Le protesi valvolari cardiache

Vittorio Pengo (Padova)

Antithrombotic treatment in patients with mechanical prostehtic heart valves

	No Treatment	Antiplatelet agents	Oral anticoagulants
Thromboembolism* Events/ 100 pt/yrs	**42.0**	**8.5**	**2.7**

*mean of reported studies

Stein PD. Chest 1992;102:445S-455S

Mechanical prostetic heart valves

- **OAT intensity?**

- **Thromboembolic Risk factors?**

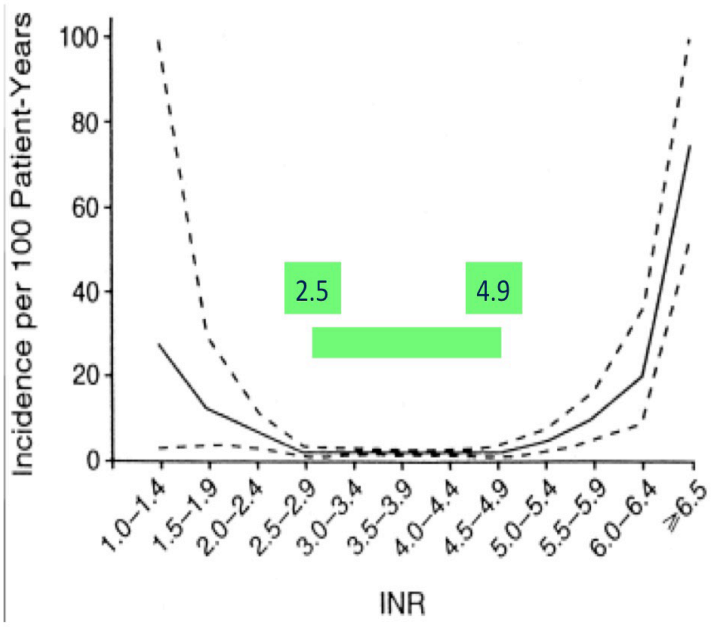
COMPARISON OF TWO LEVELS OF ANTICOAGULANT THERAPY IN PATIENTS WITH SUBSTITUTE HEART VALVES°

INR	Pz	Follow-up (pt/yrs)	TE*	Bleeding*	
2.0-2.99	51	52	1(1.92)	2(3.8)	p<0.02
3.0-4.5	48	40	2(4.94)	10(24.7)	

° patients in the two groups were also treated with Dip 150mg/die + ASA 660mg/die * events every 100 pt/yrs

Altman R. J Thorac Cardiov Surg 1991;101:427-31.

Intensity of treatment



Cannegieter SC et al. *N Engl J Med* 1995; **333:** 11-17

Prosthetic heart valves: Oral anticoagulants + antiplatelet drugs

Rationale

Clinical: high risk patients in whom OAT reduce but not eliminate thromboembolic events

Pathophysiologic: adhesion and aggregation of platelets is an invariable effect of exposure of foreign surfaces to native blood

Pharmacological: The shortened platelet survival which is related to thromboembolic events is normalized by some antiplatelet agents

A COMPARISON OF ASPIRIN WITH PLACEBO IN PATIENTS TREATED WITH WARFARIN AFTER HEART-VALVE REPLACEMENT

INR	Pts	Follow up pt/yrs	TE*	Major bleeding*	Mortality'*
3.0-4.5 + ASA 100mg/die	186	465	5(1.07)	24(5.1)	9(1.9)
3.0-4.5 + Placebo ASA	184	460	13(2.82)	19(4.1)	22(4.8)

*events every 100 pt/yrs

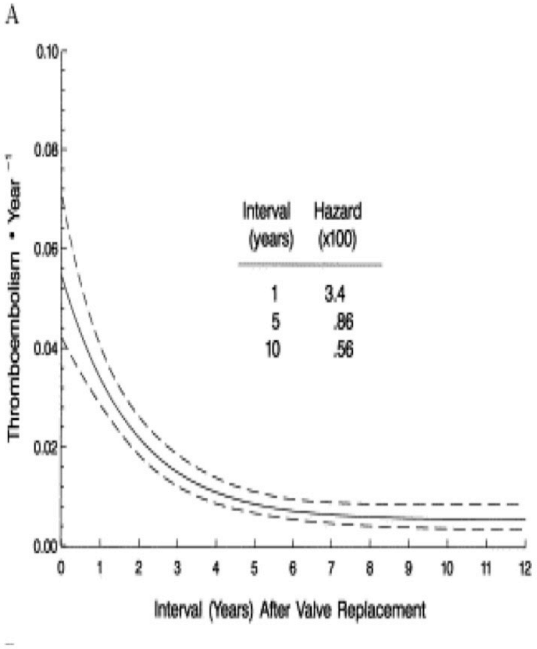
Turpie AGG. *N Engl J Med* 1993;329:524-9.

Mortality

	OAT + PLACEBO	OAT + ASA 100mg/die
Sudden death	4	1
Myocardial infarction	4	0
Heart failure	3	0
Stroke	2	1
Bleeding	4	3
Non Vascular	5	4

Turpie AGG, N Engl J Med 1993;329:524-9

Incidence of thromboembolic events after operation



Kuntze C et al, Lancet 1989

A COMPARISON OF A MODERATE WITH A MODERATE-HIGH INTENSITY ORAL ANTICOAGULANT TREATMENT IN PATIENTS WITH MECHANICAL HEART VALVE PROSTHESES§

INR target	Pts	Follow-up pt/yrs	TE*	Major bl*	Minor* bl
3.0	104	312	6(1.8)	4(1.2) p=0.02	85(26) p<0.001
4.0	101	303	6(2.1)	11(3.8)	123(43)

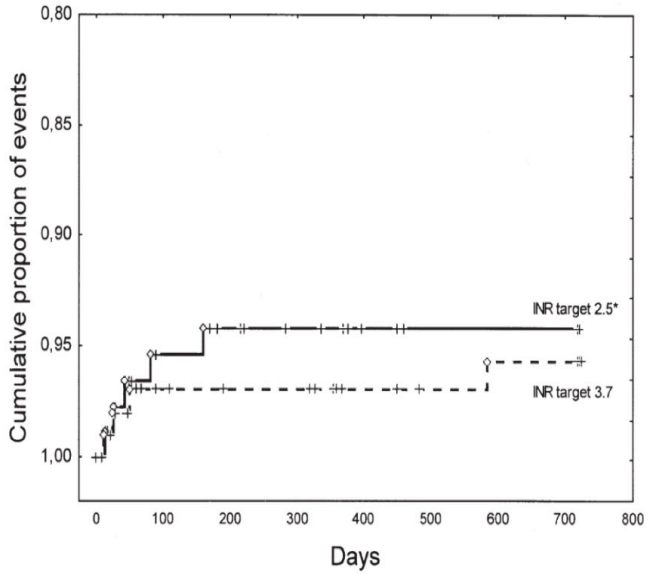
*N (n/100/pt/yrs)

§ patients were randomised at least six months after operation

Pengo V et al. Thromb Haemost 1997;77:839-44.

Low-Intensity Oral Anticoagulant Plus Low-Dose Aspirin During the First Six Months Versus Standard-Intensity Oral Anticoagulant Therapy After Mechanical Heart Valve Replacement: A Pilot
Study of Low-Intensity Warfarin and Aspirin in Cardiac Prostheses (LIWACAP)

Vittorio Pengo, Gualtiero Palareti, Umberto Cucchini, Maurizio Molinatti, Roberto Del Bono, Franco Baudo, Angelo Ghirarduzzi, Cinzia Pegoraro and Sabino Iliceto

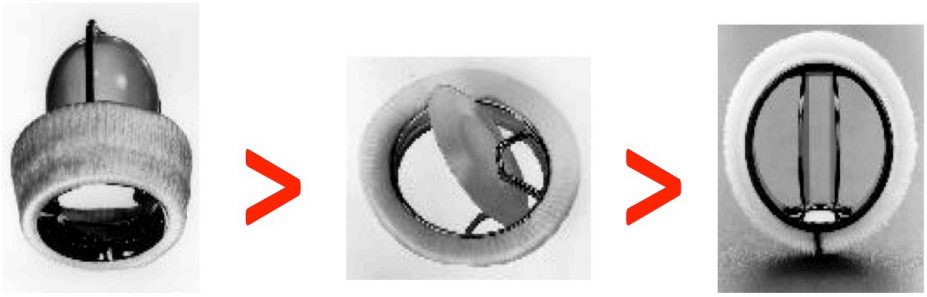


Clin Appl Thromb Hemost 2007; 13; 241

Thromboembolic risk profile in patients bearing mechanical prosthetic heart valves

- Previous thromboembolism
- Atrial fibrillation
- Atrial enlargment
- Prosthesis position
- Type of prosthesis
- Time from operation
- Age
- Thrombophilia?

Thromboembolic risk profile



2.5 %/y > 0.7 %/y > 0.5%/y

Cannegieter SC et al., M Engl J Med 1995;333:11-7

Thromboembolic risk profile

Age (yrs)

<50 < 50-69 < ≥70

0.1 %/y 0.8 %/y 1.1 %/y

Cannegieter SC et al., M Engl J Med 1995;333:11-7

Mechanical prosthetic heart valves Recommendations(I)

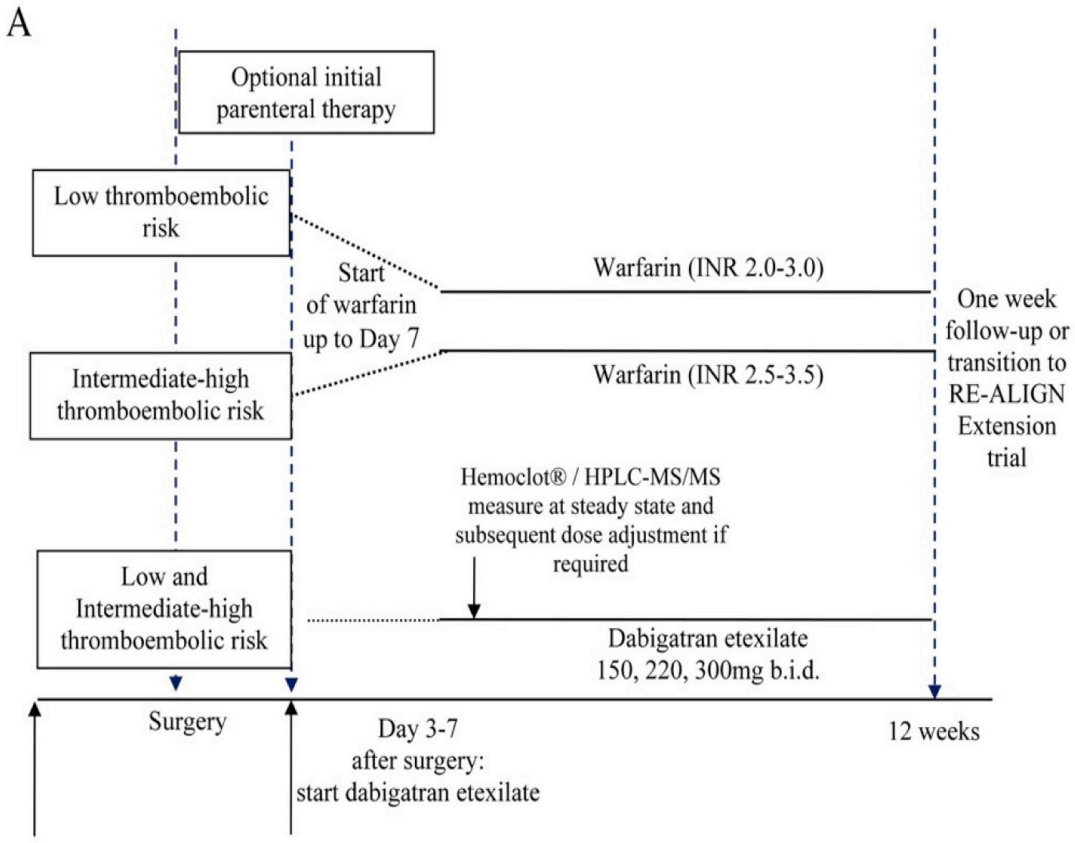
- Long term OAT at a target INR 2.5 in patients with bileaflet valves in the aortic position and no risk factors (synus rythm, normal atrial size)
- Long term OAT at a target INR 3.0 in patients with old tilting disk valves in the mitral position or aortic valvular conduit
- Long-term OAT at a target INR 3.0 in all the remaining cases

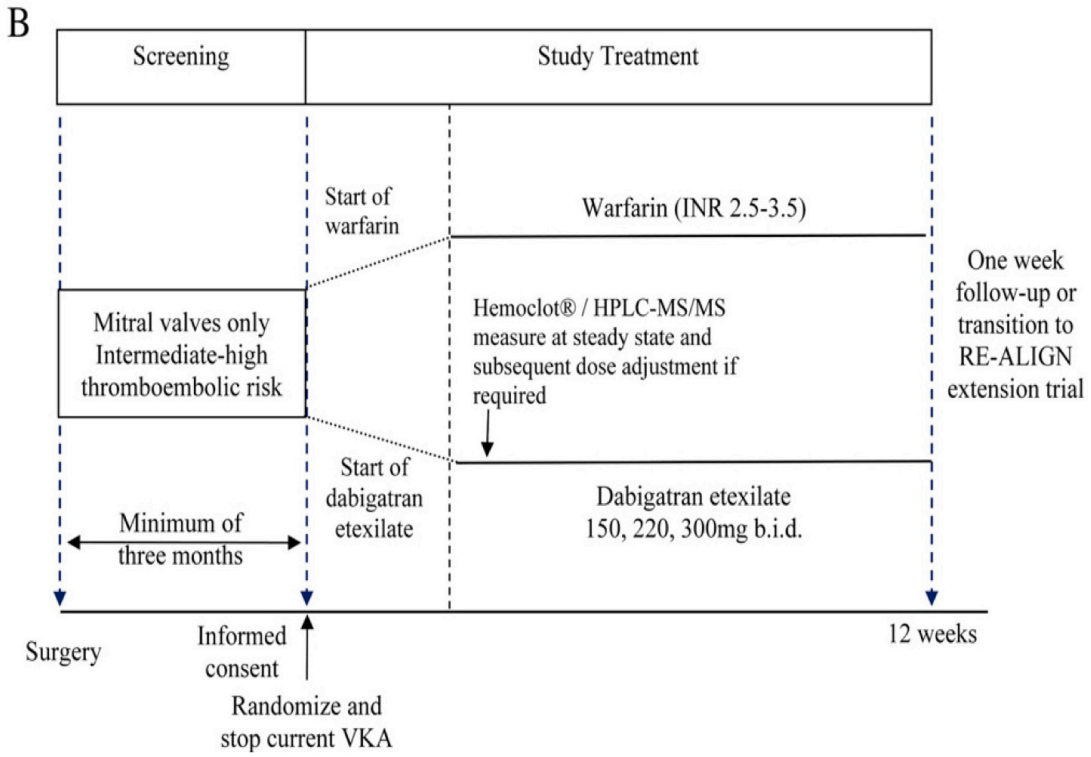
Mechanical prosthetic heart valves Recommendations(II)

- Add Aspirin 100mg/die to OAT target 3.0 in case of associated coronary artery disease
- In case of recurrent embolism despite adequate anticoagulation, consider OAT combined with low dose aspirin (100 mg/die) or valve substitution (check for thrombophilia)

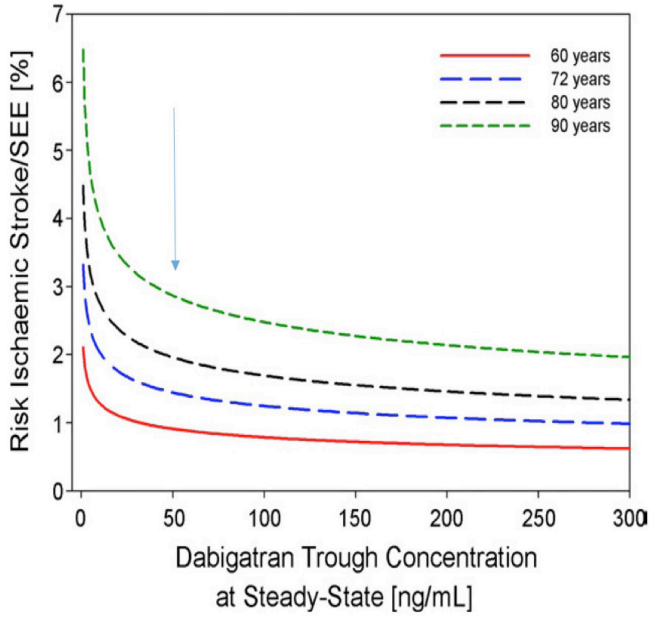
RE-ALIGN

- A prospective randomized, open label, blinded end-point phase II trial in patients with mechanical heart valves to examine the efficacy of dabigatran at 3 doses
- 150, 220, or 300 mg twice daily, with titration of doses to achieve trough plasma levels of 50 ng/ml within 1 week of dabigatran initiation for 12 weeks compared to standard dose warfarin.
- Two groups: A) immediately after mechanical bileaflet aortic or mitral valve replacement or B) at 3 months after implantation of a mechanical bileaflet mitral valve





RE-ALIGN: the choice of 50ng/ml trough



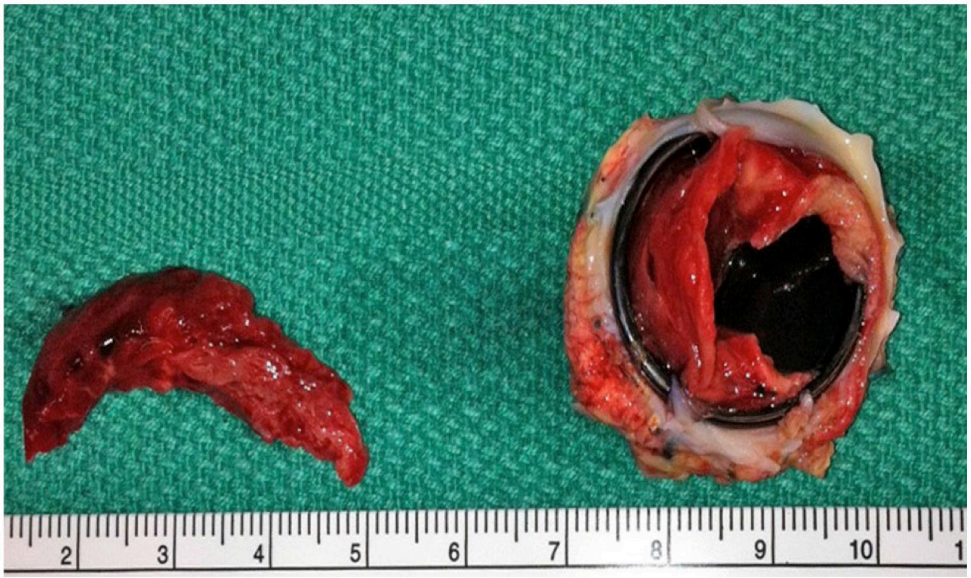
Model-predicted probability of ischemic stroke and systemic embolic event versus trough plasma concentration of total dabigatran by age in the RE-LY study

RE-ALIGN main results

Table 4. Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.*

Outcome	Population A		Population B		All Patients		Hazard Ratio (95% CI)†	P Value‡
	Dabigatran (N=133)	Warfarin (N=66)	Dabigatran (N=35)	Warfarin (N=18)	Dabigatran (N=168)	Warfarin (N=84)		
	number of patients (percent)							
Death	1 (1)	2 (3)	0	0	1 (1)	2 (2)	0.25 (0.02–2.72)	0.26
Stroke	9 (7)	0	0	0	9 (5)	0	NA	NA
Systemic embolism	0	0	0	0	0	0	NA	NA
Bleeding								
Any	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23–4.86)	0.01
Major	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.37–8.46)	0.48
Major with pericardial location	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.36–8.45)	0.48

Thrombosis on a mechanical mitral valve anticoagulated with dabigatran



Coulter S. J Thromb Thrombolysis (2014)

Pathogenesis of thrombosis in prosthetic heart valves

- Substrate
- Flow
- Coagulation

Substrate (early thrombosis)

- Perivalvular excision tissue: *thrombin generation and platelet activation*
- Dacron sewing ring
- Prosthesis
- Suture

Protein adsorption (fibrinogen, albumin), platelet activation via adsorbed complement components, contact activation of coagulation cascade

Dacron sewing rings

The majority of thrombi in patients with prosthetic heart valves appear to arise from the sewing ring which does not undergo endothelialization for at least several weeks after surgery.
Dewanjee MK J Heart Valve Dis 1999.

Prosthesis

It has been reported that platelet adhesion does not take place until the adsorbed protein film is 100–200 Å thick, about 60 s after the first blood contact.

Biomaterial structure: the less activating material is pyrolytic carbon Maximum spreading of platelets on a pyrolytic carbon surface is observed after 20–30 min.

Flow

- Atrial Fibrillation
- Left atrium size (spontaneous echo contrast)
- Design of prosthesis

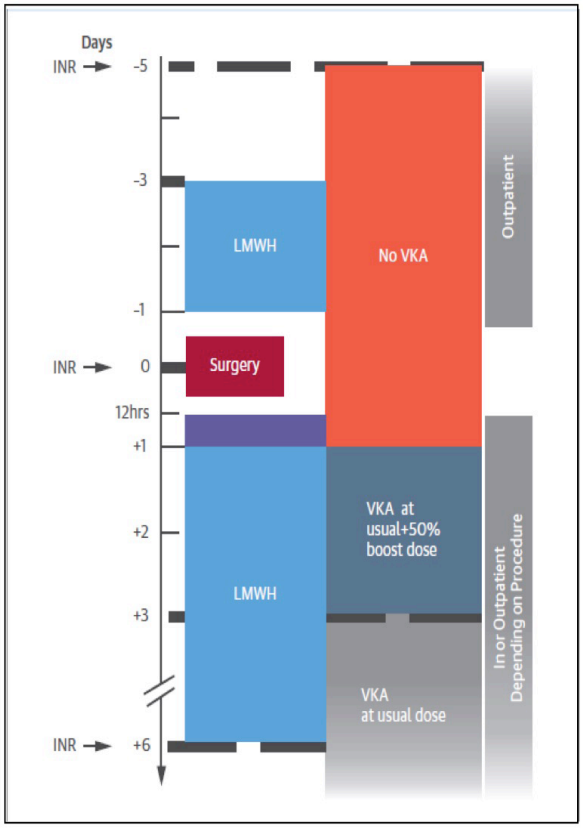
Coagulation (late thrombosis)

- INR range is inversely related to Fibrinopeptide A level
  (Pengo V. Eur J Clin Invest 1989)

- Shortened platelet survival increases the risk of thromboembolism
  (Harker LA N Engl J Med 1970)

Complications

- Valve dysfunction (thrombosis)
- Hemolysis
- Endocarditis
- Pregnancy



High risk prosthesis:
Intermediate dose LMWH

Denas G, JACC 2016

Conclusions

- VKAs are mandatory in the antithrombotic therapy in MHV
- No evidence in the timing dose and type of heparin early after operation

Modified from European Heart Journal (2014) 35, 2942–2949

Bioprosthetic heart valves Recommendations

- OAT at a target INR 2.5 for three monts
- Long term OAT in the presence of risk factors (AF, previous TE, or left atrial thrombus at surgery, left atrium >55mm)

Major bleedings: OAT + ASA

Post-operative anti-thrombotic therapy

During the first post-operative month, thromboembolic risk is markedly increased with linearized rates approximately 10 times higher than after 6 months.[27] It is higher in mitral position, with a 10–15% rate of non-obstructive prosthetic thrombosis when transesophageal echocardiography is systematically performed.[28] Bleeding risk is also high, in particular with regard to haemopericardium.
The use of heparin is favoured by AHA/ACC and ESC/EACTS guidelines before target INR is obtained but there is no graded recommendation due to the lack of controlled trials.[14,15,29] Heparin is started 12–24 h after surgery, according to the risks of thromboembolism and early bleeding. The ACCP consensus favours heparin bridging, avoiding unfractionated heparin (UFH) at

European Heart Journal (2014) 35, 2942–2949

Post-operative anti-thrombotic therapy

therapeutic doses, with a grade 2C.[16] A review of 28 studies found no difference in thromboembolic events between oral anticoagulation alone, oral anticoagulation plus UFH, and oral anticoagulation plus low-molecular-weight heparin (LMWH).[30] Bleeding was more frequent with oral anticoagulation plus UFH. The observational character of the studies and the absence of standardization of endpoints are sources of bias.
Anticoagulation is often difficult to stabilize during the early postoperative period. LMWH allows for more stable anticoagulation but is off-label in patients with mechanical prostheses. There is no consensus on the type of heparin, the dose, and the administration route because of the lack of appropriate controlled trials.
The association of low-dose aspirin raises the same problems of risk–benefit analysis as for long-term therapy. A randomized trial showed that the association of aspirin markedly decreased the risk of thromboembolic events during the year following mitral valve replacement, but also increased the risk of severe bleeding, thereby leading to a non-significant trend toward a higher all-cause mortality at 1 year.[31]

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AREVA: MULTICENTER RANDOMIZED COMPARISON OF LOW-DOSE VS STANDARD-DOSE ANTICOAGULATION IN PATIENTS WITH PROSTHETIC HEART VALVES§

INR	Pts	Follow-up	TE*	Major bl N/100 pt/yrs	Minor bl
2.0-3.0	188	412	10(2.4)	13(3.1)	34(8.2)
p<0.01					
3.0-4.5	192	425	9(2.1)	19(4.5)	56(13.3)

*events /100/pt/yrs

§ low-risk patients: aortic prostheses, synus rythm and left atrium < 50 mm

Acar J et al. Circulation 1996;94:2107-12.

Further support to low intensity treatment in patients with bileaflet prostheses

Andersen V, Aagard J. Low dose warfarin in patients with Carbomedics heart valve prostheses. *Asian Cardiovasc Thorac Ann* 2000;8:11-**4**

Retrospective, based on the INR at the time of events

INR 2.0-2.5 for Carbomedics in the aortic position

INR 2.5-3.0 for Carbomedics in the mitral position

Controversies in cardiovascular medicine

The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties

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.

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TRIAL OF DIFFERENT INTENSITIES OF ANTICOAGULATION IN PATIENTS WITH PROSTHETIC HEART VALVES

INR	Pts	Follow-up pt/yrs	TE*	Major bl*	Minor* bl
2.65	122	421	17(4.0)	4(0.9)	22(18)
					p<0.01
9.0	125	436	16(3.7)	9(2.1)	44(35.2)

*N (n/100/pt/yrs)

Saour JN. *N Engl J Med* 1990;322:428-32.

LOW INTENSITY ANTICOAGULATION IN MECHANICAL CARDIAC PROSTHETIC VALVES

101 Patients; Follow up 466.5 pt/yrs

		Thromboembolism	Major bleeding
PTR	<1.3	2.9	2.8
	1.3-1.5 low	2.5	3.8
	1.6-2.0 high	2.2	5.5
	>2.0	0	12.2

* events every 100 pt/yrs

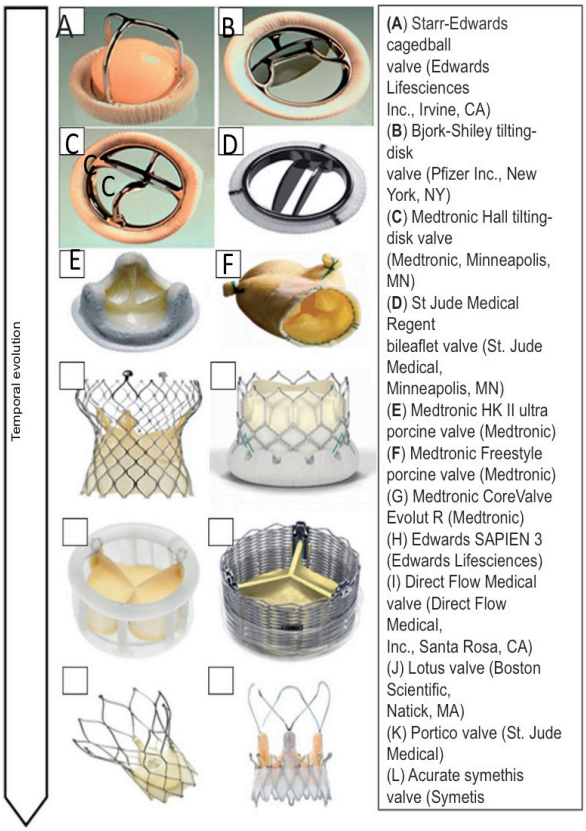
Wilson DB. *Chest* 1991;100:1533-7.

LOW INTENSITY ORAL ANTICOAGULATION PLUS LOW-DOSE ASPIRIN VERSUS HIGH INTENSITY ORAL ANTICOAGULATION ALONE: A RANDOMIZED TRAIL IN PATIENTS WITH MECHANICAL PROSTHETIC HEART VALVES

INR	Pts	Follow up pt/yrs	TE*	Major bleeding*	Mortality'*
2.5-3.5 + ASA 100mg/die	258	529	7(1.3)	6(1.1)	35(6.6)
3.5-4.5	245	471	7(1.5)	13(2.3)	41(8.7)

*events every 100 pt/yrs

Meschengieser SS J Thorac Cardiov Surg 1997:113:910-6



Antithrombotic therapy following transcatheter aortic valve implantation

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

European Heart Journal (2014) 35, 2942–2949