How to Manage Anticoagulant Therapy

After Valve Replacement

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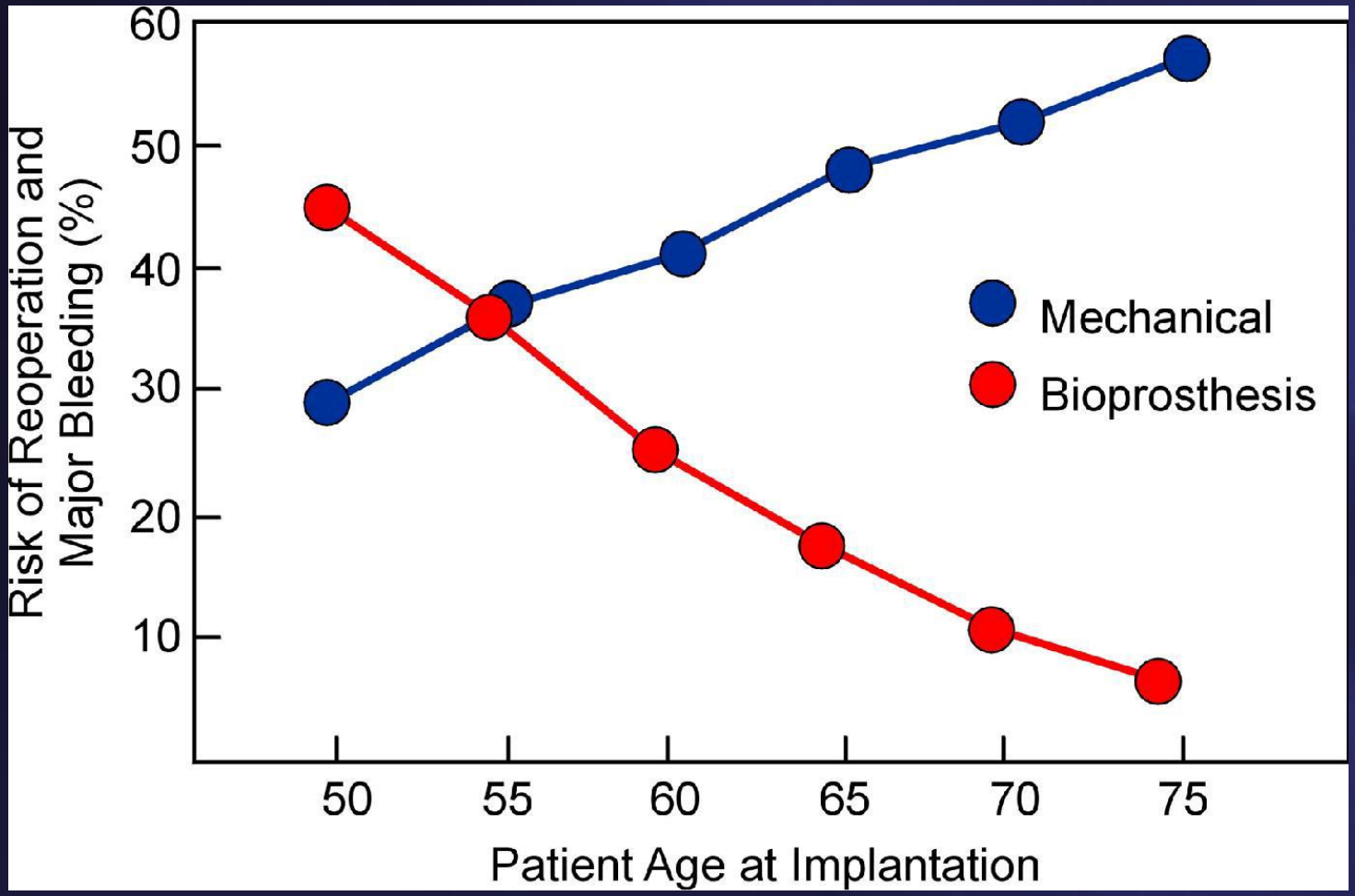
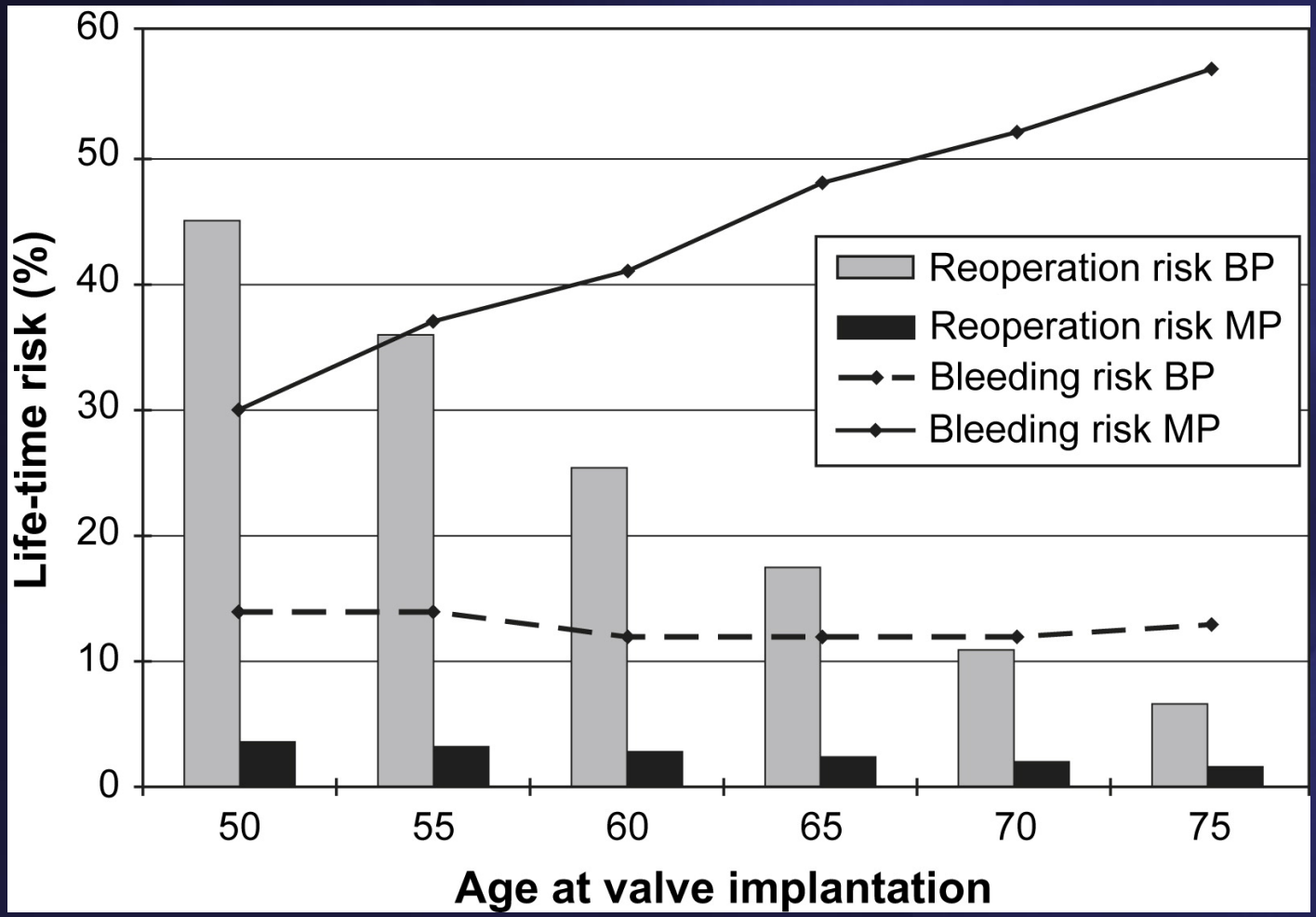
Aortic Valve Prosthesis

Risk of Major Bleeding and Reoperation



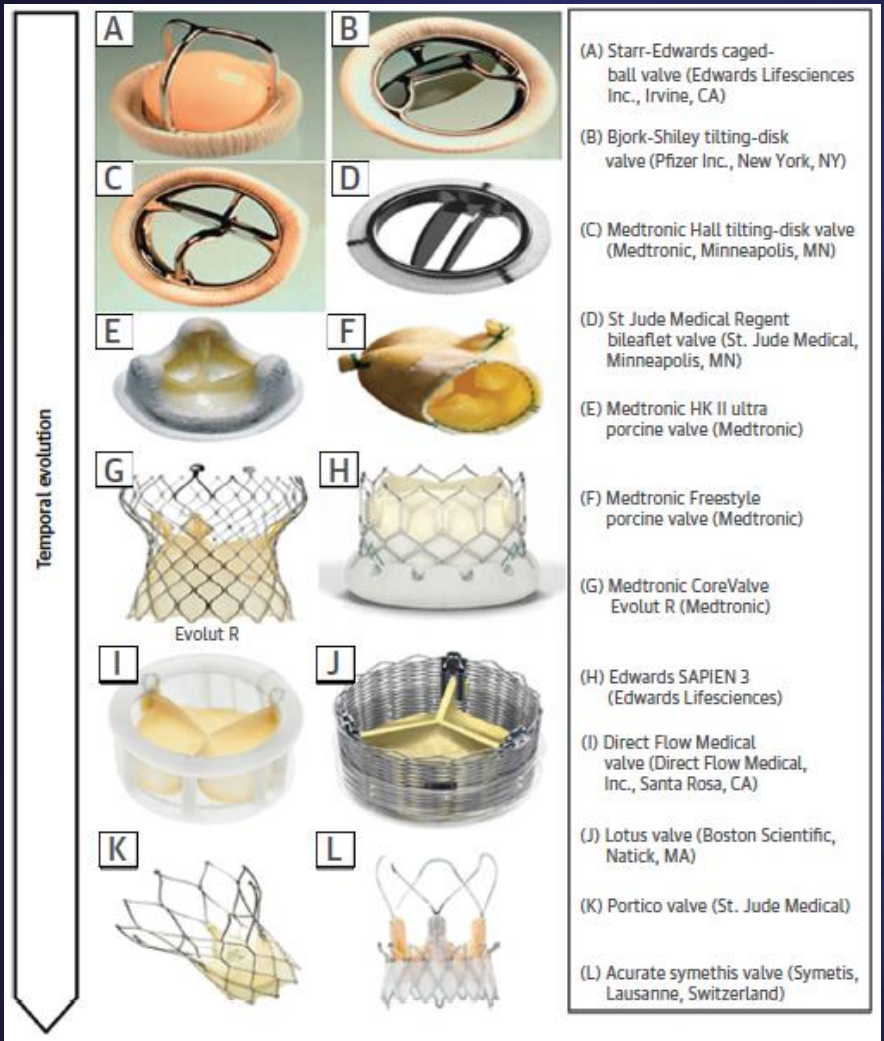
Van Geldorp MWA et al. J Thorac Cardiovasc Surg 2009;137:881– 6

Aortic Valve Prosthesis
Reoperation and Bleeding Risks



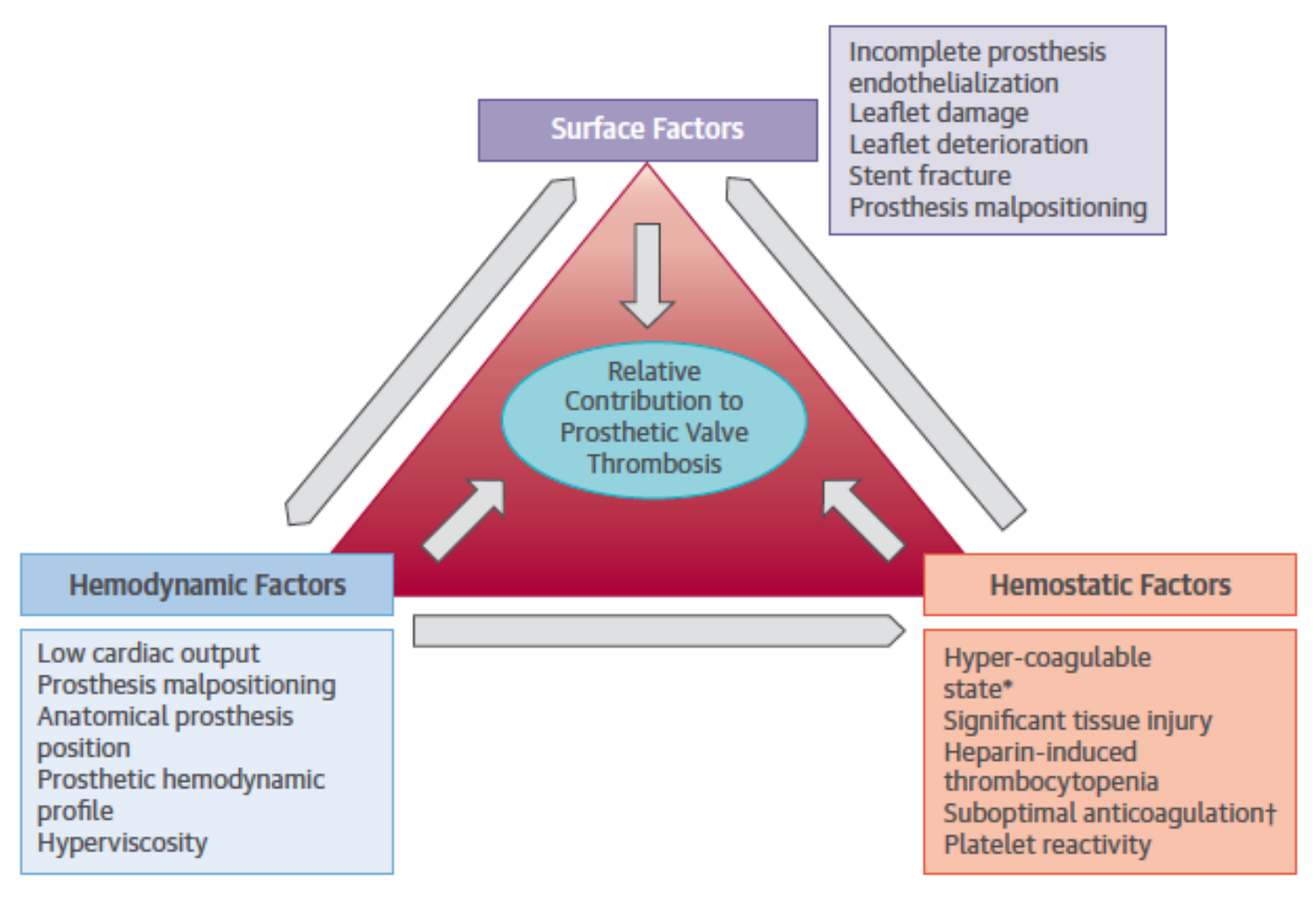
Van Geldorp M et al. J Thorac Cardiovasc Surg 2009;137:881-886

Prosthetic Heart Valve
Temporal Evolution



Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886

Prosthetic Valve Thrombosis
Mechanisms



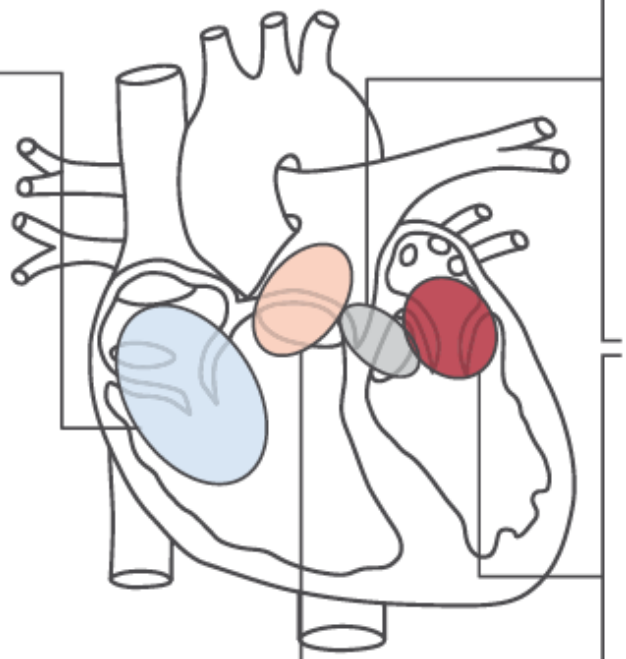
Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886

Prosthetic Valve Thrombosis
Pathophysiological Factors

Potential mechanism of prosthetic valve thrombus by anatomical location

Right-sided heart valves
Clotting pathway > platelet pathway

Left-sided heart valves
platelet pathway > clotting pathway



TRICUSPID VALVE

1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning

PULMONIC VALVE

1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
3. Surface factors
   - Valve frame fracture

AORTIC VALVE

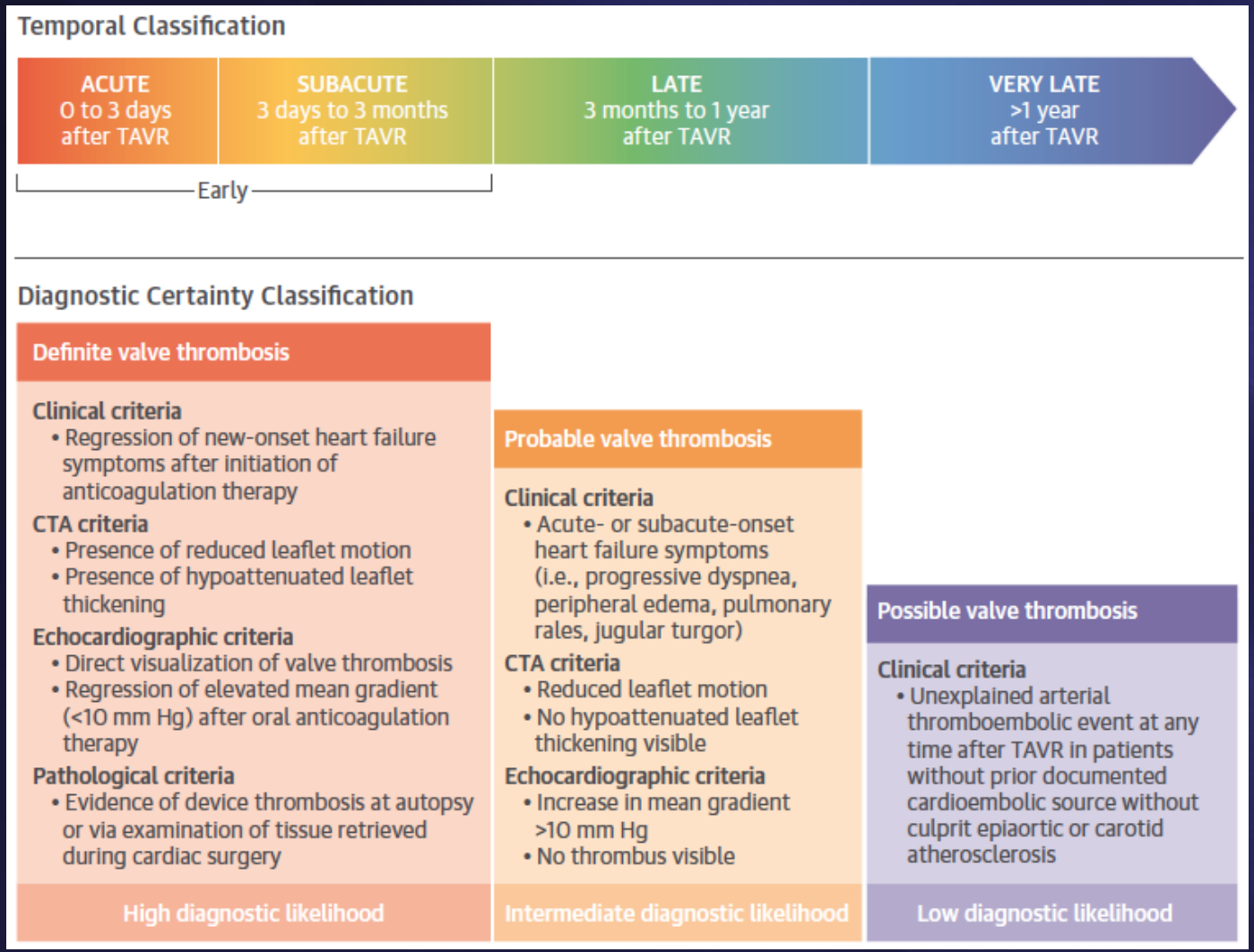
1. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
2. Hemostatic factors
   - Tissue injury
   - Prosthesis malpositioning
3. Hemodynamic factors
   - Local blood flow turbulences
   - Incomplete apposition

MITRAL VALVE

1. Hemodynamic factors
   - Relatively slow blood flow in case of AF, atrial dilation or low LV output.
   - Local blood flow turbulences
   - Incomplete apposition
2. Hemostatic factors
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
   - Leaflet injury

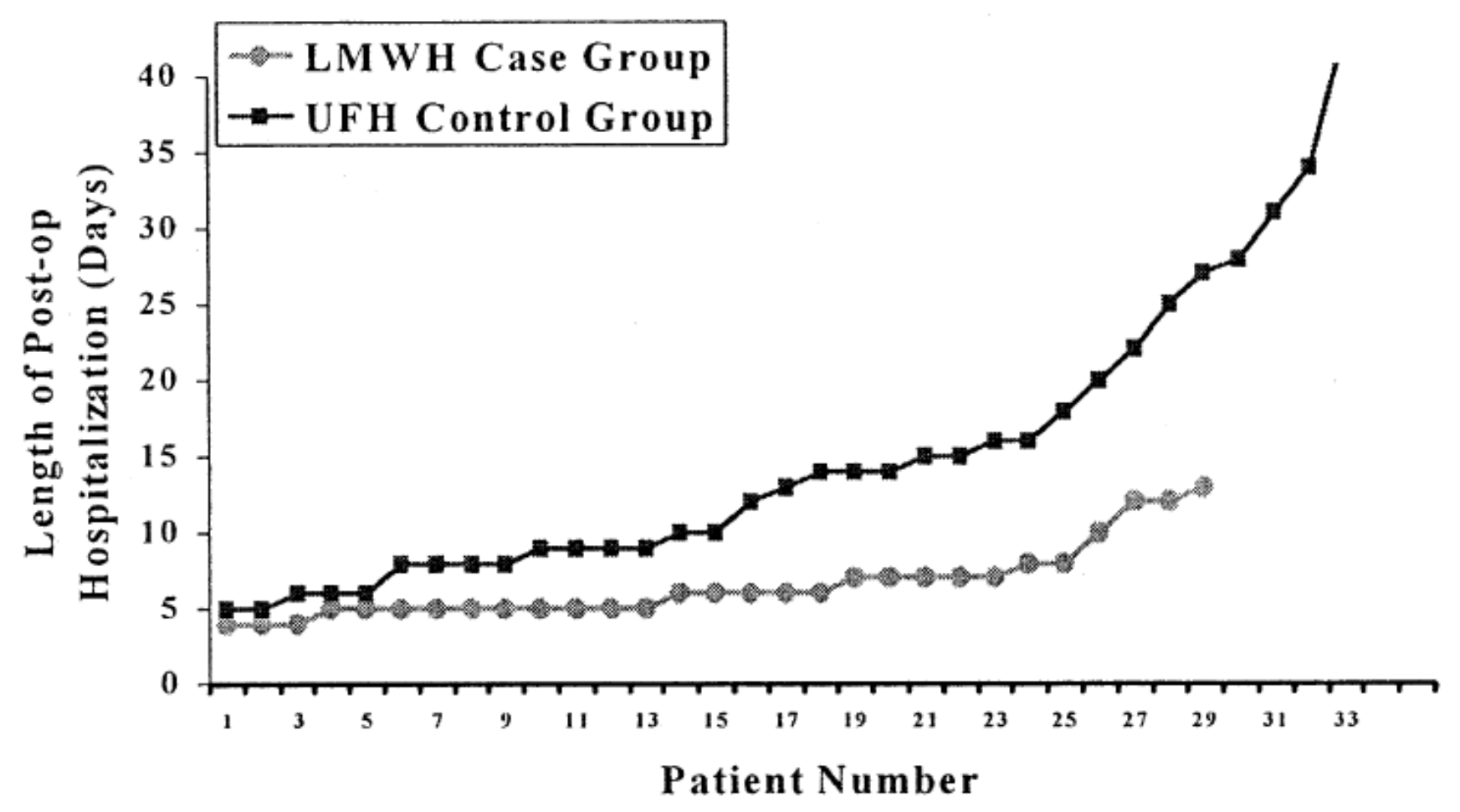
Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886

Prosthetic Valve Thrombosis
Classification



Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886

Mechanical Valve Replacement
Initiation of Anticoagulation



Fanikos J et al. Am J Cardiol 2004;93:247– 250

Biological Valve Replacement
Initial Anticoagulation Regimen

	Total population		
	Warfarin (n = 167)	Aspirin (n = 161)	p-Value
Thromboembolic complications			
MI (n(%))	2 (1.2%)	5 (3.1%)	0.267
DVT (n(%))	0	0	1.000
TCI/Stroke (n(%))	8 (4.8%)	6 (3.7%)	0.602
Other thromboembolic complication (n%)	1[b] (0.6%)	1[a] (0.6%)	1.000
Total thromboembolic events (n(%))	11 (6.6%)	12 (7.5%)	0.830

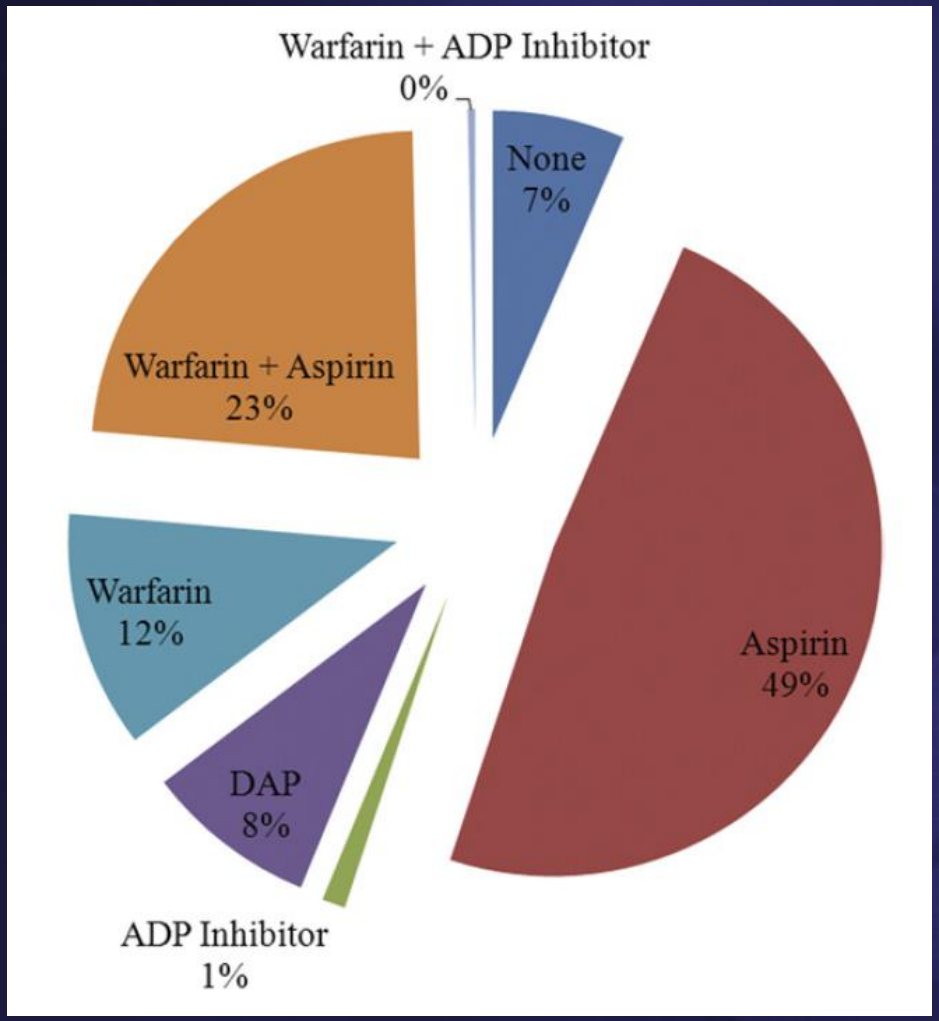
Multivariate analysis of factors associated with major bleeding events.

	OR (95% CI)	p-Value
Age	1.04 (0.94–1.14)	0.452
Hypertension	7.80 (0.96–63.08)	0.054
Gender	0.19 (0.02–1.57)	0.124
Diabetes	0.67 (0.13–3.33)	0.621
Aspirin	2.14 (0.42–10.79)	0.358
Warfarin	5.18 (1.06–25.43)	0.043

Randomized Trial
Warfarin vs Aspirin
3 months postoperative

Rafiq S et al. Thrombosis Research 2016 (in press)

Biological Valve Replacement
Initial Anticoagulation Regimen



STS Database

Brennan JM et al. J Am Coll Cardiol 2012;60:971–7

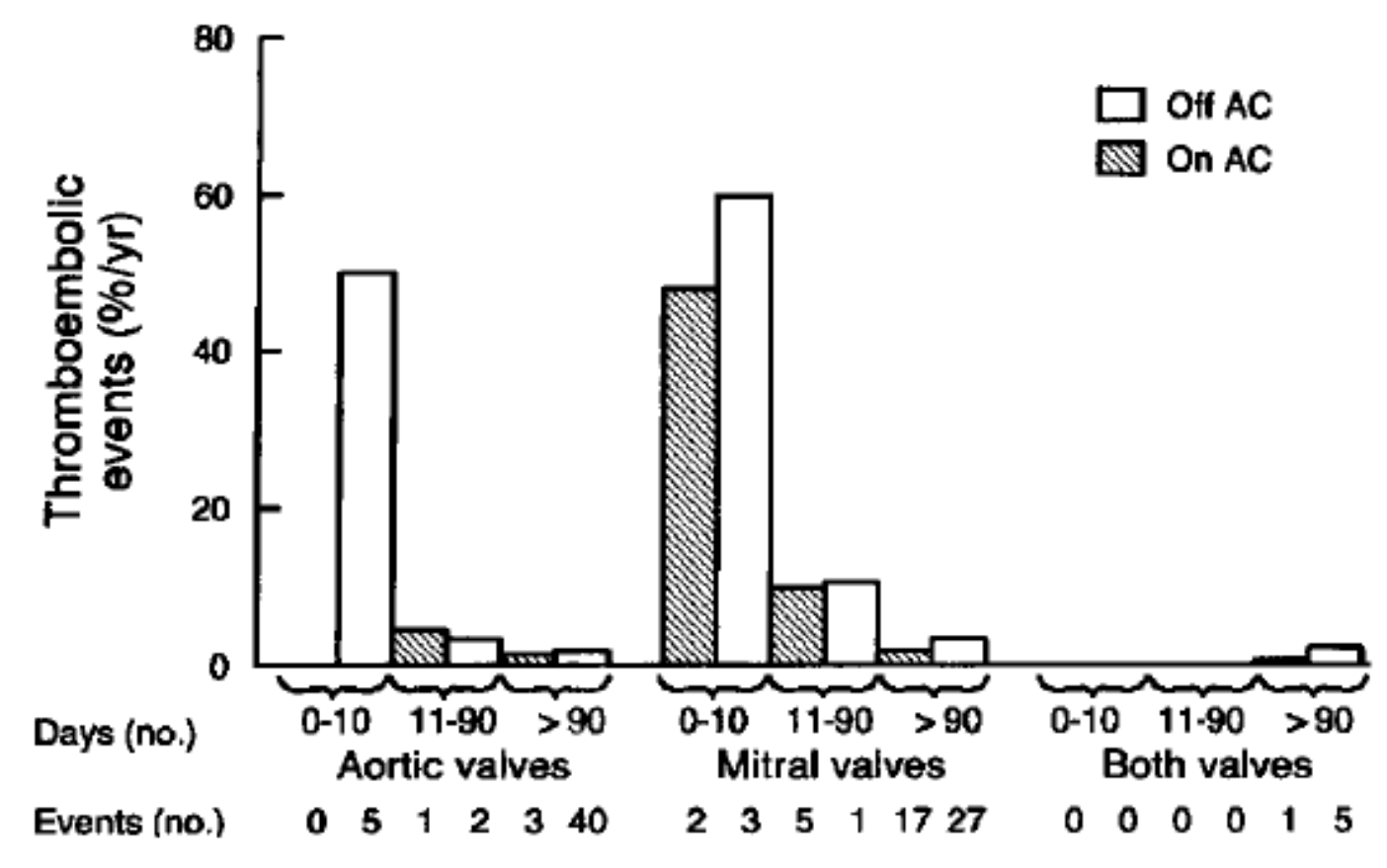
Biological Valve Replacement
Initial Anticoagulation Regimen

Table 2 Outcomes at 3 Months With Anticoagulant Strategies in the Overall Population of Patients Receiving Aortic Valve Bioprostheses

	Unadjusted 3-Month Incidence (%)			Adjusted RR (95% CI)	
	Aspirin-Only (n = 12,457)	Warfarin-Only (n = 2,999)	Aspirin + Warfarin (n = 5,972)	Warfarin-Only vs. Aspirin-Only	Warfarin + Aspirin vs. Aspirin-Only
Death	3.0	4.0	3.1	1.01 (0.80–1.27)	0.80 (0.66–0.96)
Embolism	1.0	1.0	0.6	0.95 (0.61–1.47)	0.52 (0.35–0.76)
Bleeding	1.0	1.4	2.8	1.23 (0.85–1.79)	2.80 (2.18–3.60)

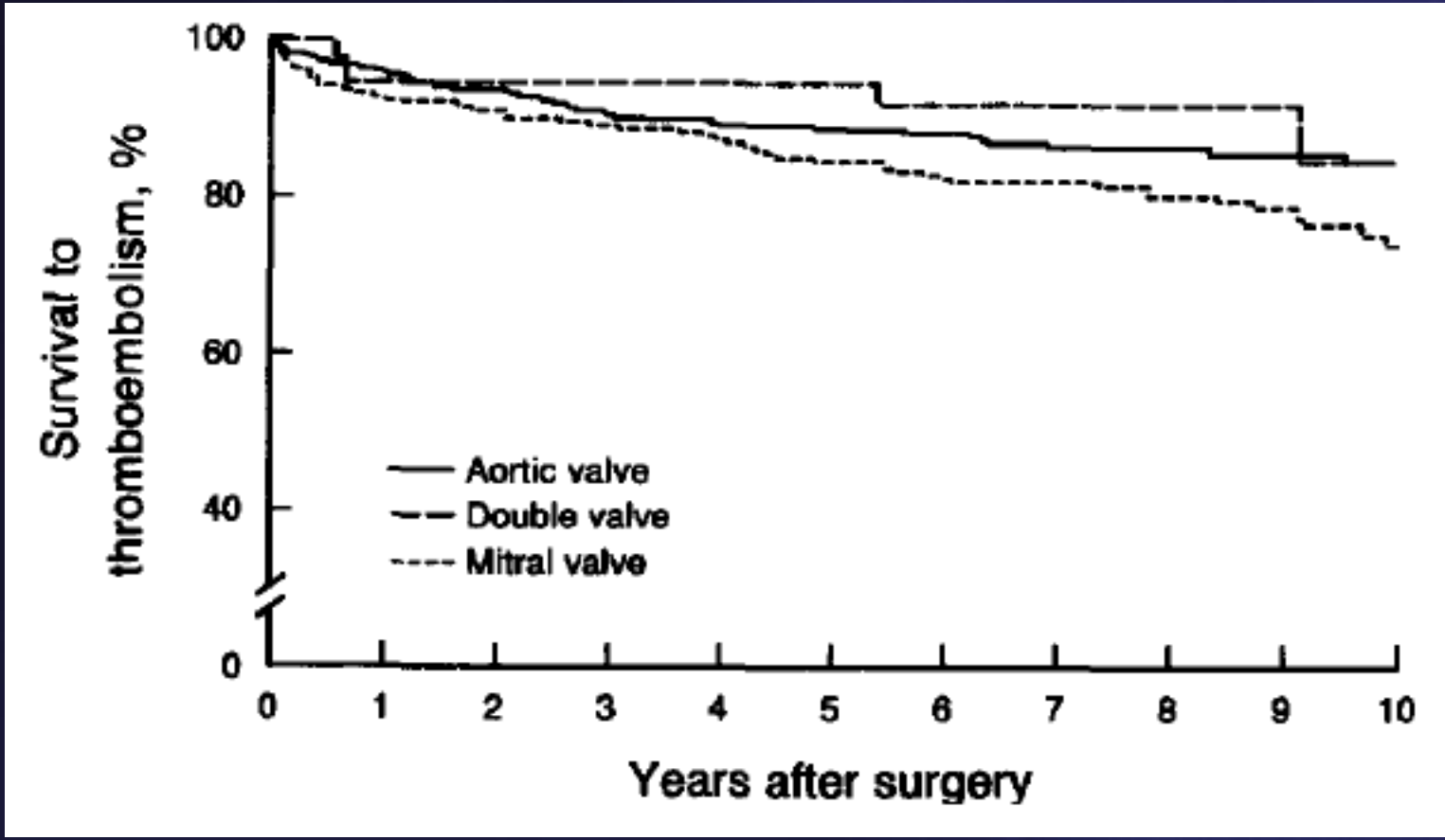
Brennan JM et al. J Am Coll Cardiol 2012;60:971–7

Biological Valve Replacement
Thromboembolic Risk



Heras M et al. J Am Coll Cardiol 1995;25:1111–1119

Biological Valve Replacement
Thromboembolic Risk



Heras M et al. J Am Coll Cardiol 1995;25:1111–1119

Valve Replacement
Anticoagulation Regimen

Table 2 Current recommendations for anti-thrombotic therapy following surgical prosthetic valve replacement

	Site	Mechanical prosthesis			Bioprosthesis	
		Target median INR		Aspirin	3 post-operative months	>3 post-operative months
		No risk factors[a]	Risk factors[a]			
ESC/EACTS guidelines[14]	Aortic	2.5	3.0 or 3.5[b]	Selected[c]	Aspirin (IIa) VKA (IIb)	-
	Mitral	3.0 or 3.5[b]	3.0 or 3.5[b]	Selected[c]	VKA	-
AHA/ACC guidelines[15]	Aortic	2.5	3.0	Systematic	Aspirin (IIa) VKA (IIb)	Aspirin
	Mitral	3.0	3.0	Systematic	VKA + aspirin	Aspirin
ACCP consensus[16]	Aortic	2.5	2.5	If low bleeding risk	Aspirin	Aspirin
	Mitral	3.0	3.0	If low bleeding risk	VKA + aspirin	Aspirin

[a]Risk factors include AF, previous thromboembolic event, left ventricular dysfunction, hypercoagulable state and for AHA/ACC Guidelines older generation prosthesis.
[b]According to whether prosthesis is at low or intermediate thrombogenicity (high-thrombogenicity prostheses are not represented here).
[c]Patients with concomitant atherosclerotic disease or with thromboembolism despite adequate INR.

Iung B, Rodes—Cabau J. Eur heart J 2014;35:2942-2949

Mechanical Valve Replacement
Bridging Anticoagulation

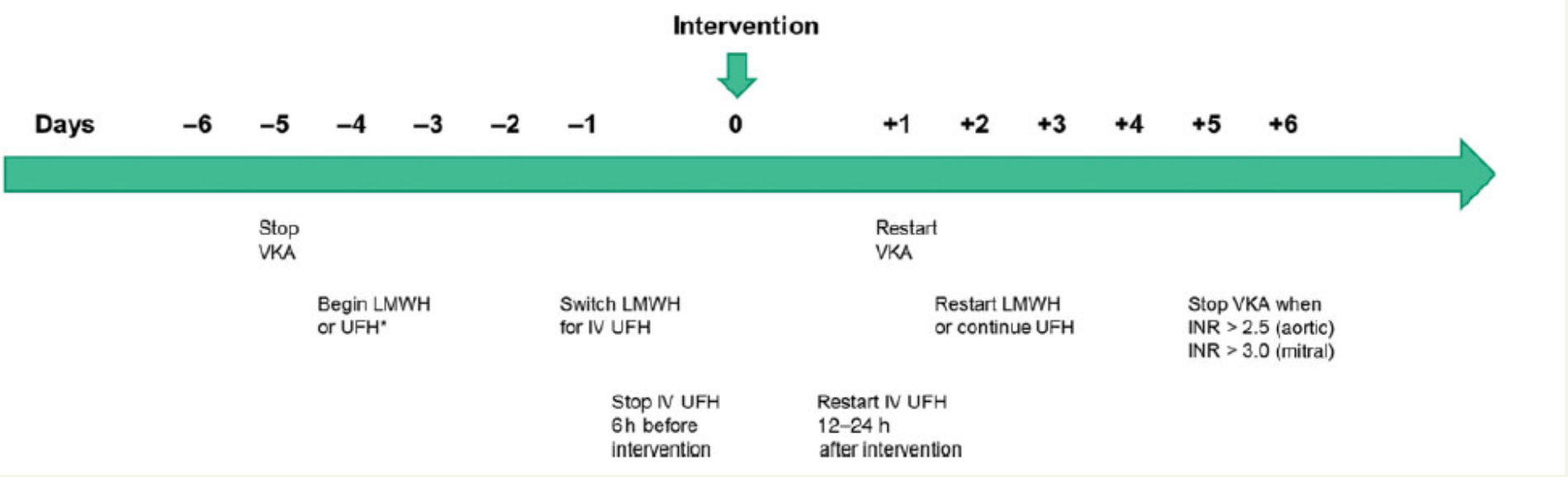


Figure 1 Main bridging steps for an intervention requiring withdrawal of oral anticoagulation in a patient with a mechanical prosthesis. *Intravenous UFH may be favoured in patients at high thromboembolic risk. Timing should be individualized according to patient characteristics, actual INR, and the type of intervention.

Iung B, Rodes—Cabau J. Eur heart J 2014;35:2942-2949

Transaortic Valve Implantation
Antithrombotic Therapy

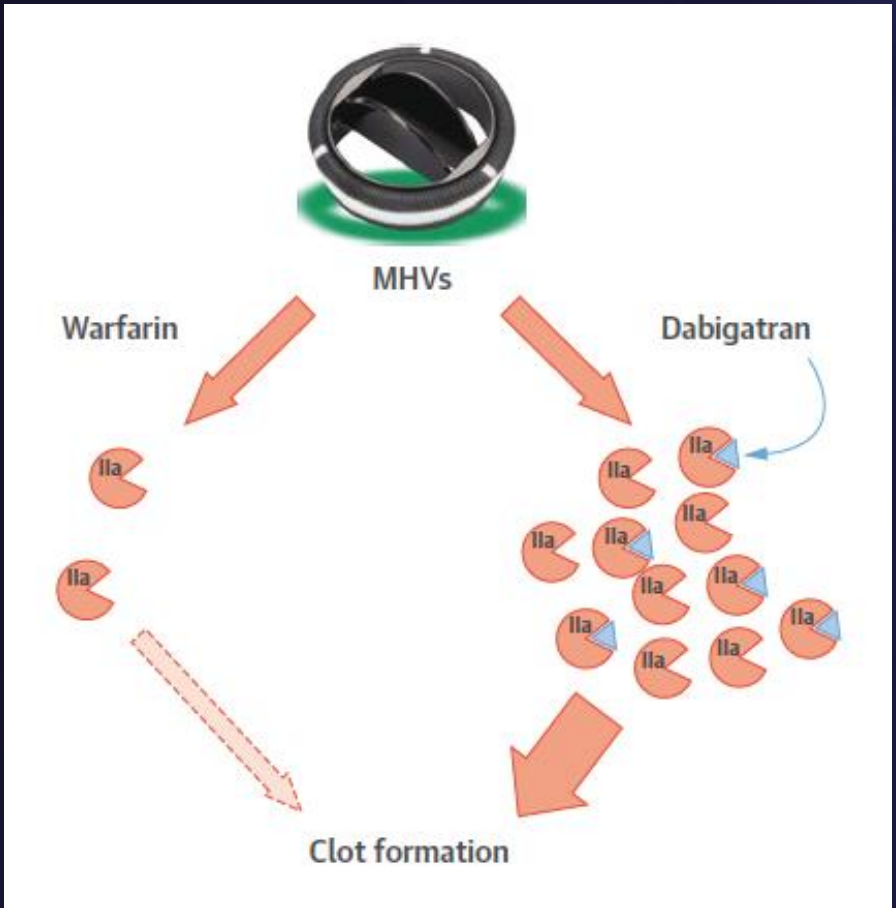
Table 3 Current recommendations for anti-thrombotic therapy following transcatheter aortic valve implantation

	ACCF/AATS/SCAI/ STS expert consensus[44]	AHA/ACC guidelines[15]	CCS position statement[45]	ESC/EACTS guidelines[14]
Long-term anti-thrombotic treatment	Aspirin 81 mg/day indefinitely	Lifelong aspirin 75–100 mg daily (Class IIb; level of evidence: C)	Low-dose aspirin indefinitely	Low-dose aspirin indefinitely
Post-procedural anti-thrombotic treatment	Aspirin 81 mg/day + clopidogrel 75 mg/day for 3–6 months If warfarin indicated (AF), then no clopidogrel	Aspirin 75–100 mg/day + clopidogrel 75 mg/day for 6 months	ASA 80 mg/day + thienopyridine for 1–3 months If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists	Low-dose aspirin + a thienopyridine early after TAVI In patients in AF, a combination of VKA and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding

Iung B, Rodes—Cabau J. Eur heart J 2014;35:2942-2949

Mechanical Valve Anticoagulation

Reason for Dabigatran Failure

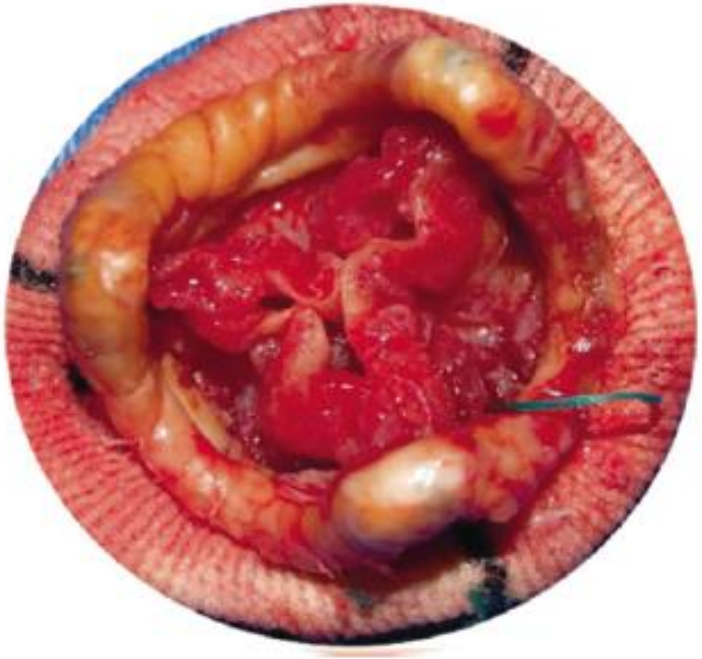
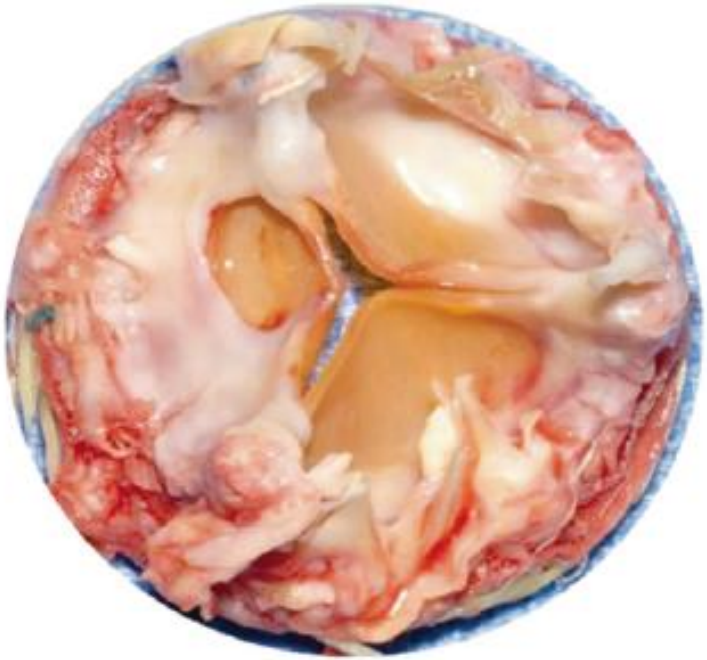


Potential pharmacodynamic explanation for the failure of dabigatran to prevent clotting in patients with MHVs. By triggering the intrinsic pathway, MHVs induce the generation of thrombin (IIa) in concentrations that overwhelm those of dabigatran. By contrast, by reducing the levels of fIX, fX, and prothrombin, warfarin attenuates fXa and thrombin generation, thereby preventing clotting. f = factor; MHV = mechanical heart valve.

Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886

Bioprosthetic Valve Failure

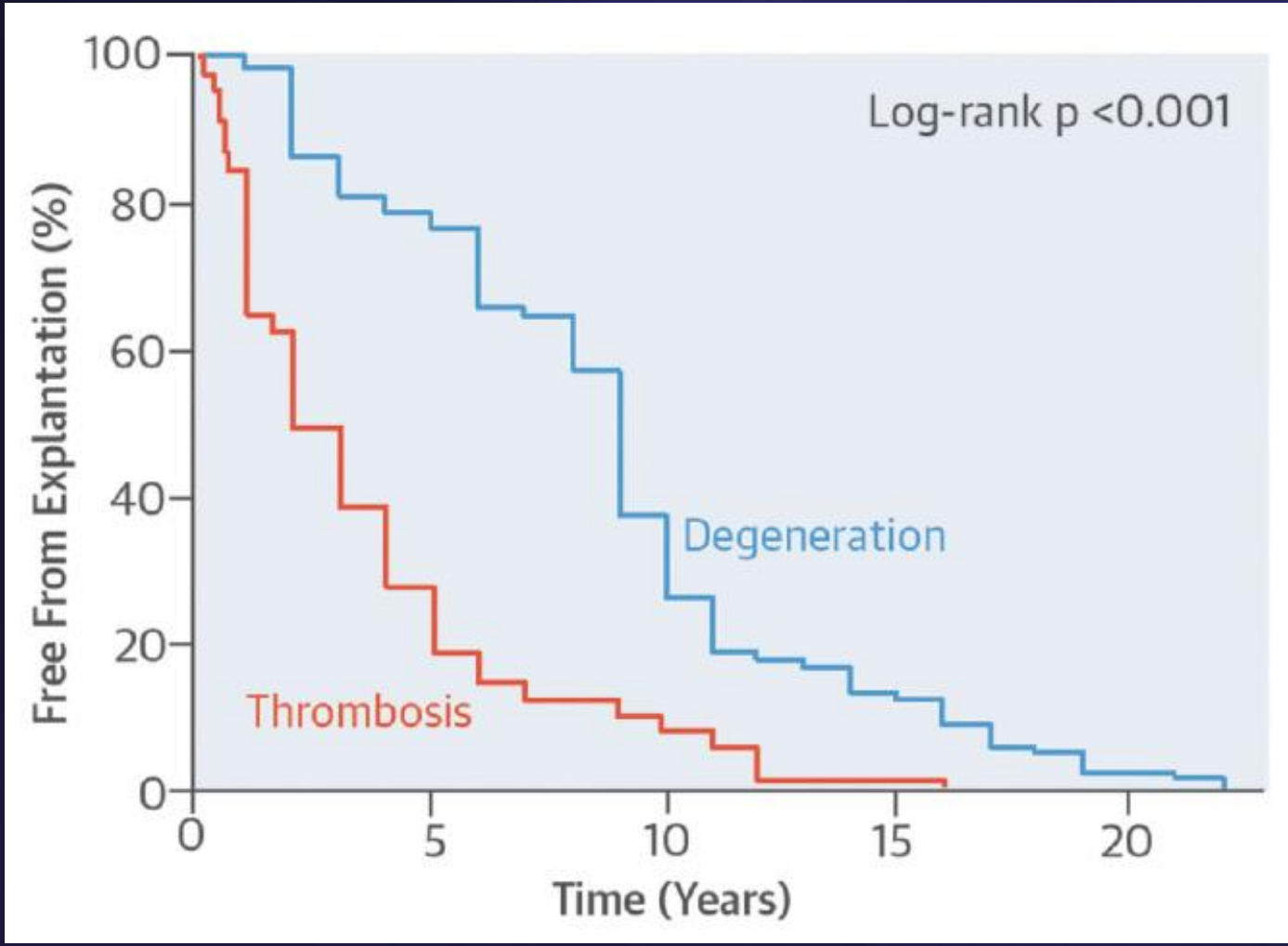
Valve Thrombosis vs Structural Failure

Bioprosthetic Thrombosis	Bioprosthetic Degeneration
	

Egbe, A.C. et al. J Am Coll Cardiol. 2015; 66(21):2285–94

Bioprosthetic Valve Failure

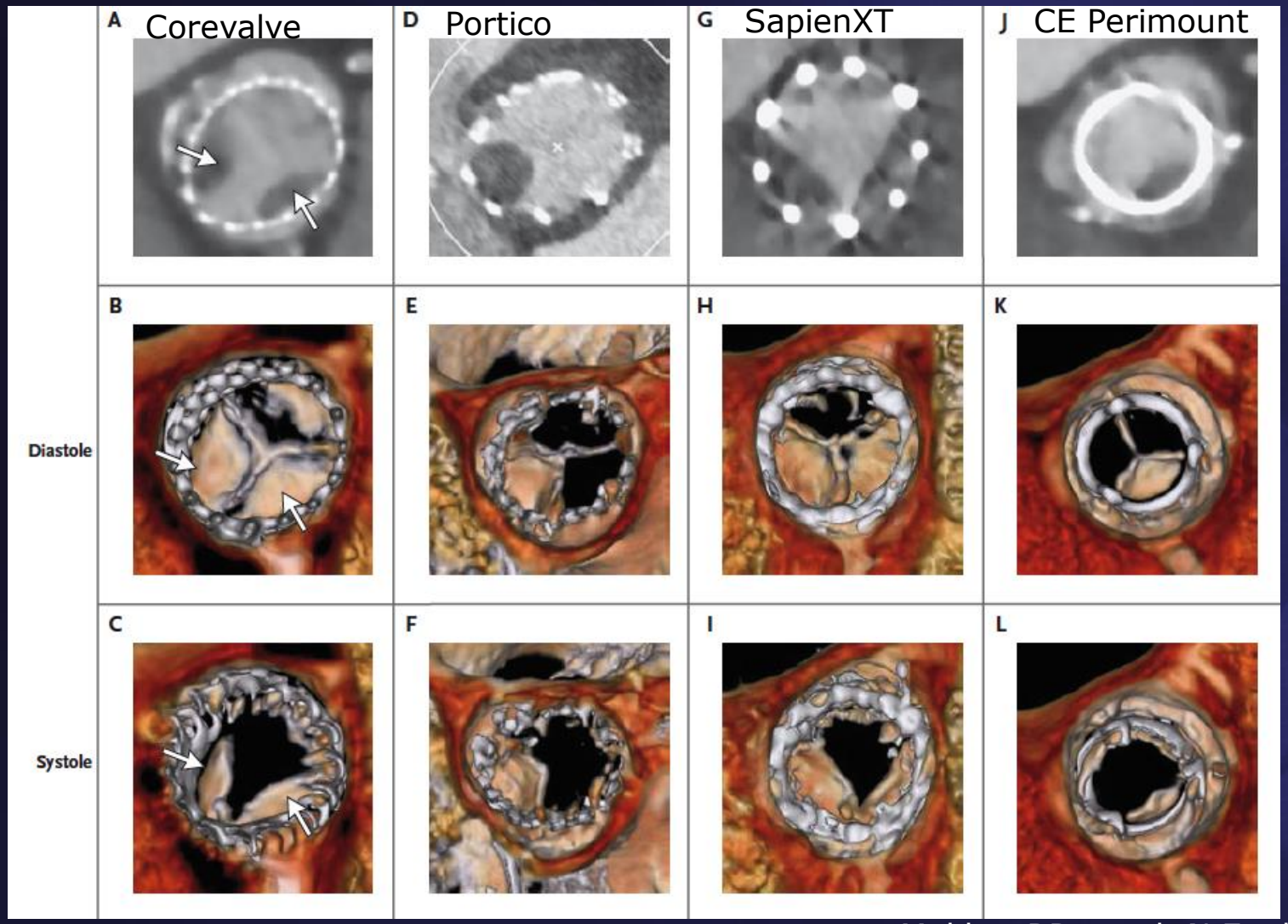
Valve Thrombosis vs Structural Failure



Egbe, A.C. et al. J Am Coll Cardiol. 2015; 66(21):2285–94

Bioprosthetic Valve Failure

Subclinical Valve Thrombosis



Reduced Leaflet Motion in 13 to 40% of pts

Makkar RR. et al. N Engl J Med. 2015; 373:2015-2024

Antithrombotic Therapy after Valve Replacement

Gaps of Evidence

- Combination of aspirin with VKA in patients with a mechanical prosthesis
- Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
- Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
- Use of DOACs in patients with a bioprosthesis
- Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF

Antithrombotic Therapy after Valve Replacement

Gaps of Evidence

Table 4 **Major gaps in evidence in anti-thrombotic therapy after valve replacement**

Combination of aspirin with VKA in patients with a mechanical prosthesis and contemporary target INRs
Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
Use of DOACs in patients with a bioprosthesis
Use of anti-Xa DOACs in patients with a mechanical prosthesis
Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF

Iung B, Rodes—Cabau J. Eur heart J 2014;35:2942-2949

Valve Replacement
Anticoagulation Regimen

TABLE 3 ACC/AHA, ACCP, and ESC Recommendations for Antithrombotic Therapy After Valve Replacement

	ACC/AHA	ACCP	ESC
Surgical MHV replacement	Anticoagulation with VKA (INR of 2.5 for AVR and no risk factors for TE; INR of 3.0 for AVR with risk factors for TE or MVR) plus aspirin 75–100 mg daily (Class I)	VKA (INR of 2.5 for AVR and 3.0 for MVR) indicated over no VKA for long-term management (Grade 1B) Aspirin 50–100 mg indicated in patients at low risk of bleeding (Grade 1B)	Anticoagulation with VKA (target INR according to prosthesis thrombogenicity and patient-related risk factors [Table 1]; Class I) Aspirin ≤100 mg daily if concomitant atherosclerotic disease and/or TE despite adequate INR (Class IIa)
Surgical BHV replacement	Anticoagulation with VKA (INR of 2.5) plus aspirin 75–100 mg for the first 3 months followed by aspirin 75–100 mg daily alone (Class IIa/IIb)	Aspirin 50–100 mg indicated in the first 3 months (Grade 2C) Aspirin 50–100 mg is indicated over VKA and over no APT for the first 3 months after AVR in patients in sinus rhythm (Grade 2C) VKA (INR: 2.5) indicated over no VKA for the first 3 months after MVR (Grade 2C)	Anticoagulation with VKA for the first 3 months after MVR, MVRep, or TVR (Class IIa) Anticoagulation with VKA for the first 3 months after AVR (Class IIb) Aspirin ≤100 mg daily for the first 3 months after AVR (Class IIa)
TAVR	Clopidogrel 75 mg plus aspirin 75–100 mg for 6 months followed by aspirin 75–100 mg daily alone (Class IIb)	Aspirin 50–100 mg plus clopidogrel 75 mg/dl is indicated over VKA and over no APT for the first 3 months (Grade 2C)	No specific recommendations

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AHA = American Heart Association; APT = antiplatelet therapy; AVR = aortic valve replacement; BHV = bioprosthetic heart valve; ESC = European Society of Cardiology; INR = international normalized ratio; MHV = mechanical heart valve; MVR = mitral valve replacement; MVRep = mitral valve repair; TAVR = transcatheter aortic valve replacement; TE = thromboembolism; TVR = target vessel revascularization; VKA = vitamin K antagonist.

Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886