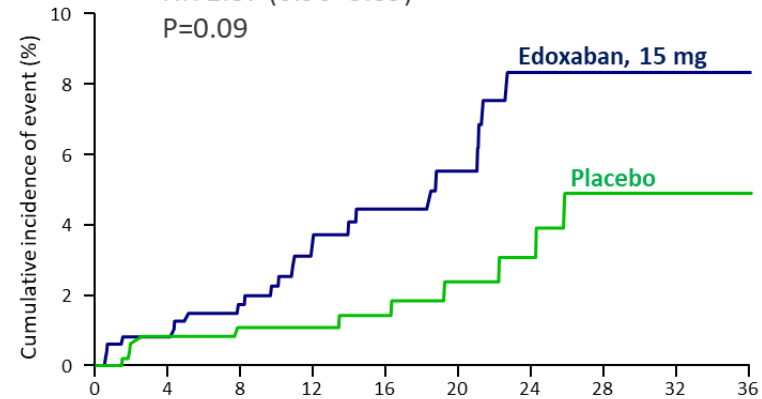
HR 0.34 (0.19–0.61)
P < 0.001, Superiority



	Number at risk									
	Months since Randomization									
	0	4	8	12	16	20	24	28	32	36
Edoxaban 15 mg	492	451	394	323	238	163	116	71	30	7
Placebo	492	439	388	314	237	170	120	74	32	6

Major Bleeding

HR 1.87 (0.90–3.89)
P = 0.09



	Number at risk									
	Months since Randomization									
	0	4	8	12	16	20	24	28	32	36
Edoxaban 15 mg	492	452	391	314	231	158	107	64	28	7
Placebo	490	451	398	322	243	173	122	74	33	7

Okumura K, et al. *N Engl J Med.* 2020 Oct 29;383(18):1735-1745.



CASE (5)

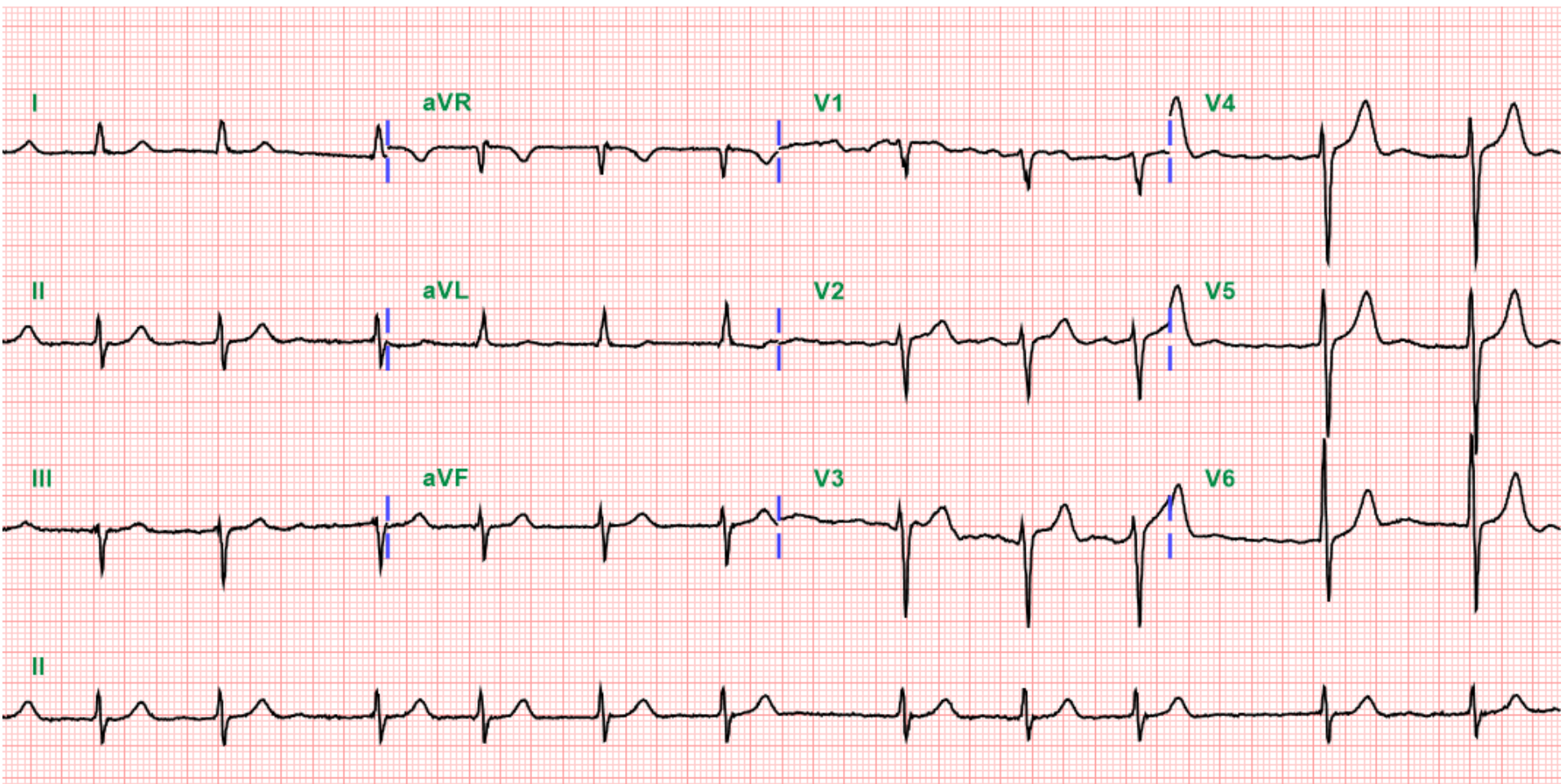
- 90-year-old male, 160 cm / 63 kg
- For preop. evaluation (melanoma), EHRA I
- Past history
 - Diagnosed with AF 20 years ago
 - HTN (+), DM (+), CHF (+), COPD (+)
 - Stroke/TIA (-), vascular disease (-)

CASE (5)

- **TFT: normal**
- **Cr = 1.37, CrCl = 32 mL/min**
- **NT-proBNP = 1,537 pg/mL**
- **TTE:**
 - **LA diameter 53.5 mm**
 - **LVEF 57%**
 - **Mild MR, Mild TR, PAP 67 mmHg**

● **CHA₂DS₂-VASc=5, HAS-BLED=1**

● 12 lead ECG



● Chest PA



- **Clinical course**

- **Apixaban 2.5mg bid since 2016**
- **In 2018, s/p Transurethral resection of bladder tumor**
- **In 2021, hematuria, bladder cancer 재발, TURB**
- **혈뇨 지속, bladder ca 재발하였으나 위험성으로 수술 못함.**
- **혈뇨 지속 fu CT 상 kidney cancer, nephrectomy 필요**
- **혈뇨 지속되어 엘리퀴스 중단.**
 - ➔ **edoxaban 15mg**

● Follow up

■ 주관적 소견

혈뇨로 엘리퀴스는 못 먹고 있음.
EHRA I

■ 객관적소견

* 활력징후

수축기혈압/이완기혈압 : 143/69mmHg, 맥박 : 74회/분

■ 검사소견

ECG: AF, 73

■ 진단명

Permanent atrial fibrillation
Diabetes mellitus (DM)
Chronic kidney disease, stage 3
Hypertension
Permanent AF
DM (EC)
HTN (EC)
CKD (stage 3)
s/p Bladder ca. op (2018.7.3)
CHADS-VASc 4

LA 51.4 EF 57.5, 2016.9.9

송파

■ 진료계획

3m later
릭시아나 15mg으로 변경.

■ 주관적 소견

Doing well
EHRA I
Bleeding (-)
혈뇨 안나온다. 다리가 붓는다.

■ 객관적소견

* 활력징후

수축기혈압/이완기혈압 : 141/75mmHg, 맥박 : 74회/분

■ 검사소견

ECG: AF, 73

■ 진단명

Permanent atrial fibrillation
Diabetes mellitus (DM)
Chronic kidney disease, stage 3
Hypertension
Permanent AF
DM (EC)
HTN (EC)
CKD (stage 3)
s/p Bladder ca. op (2018.7.3)
CHADS-VASc 4

LA 51.4 EF 57.5, 2016.9.9

송파

■ 진료계획

3m later
이노제 prn

Lixiana's Good Points

- Once daily
 - ➔ Adherence
- A variety of dosing options (60-30-15mg)
 - ➔ Frailty, comorbidities
- Low body weight as dose reduction criteria
 - ➔ Asian patients
- Less drug-drug interaction
 - ➔ Polypharmacy

Standard

HDER
(60/30)

Individualized, shared decision

LDER
(30/15)

VLDER
(15)



