EuroValve

Faculty Disclosure

Bernard Iung

I disclose the following financial relationships:

Consultant forr Abbott, Boehringer Ingelheim, Valtech

Paid speaker for Edwards Lifesciences

Veterans Study

- 575 patients randomised between 1977 and 1982 (Bjork-Shiley or Hancock)
- 15-year FU

PROSTHESIS	AORTIC			MITRAL		
	MEC n=198	BIO n=196	p	MEC n=88	BIO n=93	p
Death	66±3	79±3	0.02	81±4	79±4	0.30
Embolism	18±4	18±4	0.66	18±5	22±5	0.96
Prosthetic thrombosis	2±1	1±1	0.33	1±1	1±1	0.95
Bleeding	51±4	30±4	0.0001	53±7	31±6	0.01
Valve failure	0±0	23±5	0.0001	5±4	44±8	0.0002
Reoperation	10±3	29±5	0.0004	25±6	50±8	0.15

(Hammermeister et al. J Am Coll Cardiol 2000;36:1152-8)

Edinburgh Heart Valve Trial

- 541 patients randomised between 1975 and 1979 (Bjork-Shiley or Hancock / Carpentier Edwards prosthesis)
- 20-year FU

PROSTHESIS	AORTIC			MITRAL		
	MEC n=109	BIO n=102	p	MEC n=129	BIO n=132	p
Survival	28±4	31±5	0.57	22±4	18±4	0.41
Embolism	24±6	39±9	0.13	53±7	32±6	0.32
Bleeding	61±8	42±12	0.001	53±8	37±11	0.39
Reoperation	7±3	56±8	0.0001	13±4	78±7	0.0001

(Oxenham et al. Heart 2003;89:715-21)

Mechanical and Biological Aortic Prostheses in Patients Aged 55-70 Years

Linearized rates of valve-related events

Variables	MP (n = 149) %/pt-yr (95% CI)	BP (n = 147) %/pt-yr (95% CI)	p Value
Thromboembolism	0.54 (0.14–0.94)	0.24 (0.03–0.51)	0.3
Bleeding	1.47 (0.81–2.13)	0.72 (0.25–0.19)	0.08
Endocarditis	0.38 (0.04–0.72)	0.24 (0.03–0.51)	0.7
Valve failure	0	2.17 (1.35–2.98)	0.0001
Valve thrombosis	0.23 (0.03–0.49)	0	0.2
Nonstructural dysfunction	0.23 (0.03–0.49)	0.24 (0.03–0.51)	0.6
Reoperation	0.62 (0.19–1.05)	2.32 (1.48–3.18)	0.0003

(Stassano et al. J Am Coll Cardiol 2009;54:1862-8)

Optimizing the Choice of the Prosthesis

- **Mechanical prosthesis** → **Risk of Bleeding**

  – Optimizing the choice of target INR

  – Antiplatelet drugs

  – Role of INR stability

- **Bioprosthesis** → **Risk of Reoperation**

  – ↓ primary failure with ↑ in age

  – ↑ in reoperation risk with age and comorbidity

Risk factors for thromboembolism

- **Prosthesis thrombogenicity**
  - Low
    - Carbomedics (aortic position), Medtronic Hall, St.Jude Medical, ON-X.
  - Medium
    - Other bileaflet valves.
  - High
    - Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley, other tilting-disc valves.

- **Patient-related risk factors**
  - Mitral, tricuspid, or pulmonary valve replacement.
  - Previous thromboembolism.
  - Atrial fibrillation.
  - Mitral stenosis of any degree.
  - Left ventricular ejection fraction < 35%.

Target international normalized ratio (INR) for mechanical prostheses

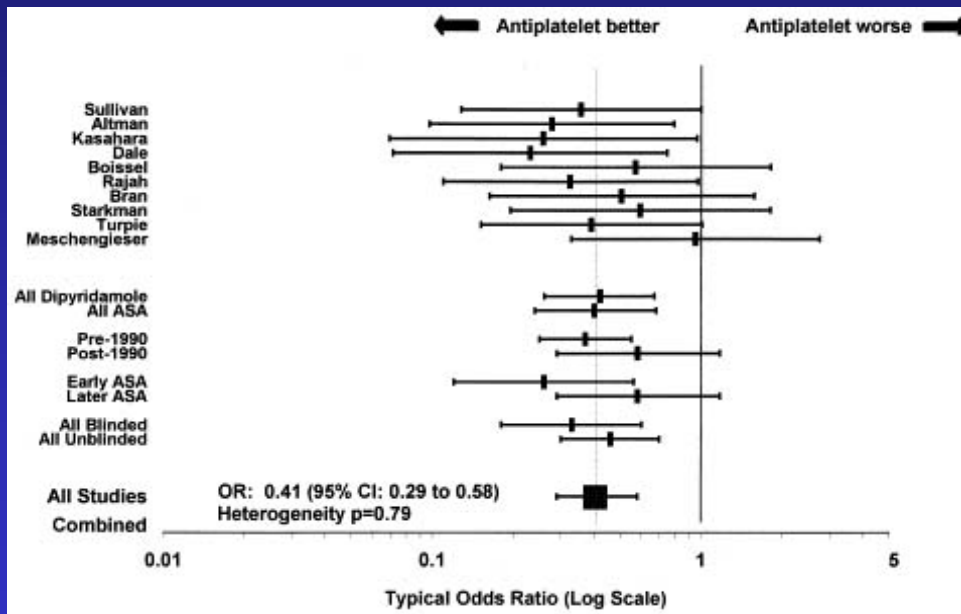| Prosthesis thrombogenicity	Patient-related risk factors	
	No risk factor	≥ 1 risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis:
- and concomitant atherosclerotic disease   IIaC
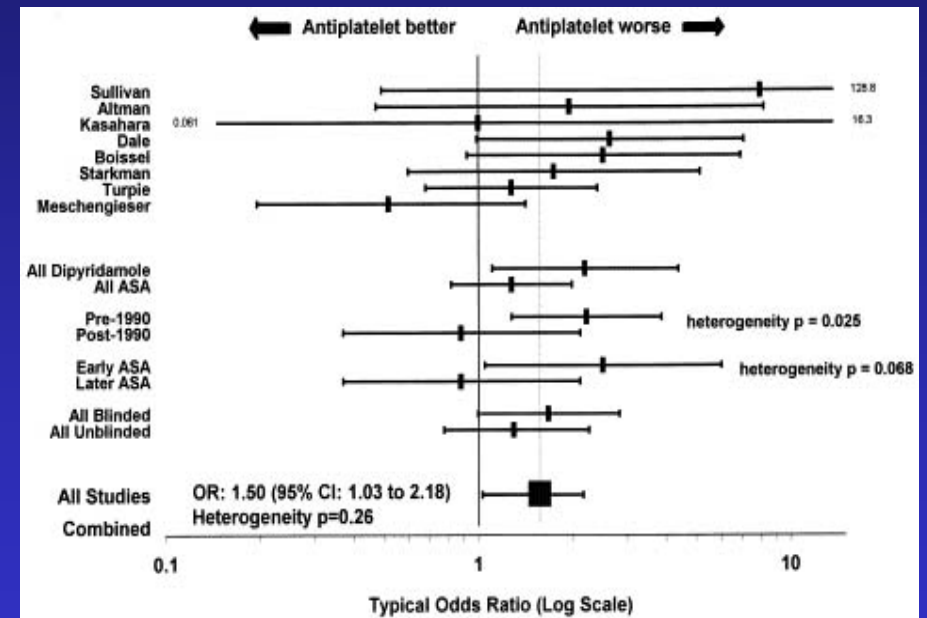- after thromboembolism despite adequate INR   IIaC

Antiplatelets + vit. K Antagonists
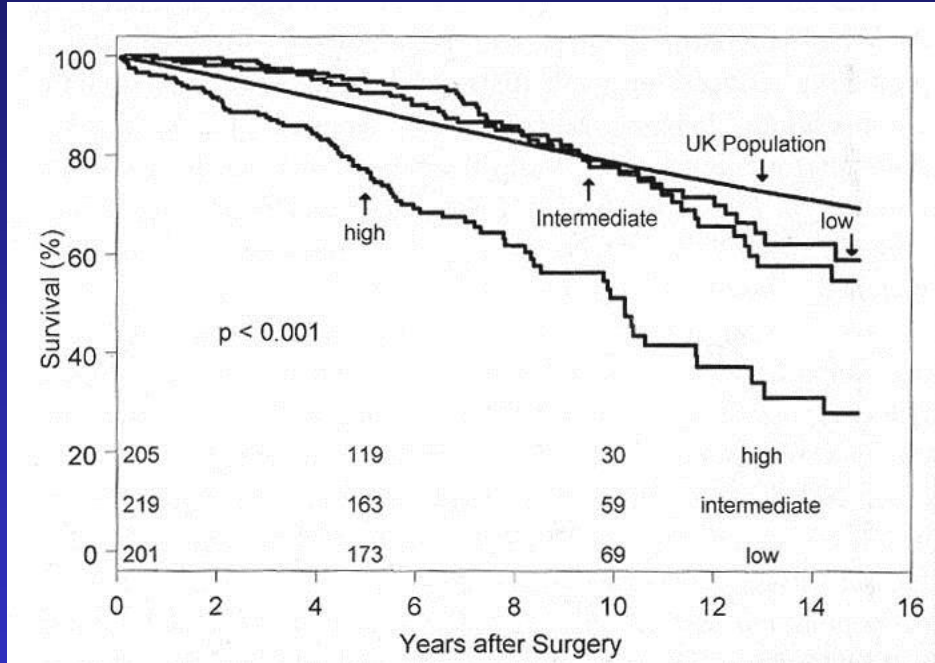## Meta - Analysis
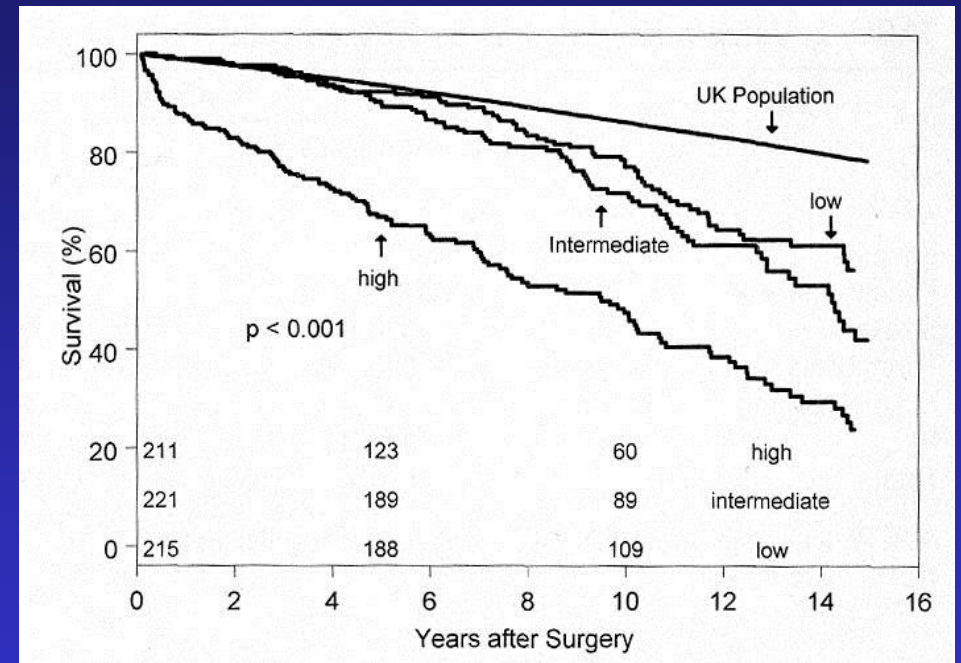

Thromboembolism

Major Bleeding

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

Anticoagulation Variability

1272 patients with Medtronic-Hall prosthesis

Aortic Prosthesis

Mitral Prosthesis

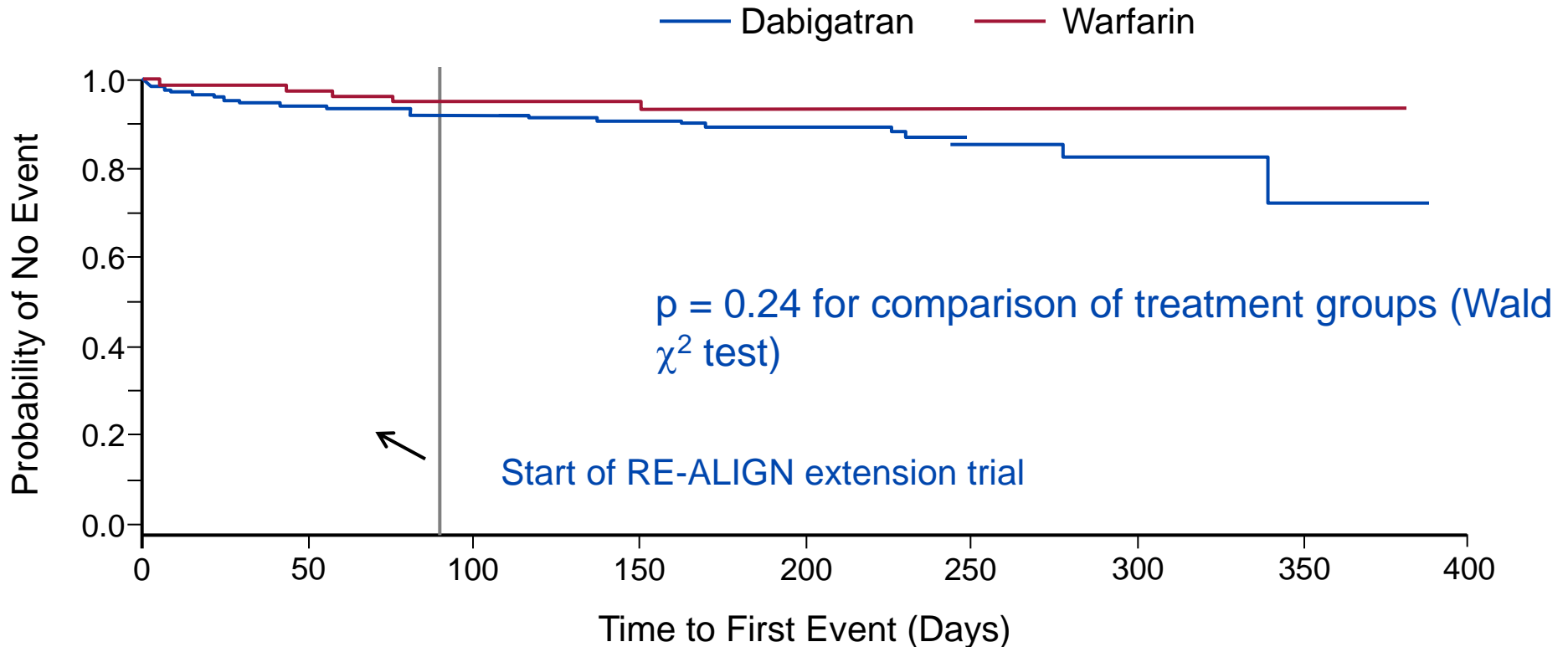*(Butchart et al. J Thorac Cardiovasc Surg 2002;123:715-23)*

Anticoagulation Variability
Survival – Multivariate Analysis

	Relative Risk	P <
INR Variability (↑ 20%)	1.81	0.001
Diabetes	1.64	0.007
Age (↑ 10 yrs)	1.63	0.001
Associated CABG	1.51	0.002
Male Gender	1.49	0.001
HTN	1.43	0.01
Thromboembolism / Bleeding	1.32	0.02
Prosthetic Regurgitation	1.28	0.016
NYHA Class III / IV	1.27	0.02
Small Prosthetic ∅	1.07	0.001

Re-Align trial: composite of a first thromboembolic event or death

Legend: —— Dabigatran —— Warfarin

Y-axis: Probability of No Event (0.0 to 1.0)

X-axis: Time to First Event (Days) (0 to 400)

p = 0.24 for comparison of treatment groups (Wald χ^2 test)

Start of RE-ALIGN extension trial

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

First thromboembolic event includes stroke, systemic embolism, transient ischemic attack, myocardial infarction.

(Eikelboom et al. N Engl J Med 2013;36:1206-14)
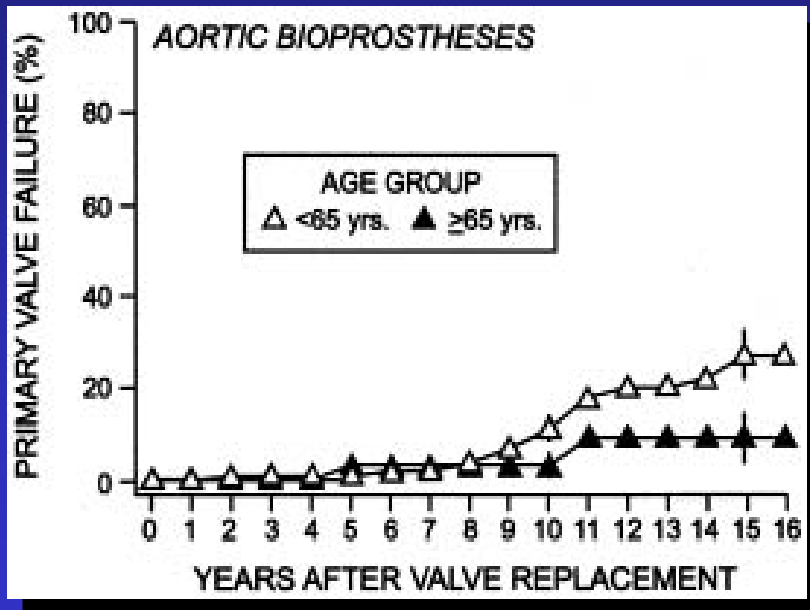
Primary Bioprosthesis Failure
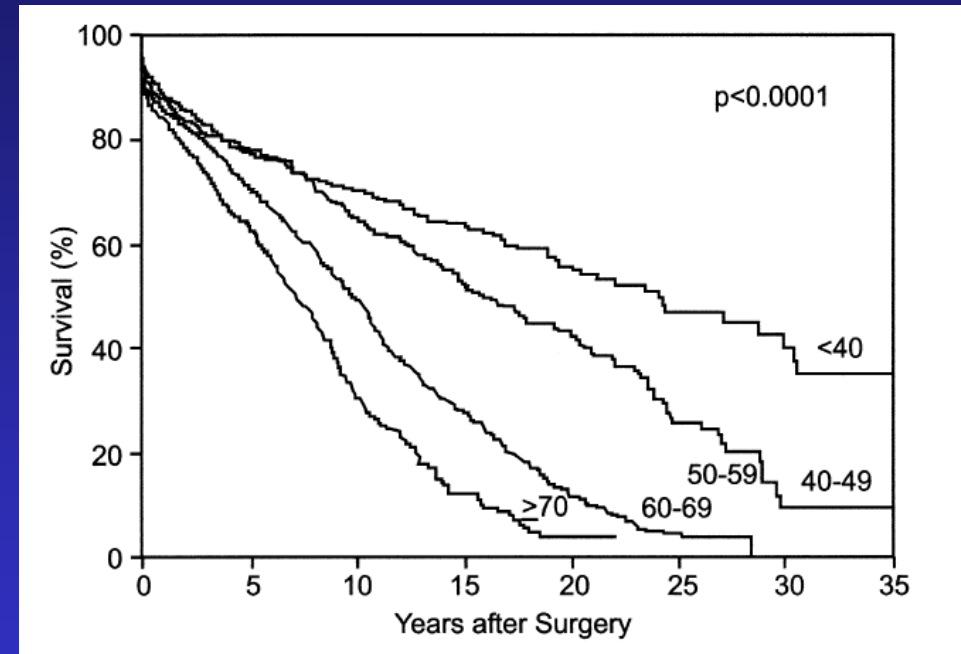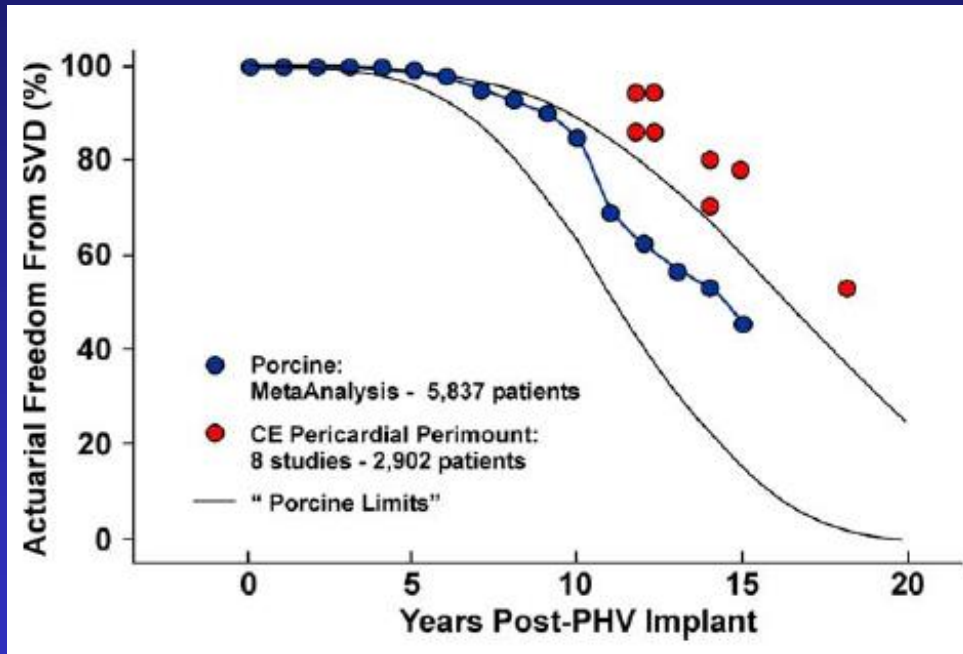
*(Rahimtoola
J Am Coll Cardiol 2010;55:2413-26)*

*(Grunkemeier et al.
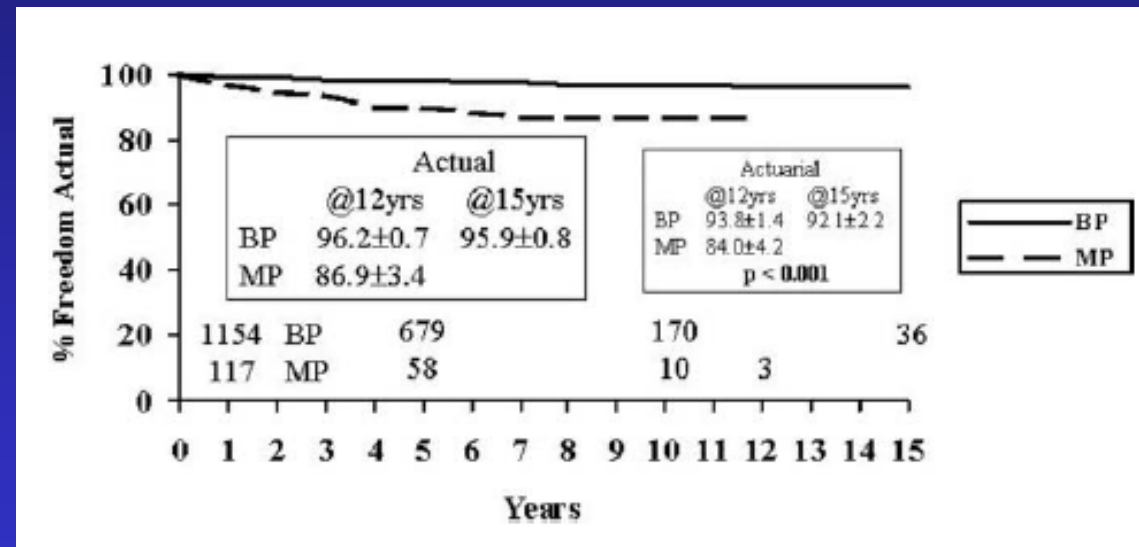J Heart Valve Dis 1999;8:466-71)*

Deterioration of Bioprosthesis

- **Decrease in the risk of primary deterioration**
    - To be compared with life expectancy
    - Take into account the risk related to reoperation

Freedom from valve-related mordidity in pts >70y.

(Hammermeister et al.
J Am Coll Cardiol 2000;36:1152-8)

(Chan et al.
J Thorac Cardiovsc Surg 2006;131:1267-73)

"Valve-in-Valve"

Herzzentrum Leipzig

Herzzentrum Leipzig
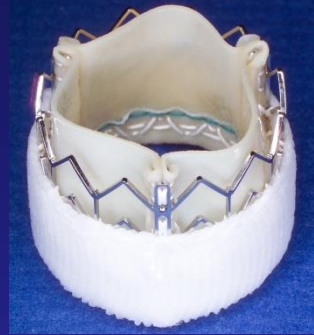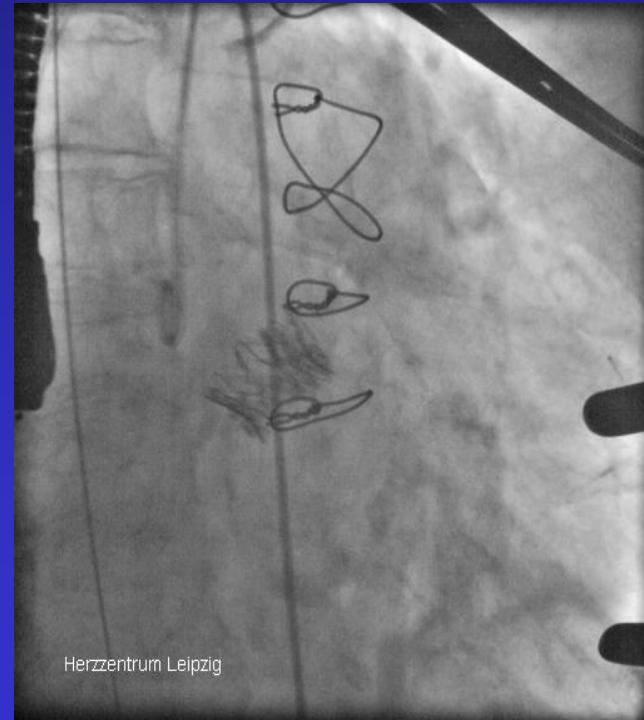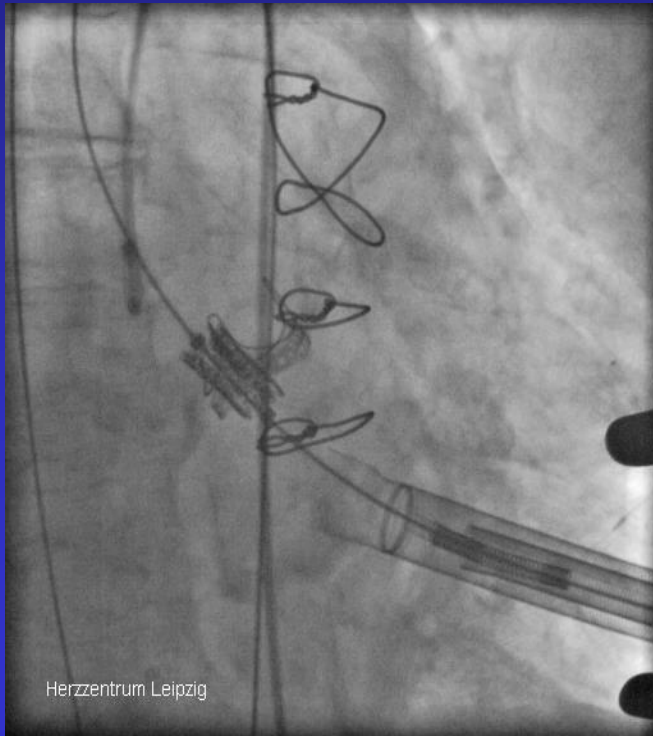
Outcome Simulation
Predited Events vs. Age
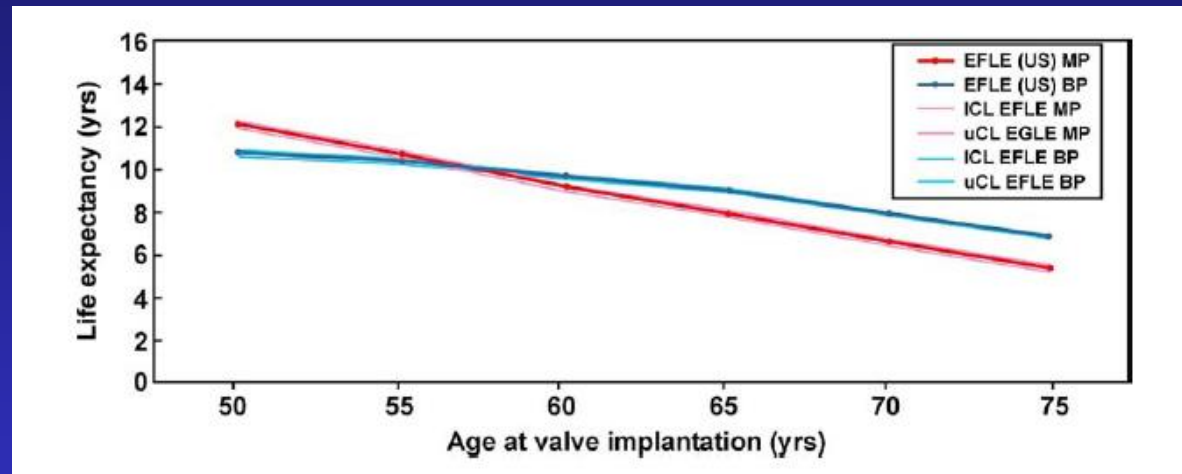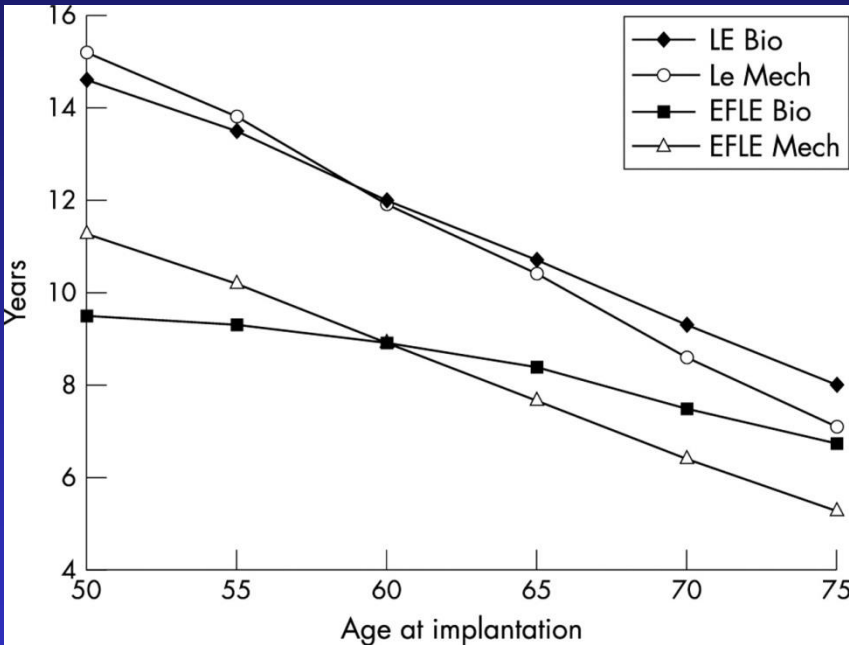
(Puvimanasinghe et al.
Heart 2004;90:1172-8)

(Van Geldorp et al.
J Thorac Cardiovasc Surg 2009;137:881-6)

Other Biological Substitutes

- Homografts
  - Similar durability
  - Increased complexity
    of reinterventions
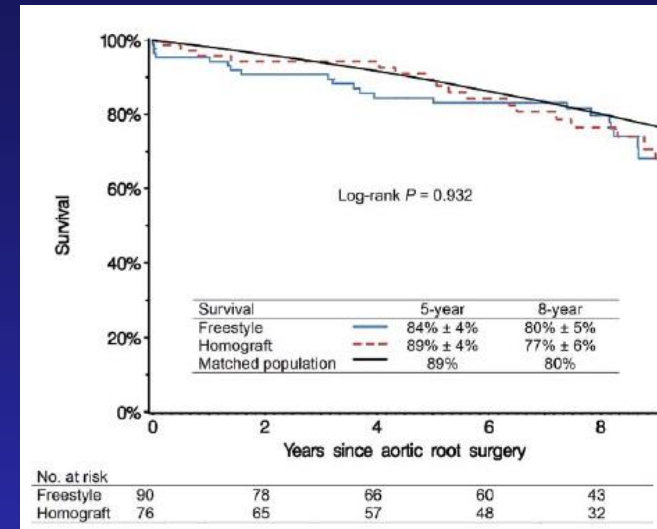
(El Hamamsy et al.
J Am Coll Cardiol 2010;55:368-76)

- Autografts
  - Complexity of intervention
  - 51% freedom from autograft
    reintervention at 18 years
    (Mokhles et al.
    Eur Heart J 2012;33:2213-24)
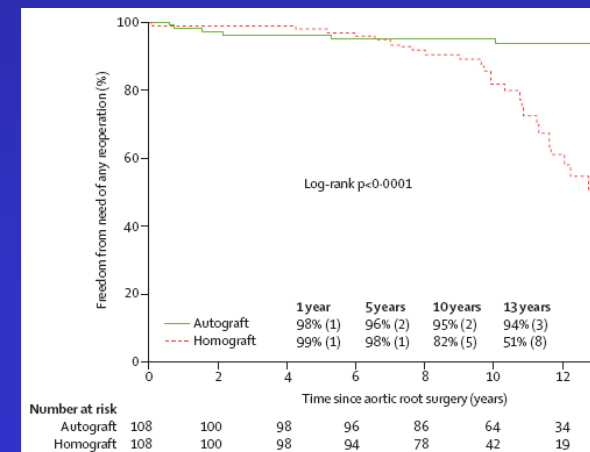
(El Hamamsy et al. Lancet 2010;376:624-31)

Mechanical Prosthesis and Pregnancy

1234 pregnancies in 976 patients (2/3 mitral prosthesis)

Anticoagulation	Embryopathy (%)	Spontaneous Abortion (%)	Thrombo-Embolism (%)	Maternal Death (%)
Vit.K blockers throughout pregnancy	6.4	25	3.9	1.8
Heparin throughout pregnancy	0	24	33	15
- low-dose	0	20	60	40
- adjusted-dose	0	25	25	6.7
Heparin during the first trimester, then vit.K blockers	3.4	25	9.2	4.2

(Chan et al. Arch Interm Med 2000;160:191-6)

Desire of Pregnancy

- **Difficulties of management of mechanical protheses**
  - embryopathy with vit K antagonists
  - increased risk of thromboembolism with heparin
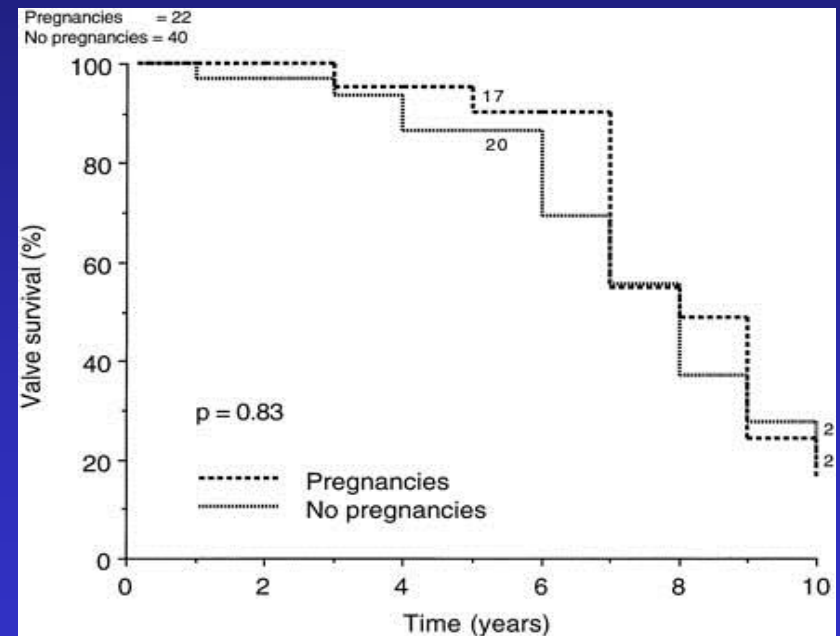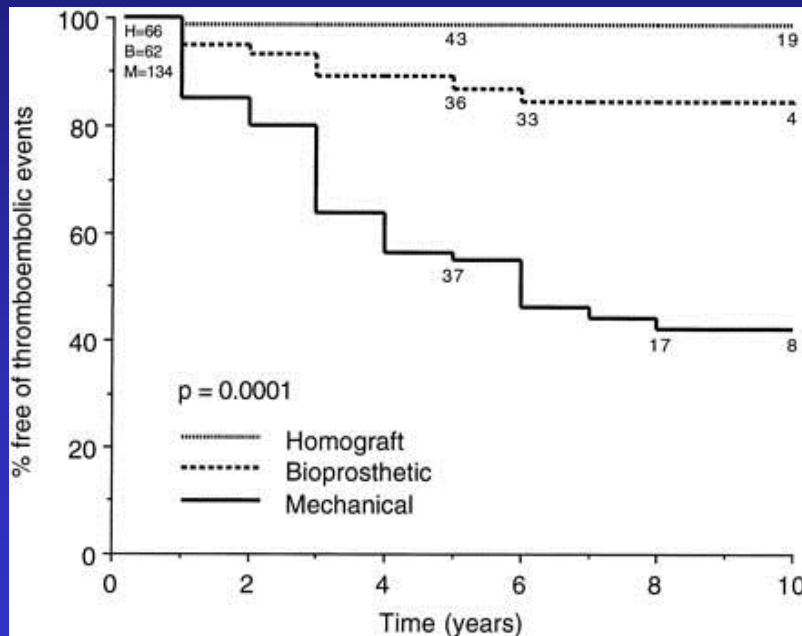
(North et al. Circulation 1999;99:2669-76)

➤ *Favour biological subtitutes in young women*

Dialysis

5858 dialysis patients undergoing valve surgery
(Aortic valve replacement in 3415 patients (58%)
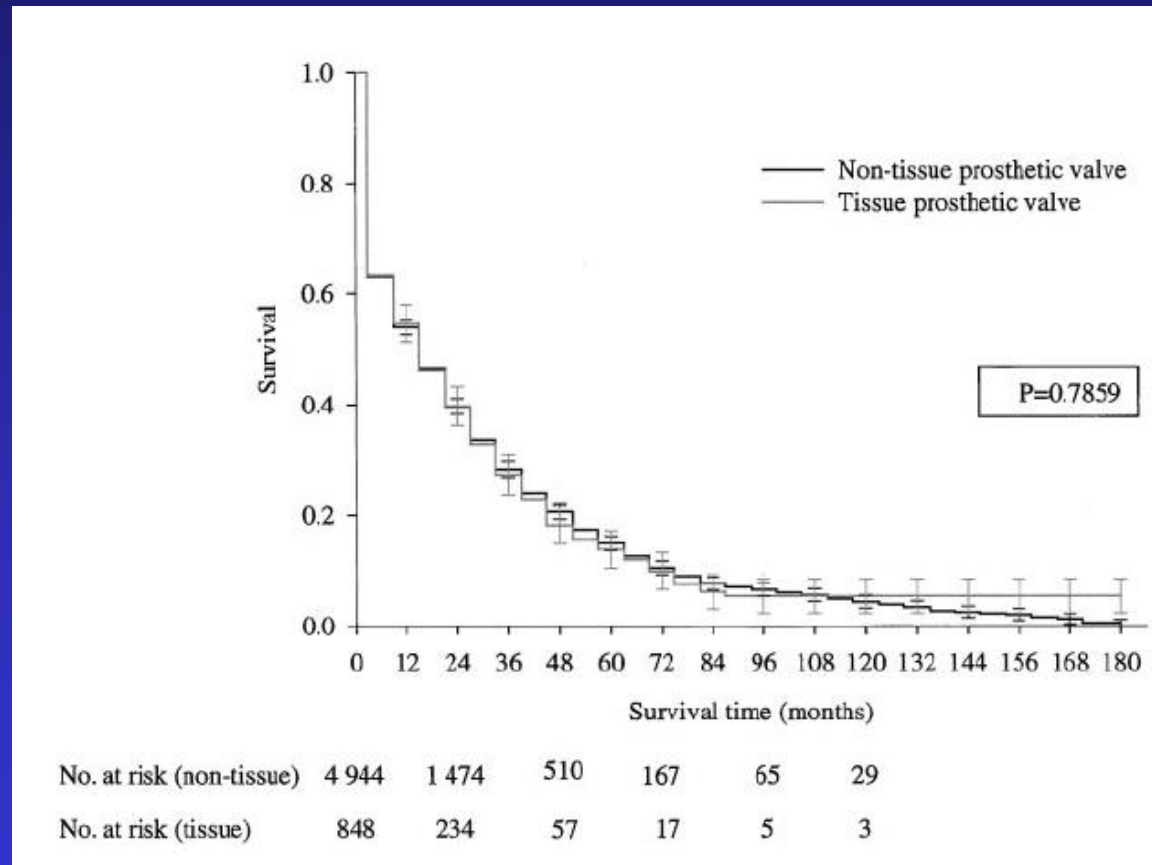
(Herzog et al. Circulation 2002;105:1336-41)

Choice of the aortic/mitral prosthesis : in favour of a mechanical prosthesis

	Class	Level
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications for long-term anticoagulation.	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration.	I	C
A mechanical prosthesis is recommended in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	I	C
A mechanical prosthesis should be considered in patients aged < 60 years for prosthesis in the aortic position and < 65 years for prosthesis in the mitral position.	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy, for whom future redo valve surgery would be at high risk.	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to high risk for thromboembolism.	IIb	C

EACTS

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Choice of the aortic/mitral prosthesis : in favour of a bioprosthesis

	Class	Level
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good quality anticoagulation is unlikely (compliance problems, not readily available) or contraindicated because of high bleeding risk (prior major bleed, comorbidities, unwillingness, compliance problems, lifestyle, occupation).	I	C
A bioprosthesis is recommended for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C
A bioprosthesis should be considered in patients for whom future redo valve surgery would be at low risk.	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	C
A bioprosthesis should be considered in patients aged > 65 years for prosthesis in aortic position or > 70 years in mitral position, or those with life expectancy lower than the presumed durability of the bioprosthesis.	IIa	C

Type of Valve Substitute / Age in Aortic Stenosis

(Iung et al. Eur Heart J 2003;24:1231-43)
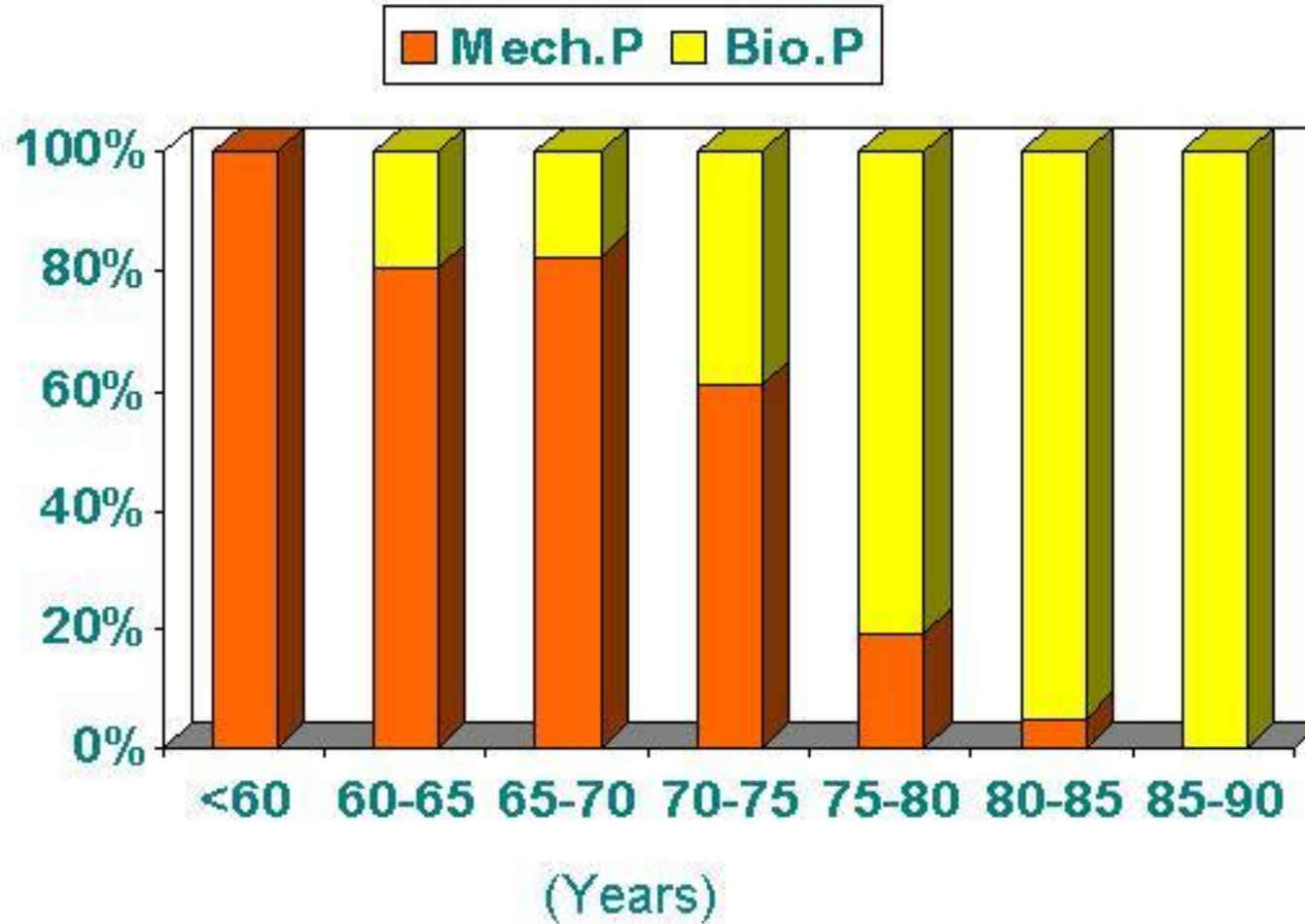
Valve Replacement for AS in the Elderly

Reasons for Choosing a Mechanical Prosthesis
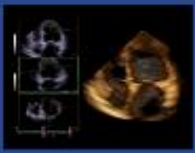
	(%)
Renal Failure, dialysis, or hypercalcemia	1
Need for Anticoagulation because of risk factors for thrombo-embolism	1
Physician's preference	75
Patient's Preference	19
Other	0

Temporal Trends and Type of Prosthesis
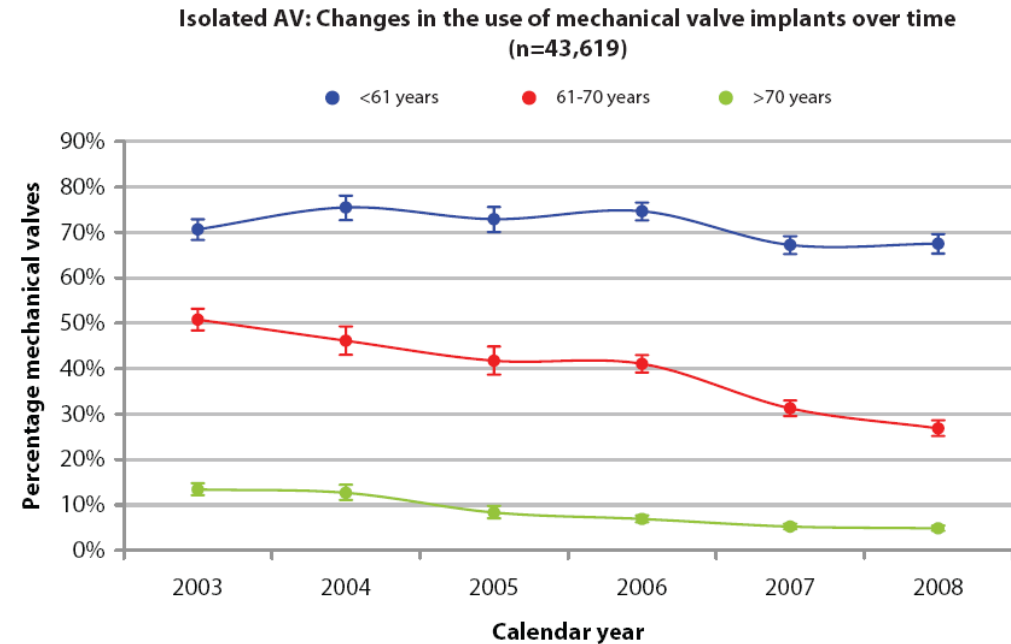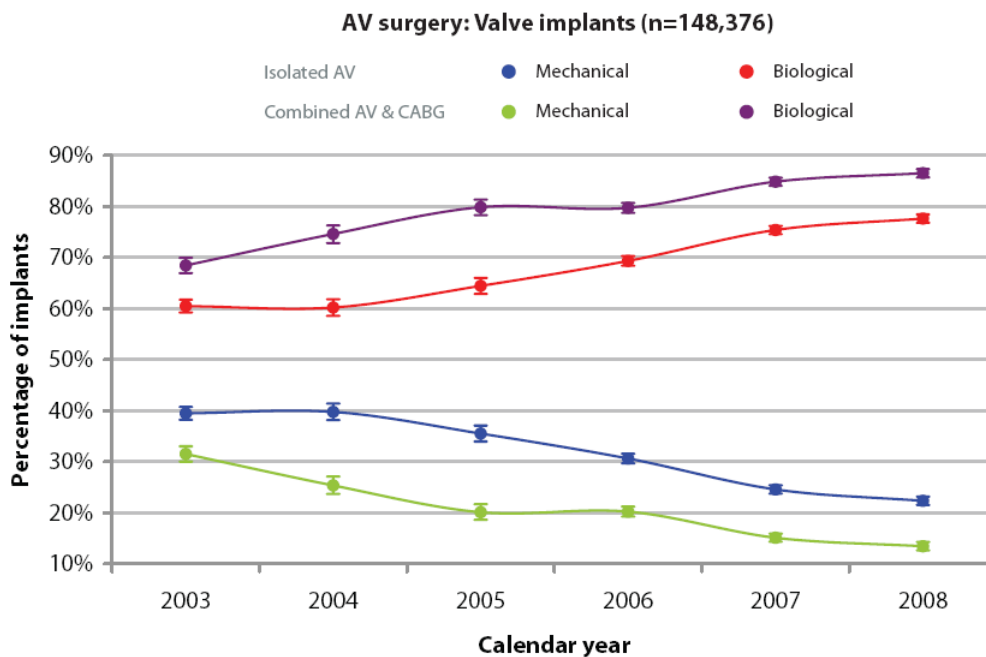
(Fourth EACTS Adult Cardiac Surgical Database Report 2010)

Conclusion

- Long-term follow-up data tend to increase indications of bioprostheses, in particular by lowering the age limit.

- ESC/EACTS Guidelines favour age ranges over thresholds.

- The choice of the type of prosthesis should not stress the role of age, but take into account patient wishes and specific situations.

- Transcatheter valve-in-valve implantations may further increase the percentage of bioprostheses.

- Importance of patient information and individualized approach.

Anticoagulant Therapy in the Elderly
Role of Age

(Palaretti et al. Arch Intern Med 2000;160:470-8)

- **Prospective study : 461 pts > 75 yrs vs. 460 yrs ≤ 70 yrs**
  matched for : sex, indications, centre

Incidence for 100 pts-yrs	> 75 yrs	≤ 70 yrs	p
All bleeding	9.9	6.9	0.07
- INR 2-3	4.5	3.9	
- INR 3-4.5	15	2.6	
Major bleeding	2.1	1.1	0.19

→ **Increase in bleeding risk with age**

→ **But moderate with low anticoagulation**

Anticoagulation: Randomized Trials

	Age (yrs)	MVR or double (%)	ASA (%)	Target INR	n=	TE	Maj bleed	All bleed
Saour	91% < 40	62	0	2.65	122	4.0	3.3	21.3
				9	125	3.7	7.2	42.4
Altman	52	32	100	2.0-3.0	51	1.9	-	3.9
				3.0-4.5	48	4.9	-	24.7
AREVA	59	4	0	2.0-3.0	188	1.9	4.0	11.2
				3.0-4.5	192	1.7	5.6	20.5
GELIA Ao	60	0	-	2.0-3.5	675	0.45	0.92	19.5
				3.0-4.5	672	0.66	0.78	25.4
GELIA Mi	61	100	-	2.0-3.5	182	2.75	0.92	34.6
				3.0-4.5	178	1.21	0.24	49.7
ESCAT Ao	60	0	7.6	1.8-2.8	2164	0.24	1.42	-
				2.5-4.5		0.46	1.78	-
ESCAT Mi	60	100	7.6	2.5-3.5	392	0	1.41	-
				2.5-4.5		0	0.50	-

Aspirin : Randomized Trials

	Age (yrs)	MVR or double (%)	Target INR	n=	TE	Maj bleed	All bleed
Turpie	58	54	3.0-4.5	184	1.9*	6.6	22
			3.0-4.5 + ASA	186	8.5*	8.5	35
Altman	57	29	2.0-3.0 + ASA 100mg	207	0.5	3.6	-
			2.0-3.0 + ASA 650 mg	202	1.1	5.1	-
Meschengieser	53	33	2.5-3.5 + ASA	258	1.3	1.1	-
			3.5-4.5	245	1.5	2.3	-

* Major embolism or vascular death

Anti-IIa et Anti-Xa

Intrinsic tenase (surface contact)

Extrinsic tenase (tissue damage)

Factor XII → Factor XIIa

Factor XI → Factor XIa

Factor IX → Factor IXa | Factor VIIIa | Factor VIIa | Tissue factor ← Factor VII

Factor X → Factor Xa | Factor Va

Factor II → Factor IIa (thrombin)

Fibrinogen → Fibrin
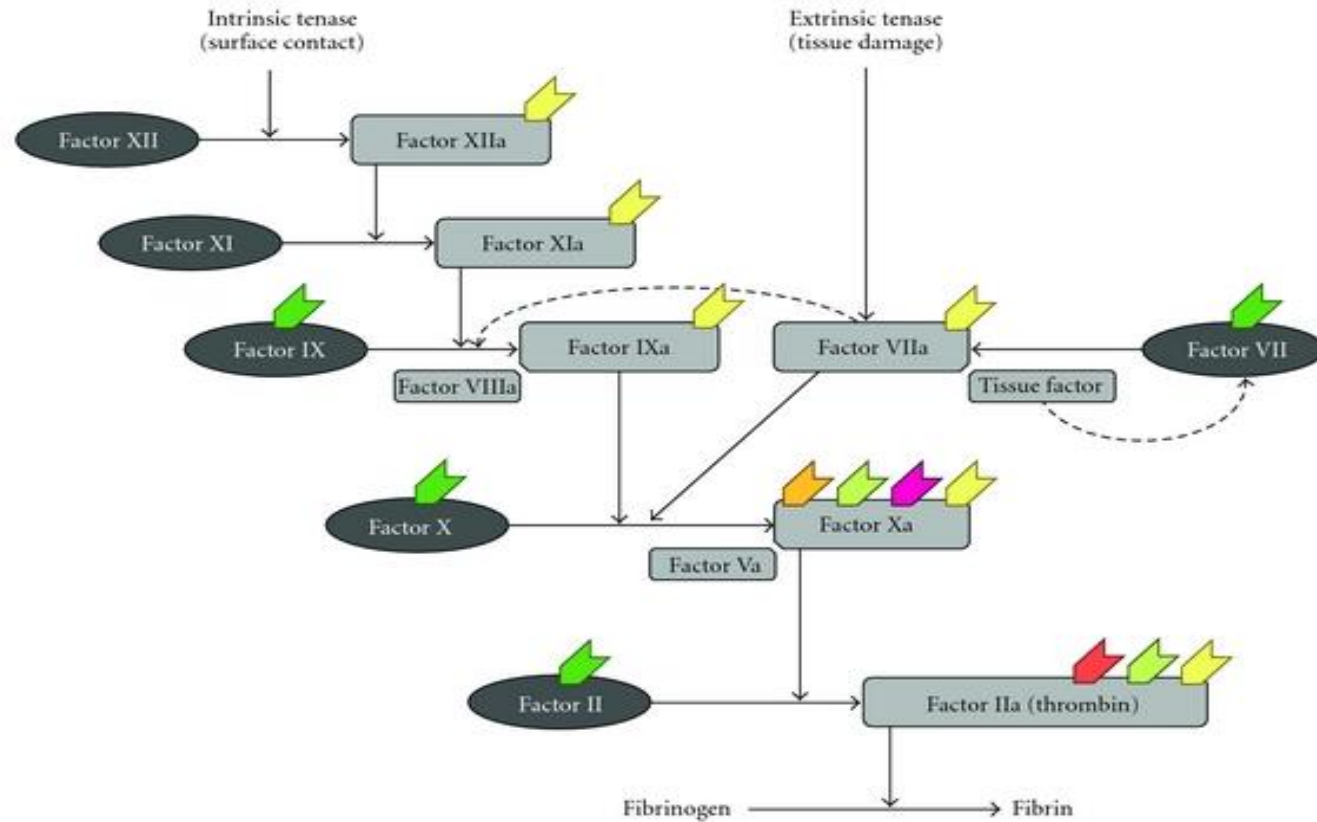
Rivaroxaban, Apixaban
Dabigatran

Direct Factor Xa inhibitor
Direct thrombin inhibitor
Fondaparinux (+AT)

Low molecular weight heparin (+AT)
Unfractionated heparin (+AT)
Vitamin K antagonist

Thromboses de Prothèses Mécaniques sous Dabigatran

Survenues 2 et 3 mois après introduction Dabigatran 150 mg x 2
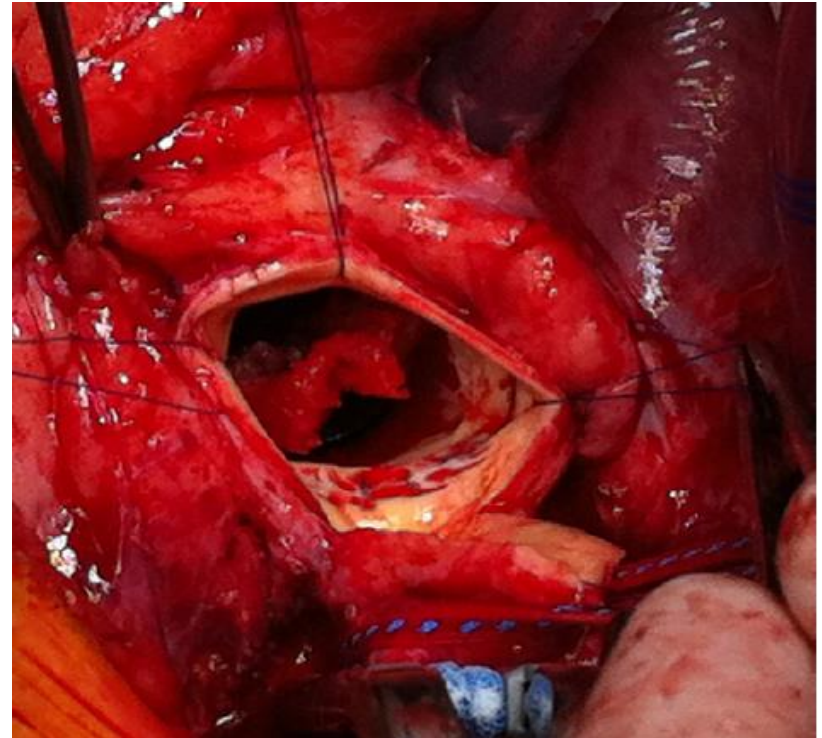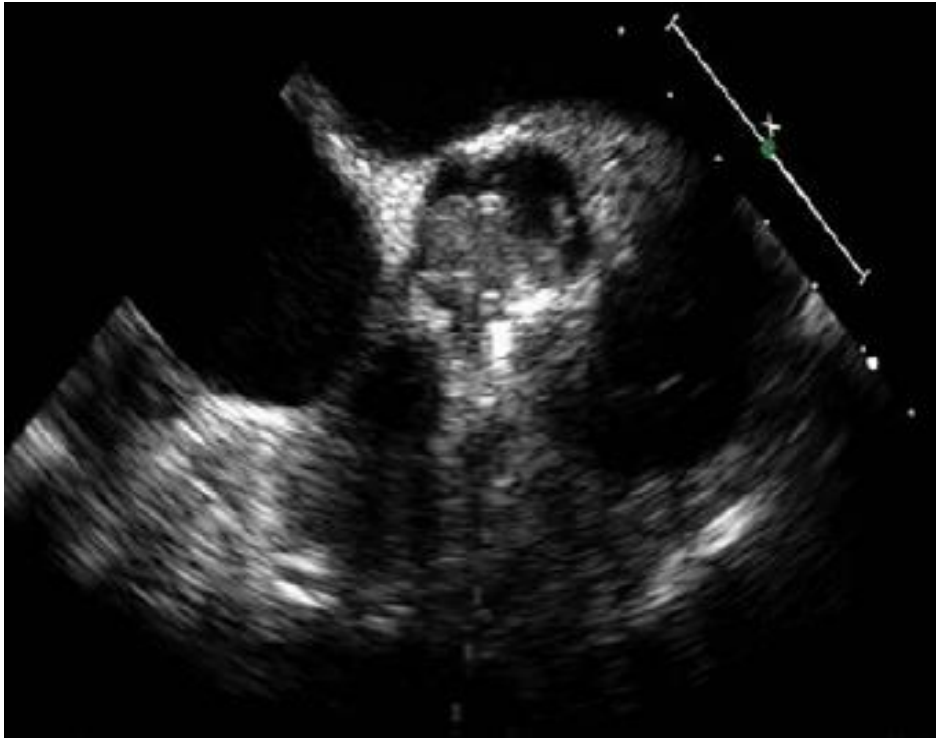
"The message is that dabigatran has really been approved only for patients who have non-valvular AF, but people are starting off-label use because of the perceived convenience of the medication"

(J Am Coll Cardiol 2012; DOI:10.1016/j.jacc.2012.06.039)

Indications for antithrombotic therapy after valvular surgery

	Class	Level
Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.	I	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C
Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation should be considered for the first 3 months after mitral valve repair.	IIa	C
Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIa	C
Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIb	C

INR Self-Management
Thrombo-Embolic Events

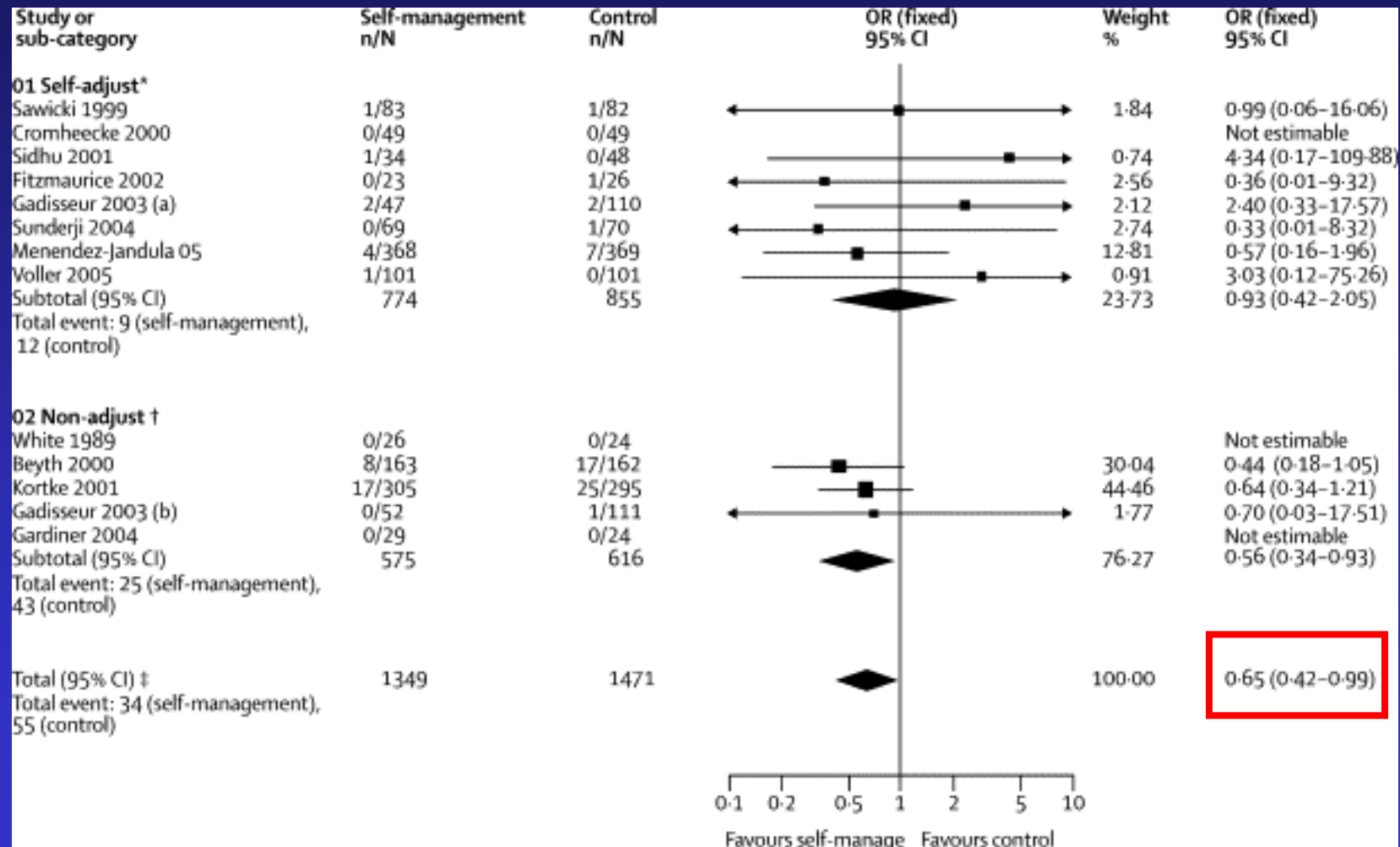| Study or sub-category	Self-management n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
01 Self-adjust*					
Sawicki 1999	0/83	2/82		3·50	0·19 (0·01–4·08)
Cromheecke 2000	0/49	1/49		2·08	0·33 (0·01–8·22)
Sidhu 2001	1/34	0/48		0·56	4·34 (0·17–109·88)
Fitzmaurice 2002	0/23	0/26			Not estimable
Gadisseur 2003 (a)	0/47	0/110			Not estimable
Sunderji 2004	0/69	2/70		3·45	0·20 (0·01–4·18)
Menendez-Jandula 05	4/368	20/369		27·68	0·19 (0·06–0·57)
Voller 2005	0/101	1/101		2·09	0·33 (0·01–8·20)
Subtotal (95% CI)	774	855		39·37	0·27 (0·12–0·59)
Total event: 5 (self-management), 26 (control)					
02 Non-adjust †					
White 1989	0/26	1/24		2·14	0·30 (0·01–7·61)
Horstkotte 1998	1/75	3/75		4·15	0·32 (0·03–3·19)
Beyth 2000	14/163	21/163		26·98	0·63 (0·31–1·29)
Kortke 2001	12/305	20/295		27·37	0·56 (0·27–1·17)
Gadisseur 2003 (b)	0/52	0/111			Not estimable
Gardiner 2004	0/29	0/24			Not estimable
Subtotal (95% CI)	650	691		60·63	0·57 (0·35–0·93)
Total event: 27 (self-management), 45 (control)					
Total (95% CI) ‡	1424	1546		100·00	**0·45 (0·30–0·68)**
Total event: 32 (self-management), 71 (control)					

0·1 0·2 0·5 1 2 5 10

Favours self-manage   Favours control

(Heneghan et al. Lancet 2006;367:404-11)
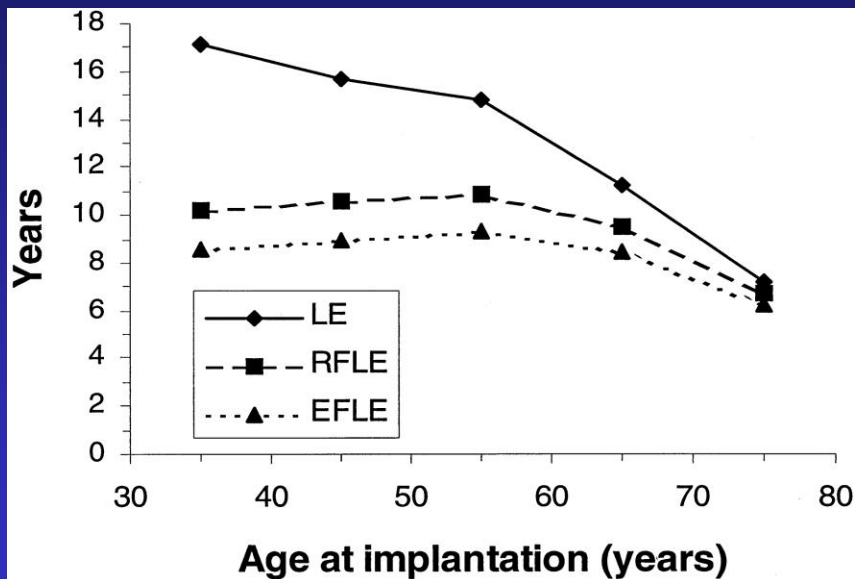
INR Self-Management

Severe Bleeding

(Heneghan et al. Lancet 2006;367:404-11)

Bioprosthesis Failure
In Patients 40 to 75 Years Old

- **Life expectancy vs. reoperation-free life expectancy**

Aortic bioprosthesis

(Puvimanasinghe et al. Circulation 2001;103:1535-41)

- **Opinion of the patient**

Difficulties in Valve Selection

- The incidence of thrombo-embolism and bleeding is approximately linear, but varies according to a number of factors :
    - Patient
    - Prosthesis (type, site)
    - Modalities of anticogulant therapy

    And should be interpreted by comparison with a general population

- The risk of bioprosthetic failure is not linear

- The risk linked to reoperation is variable

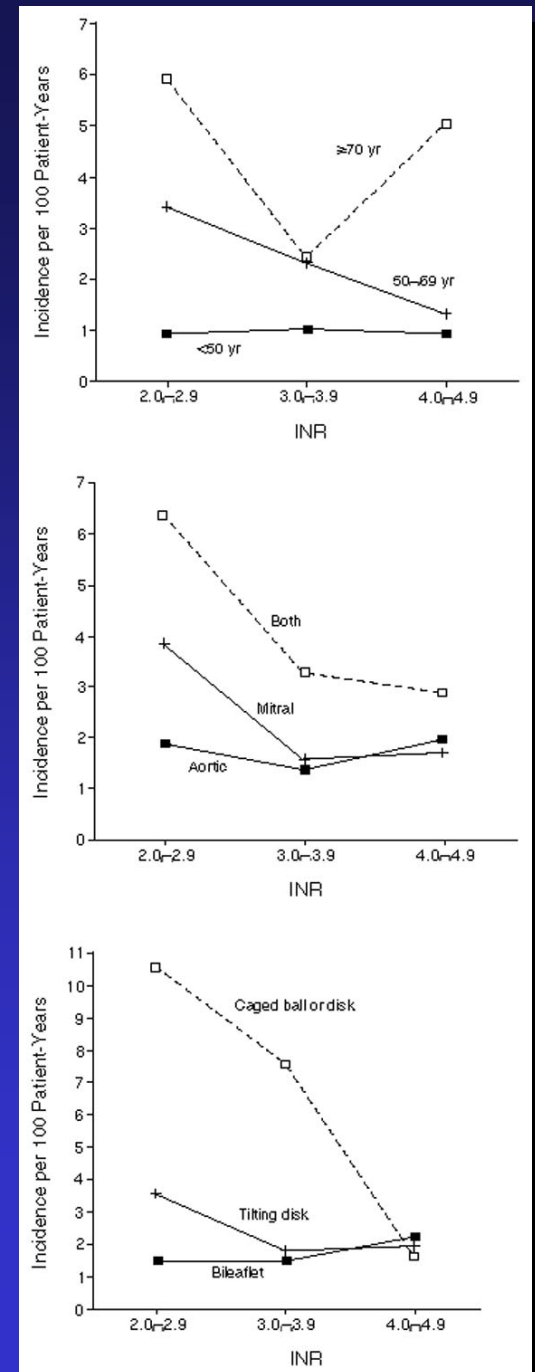   → ***Need for randomised series with a long follow-up***

Factors Influencing the Thromboembolic Risk

– age
– rhythm
– previous embolism
– prosthesis
  • site
  • type

→ **2 categories**
– Low risk (recent aortic prostheses with sinus rhythm)
– High risk (others)

(Cannegieter et al. N Engl J Med 1995;333:11-7)

ACC/AHA Guidelines

Table 37. Recommendations for Antithrombotic Therapy in Patients With Prosthetic Heart Valves

|	Aspirin (75–100 mg)	Warfarin (INR 2.0–3.0)	Warfarin (INR 2.5–3.5)	No Warfarin
Mechanical prosthetic valves				
AVR—low risk				
Less than 3 months	Class I	Class I	Class IIa	
Greater than 3 months	Class I	Class I		
AVR—high risk	Class I		Class I	
MVR	Class I		Class I	
Biological prosthetic valves				
AVR—low risk				
Less than 3 months	Class I	Class IIa		Class IIb
Greater than 3 months	Class I			Class IIa
AVR—high risk	Class I	Class I		
MVR—low risk				
Less than 3 months	Class I	Class IIa		
Greater than 3 months	Class I			Class IIa
MVR—high risk	Class I	Class I		

Depending on patients' clinical status, antithrombotic therapy must be individualized (see special situations in text). In patients receiving warfarin, aspirin is recommended in virtually all situations. Risk factors: atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable condition. International normalized ratio (INR) should be maintained between 2.5 and 3.5 for aortic disc valves and Starr-Edwards valves. Modified from McAnulty JH, Rahimtoola SH. Antithrombotic therapy in valvular heart disease. In: Schlant R, Alexander RW, editors. Hurst's The Heart. New York, NY: McGraw-Hill, 1998:1867–74 (934). Reprinted with permission from the McGraw-Hill Companies.

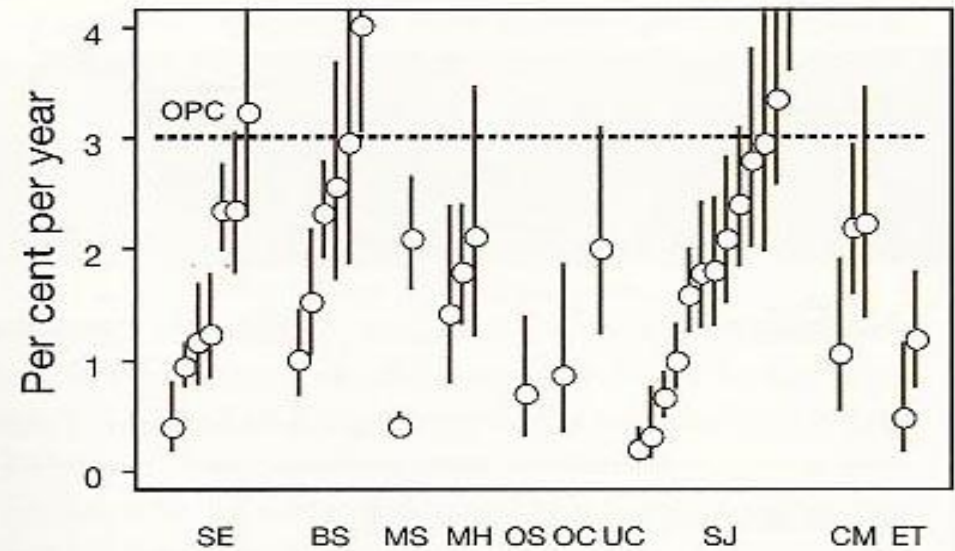   AVR indicates aortic valve replacement; and MVR, mitral valve replacement.

(Circulation 2008;118:e523-661)

Thromboembolism and Mechanical Prostheses

Observational Data
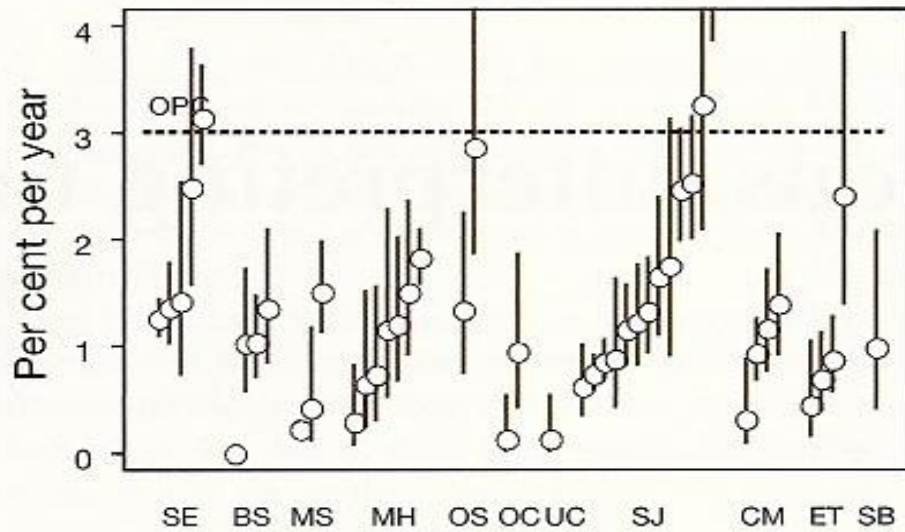
(Butchart et al. Heart Valve Disease.

A guide to patient management after surgery. Informa Heathcare 2006)