Antithrombotic Therapy for TAVI

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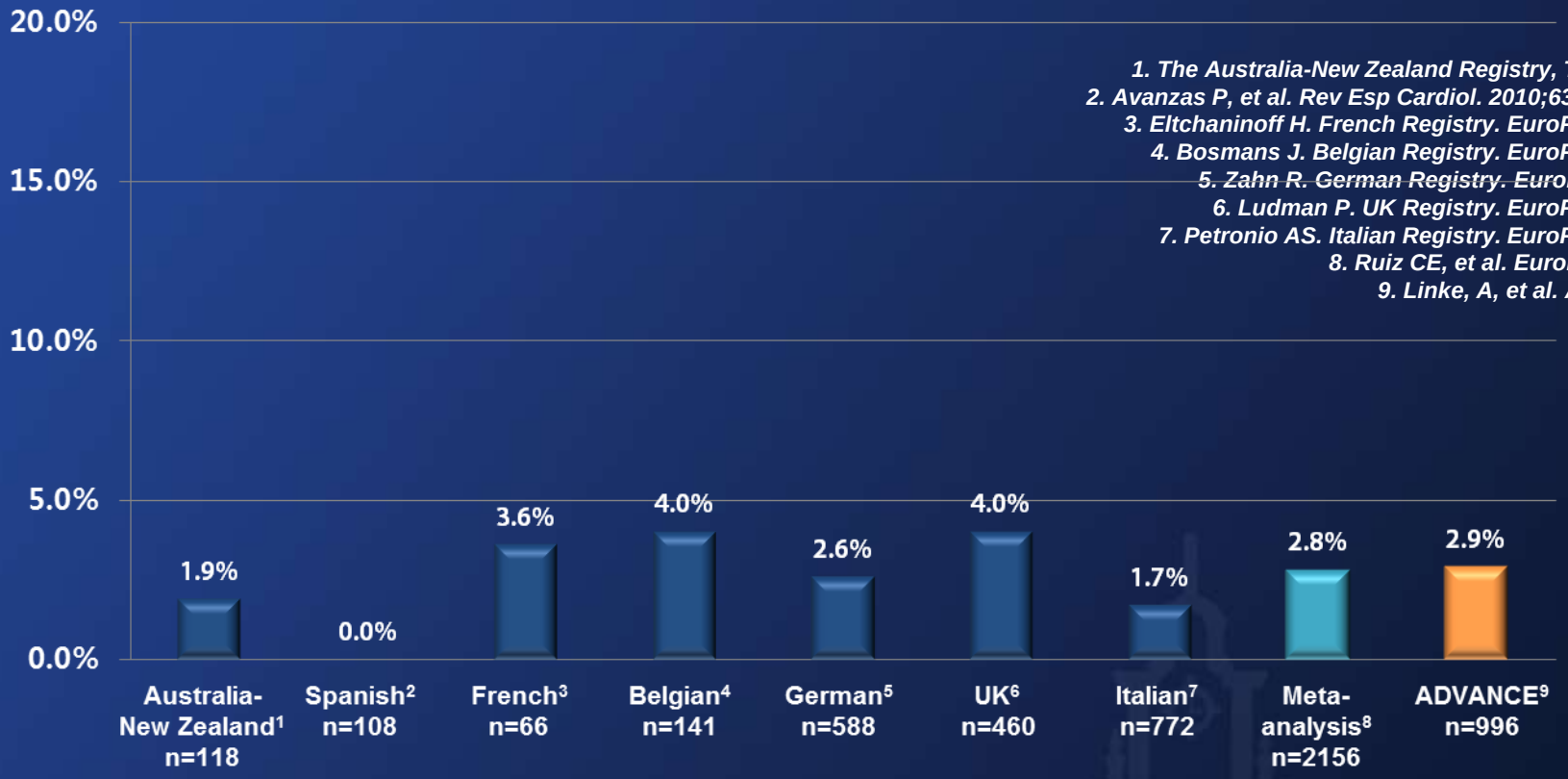
Issue #1.

peri-TAVI stroke prevention

Peri-procedural Stroke in TAVI
- Pooled CoreValve Data at 30-day



1. The Australia-New Zealand Registry, TCT 2010.
2. Avanzas P, et al. Rev Esp Cardiol. 2010;63:141-148.
3. Eltchaninoff H. French Registry. EuroPCR 2010.
4. Bosmans J. Belgian Registry. EuroPCR 2010.
5. Zahn R. German Registry. EuroPCR 2010
6. Ludman P. UK Registry. EuroPCR 2010.
7. Petronio AS. Italian Registry. EuroPCR 2010.
8. Ruiz CE, et al. EuroPCR 2011
9. Linke, A, et al. ACC 2012

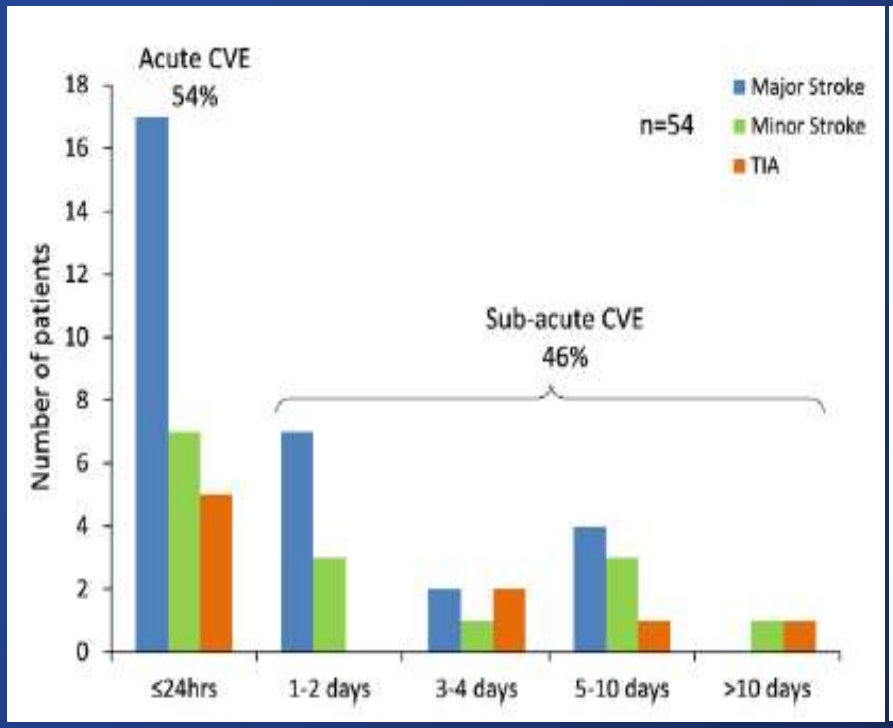
New Ischemic Defects after TAVI : 66-86%

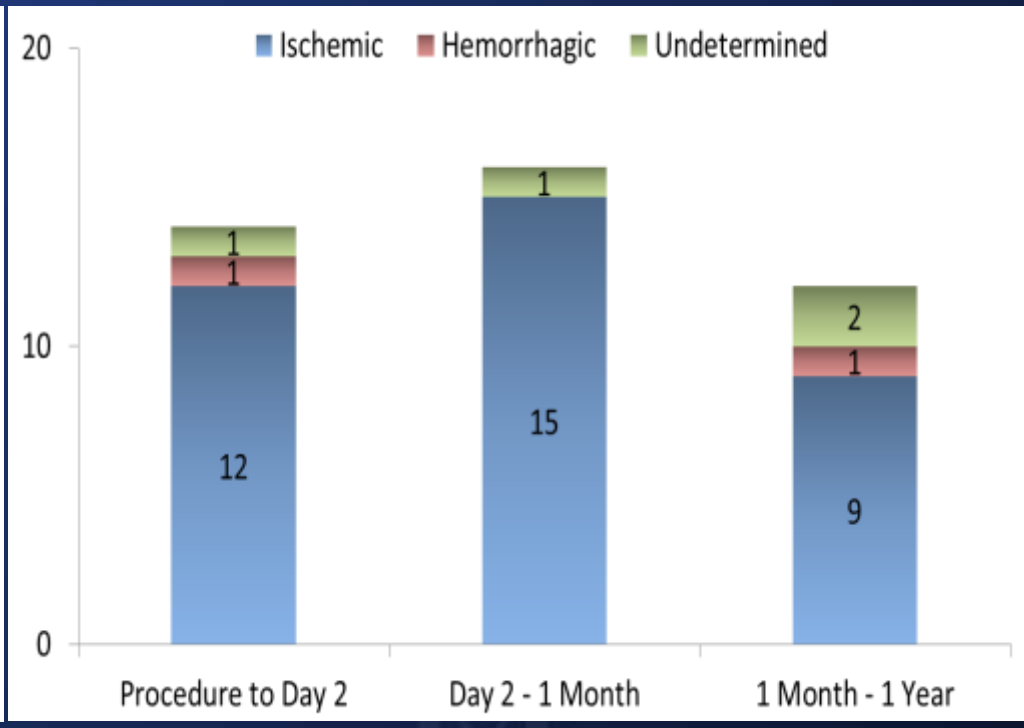
➔ Regardless of valve type or access route (trans-femoral or trans-apical)

➔ Most new ischemic defects are clinically silent

Clinically Apparent Stroke after TAVI : 3% (0-6%)

Peri-procedural Stroke in TAVI
- Timing of Stroke After TAVI



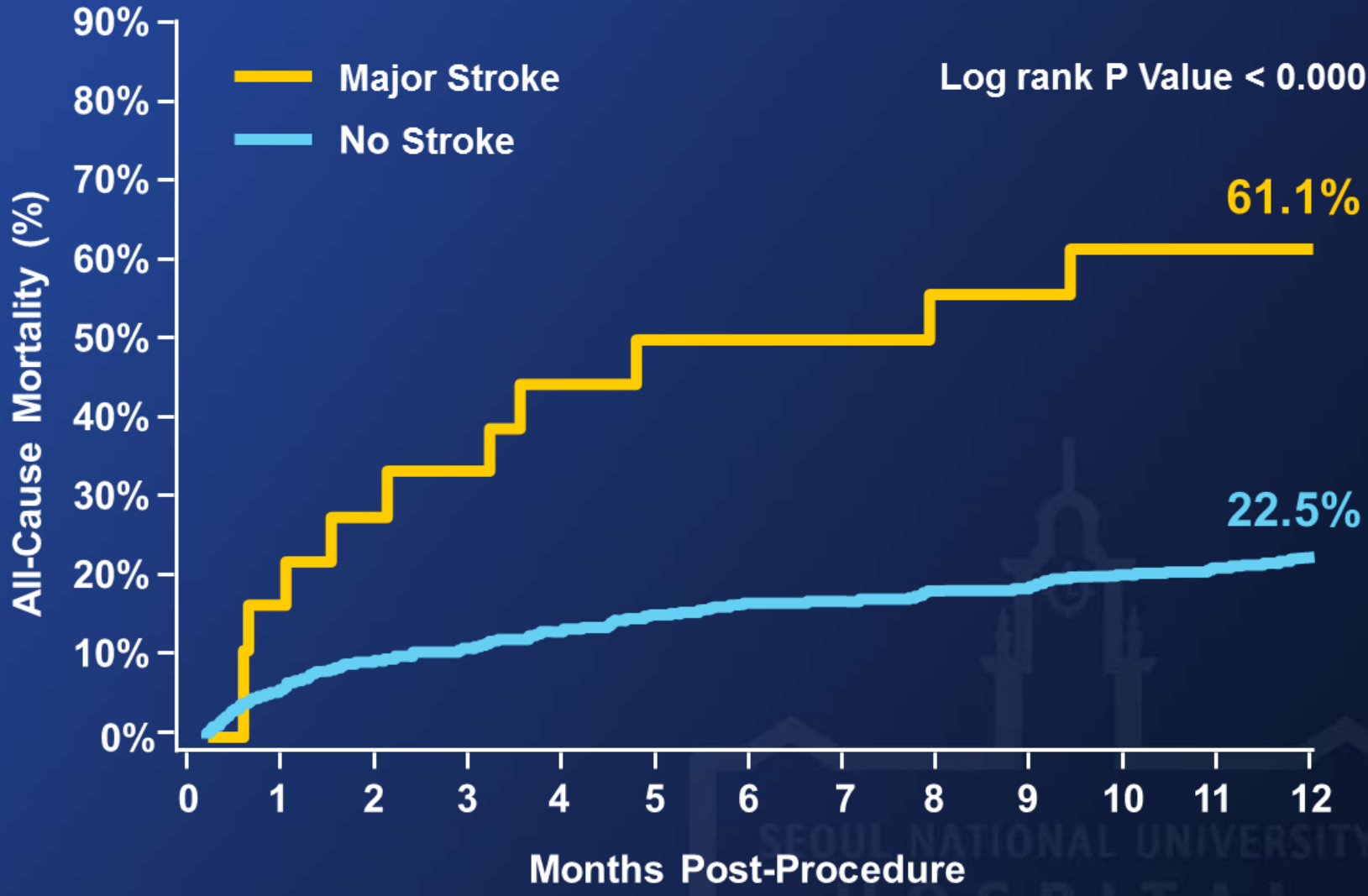


- Timing
  - About Half of Cerebrovascular Events occurs < 24 hrs
  - But, Another half of events occurs “after” 24 hrs
- Etiology
  - Most of Cerebrovascular Events are “Ischemic” events

➔ Stroke prevention is IMPORTANT both at peri- & post-procedure periods

Rodes-Cabau et al. JACC 2013;62:2349-59
Bosmans et al. EUROPCR 2013

Peri-procedural Stroke in TAVI
- One year Mortality in Patients with Major Stroke



CoreValve US Clinical Trial (Extreme-Risk Iliofemoral Pivotal), TCT 2013

Current Recommendations
- Antithrombotic Agents and Strategies for TAVI

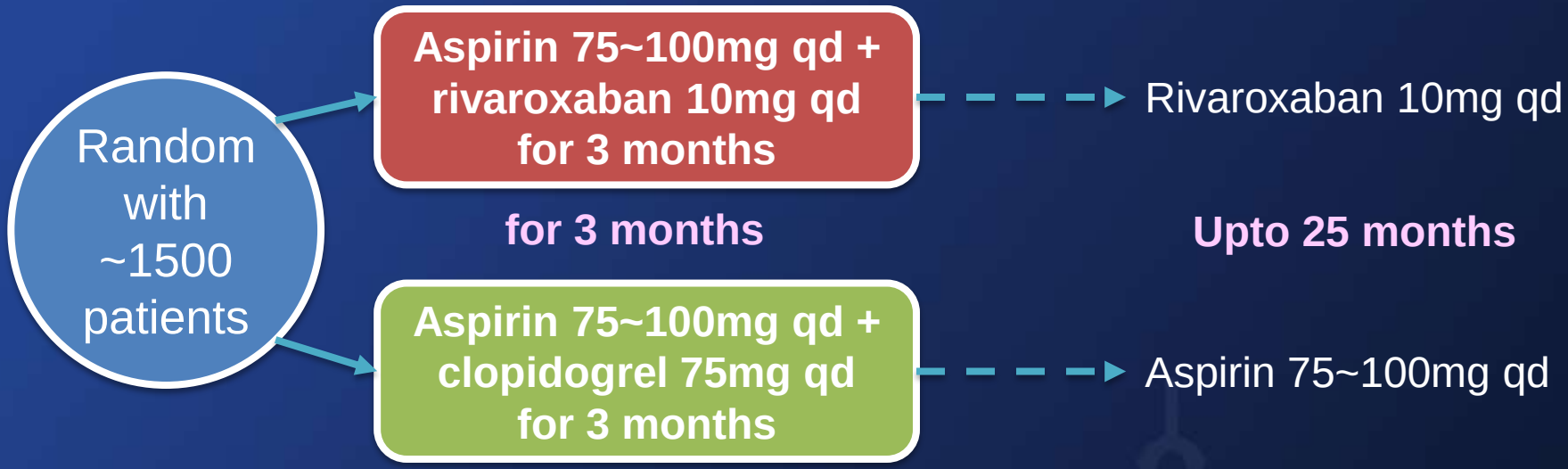
PARTNER Trial (17,18)	ACC/STS Recommendations	CCS Statement	PARTNER Trial
Pre-procedural	Aspirin 80 mg		
	Clopidogrel 300 mg		
Procedural	Unfractionated heparin	Unfractionated heparin	—
	Goal ACT: 250 s	Goal ACT: 300 s	
	Reversal with protamine	Reversal with protamine	
	Bivalirudin (?)	Bivalirudin (?)	
Post-procedural	Aspirin 81 mg/day indefinitely +	Aspirin 81 mg/day indefinitely +	Indefinite low-dose Aspirin gen erally recommended +
	Clopidogrel 75 mg/day × 3M	Clopidogrel 75 mg/day × 3–6M	Thienopyridine × 1–3M
	If AF, Lifelong warfarin	If warfarin indicated (AF), then no clopidogrel	If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists

ACC = American College of Cardiology; ACT = activated clotting time; AF = atrial fibrillation; CCS = Canadian Cardiovascular Society; STS = The Society for Thoracic Surgeons; TAVI = transcatheter aortic valve implantation.

J Am Coll Cardiol. 2013;62(25):2349-2359. doi:10.1016/j.jacc.2013.03.029

NOAC after TAVI ; GALILEO trial (phase III) for rivaroxaban

After successful TAVI, for patients who do not have AF,



Time frame : 25 months

Primary efficacy end-point : composite of all-cause death, stroke, MI, valve thrombosis, pulmonary embolism or DVT, systemic embolism

Safety end-point : major bleeding including life threatening or disabling bleeding

Subclinical leaflet thrombosis is not specified as an efficacy outcome in advance, but imaging substudy may be feasible in small subset

Issue #2.

TAVI patients with Atrial Fibrillation

Incidence of A.fib in TAVI patients

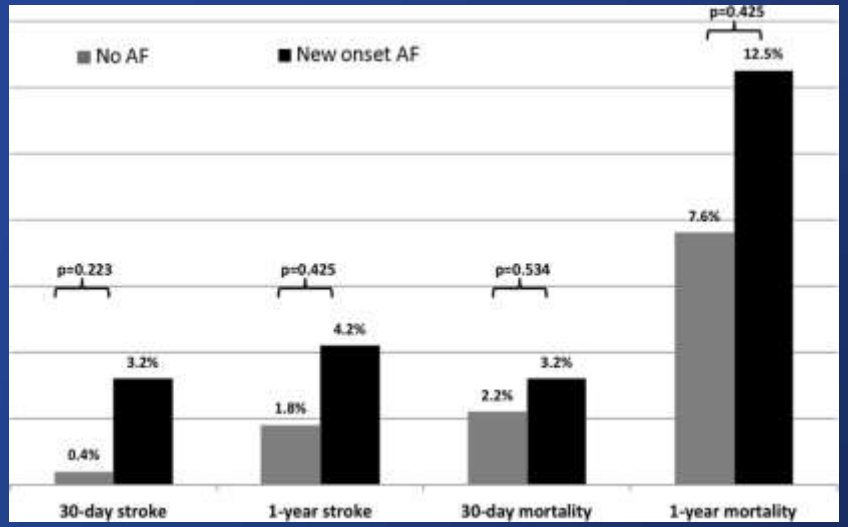
- Afib is one of the most frequent co-morbidity in TAVI patients
  - The overall rate of previous A.fib in TAVI patients was 30-50%
  - The rate of new-onset A.fib (NOAF) within 1 month of TAVI was 8-32%
- TAVI Patients with Afib frequently had “high” CHA2DS2-VASC score
  - Average CHA2DS2-VASC score was 4.7

JACC 2012;59:178-88
Am J Cardiol 2014;114:1861-1866
World J Cardiol 2012;4:8-14

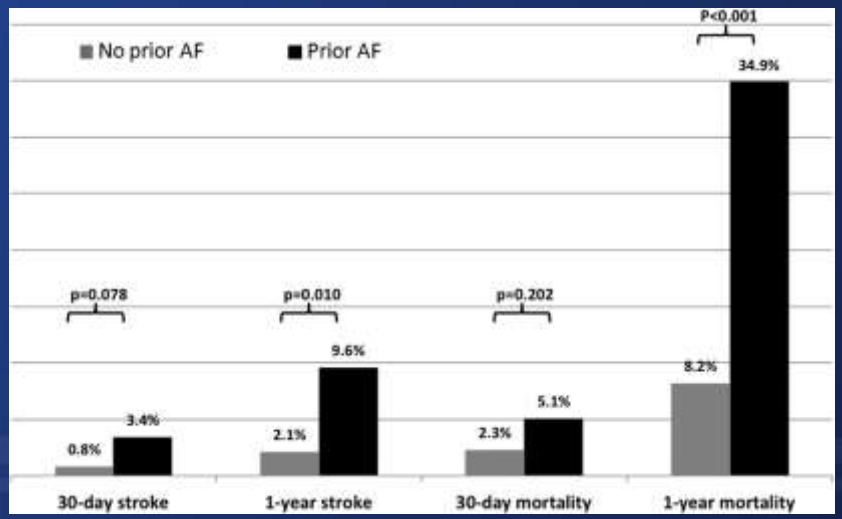
Clinical Impact of A.fib after TAVI

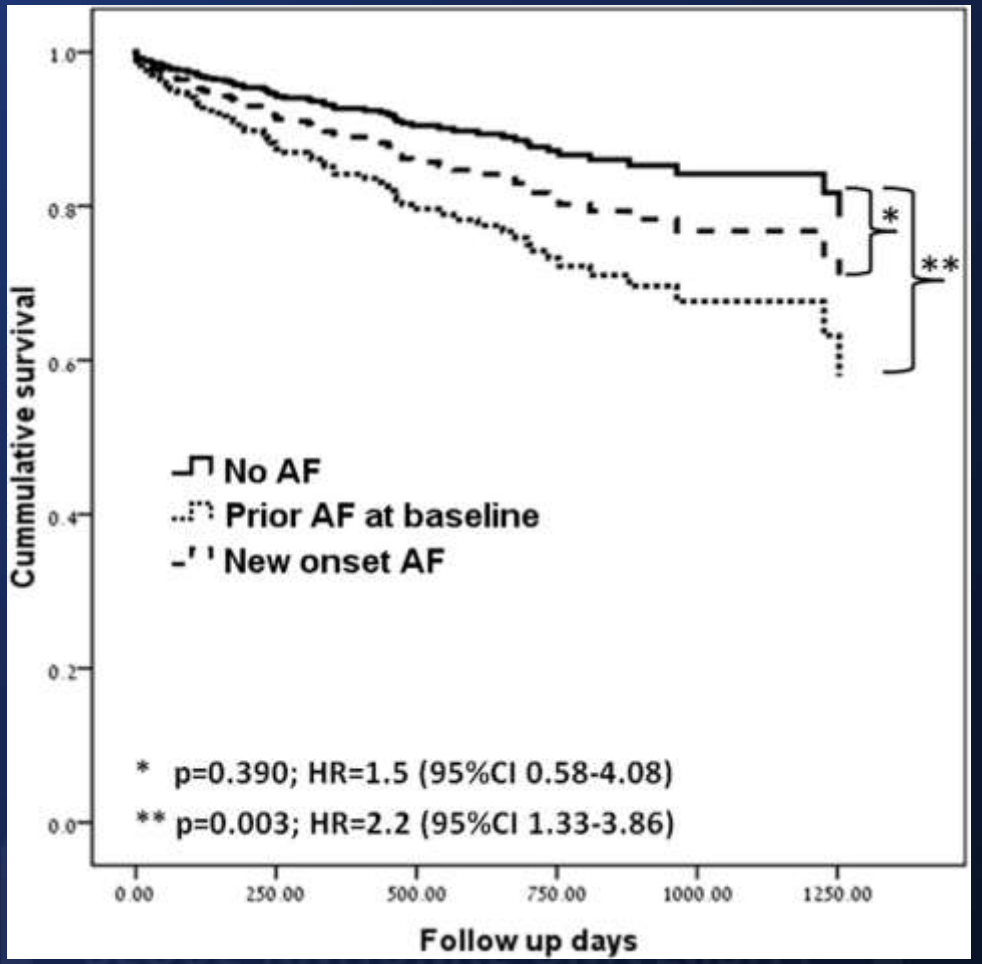
Cumulative rate of mortality or stroke

(1) Mortality / stroke : New-onset A.fib



(2) Mortality / stroke : Chronic A.fib





Am J Cardiol 2014;114:1861-1866

Clinical Impact of A.fib after TAVI

All-cause mortality at 12 months according to Afib classification

	n	events (%)	HR (95% CI)	Hazard ratio (95% CI) 5 1 2 4 8 12	p - value
No Atrial Fibrillation (Pre and Post)	258	31 (12.0%)	reference		
Permanent Atrial Fibrillation	70	19 (27.1%)	2.47 (1.40-4.38)		0.002
Persistent Atrial Fibrillation	8	3 (37.5%)	3.60 (1.10-11.78)		0.034
Permanent / Persistent Atrial Fibrillation	78	22 (28.2%)	2.59 (1.50-4.47)		0.001
Paroxysmal Atrial Fibrillation / Atrial Flutter	31	9 (29.0%)	2.88 (1.37-6.05)		0.005
Any Atrial Fibrillation (Pre or Post)	131	35 (26.7%)	2.45 (1.51-3.98)		<0.0001

Stratified IPTW adjusted analyses of all-cause mortality across subgroups

	No AF N = 258	AF N = 131	Hazard ratio (95% CI)	Hazard ratio (95% CI) 5 1 2 4 8 16	p value	p value interaction
Age						0.870
≤80 years	5/66	7/31	2.53 (0.78-8.22)		0.124	
>80 years	26/192	28/100	2.29 (1.32-3.98)		0.003	
Gender						0.469
Male	13/110	17/55	2.86 (1.35-6.03)		0.006	
Female	18/148	18/76	1.97 (1.01-3.84)		0.047	
Diabetes mellitus						0.462
No	22/188	22/96	2.05 (1.12-3.78)		0.020	
Yes	9/70	13/35	3.22 (1.36-7.62)		0.008	
Renal Function						0.691
GFR < 60ml/min/1.73m^2	8/86	6/35	1.93 (0.65-5.72)		0.233	
GFR ≥ 60ml/min/1.73m^2	23/172	29/96	2.48 (1.41-4.37)		0.002	
Coronary Artery Disease						0.366
No	11/93	11/58	1.70 (0.73-3.97)		0.222	
Yes	20/165	24/73	2.81 (1.52-5.19)		0.001	
Left ventricular ejection fraction						0.610
>40%	21/195	23/92	2.55 (1.39-4.68)		0.003	
≤40%	10/62	12/39	1.98 (0.83-4.69)		0.122	

Circ Cardiovasc Interv 2013;6:77-84

Clinical Impact of A.fib after TAVI

All-cause mortality at 12 months according to Afib classification

Regardless of New-onset or Chronic A.fib,

Patients with A.fib have higher risk of mortality or stroke, than those without A.fib,

Especially in patients with old age, DM, male, or coronary artery disease.

Stratified IPTW adjusted analyses of all-cause mortality across subgroups

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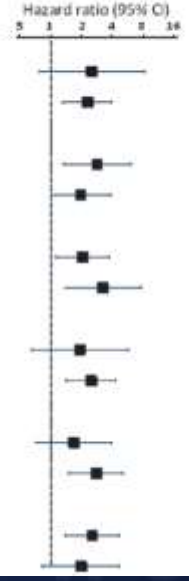
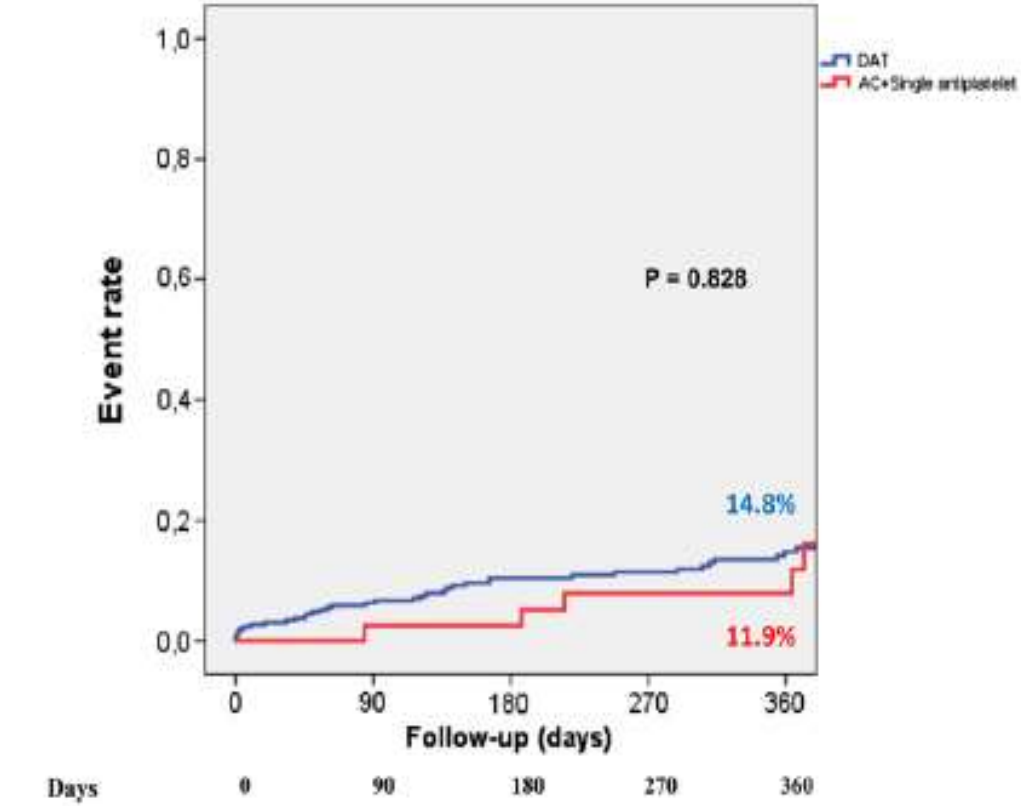


Circ Cardiovasc Interv 2013;6:77-84

Efficacy of warfarin/aspirin in TAVI patients with A.fib

343 patients with aortic stenosis underwent TAVI (Retrospective)
16.7% of patients were indicated anticoagulation (mainly due to A.fib)
Comparison Group
① Warfarin + SAPT (Patients with indication of anticoagulation, n=43)
② DAPT (Patients with no indication of anticoagulation, n=300)



No significant differences in mortality, CV events, bleeding between groups

①Warfarin + SAPT (Pts/Af)

②DAPT (Pts/SR)

up to 1-year after TAVI

Am J Cardiol 2013;111:237-242

Current Recommendations
- Antithrombotic Agents and Strategies for TAVI

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Pre-procedural	Aspirin 80 mg		
	Clopidogrel 300 mg		
Procedural	Unfractionated heparin	Unfractionated heparin	—
	Goal ACT: 250 s	Goal ACT: 300 s	
	Reversal with protamine	Reversal with protamine	
	Bivalirudin (?)	Bivalirudin (?)	
Post-procedural	Aspirin 81 mg/day indefinitely +	Aspirin 81 mg/day indefinitely +	Indefinite low-dose Aspirin gen erally recommended +
	Clopidogrel 75 mg/day × 90 days	Clopidogrel 75 mg/day × 3–6M	Thienopyridine × 1–3M
	If AF, Lifelong warfarin	If warfarin indicated (AF), then no clopidogrel	If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists

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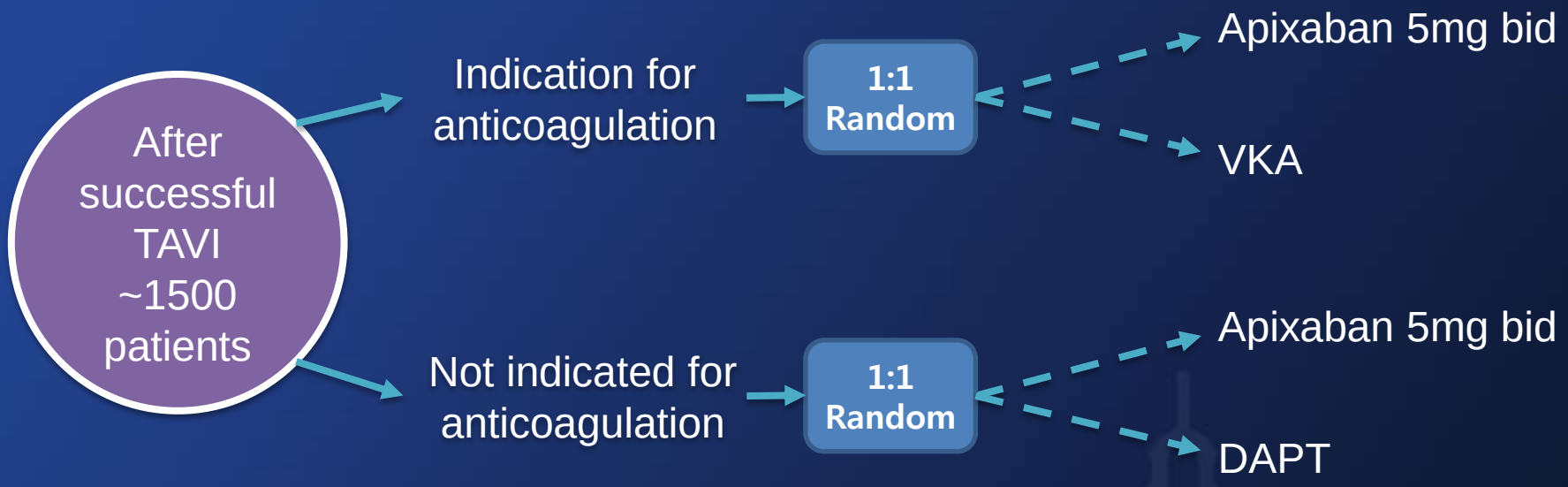
J Am Coll Cardiol. 2013;62(25):2349-2359. doi:10.1016/j.jacc.2013.03.029

NOAC after TAVI ; ATLANTIS trial (phase III) for apixaban

After successful TAVI,



Time frame : upto 6 months

Primary efficacy end-point : composite of all-cause death, stroke/TIA, MI, intracardiac or valve thrombosis, pulmonary embolism or DVT, systemic embolism

Safety end-point : major bleeding including life threatening or disabling bleeding

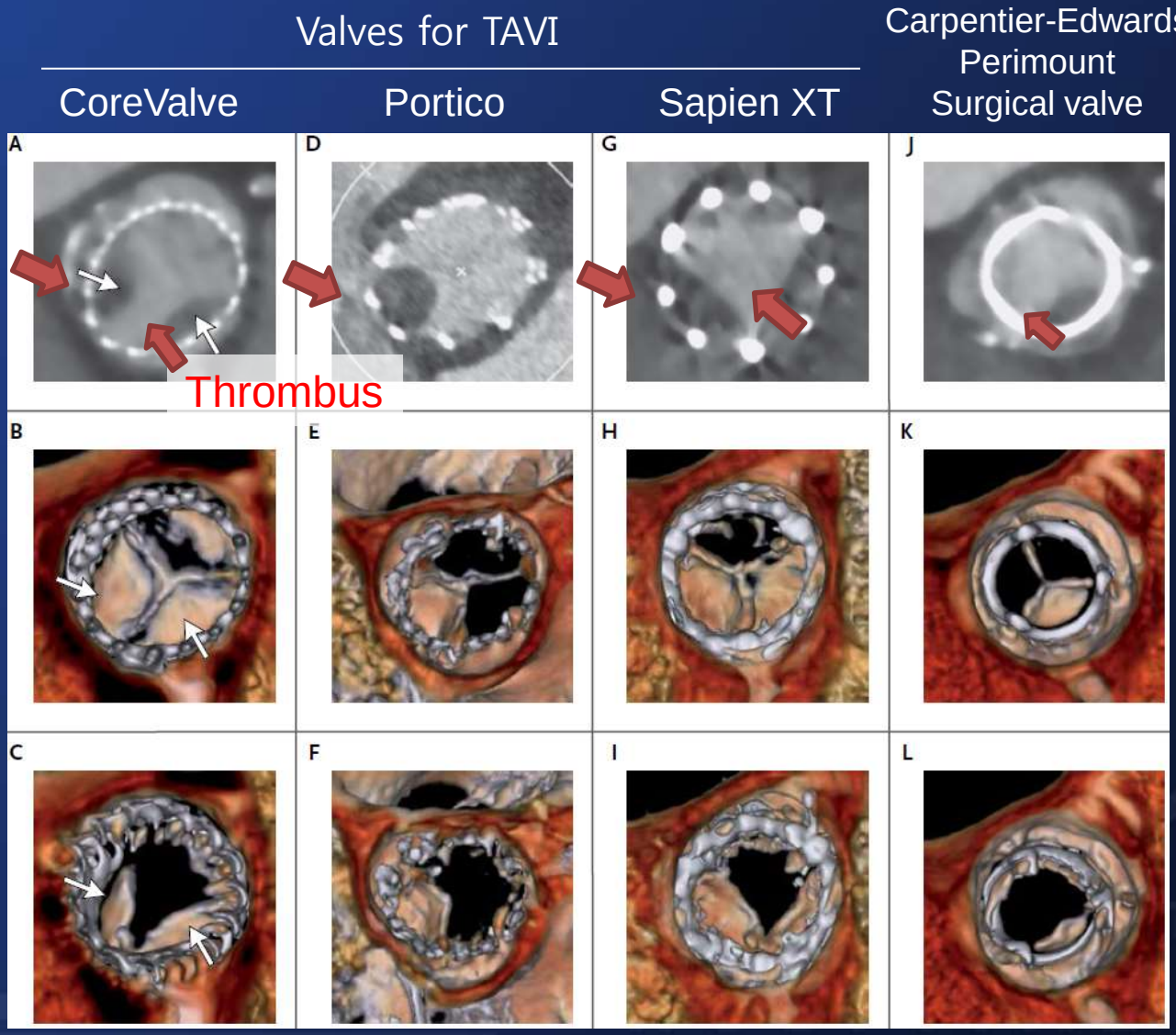
Subclinical leaflet thrombosis is not specified also in this trial

Issue #3.

Valve Leaflet thrombosis After TAVI

Imaging evidences of reduced leaflet motion

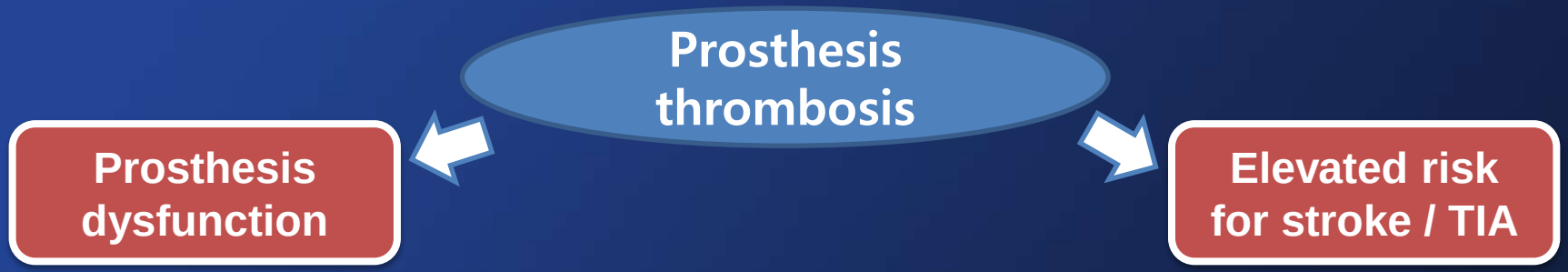
Reduced leaflet motion is not derived from structural deformation, but is directly linked to subclinical leaflet thrombosis



* 4D volume-rendered CT scans

R.R. Makkar et al., *N Engl J Med* 2015;373:2015-24.

Prosthesis thrombosis : now in the spotlight



To date, occasional reports (at least 24 cases) for early valve thrombosis say…

- from 3 days ~ 7 years after the procedure
- more prevalent in Sapien valve, but also in others such as CoreValve
- frank thrombosis and restricted leaflet opening : very rare

  cf. annual risk for surgical valve thrombosis : ~0.3%

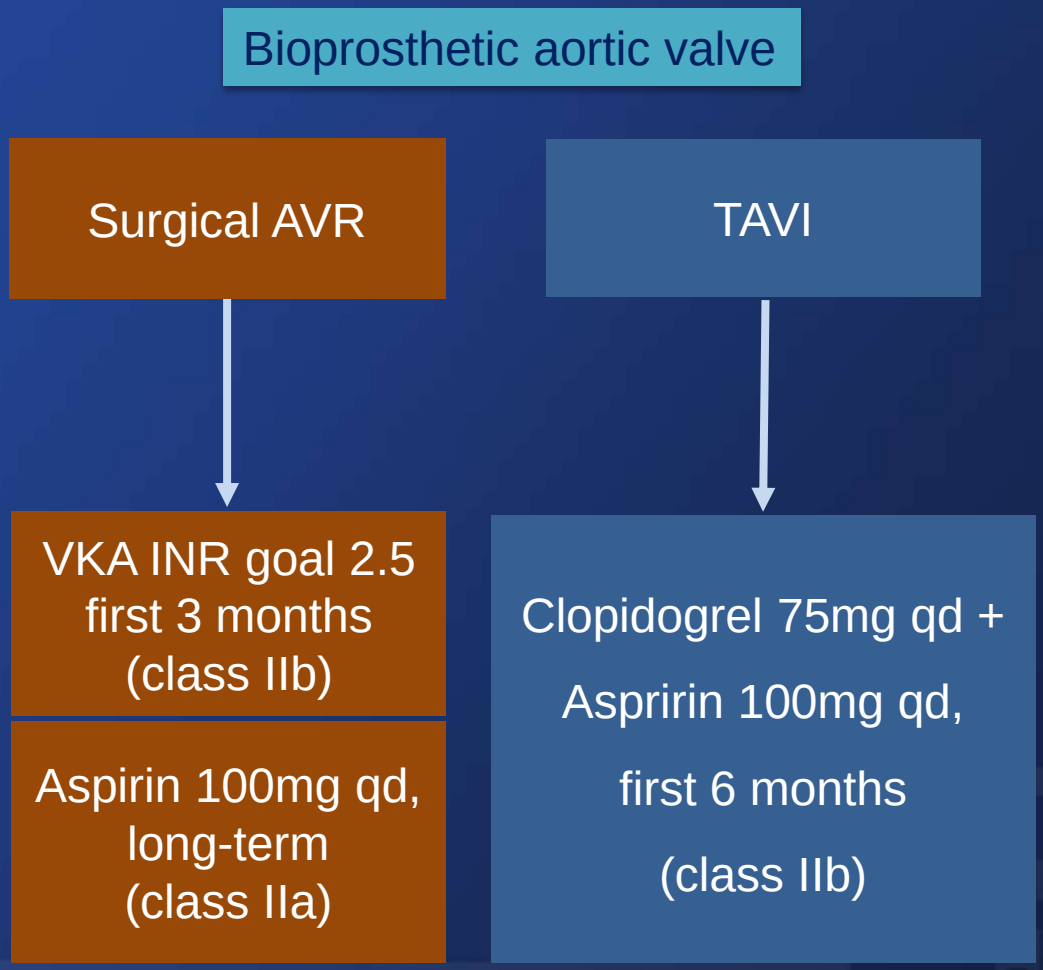
- TAV thrombosis may happen even with DAPT ± anticoagulation

Descoux et al., *J Cardiothoracic Surgery* 2015;10:50.

Current guidelines for antithrombotic therapy

Current guidelines are the legacy of the past experiences,
but are not enough to answer to the unmet clinical needs

2014 ACC/AHA guideline and 2012 ESC guideline



Lifelong oral anticoagulation : only for patients with bioprostheses who have other indications such as atrial fibrillation (class IC)

In practice, actual use of anticoagulation following bioprosthetic AVR is highly variable

Recent registry showed 38% of all patients and 49% of those at high risk were given anticoagulation

Nishimura RA et al. *Circulation* 2014;129:2440-92. / Vahanian A et al. *Eur Hear J* 2012;33:2451-96.
Brennan JM et al., J Heart Valve Dis 2012;21:78-87.

Future of Anticoagulation After TAVI

NOAC vs Warfarin (Af), NOAC vs DAPT (SR) ?

Study name	Phase	Indication	Cases	Remarks
RE-ALIGN **Dabigatran** **Vs** **warfarin**	Phase 2	**Mechanical Heart Valves**	252	**Terminated** because of adverse safety events related to dabigatran
GALILEO **Rivaroxaban** **Vs** **antiplatelet**	Phase 3	**TAVI** **Excluding pre-existing Af**	1,500	Rivaroxaban 10mg + ASA 75-100mg for 3 m followed by rivaroxaban 10mg alone vs Clopidogrel 75mg + ASA 75-100mg for 3 m, followed by ASA 75-100mg alone
ATLANTIS **Apixaban** **Vs** **Warfarin** **Vs** **antiplatelet**	Phase 3	**TAVI** **Including Af**	1509	Apixaban 5mg bid Vs. Warfarin Vs. DAPT/MAPT

1. *John W. Eikelboom, et al, Dabigatran versus Warfarin in Patients with Mechanical Heart Valves, NEJM 369;13*
2. *Source from clinicaltrials.gov*

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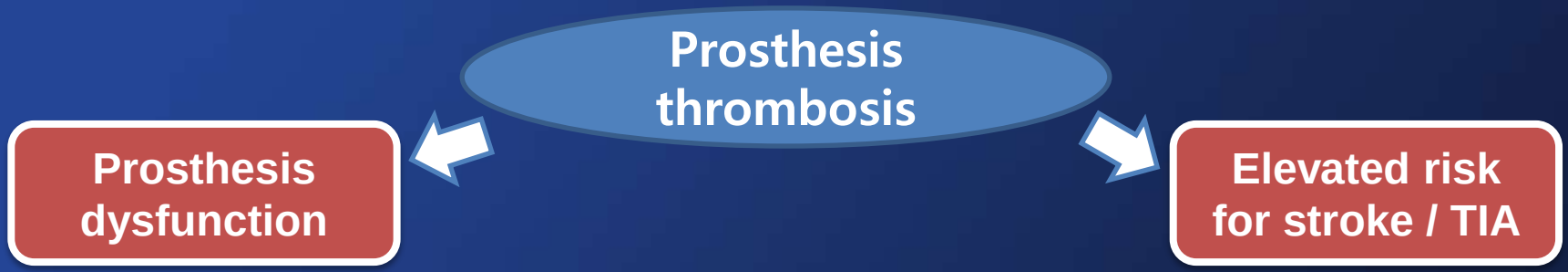
Prosthesis thrombosis : now in the spotlight



Prosthesis dysfunction :

subclinical or clinically significant reduced leaflet motion

→ Symptom : aggravated/reappeared dyspnea >> chest pain

→ Detection :

① echocardiography

(TEE >> TTE, ↑ transprosthetic pressure gradient)

② ECG-gated volume-rendered CT

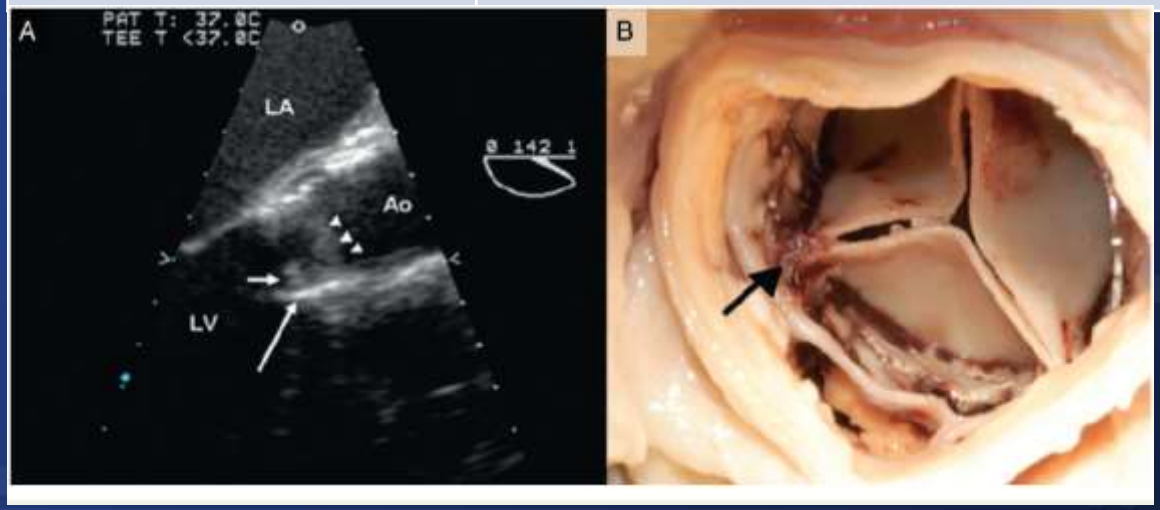
(direct visualization of thrombosis and reduced leaflet motion)

Descoux et al., *J Cardiothoracic Surgery* 2015;10:50.

Past experiences for antithrombotic therapy in TAVI

Antithrombotic regimens of pivotal clinical trials are mainly borrowed from the experiences of coronary stenting/surgical tissue valves

	PARTNER Trial (**SAPIEN**)	PIVOTAL Trial (**CoreValve**)
Antiplatelet therapy	DAPT (aspirin and clopidogrel) for 6 months	DAPT with aspirin (81mg daily) and clopidogrel (75mg daily) for 3 months
	Followed by antiplatelet monotherapy (aspirin is preferred)	
If warfarin is indicated		Aspirin (at least 81mg daily) and warfarin *without* clopidogrel

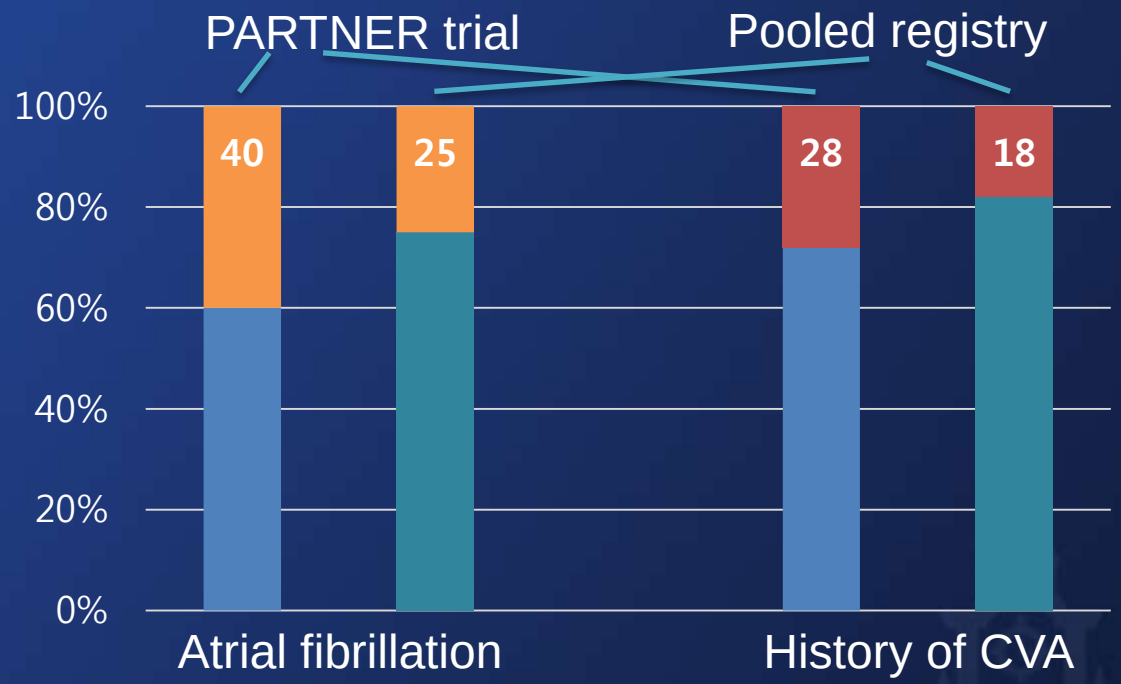


Thrombus
on the exposed scaffold strut

Mylotte D et al., Eur Heart J 2015;36:1306-27.
Leon MB et al., *N Engl J Med* 2010;363:1597-1607. / Adams DH et al., *N Engl J Med* 2014;370:1790-98.

Patients with need for anticoagulation?

Anticoagulation is also needed for many TAV-recipients with atrial fibrillation



cf. average $CHADS_2$ score of in one TAVI registry : **3**

→ substantial patients will benefit from anticoagulation

Leon MB et al., *N Engl J Med* 2010;363:1597-1607.
Luis NF et al., *Circulation* 2012;126:3041-53. / Jeffrey ER. 2015 ACC editorial for 'Anticoagulation in TAVR'

Potential role of indication expansion for anticoagulation

But, who stands to benefit from the expanded indications?

There are not enough data to propose other factors.

- Prosthetic factors? :
  - porcine vs. bovine pericardial leaflet
  - stented vs. non-stented
  - small valves vs. large valves

- Patient factors? :
  - patients who have a very low LV EF (possibly)
  - severe calcification in native valve?
  - enlarged sinus of Valsalva?

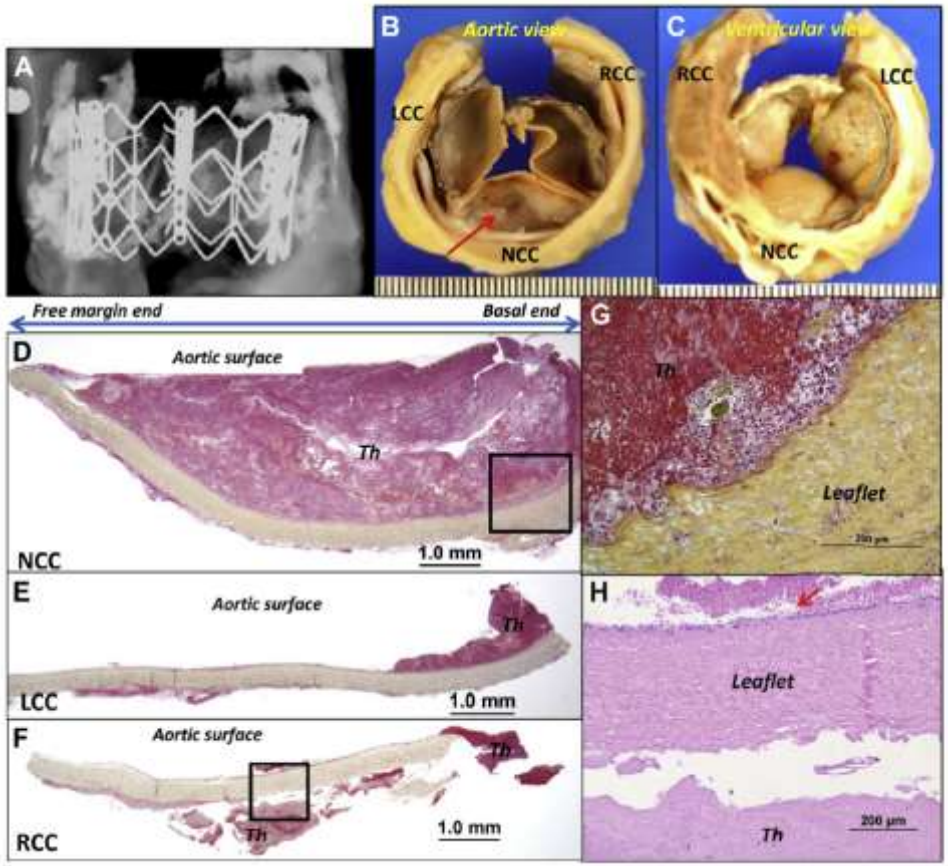
Leon MB et al., *N Engl J Med* 2010;363:1597-1607.
Luis NF et al., *Circulation* 2012;126:3041-53. / Jeffrey ER. 2015 ACC editorial for 'Anticoagulation in TAVR'

Lesson #1 from pathologic findings

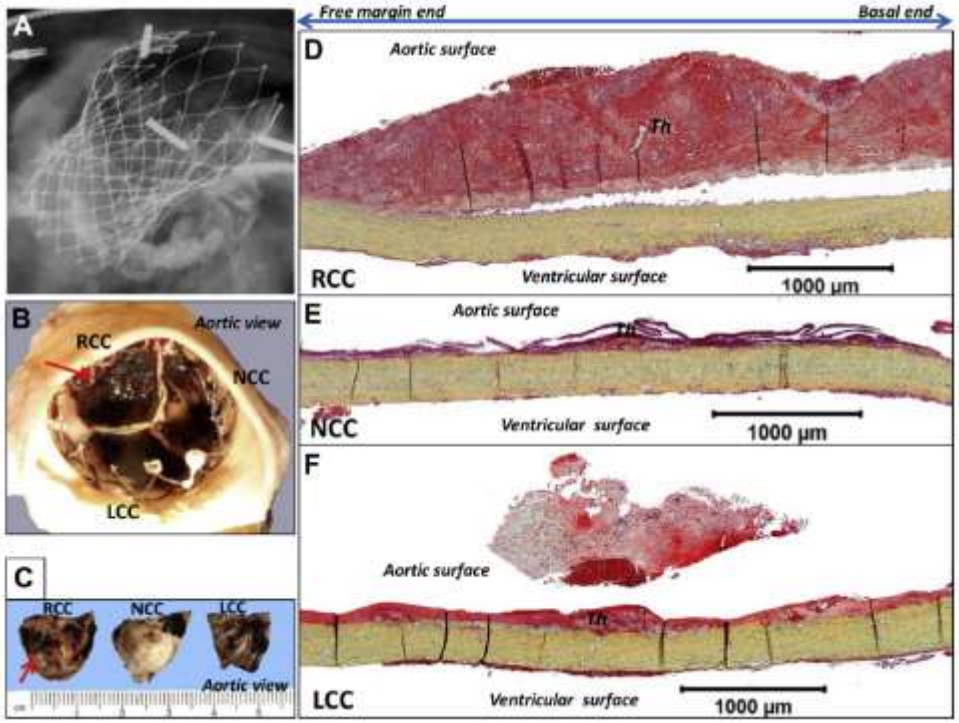
Potential triggers : valve injury during the procedure, autoimmune reaction, mal-apposition or under-expansion, valve-in-valve procedure, …

→ but, (unrecognized or potential) hypercoagulable status rather than valve injury may be a most important factor, most prosthetic leaflets were intact even in the case of frank TAV thrombosis

Edward Sapien



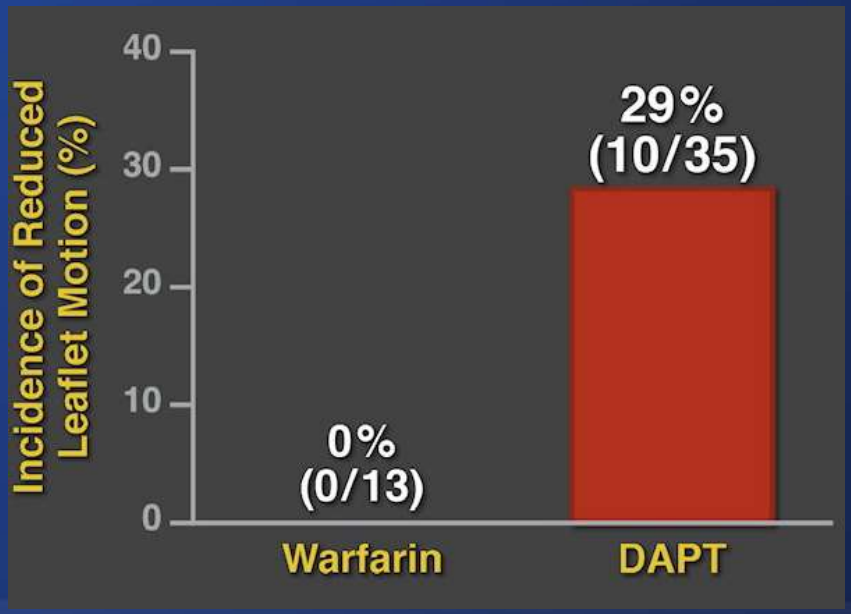
Medtronic CoreValve



Eduardo De Marchena et al., *J Am Coll Cardiol* 2015;8:728-39.

Lesson #2 from clinical data

Most TAV thrombosis does not occur in the initial phase of follow-up
In case series of TAV thrombosis, most cases occurred beyond 3 months



Anticoagulation can absolutely reduce the risk of subclinical leaflet thrombosis at 6 months check-up

And, anticoagulation was not implemented in more than 60% of patients with late (>1 month) cerebrovascular events after the TAVI in one registry

Descoux et al., *J Cardiothoracic Surgery* 2015;10:50. / R.R. Makkar et al., N Engl J Med 2015;373:2015-24.
Luis NF et al., *Circulation* 2012;126:3041-53.

Guidelines and experiences from surgical AVR with bioprosthesis

- ✓ Even without VKA,
  annual risk for clinically significant thromboembolism
  in patients with sinus rhythm = 0.7%

- ✓ warfarin vs. aspirin
  prospective comparison study upto 3 months f/u
  : no differences in thromboembolic events (2.9% in both groups),
  bleeding (2.9% in aspirin, 3.8% in warfarin group, p=0.36),
  and death (2.9% in both groups)

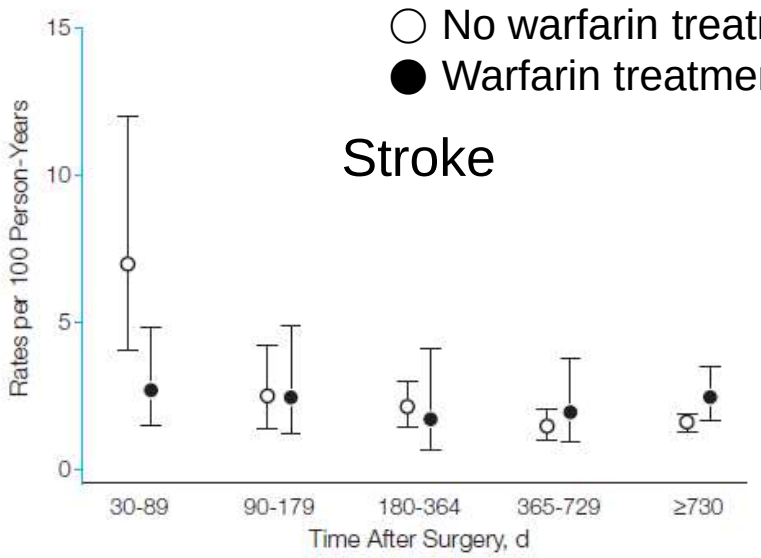
- ✓ But, patients with bioprosthetic AV in the first 90 days after valve replacement,
  at a higher risk of ischemic stroke or peripheral embolism than normal patient

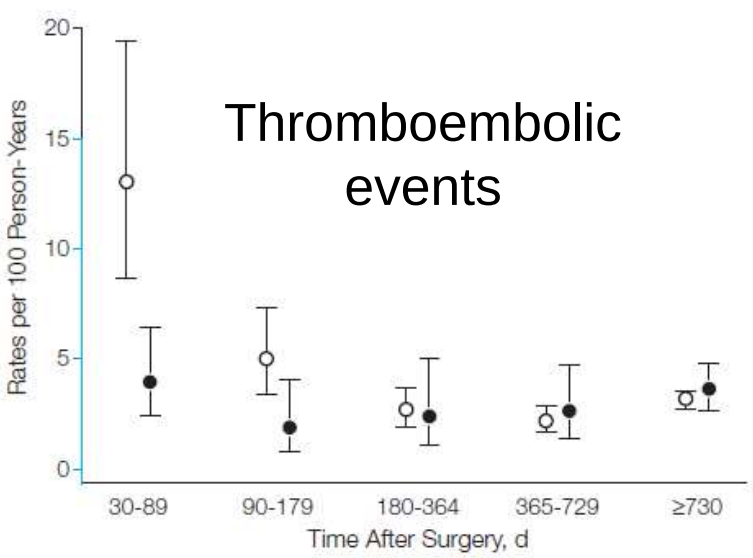
→ Anticoagulation early after valve implantation upto 3 months
: to decrease thromboembolism risk until the prosthesis is fully endothelialized

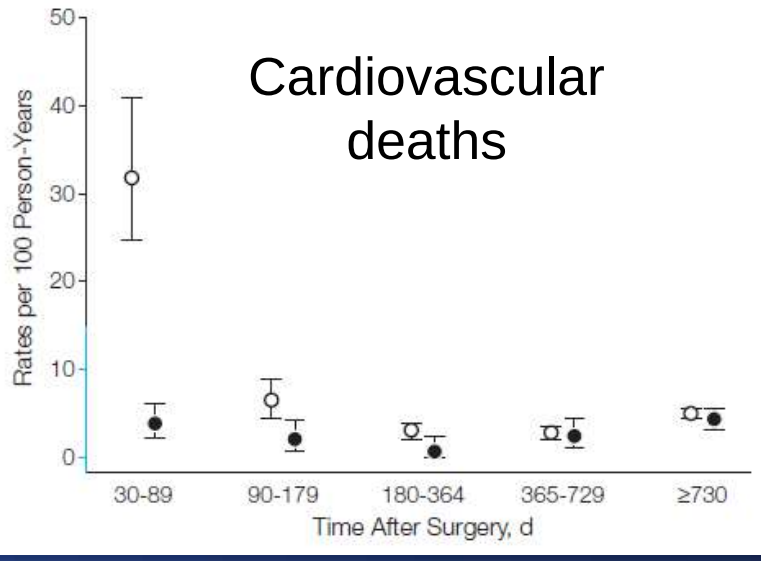
→ In low risk patients for bleeding
: anticoagulation as long as 6 months may be reasonable

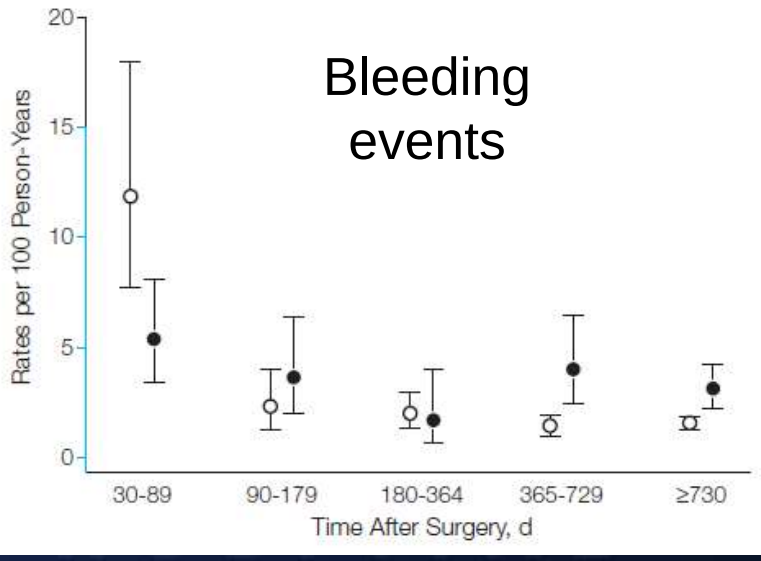
Nishimura RA et al. *Circulation* 2014;129:2440-92.

SAVR Registry data of extended anticoagulation duration









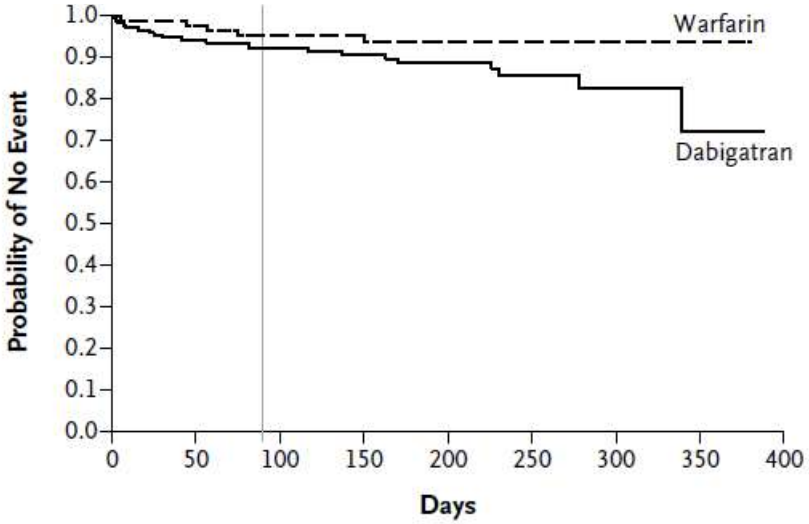
Charlotte Merie et al. *JAMA* 2012;308:2118-25.

How about NOAC?

No randomized trials comparing warfarin vs. NOAC, or aspirin vs. NOAC for TAVI

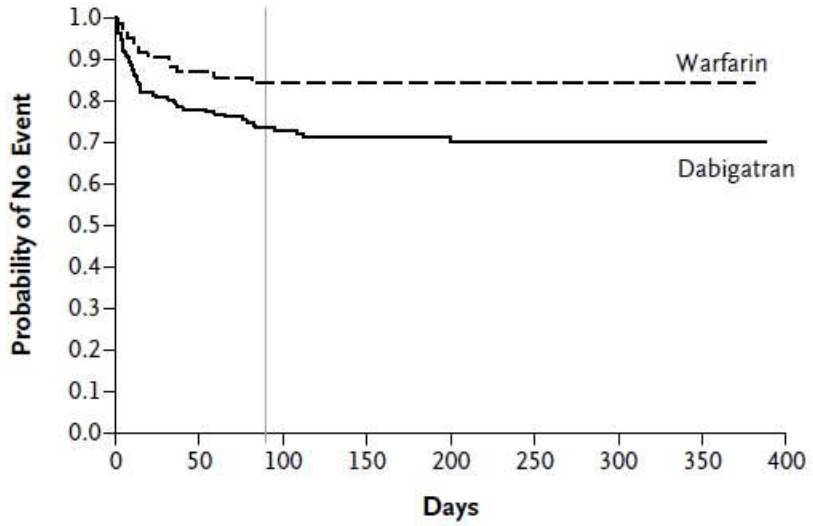
After the failure of the **RE-ALIGN** trial
(warfarin vs. dabigatran for mechanical mitral valve prosthesis),
rivaroxaban, apixaban, edoxaban have not been tested in patients with prosthetic heart valves and are not approved for that indication

First thromboembolic event



No. at Risk								
Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

First bleeding event



No. at Risk								
Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

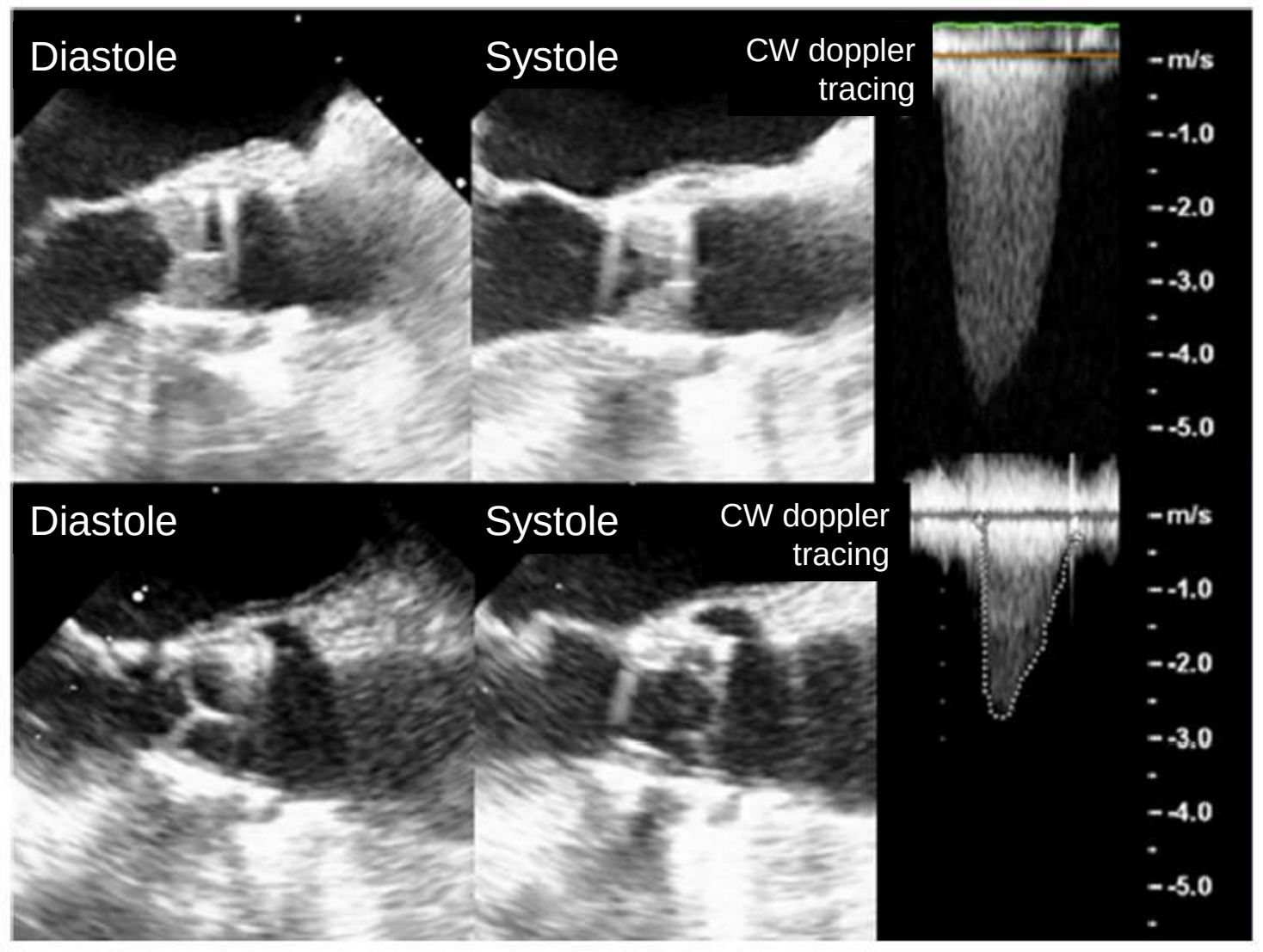
Is there any chance for TAV-recipients?

John WE et al. *N Engl J Med* 2013;369:1206-14.

Anecdotal reports of bioprosthetic thrombosis using VKA

Before anticoagulation

After anticoagulation



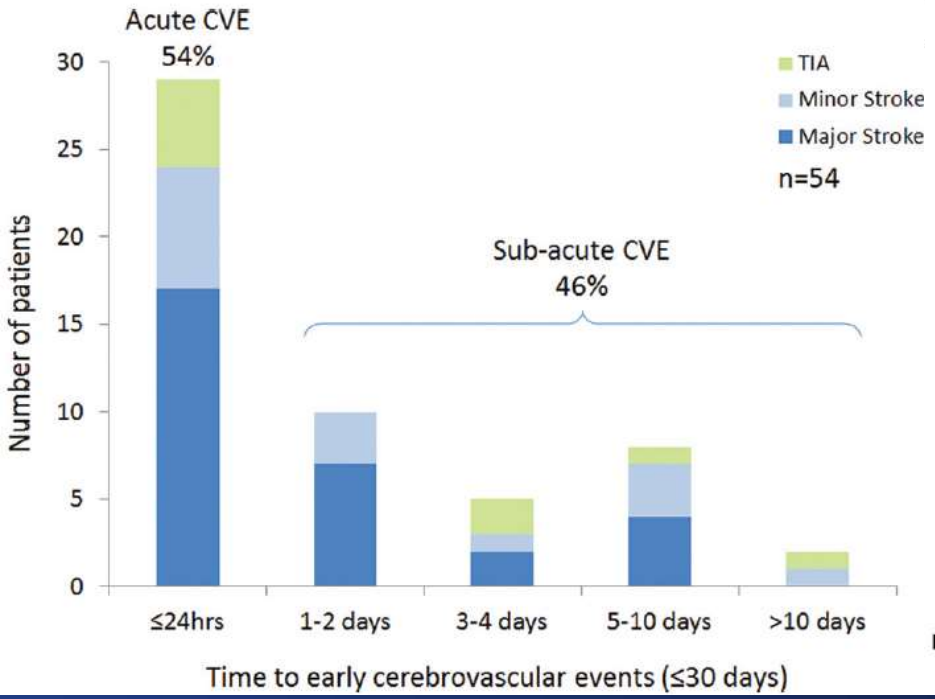
But, no reliable data on the use of NOACs even for the preventive purpose

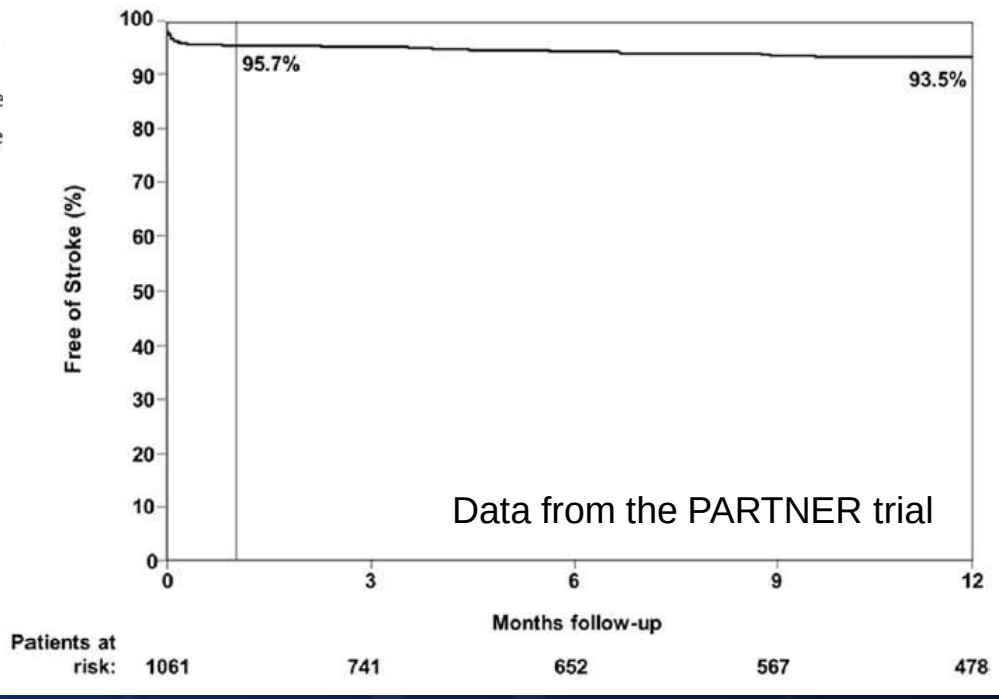
Descoux et al., *J Cardiothoracic Surgery* 2015;10:50.

Bright future for NOAC?

Some potential niche for NOACs in TAV-recients

1) Most ischemic events after TAVI : ischemic CVA
   atrial arrhythmias might play an important role in their occurrences
2) Majority of cerebrovascular events occurs in the initial phase of follow-up





3) Cardioembolic risk of TAV-recipient is very high, and ~30% of patients have chronic atrial fibrillation (even in sinus rhythm, mean $CHADS_2$ score is 3!!)

Promising for short-term NOACs for TAV-recipients?

Josep RC et al., *J Am Coll Cardiol* 2013;62:2349-59.

Lessons from the past

In a small RCT, DAPT vs. aspirin alone was compared after successful TAVI,

	Overall (n=79)	DAPT (n=40)	Aspirin (n=39)	P-value
30 days				
Cardiovascular death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	2 (5%)	0.49
Minor stroke	0	0	0	-
Transient ischemic attack	2 (3%)	1 (3%)	1 (3%)	0.75
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55
6 months				
Cardiovascular death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	0	0.49
Minor stroke	0	0	0	-
Transient ischemic attack	2 (3%)	1 (3%)	0	0.75
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55

Aspirin monotherapy might be adequate in elderly patients who do not have other compelling indications for the use of DAPT

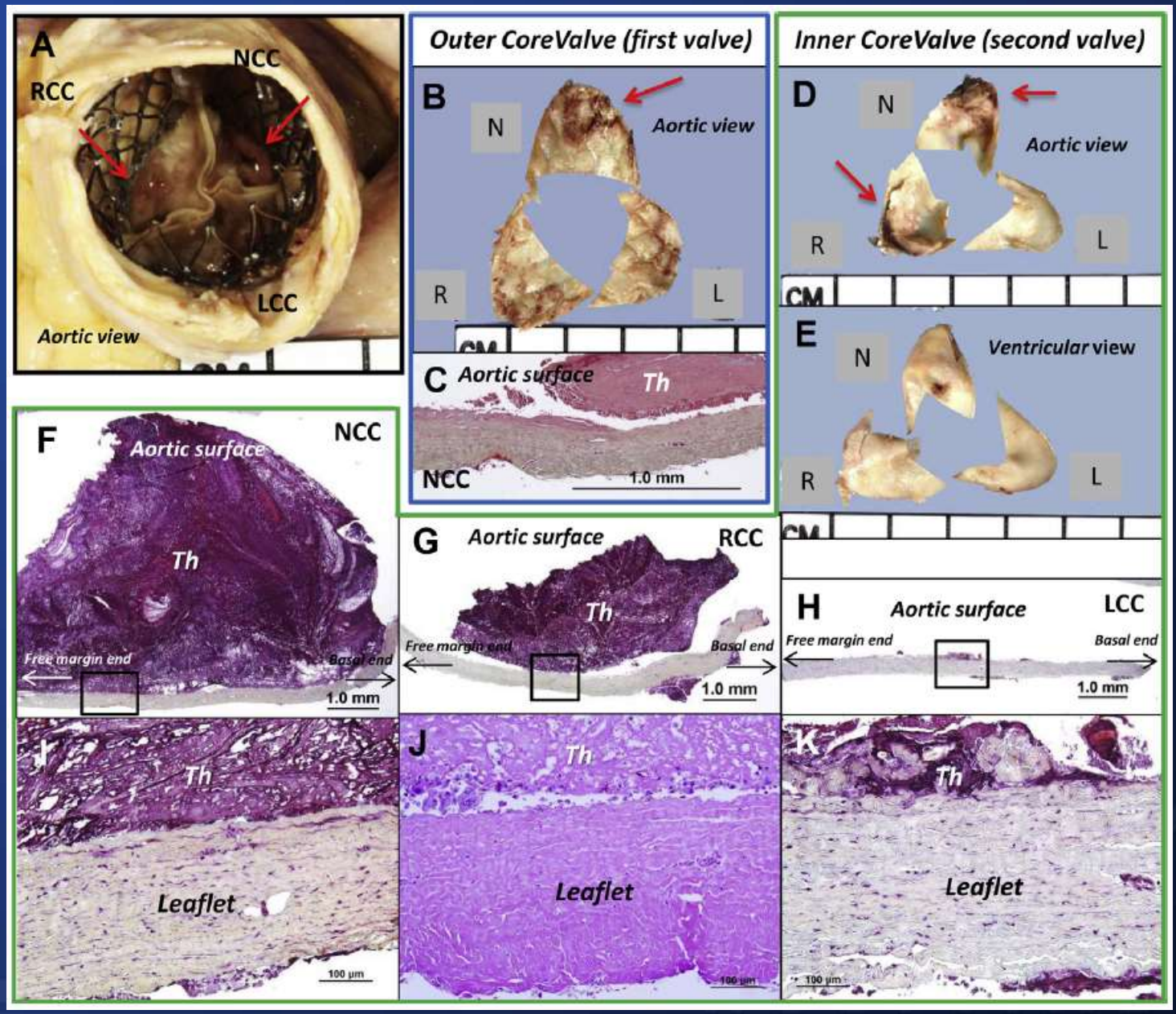
Gian PU et al., *Am J Cardiol* 2011;108:1772-6.

Strategy for now

- ✓ Subclinical leaflet thrombosis and its consequences
  (e.g., limited leaflet motion) have come to the focus as a major issue.
- ✓ NOACs may have a role for this interesting problem.
- ✓ But, to date, no tangible evidence is available.
  Before we can claim the evidence of routine anticoagulation,
  judicious patient selection is essential to expand the indication of NOAC
- ✓ Potential candidates for NOAC in TAV-recipient
  : reduced LV function but with sinus rhythm?
  : valve-in-valve implantation?

John CL et al., *N Engl J Med* 2015;373:1996-8.

TAV thrombosis in a case of valve-in-valve implantation



Eduardo De Marchena et al., *J Am Coll Cardiol* 2015;8:728-39.

Limitations of VKA therapy

VKA therapy has several limitations

- Slow onset/offset of action
- Narrow therapeutic window (INR range 2–3)
- Warfarin resistance
- Unpredictable response
- Numerous drug–drug interactions
- Numerous food–drug interactions
- Frequent dose adjust ments
- Routine coagulation monitoring

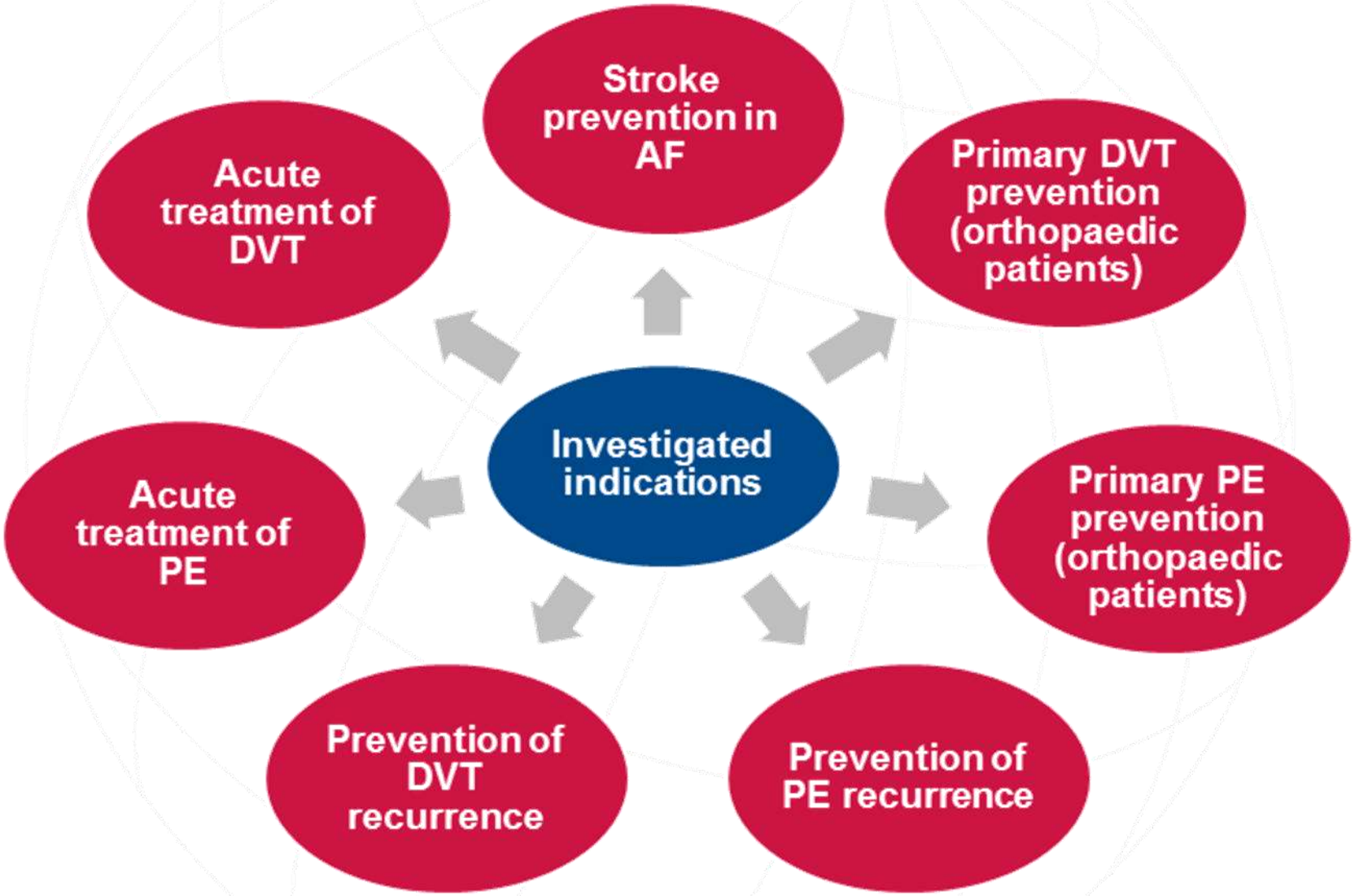
- *Ansell J et al. Chest 2008;133(Suppl);160S–98S; Umer Ushman MH et al. J Interv Card Electrophysiol 2008;22:129–37;*
- *Nutescu EA et al. Cardiol Clin 2008;26:69–87*

Advantages of NOACs

NOACs has several advantages

- High Specificity
- Fixed Daily Dose
- Good Efficacy and Tol erability Balance
- Predictable Phamacokinetics
- Fewer drug–drug interactions
- Fewer food–drug interactions
- NO Dose Adjustment
- No Routine Blood Lab Monitoring

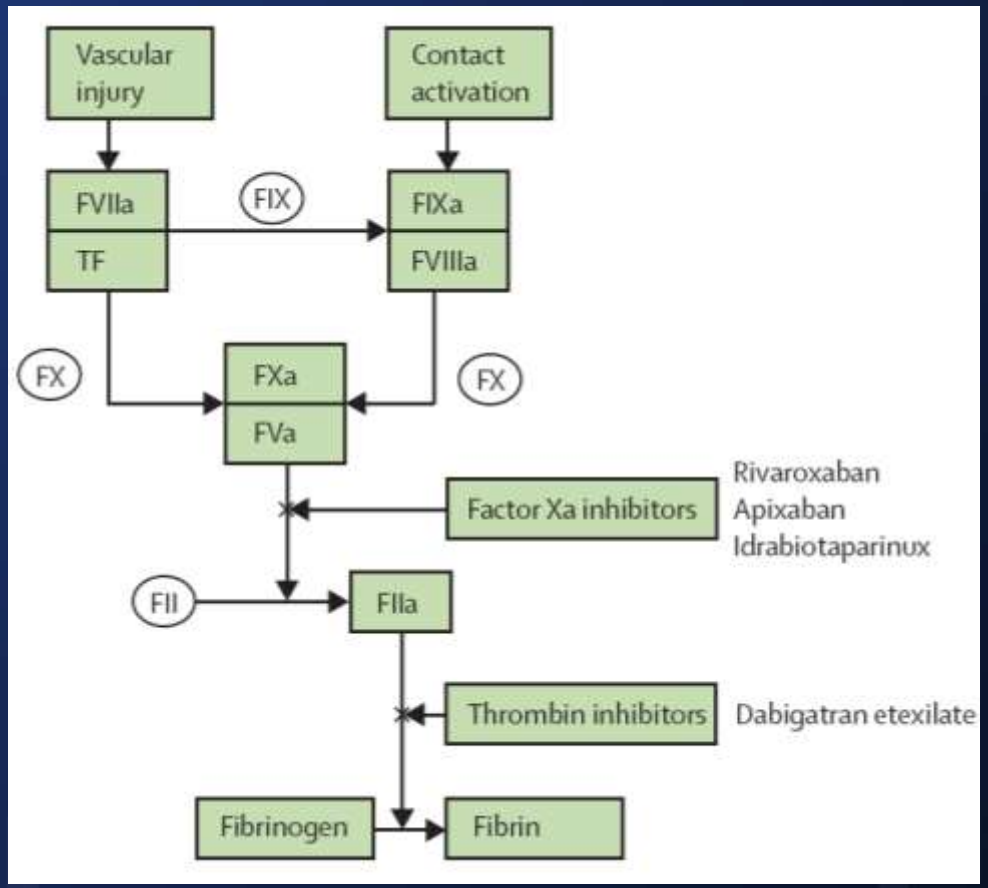
NOAC is Already with Us…



AF = atrial fibrillation; DVT = deep vein thrombosis; NOAC = novel oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolism

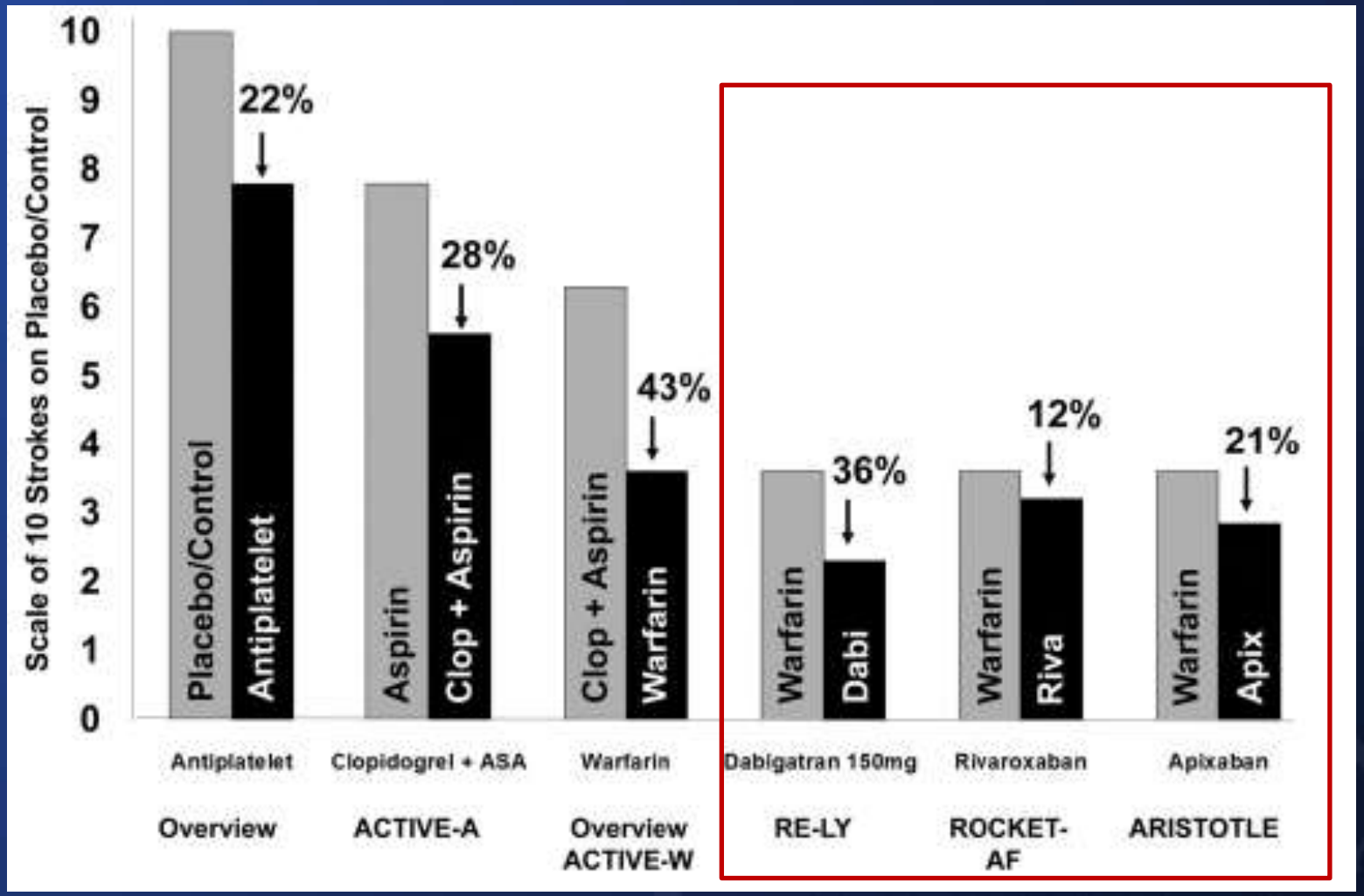
Clinical trials of NOAC in prevention of stroke in A.fib patients

- Dabigatran (RE-LY, 2009)
- Rivaroxaban (ROCKET-AF, 2011)
- Apixaban (ARISTOLE, 2011)



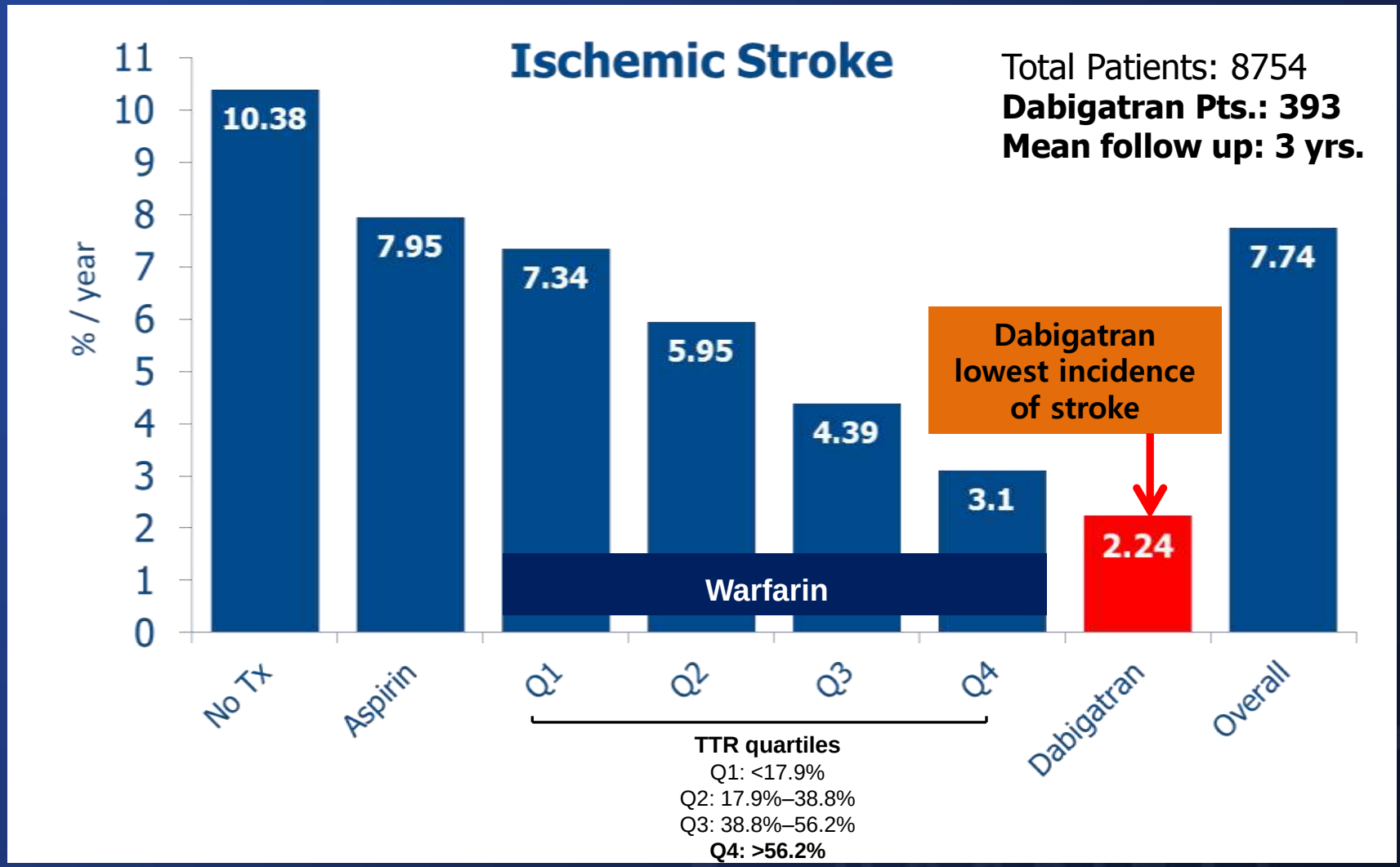
Hankey GJ et al. Lancet Neur 2010

Clinical trials of NOAC in prevention of stroke in A.fib patients



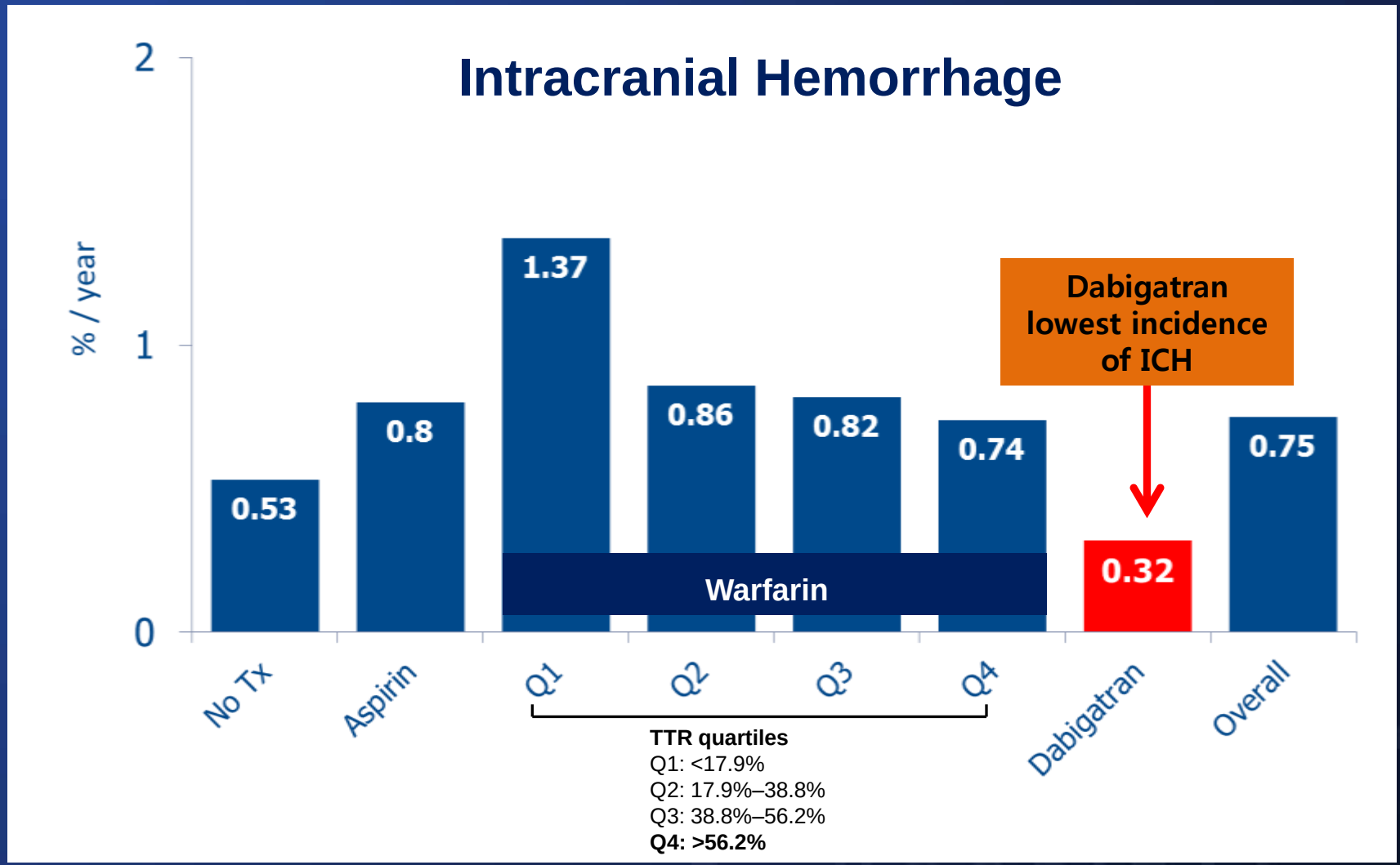
Christopher B. Granger, et al. Circulation. 2012;125:159-164

Incidence of ischemic stroke in A.fib Patients
- Hong Kong Registry



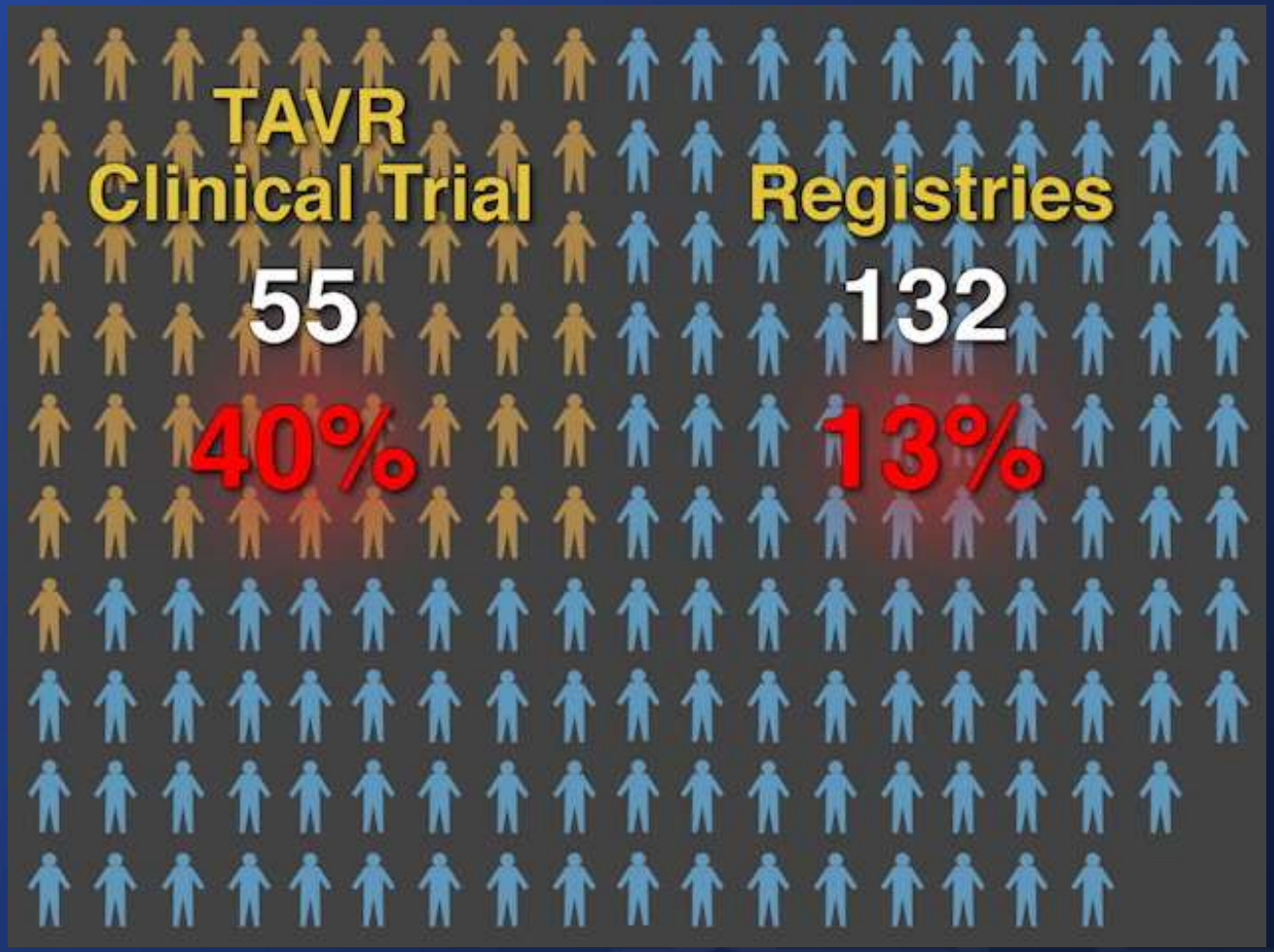
Ho CW et al. Stroke published online November 18, 2014;

Incidence of "ICH" in A.fib Patients
- Hong Kong Registry



Ho CW et al. Stroke published online November 18, 2014;

Subclinical leaflet thrombosis is more common than you think



Reduced leaflet motion is quite common in TAV-recipients
(mean CT acquisition time : about 6 mo. after the TAVI procedure)

R.R. Makkar et al., *N Engl J Med* 2015;373:2015-24.

Potential Future Antithrombotic Strategy in TAVI patient

Table 6 Possible Future Antithrombotic Strategies for TAVI That Have Not Yet Been Evaluated

	Potential Advantages	Potential Disadvantages
Procedural		
Bivalirudin	Predictable antithrombotic response; can be used in heparin-induced thrombocytopenia.	Quick onset of action; short half-life. Not reversible with protamine.
Argatroban	Can be used in heparin-induced thrombocytopenia or renal dysfunction (metabolized by liver).	Longer half-life than bivalirudin and requires 1–3 h to achieve steady-state.
Aptamers	Completely reversible; partly reversible.	Modest experience in PCI to date.
Post-procedural		
Apixaban or rivaroxaban	More rapid onset and predictable levels of anticoagulation as compared with warfarin.	No antidote.
Dabigatran	More rapid onset and predictable levels of anticoagulation as compared with warfarin.	No antidote. Twice daily dosing.
Prasugrel	More rapid onset, higher degrees of platelet inhibition, and less interpatient variability as compared with clopidogrel.	Unknown if higher degrees of platelet inhibition are beneficial post-TAVI. Contraindicated in patients with history of stroke or TIA.
Ticagrelor	More rapid onset, higher degrees of platelet inhibition, and less interpatient variability as compared with clopidogrel.	Unknown if higher degrees of platelet inhibition are beneficial post TAVI. Twice daily dosing. Dyspnea.

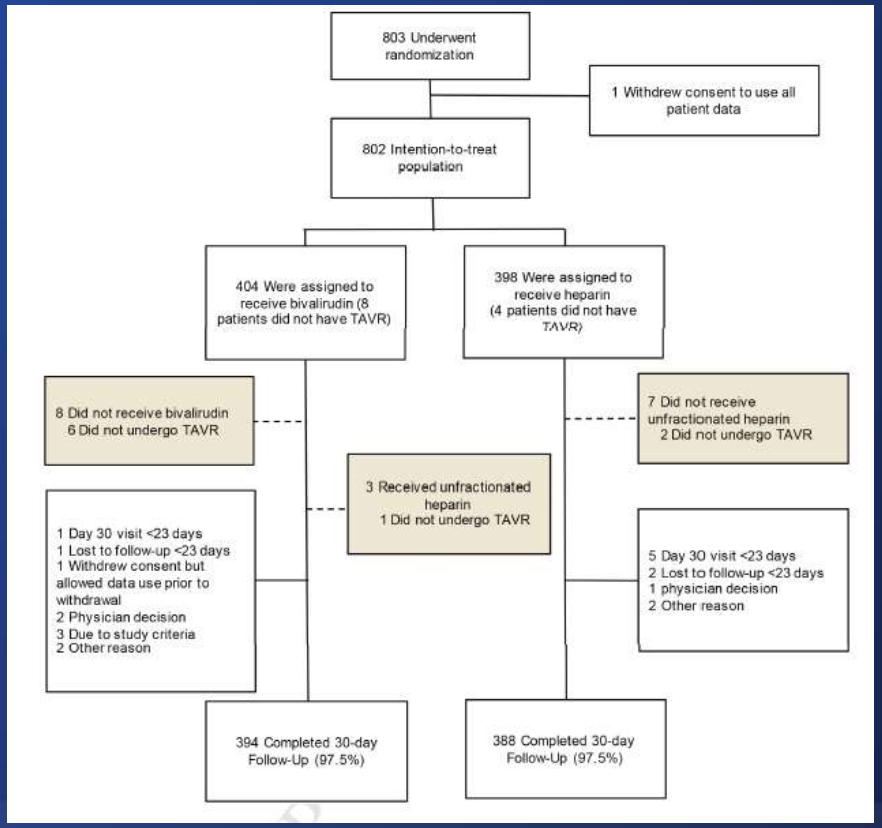
AF = atrial fibrillation; CHADS2 = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TAVI = transcatheter aortic valve implantation.

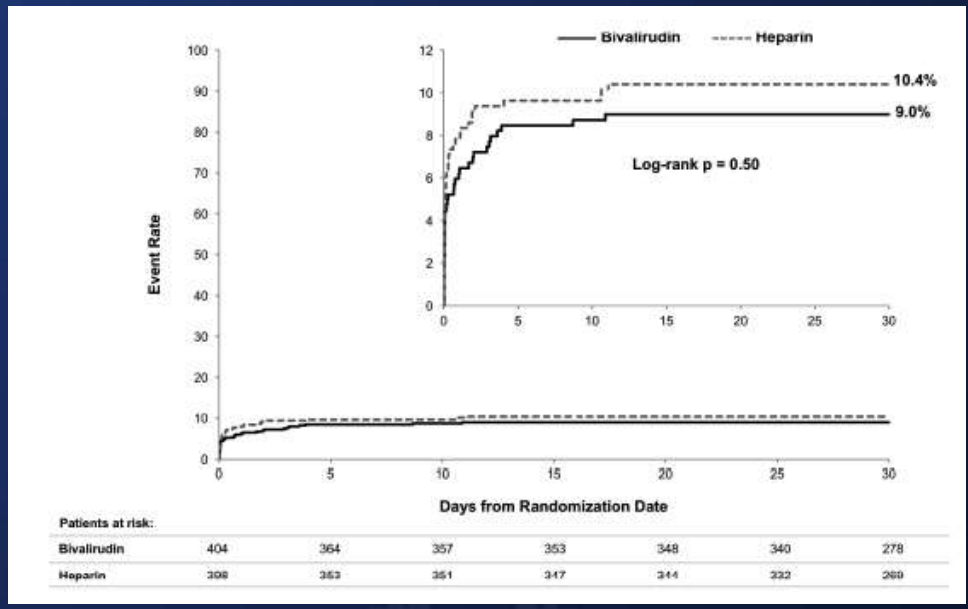
J Am Coll Cardiol. 2013;62:2349-2359

Area of Uncertainty
- Heparin vs Bivalirudin During TF-TAVI

802 patients with aortic stenosis undergoing TF-TAVI
Randomized 1:1 into Bivalirudin vs. Unfractionated heparin
Primary Endpoint

- **Major bleeding (48hrs or before discharge)**
- **Net adverse clinical events (death, MI, stroke, major bleeding) at 30-day**





Secondary endpoint at 30 days				
Major bleeding (BARC ≥3b)	36 (8.9)	42 (10.6)	0.84 (0.55–1.29)	0.43
Major adverse cardiovascular events	31 (7.7)	32 (8.0)	0.95 (0.59–1.53)	0.85
Death	19 (4.7)	19 (4.8)	0.99 (0.53–1.83)	0.96
Myocardial infarction	2 (0.5)	7 (1.8)	0.28 (0.06–1.35)	0.11
Stroke	14 (3.5)	11 (2.8)	1.25 (0.58–2.73)	0.57

Dangas et al. J Am Coll Cardiol. 2015, Accepted manuscript

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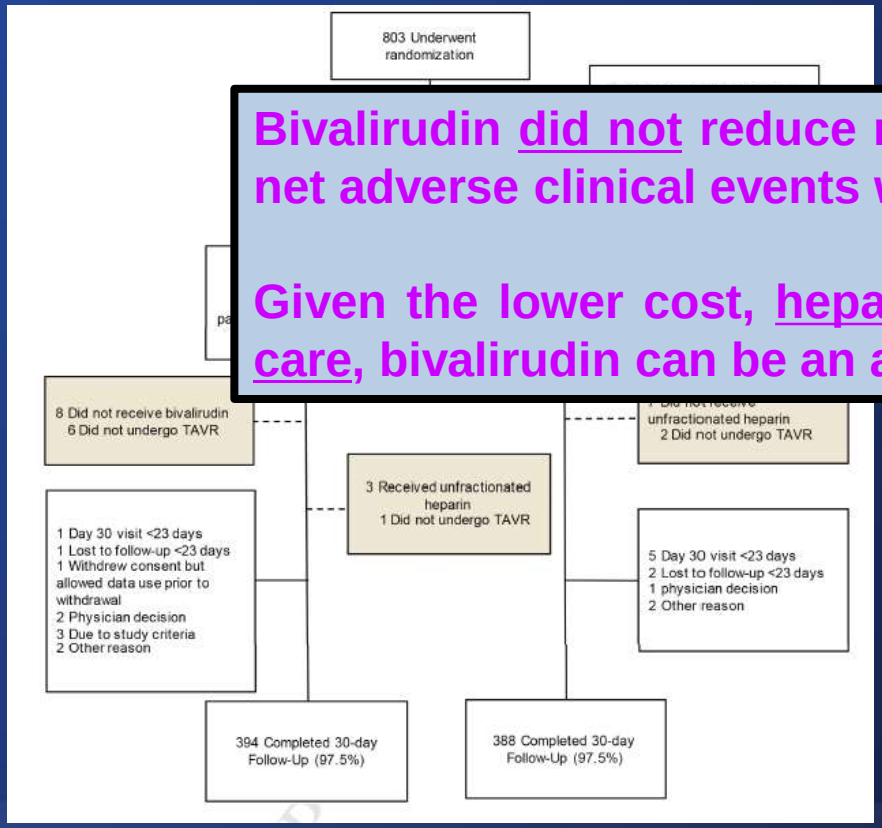

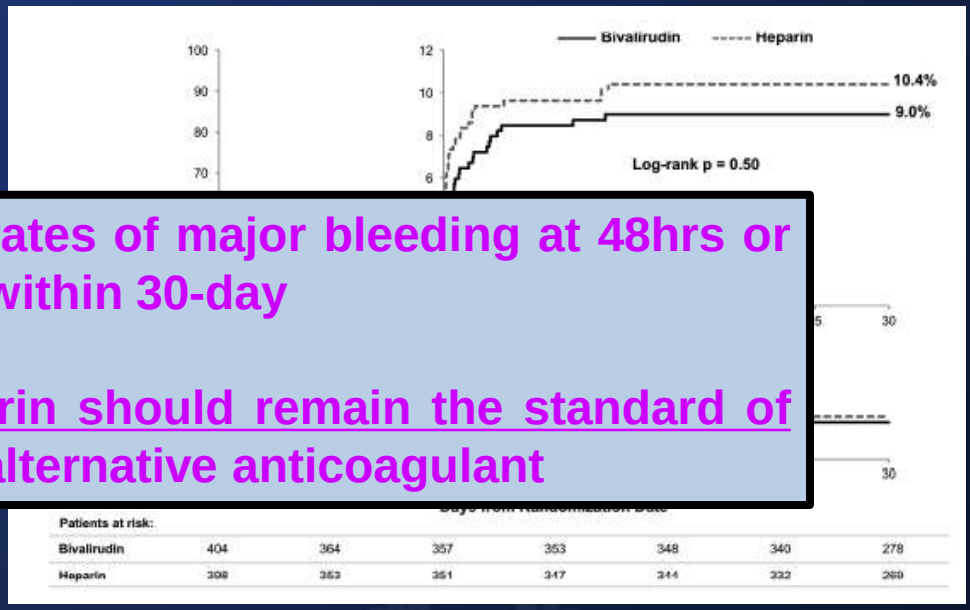

Bivalirudin did not reduce rates of major bleeding at 48hrs or net adverse clinical events within 30-day

Given the lower cost, heparin should remain the standard of care, bivalirudin can be an alternative anticoagulant

Secondary endpoint at 30 days				
Major bleeding (BARC ≥3b)	36 (8.9)	42 (10.6)	0.84 (0.55–1.29)	0.43
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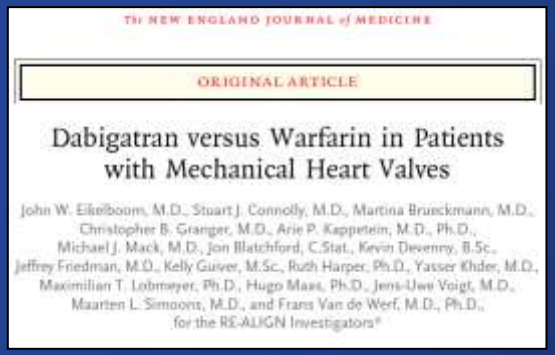
Dangas et al. J Am Coll Cardiol. 2015, Accepted manuscript

Post-procedural Anticoagulation After SAVR

RE-ALIGN (Dabigatran)


THE NEW ENGLAND JOURNAL of MEDICINE

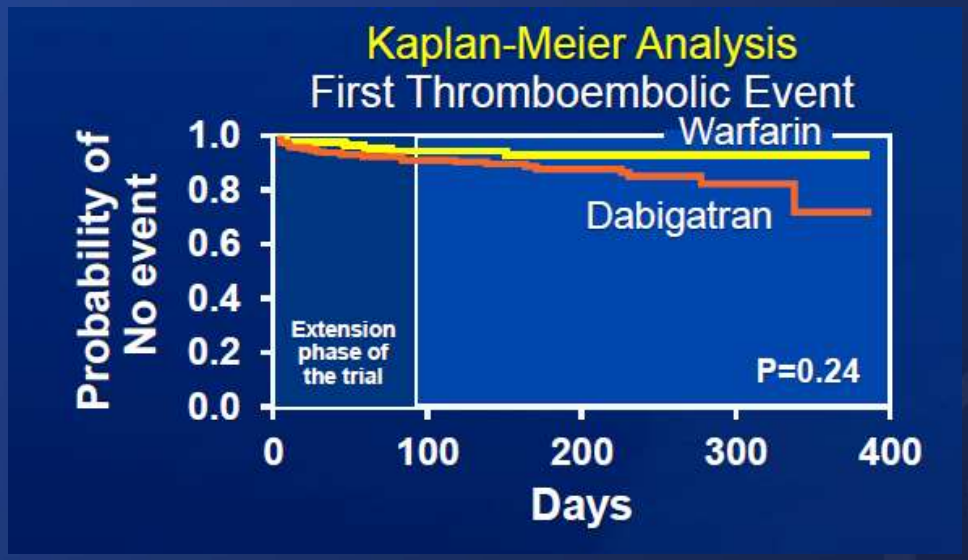
ORIGINAL ARTICLE

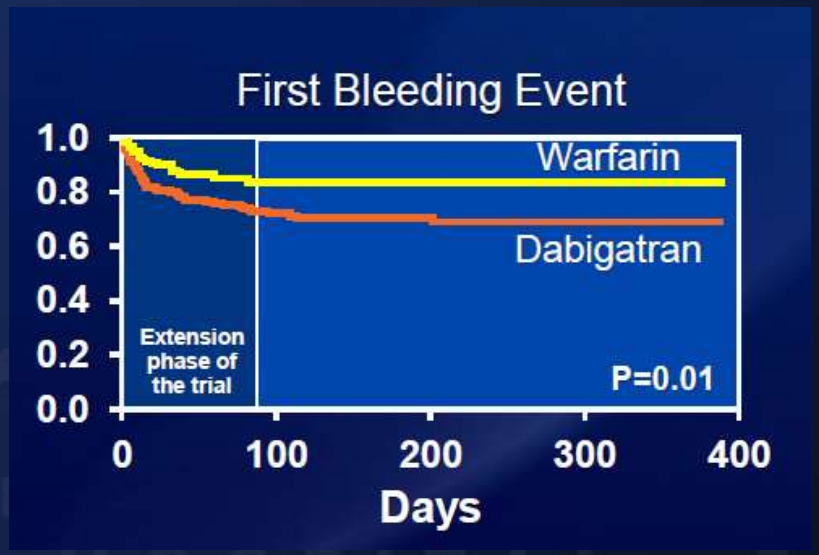
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*

"NOT" TAVI patients
(Surgical Valvular Replacement Patients)

Dabigatran was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.



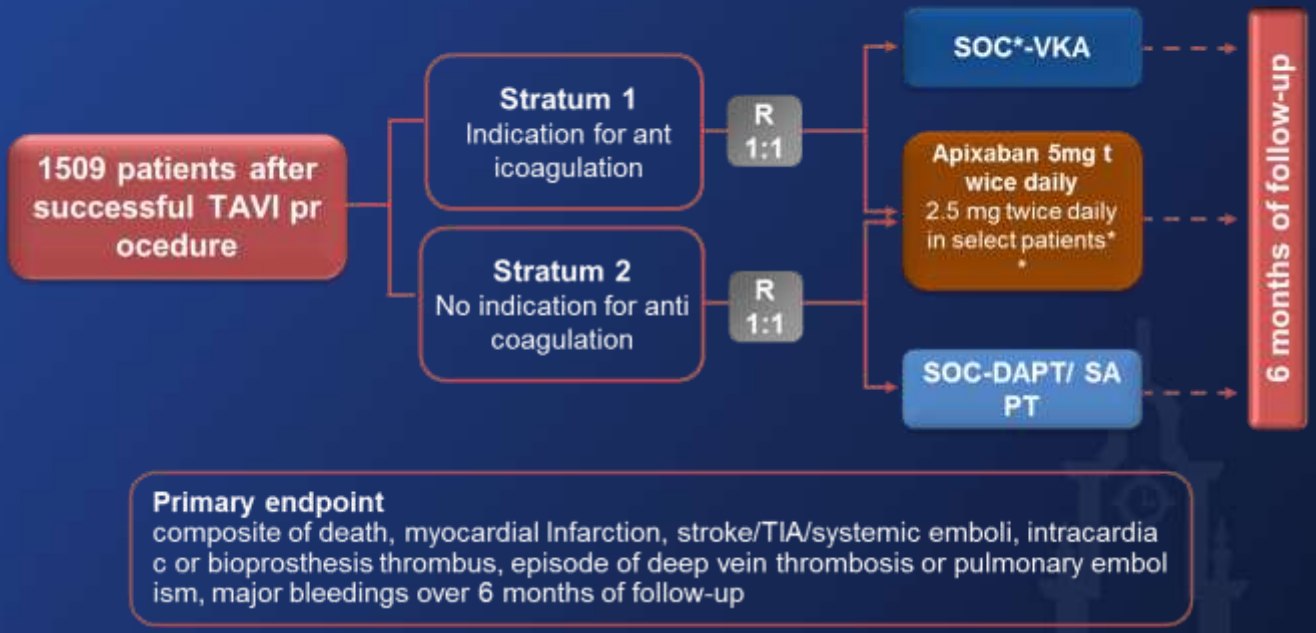


NEJM, 2013 Sep, 26; 369:1206-14

Area of Uncertainty
- Anticoagulation After TAVI in A.fib

Potential Role of NOAC

ATLANTIS (Apixaban) - Ongoing

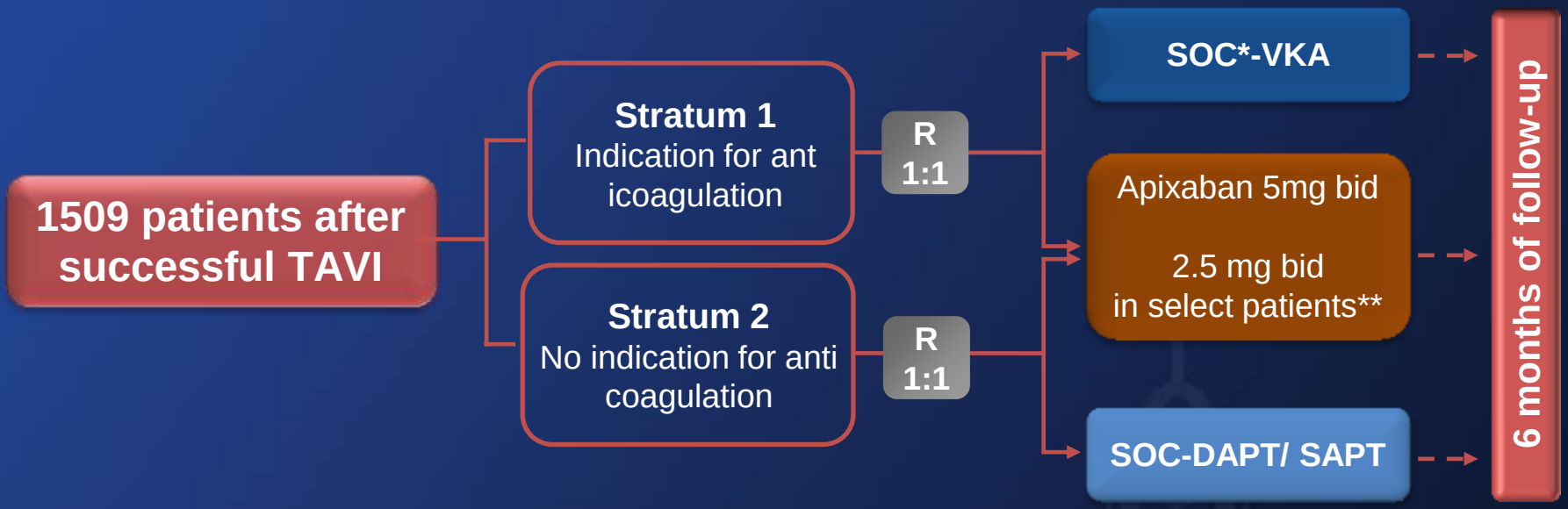


Clear Advantages of NOAC in Stroke Prevention in non-TAVI population has already well-validated.

Whether NOAC will show Similar Benefit in TAVI population still be clarified in the ATALANTIS trial.

Post-procedural Anticoagulation After TAVI

ATLANTIS (Apixaban) - Ongoing



Primary endpoint
composite of death, myocardial Infarction, stroke/TIA/systemic emboli, intracardiac or bioprosthesis thromb us, episode of deep vein thrombosis or pulmonary embolism, major bleedings over 6 months of follow-up

Post-procedural Anticoagulation After TAVI

GALILEO (Rivaroxaban) - Ongoing

Objective: Death or first adjudicated thromboembolic event (DTE)

Design: Randomized, Parallel Assignment, Open Label

Rivaroxaban 10mg + ASA 75-100mg for 3 months followed by rivaroxaban 10mg alone thereafter	**VS.**	**Clopidogrel 75mg + ASA 75-100mg for 3 months, followed by ASA 75-100mg alone**

Primary Outcome: Composite of all-cause death, stroke, myocardial infarction, valve thrombosis, pulmonary embolism, deep vein thrombosis and systemic embolism. Safety endpoint is life threatening, disabling or major bleeding events

Exclusion Criteria: Atrial fibrillation (AF)