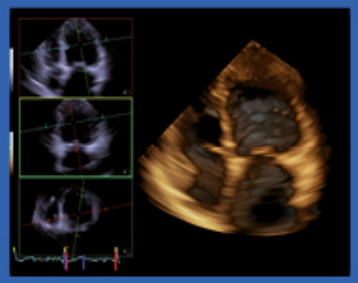
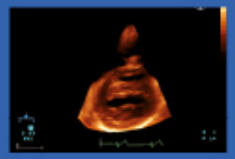
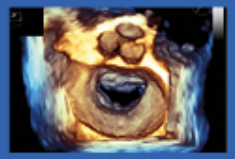
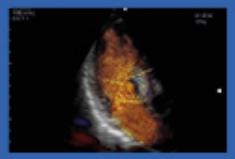


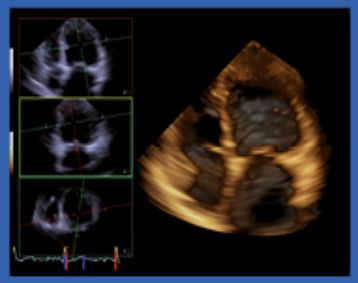
EuroValve

March 27 - 28, 2015

How to Manage Anticoagulant Therapy in Valve Disease After Valve Replacement

Bernard Iung
Bichat Hospital, AP-HP
Paris Diderot University
DHU FIRE



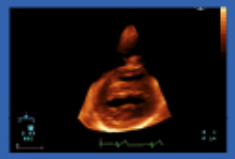
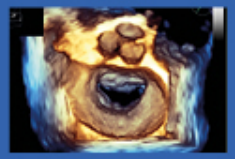
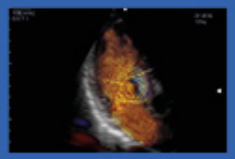
EuroValve
March 27 - 28, 2015

Faculty disclosure

Bernard Iung

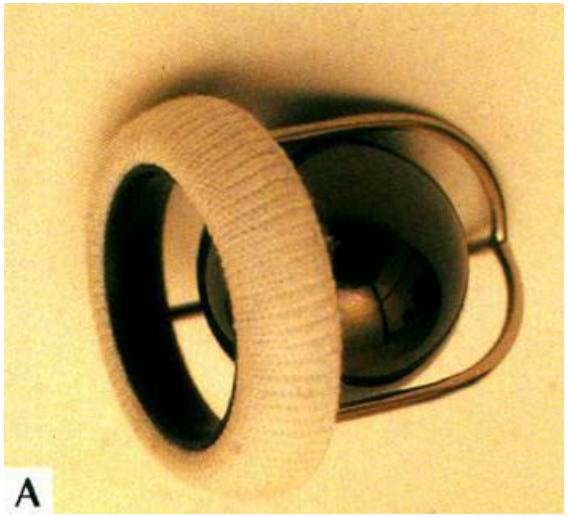
I disclose the following financial relationships:

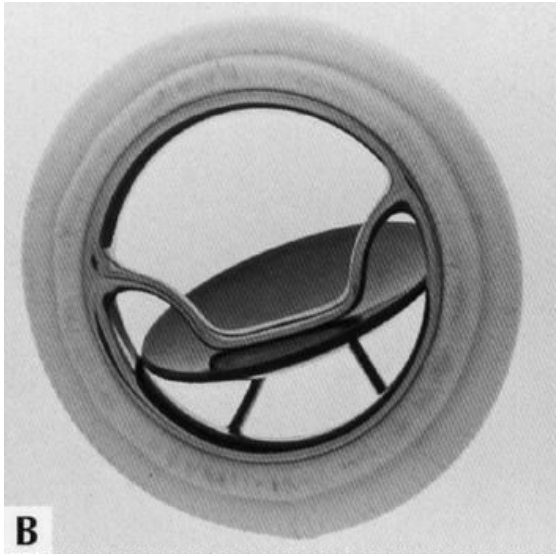
Consultant for Abbott Boehringer Ingelheim, Valtexch
Paid speaker for Edwards Lifesceinces

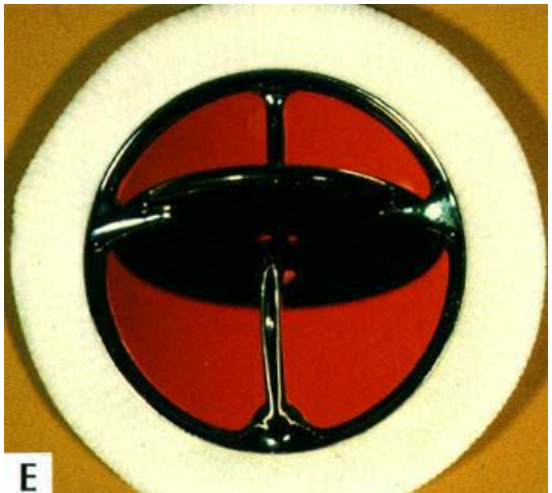





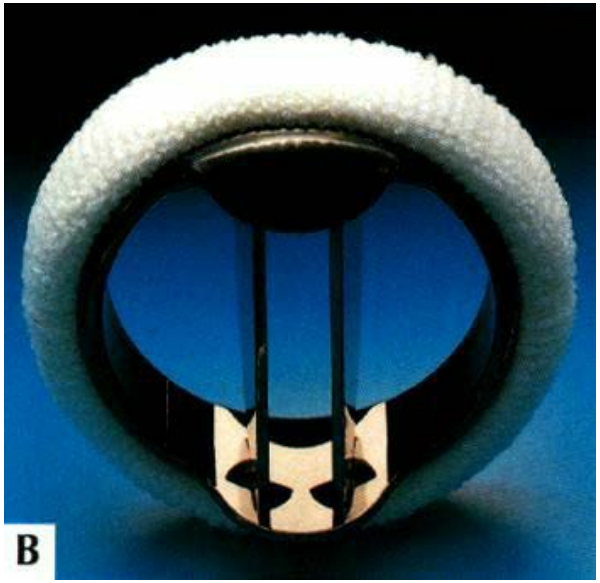
www.eurovalvecongress.com

Mechanical Prostheses









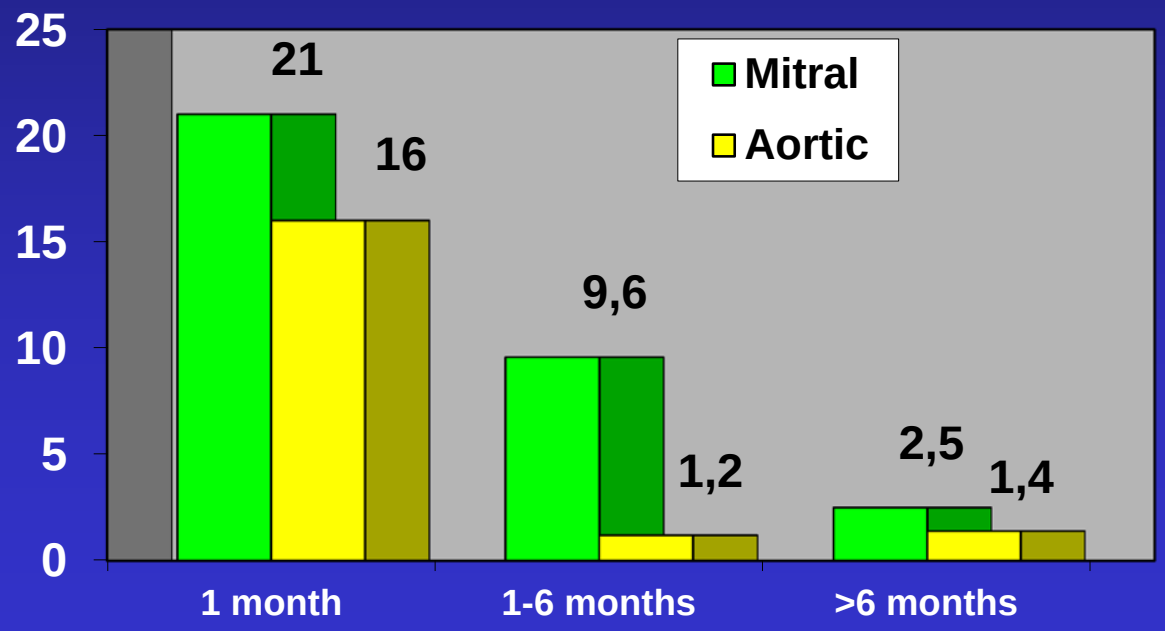
Thromboembolic Risk of Mechanical Prostheses

Post-Operative Period

Additional factors:

- endothelialization of the ring
- inflammation
- impaired hemostasis

Linearized rates per 100 pts-year :

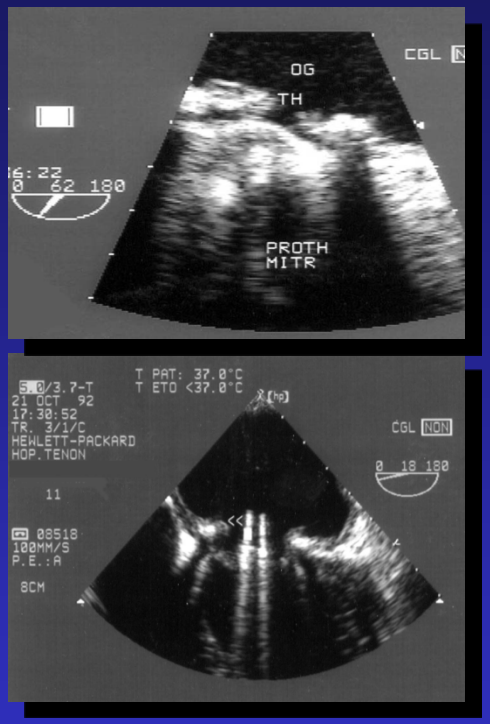


(Butchart et al. Circulation 1991;84(suppl.III):61-69)

Post-Operative Prosthetic Thrombosis

- **Occlusive thrombosis (1-2%)**

- **Non-occlusive thrombosis**
  - revealed only by TEE
  - frequency > clinical events



Series of MVR	*Gueret*	*Malergue*	*Iung*	*Laplace*
n=	56	200	331	680
Non-occlusive Thrombosis (%)	12.5	15	16	9.4

Components of Thromboembolic Risk

	Mitral	Aortic
Blood stasis	+++	+
Flow velocity	low	high
Valve opening	passive	active
Atrial fibrillation	frequent	rare
High shear stress	+	+++
Arterial risk factors	+	++

Anticoagulant Therapy Early After Heart Valve Replacement

- Prosthetic surface area

  Absence of endothelialization of the prosthetic ring
  $\rightarrow$ platelet aggregation
  (Dewanjee et al. Mayo Clin Proc 1983;58:307-14)

- Changes related to cardiopulmonary bypass, neutralization of heparin, hemostatic factors
  (Koppensteiner et al. Am J Cardiol 1991;67:79-83)

- Difficulties in obtaining stable anticoagulation with heparin, delayed effect of vit. K antagonists

- Risk and severity of bleeding (tamponade…)

Modalities of Post-Operative Anticoagulant Therapy

- **Vitamin K-blockers alone**
  - effective anticoagulation delayed (> 48 h.)
  - target INR ?
    - 1.5 - 2.6 *(Ageno et al. Am J Cardiol 1999;84:905-8)*
    - 2.5 - 3.5 *(ACC/AHA Guidelines)*
- **Heparin before vitamin K-blockers**
  - early and effective anticoagulation
  - difficulties in achieving stable ACT
- **Low-Molecular weight heparins**
  - widely used, but off label
  - observational series suggest feasibility ± safety
    (Fanikos et al. Am J Cardiol 2004;93:347-50)
    (Rivas-Gandara et al. Heart 2008;94:205-10)
- **Antiplatelet drugs**

Post-Operative Anticoagulant Therapy

- Review of 28 studies
- No difference in thromboembolic events between: warfarin alone, UFH + warfarin, LMWH + warfarin
- More frequent bleeding with UFH + warfarin than with warfarin alone and LMWH + warfarin
- Limitations:
  - observational studies
  - no standardized treatments or endpoints

(Kulik et al. Ann Thorac Surg 2006;81:770-81)

Early Thromboembolic Events

- 301 patients undergoing valve replacement with a mechanical prosthesis (2005-2007)
- Standardization
  - Intravenous UFH then VKA blockers
  - UFH dose adaptation using a nomogram
  - TEE around post-op. day 10
- Thromboembolic events

	n=	Th. Emb. % [95%CI]	n=
AVR	151	1.3 [0-3]	2
MVR	108	14 [7-20]	15
AVR+MVR	41	17 [10-24]	7

(Allou et al. Heart 2009;95:1694-700)

Early Thromboembolic Events

Factors associated with thromboembolic events after MVR

	OR [95% CI]	p
Diabetes	3.3 [1.0-10.9]	0.049
Effective anticoagulation at post-op. day 3	0.3 [0.1-0.8]	0.018
HIT or permanent pacemaker	13 [3-53]	0.001

(Allou et al. Heart 2009;95:1694-1700)

Predictors of Post-Operative Thrombo-Embolic Events

Antiplatelet Drugs

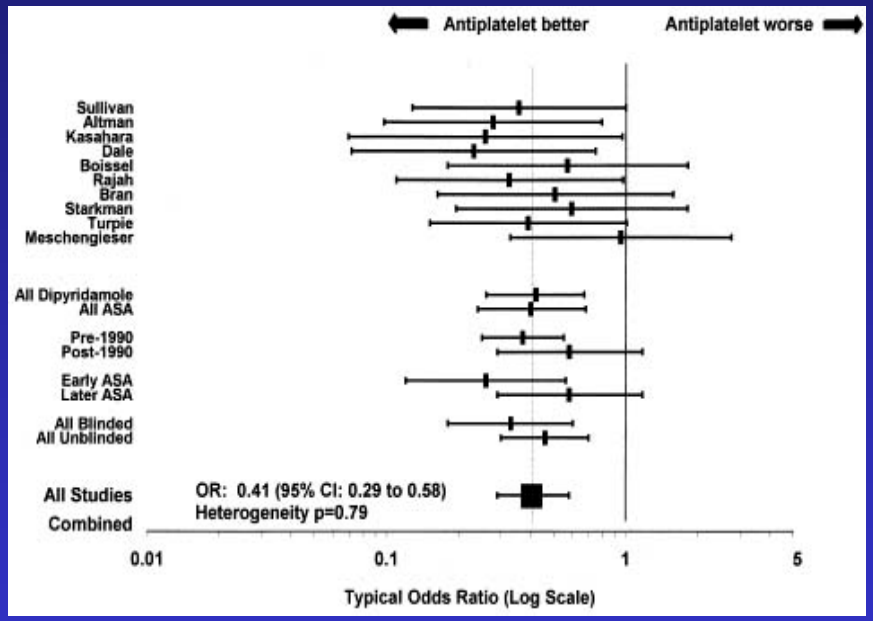
- 229 pts randomised after MVR (ASA 200 mg/24h or placebo) Multiplane TEE at day 9 and 5 months; 1-yr clinical FU)

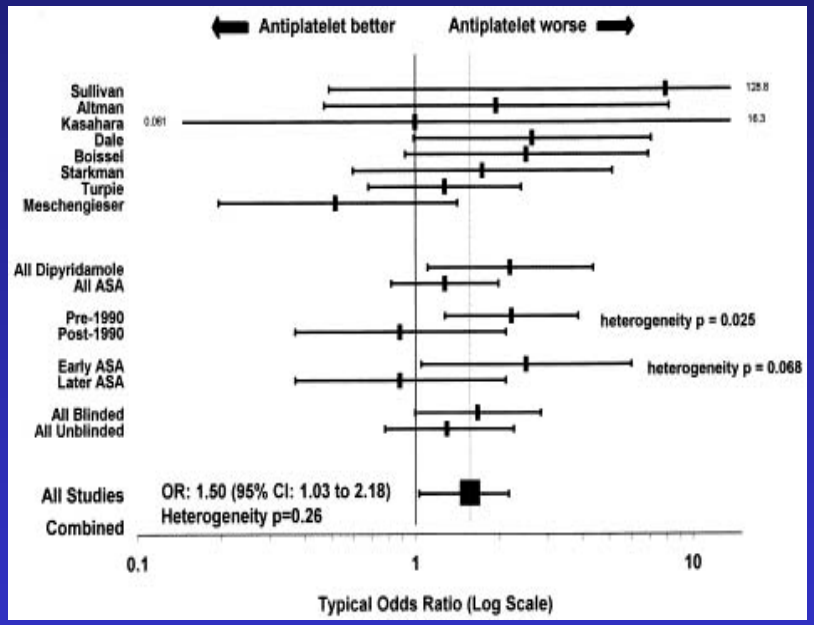
	INR	*Thrombus (% at Day 9)*	*Thrombus (% at 5 months)*	*All TE (% à 1 yr)*	*GI bleeding (% at 1 yr)*	*Mortality (% at 1 yr)*
Asp + (n=109)	3.0	4.8	4.5	9.1	3.4	9.1
Asp - (n=120)	3.0	13.1	8	25	0	4.1
p		0.03	NS	0.001	0.003	0.13

(Laffort et al. J Am Coll Cardiol 2000;35:739-46)

Antiplatelets + vit. K Antagonists

Meta - Analysis





Thromboembolism **Major Bleeding**

(Massel et al. J Am Coll Cardiol 2001;37:569-78)

Post-Operative Anticoagulation for Mechanical Protheses

Guidelines

When postoperative anticoagulant therapy is indicated, oral anticoagulation should be started during the first postoperative days. Intravenous unfractionated heparin (UFH), monitored to an activated partial thromboplastin time (aPTT) of 1.5–2.0 times control value, enables rapid anticoagulation to be obtained before the INR rises. Low molecular weight heparin (LMWH) seems to offer effective and stable anticoagulation and has been used in small observational series.[216] This is off-label use. The limit-

2012 ESC/EACTS Guidelines (Eur heart J 2012;33:2451-96)

Many centers initiate heparin early after surgery for anticoagulation until the INR reaches the therapeutic range. Bridging anticoagulation is typically started once postoperative bleeding is no longer an issue. Some centers use subcutaneous low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), whereas other centers continue to prefer intravenous UFH.

ACC/AHA Guidelines 2014 (Circulation 2014;129:e521-e643)

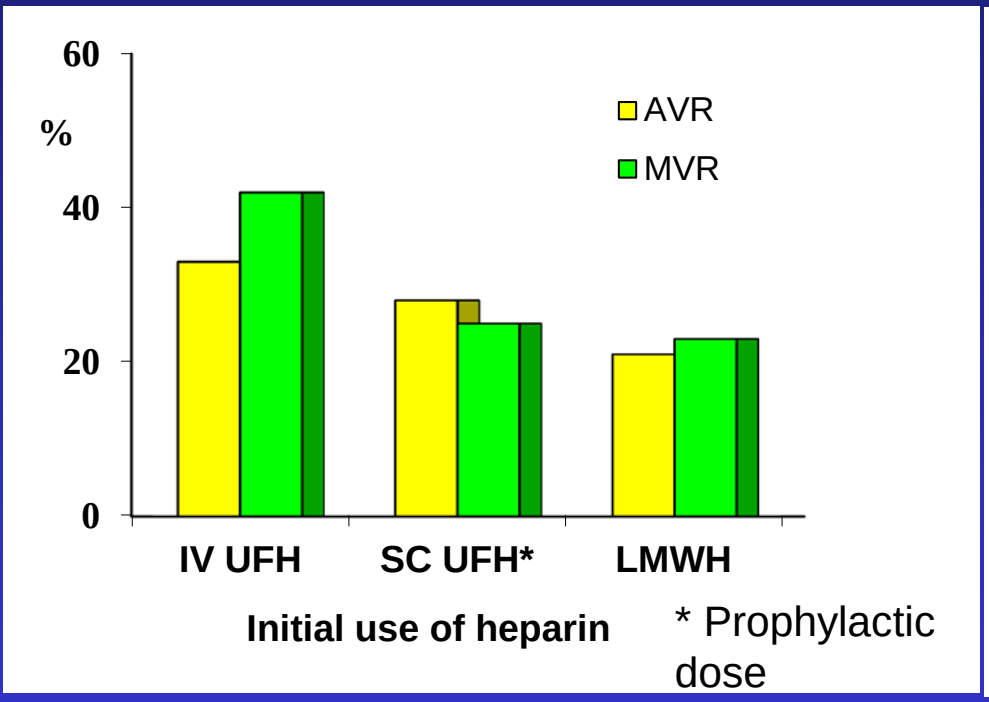
In patients with mechanical heart valves, we suggest bridging with UFH (prophylactic dose) or LMWH (prophylactic or therapeutic dose) over IV therapeutic UFH until stable on VKA therapy (Grade 2C).

9th ACCP Consensus Chest 2012;141:e575S-e600S)

Post-Operative Anticoagulant Therapy

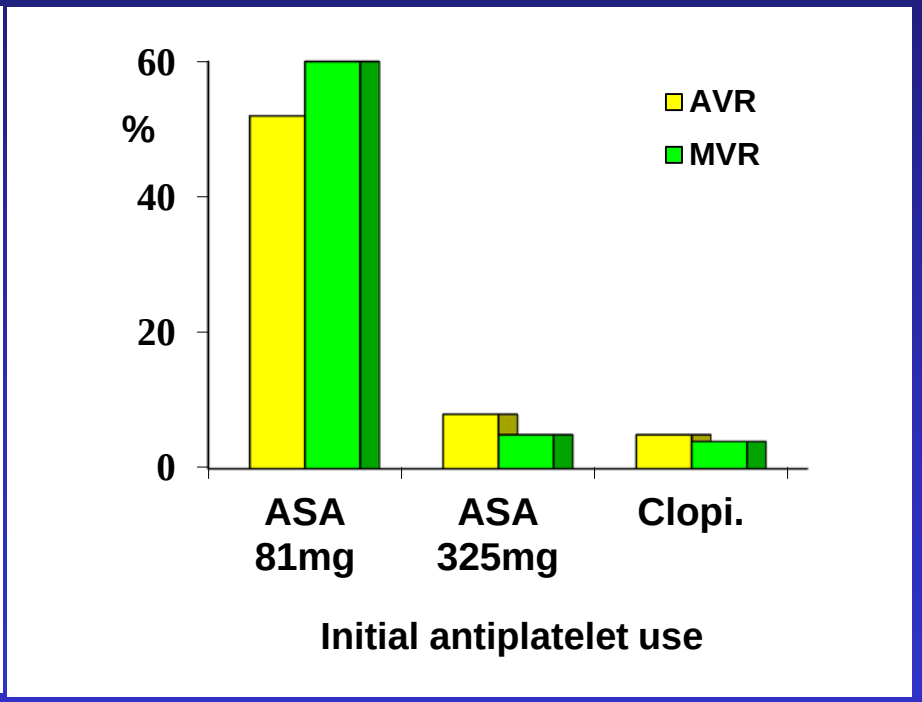
Use of Heparin and antiplatelet drugs

Survey based on case scenarios (57 Canadian surgeons)



Initial use of heparin

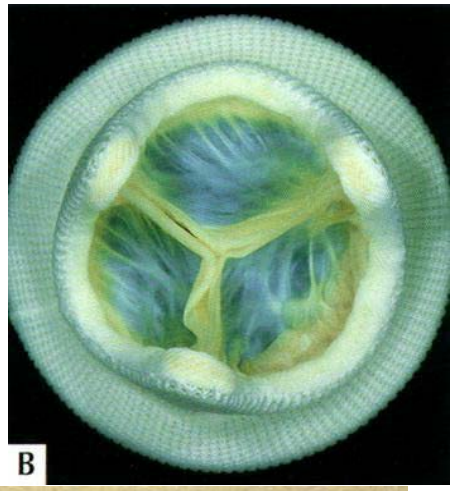
* Prophylactic dose

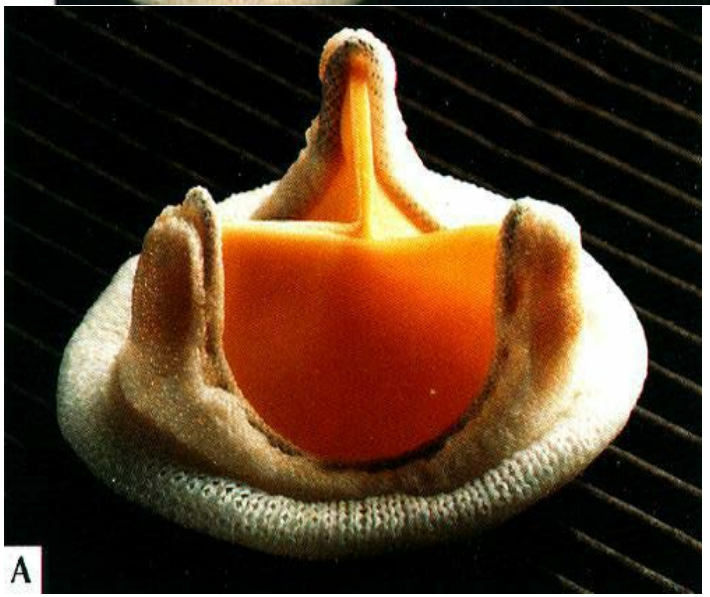


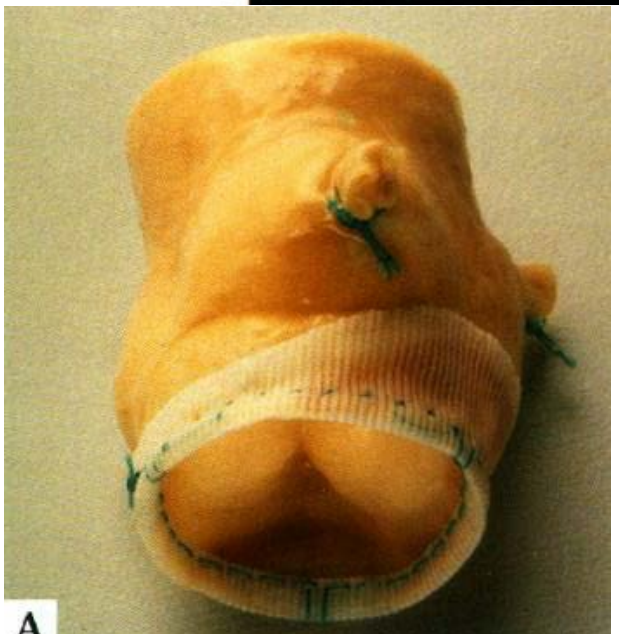
Initial antiplatelet use

(Kulik et al. J Heart Valve Dis 2006;15:581-7)

Bioprostheses







ESC 2007 Guidelines

Oral anticoagulation is recommended for the following situations:

- Lifelong for all patients with mechanical valves.[5,14,178]
- Lifelong for patients with bioprostheses who have other indications for anticoagulation, e.g. atrial fibrillation, or with a lesser degree of evidence, e.g. heart failure, impaired LV function (EF <30%).
- For the first 3 months after insertion in all patients with bioprostheses with a target INR of 2.5. However, there is widespread use of aspirin (low dose: 75–100 mg) as an alternative to anticoagulation for the first 3 months, but there are no randomized studies to support the safety of this strategy.[179]

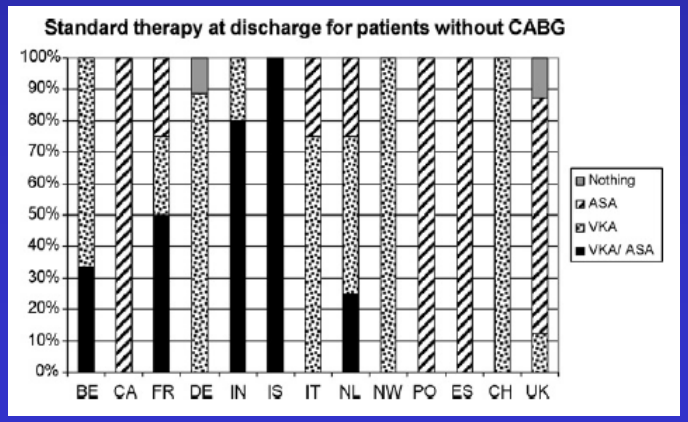
(Eur Heart J 2007;28:230-68)

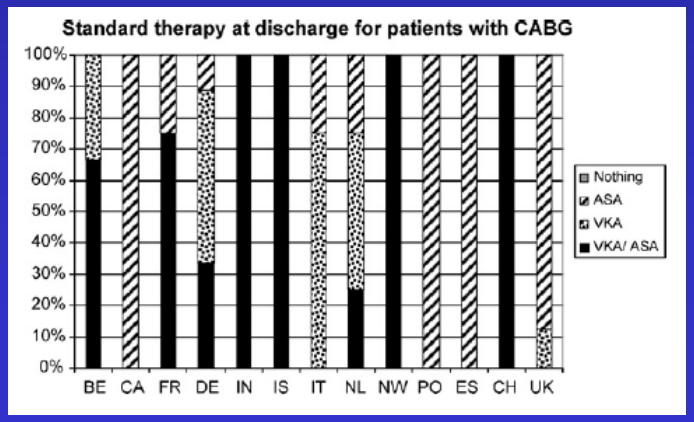
Anticoagulant Therapy after AVR with a Bioprosthesis: ACTION Registry

- Survey analysing anticoagulation in 48 centres from 13 countries after AVR using a Saint-Jude Epic bioprosthesis

	No CABG	CABG
VKA + ASA	20	39
VKA alone	43	24
ASA alone	33	37
Nothing	4	0

} VKA 63%



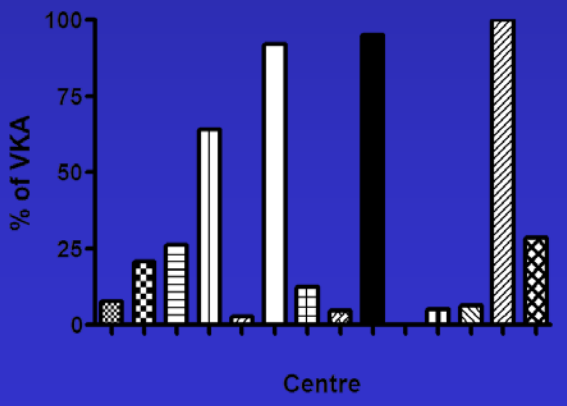


(Colli et al. Eur J Cardiothorac Surg 2008;33:531-6)

Anticoagulant Therapy after AVR with a Bioprosthesis: ARVA Registry

- Prospective French registry:
- 434 patients included in 14 centres
- Post-operative antithrombotic therapy
  - UFH or LMWH 99.5%
  - Aspirin 65%
  - VKA 9%
  - VKA + aspirin 19%
  - No antithrombotic 7%
- Factors associated with VKA use

	Odds Ratio	CI 95%	p
Coronary disease	1.2	0.4-3.5	0.77
AVR+ CABG	2.1	0.6-7.1	0.22
SV Arrhythmias	18.1	5.4-80.5	<0.0001
Center effect 10-60% >60%	 6 68	 3-14 19-240	 <0.0001 <0.0001



(Bouleti et al. ESC 2012)

Data from the Literature

- 28 series

- Limitations
  - Few comparatives studies
  - Mix of aortic and mitral bioprosthesis
  - Confounding factors
  - Only 2 prospectives series
    - One non-randomised comparative series
    - Only one randomised trial

(Nowell et al. Eur J Cariothoracic Surg 2007;31:578-85)

Anticoagulant Therapy after AVR with a Bioprosthesis

Non-Randomized Comparative Series

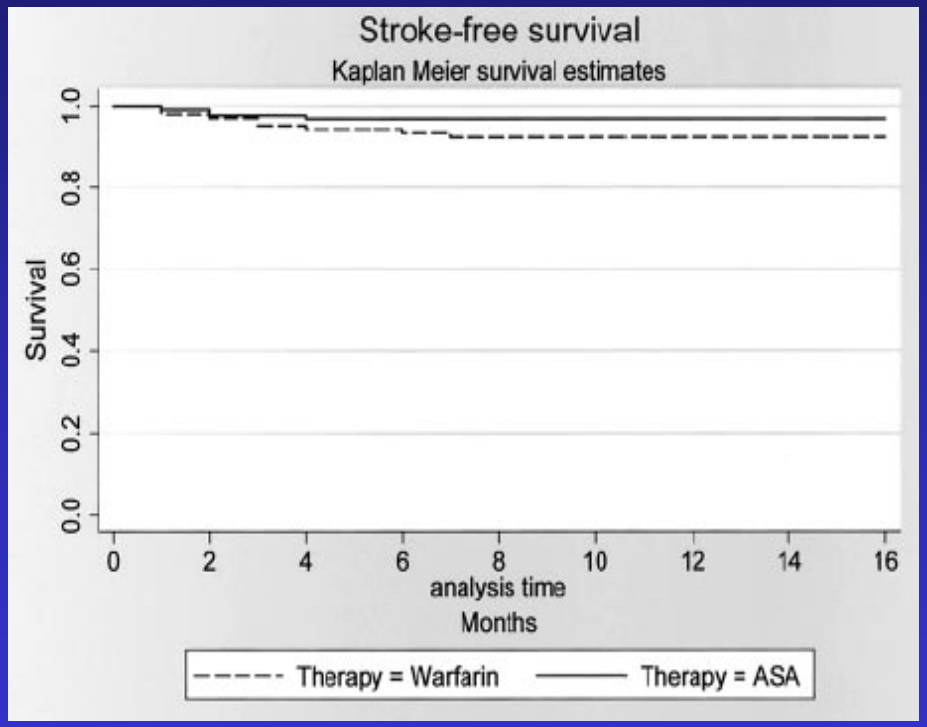


TABLE 3. Postoperative Data

	ASA (n=141)	Warfarin (n=108)	*P*
Perioperative (30-day) death	1 (0.7)	2 (1.9)	0.581*
Death at follow-up	3 (2.1)	5 (4.6)	0.299*
NYHA at follow-up (III–IV)	6 (4.3)	8 (7.4)	0.285
Postoperative cerebral ischemia (first episode)			
24 h to 3 mo	3 (2.1)	5 (4.6)	0.299*
>3 mo	1 (0.7)	3 (2.8)	0.319*
Major bleeding	3 (2.1)	4 (3.7)	0.473*
Need for AVR redo	2 (1.4)	1 (0.9)	1.000*

Values are number (%). AVR indicates aortic valve replacement.
*Fisher exact test.

(Gherli et al. Circulation 2004;110:496-500)

Anticoagulant Therapy after AVR with a Bioprosthesis

Non-Randomized Comparative Series

- Only prospective randomised trial
- 193 patients after bioprothetic valve replacement (181 AVR)
- Triflusal vs. AVK
- Composite endpoint of death, embolism, or severe bleeding at 3 months
  - 8.8% per 100 pts-year with triflusal
  - 11% per 100 pts-year under vit.K blockers *(p=0.57)*

(Aramendi et et al. Eur J Cardiothorac Surg 2005;27:854-60)

STS Database

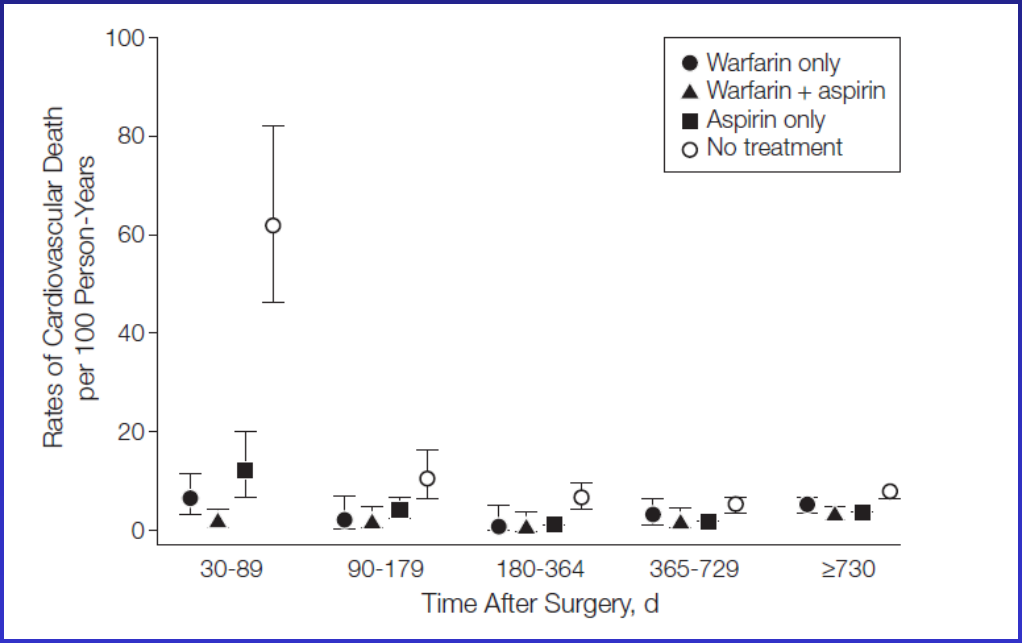
- 26 656 patients ≥ 65 yrs undergoing AVR (1997-2009)

	Aspirin (58%)	Warfarin (14%)	Warfarin + Aspirin (28%)
Death	3.0	4.0	3.1
Embolism	1.0	1.0	0.6
Bleeding	1.0	1.4	2.8

(Brennan et al. J Am Coll Cardiol 2012;60:971-7)

Danish Registry

- 4075 patients undergoing AVR (1997-2009)
- Higher incidence of thrombombolism and cardiovascular death when warfarin was discontinued within the first 6 mo.
- Of 881 pts without post-op warfarin, 181 received ASA



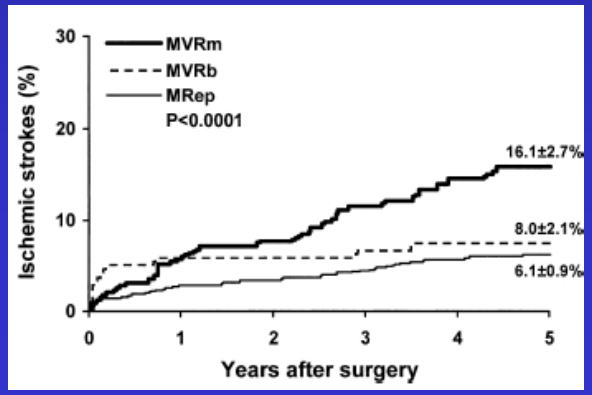
(Merie et al. JAMA 2012;308:2118-25)

Thromboembolic Events After Mitral Valve Surgery

- 1344 pts operated on for mitral valve disease
  897 valve repair, 447 MVR (mechanical: 231, biological: 216)
- Linearized rates of ischaemic strokes

	0-30 days	30-180 days	> 180 days
Repair	18±5	1.5±0.6	0.9±0.1
MVR mech	17±10	4.7±2.3	2.5±0.4
MVR bio	60±20	1.5±1.5	0.9±0.3

- Incidence of any first ischaemic stroke



(Russo et al. J AmColl Cardiol 2008;51:1203-11)

Early Thromboembolic Events after Valve Repair

- 350 patients undergoing mitral valve repair (2002-2005)
- Anticoagulation modalities according to the choice of the surgical team
- 12 thromboembolic events (11 TIA) over 44 ± 6 days [35-60]

	ASA	VKA	VKA + ASA	None
n=	66	230	19	35
Th.Emb.	0	7 (3%)	0	5 (14%)*
Bleeding	1 (1.5%)	1 (0.4%)	0	0

(p=0.03)*

(Meurin et al. Int J Cardiol 2008;126:45-52)

Post-Operative Anticoagulation for Bioprotheses

Guidelines

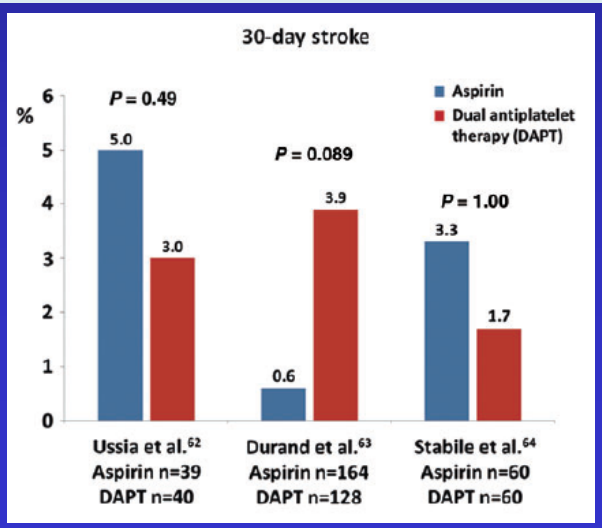
	Site	Bioprosthesis	
		3 post-operative months	>3 post-operative months
ESC/EACTS guidelines[14]	Aortic	Aspirin (IIa) VKA (IIb)	-
	Mitral	VKA	-
AHA/ACC guidelines[15]	Aortic	Aspirin (IIa) VKA (IIb)	Aspirin
	Mitral	VKA + aspirin	Aspirin
ACCP consensus[16]	Aortic	Aspirin	Aspirin
	Mitral	VKA + aspirin	Aspirin

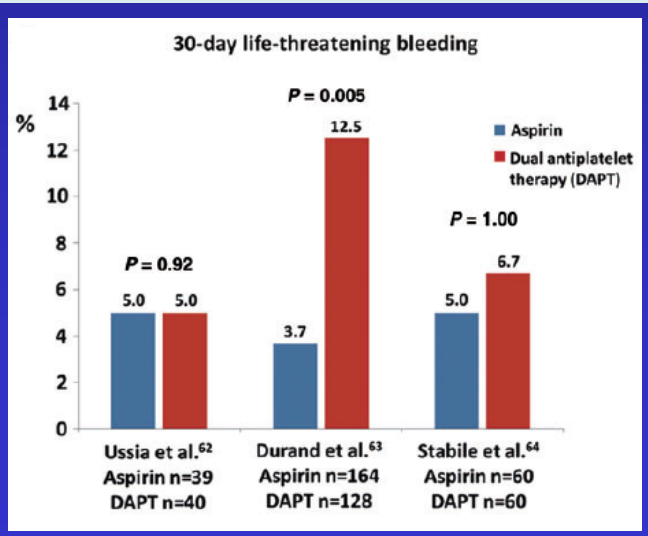
(Iung and Rodés-Cabau Eur Heart J 2004;35:2942-9)

Antithrombotic Therapy for TAVI

Guidelines

	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 and Rodés-Cabau Eur Heart J 2004;35:2942-9)

Conclusion

- Early heparin followed by vit.K blockers is favoured after mechanical valve replacement, but significant residual thromboembolism persistsfollowing MVR
- Aspirin alone is now favoured after bioprosthetic AVR
- Dual antiplatelet therapy is favoured after TAVI

  - Low level of evidence
  - Lack of standardization
  - Need for controlled trials