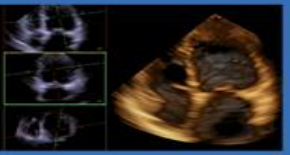

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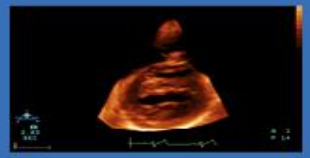
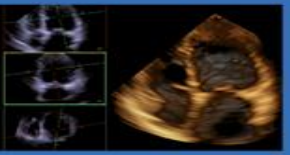


Spotlight on valvular heart disease guidelines. Prosthetic heart valves.

Bernard Iung
Bichat Hospital, Paris Diderot University
Paris, France

www.eurovalvecongress.com



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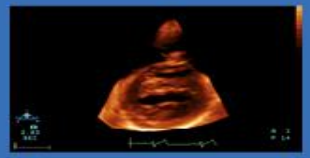

Faculty disclosure

First name - last name

I disclose the following financial relationships:

Consultant for Edwards Lifesciences
Paid speaker for Boehringer Ingelheim, Novartis

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

Recommendations	Class	Level
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contra-indications to long-term anticoagulation*.	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration**.	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	IIa	C

** Increased bleeding risk because of comorbidities, compliance concerns or geographic, lifestyle or occupational conditions*

*** Young age (<40 years), hyperparathyroidism*

Choice of the aortic/mitral prosthesis in favour of a mechanical prosthesis *(continued)*

Recommendations	Class	Level
A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and <65 years for prostheses 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 thrombo-embolism.	IIb	C

** Between 60 and 65 (aortic prosthesis) / 65 and 70 years (mitral prosthesis), both valves are acceptable and the choice requires careful analysis of factors other than age*

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

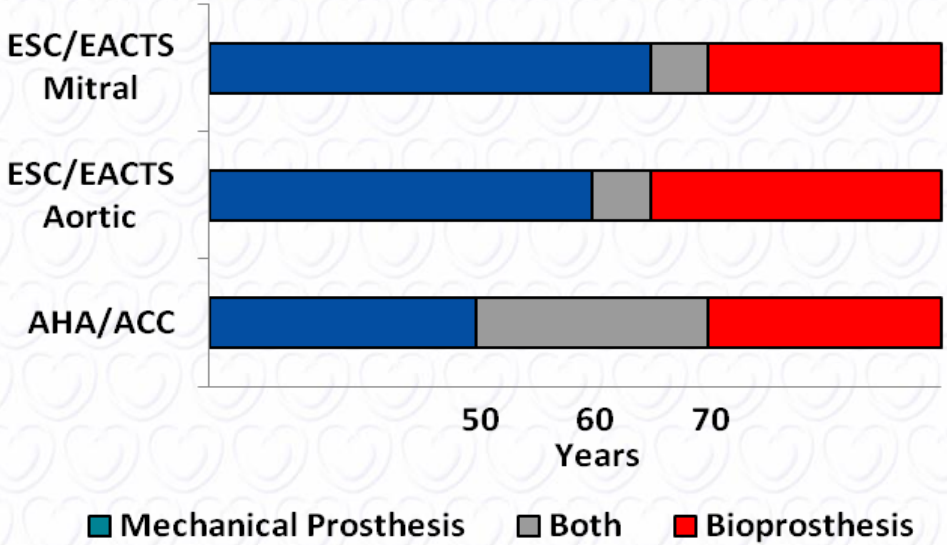
Recommendations	Class	Level
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good-quality anticoagulation is unlikely (compliance problems, not readily available) or contra-indicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, compliance problems, lifestyle, occupation).	I	C
A bioprosthesis is recommended for reoperation for mechanical valve thrombosis despite good long-term anti-coagulant control.	I	C

Choice of the aortic/mitral prosthesis in favour of a bioprosthesis *(continued)*

Recommendations	Class	Level
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery.	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 a prosthesis in the aortic position, or age >70 years in a mitral position*, or those with life expectancy lower than the presumed durability of the bioprosthesis.	IIa	C

** Between 60 and 65 (aortic prosthesis) / 65 and 70 years (mitral prosthesis), both valves are acceptable and the choice requires careful analysis of factors other than age*

Age thresholds and choice of the type of prosthesis



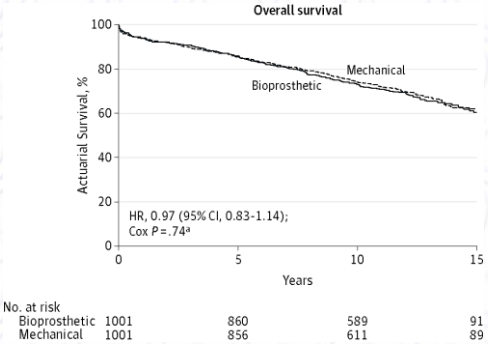
2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx391)

Long-term survival and type of prosthesis

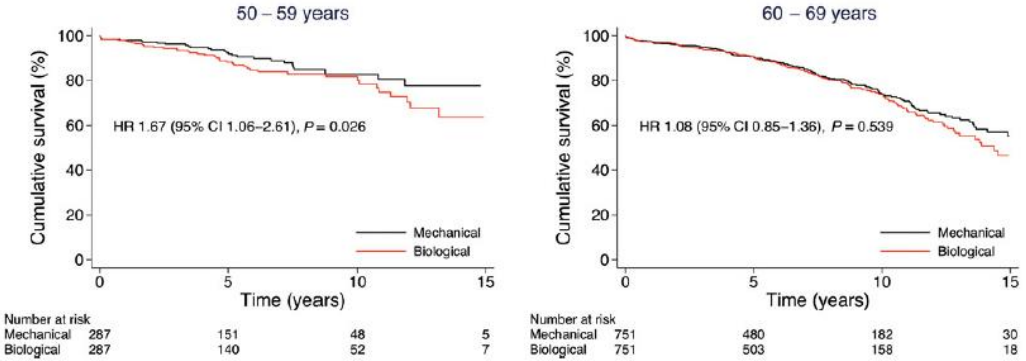
Observational series in pts aged 50-69 yrs with mechanical or biological aortic prostheses.

Comparison of survival in propensity-matched groups.

2 groups of 1001 pts



2 groups of 1099 pts



No difference for 50-59 and 60-69 yrs

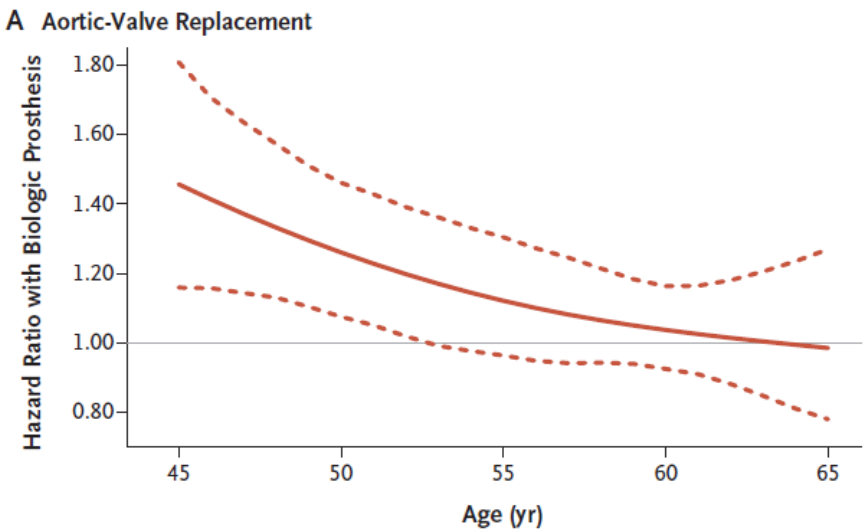
(Chiang et al. JAMA 2014;312:1323-29)

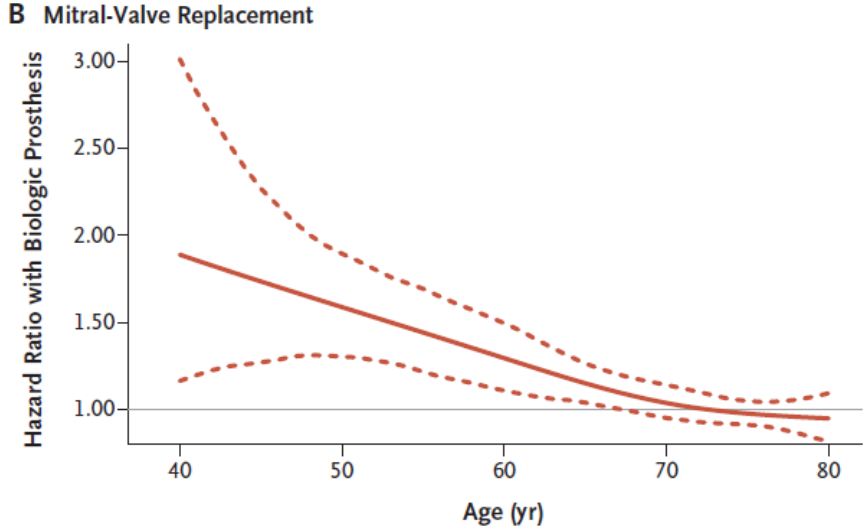
(Glaser et al. Eur Heart 2016;37:2658-67)

Survival with mechanical or biologic prostheses

9 942 patients with AVR

15 503 patients with MVR





Age-dependent hazard of death with bioprosthesis vs. mechanical prosthesis

(Goldstone et al. N Engl J Med 2017;377:1847-57)

Indications for antithrombotic therapy for mechanical prostheses

Recommendations	Class	Level	
Mechanical prosthesis			
Oral anticoagulation using a VKA is recommended lifelong for all patients.	I	B	
Bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted.	I	C	
The addition of low-dose aspirin (75-100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C	
The addition of low-dose aspirin (75-100 mg/day) to VKA may be considered in the case of concomitant atherosclerotic disease.	IIb	C	New
INR self-management is recommended provided appropriate training and quality control are performed.	I	B	New

(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx391)

Target INR for mechanical prostheses

Prosthesis thrombogenicity	Patient-related riskfactors[a]	
	None	≥1 risk factor
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

[a] *Mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis of any degree, LVEF <35%*

[b] *Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St. Jude Medical, On-X, Sorin Bicarbon*

[c] *Other bileaflet valves with insufficient data*

[d] *Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Björk-Shiley and other tilting-disc valves*

Lower target INR for mechanical aortic prostheses ?

IIb	B-R	A lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors (209).

(Nishimura et al. J Am Coll Cardiol 2017;70:252-89)

PROACT trial

- **375 pts randomized after AVR (ON-X valve): INR [1.5-2.0] vs. [2.0-3.0] (+ASA 81 mg/j). Decrease of major (1.5% vs. 3.3%, p=0.047) and minor bleeding (1.3% vs. 3.4%, p=0.021) with no difference in thromboembolic events (3.0% vs. 1.8%, p=0.18).**

- **Limitations**
  - Single type of prosthesis
  - Lack of statistical power for thromboembolic risk
  - Weekly INR self-monitoring

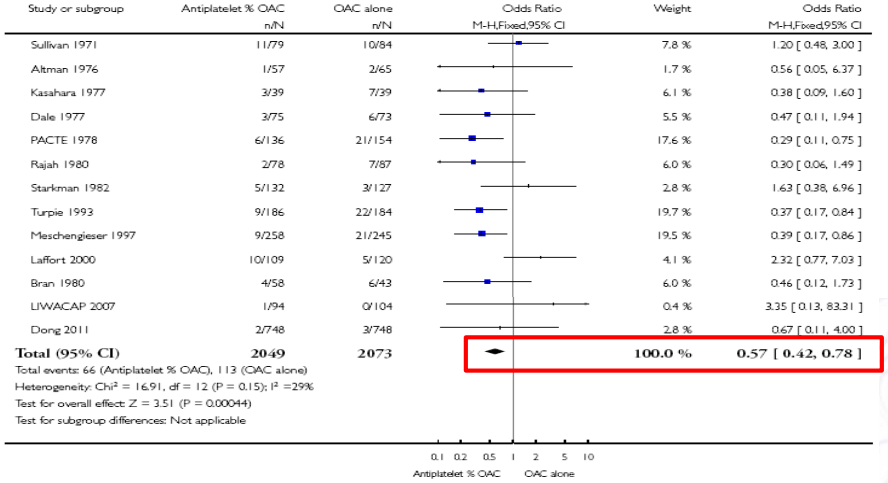
(Puskas et al. J Thorac Cardiovasc Surg 2014;147:1202-11)

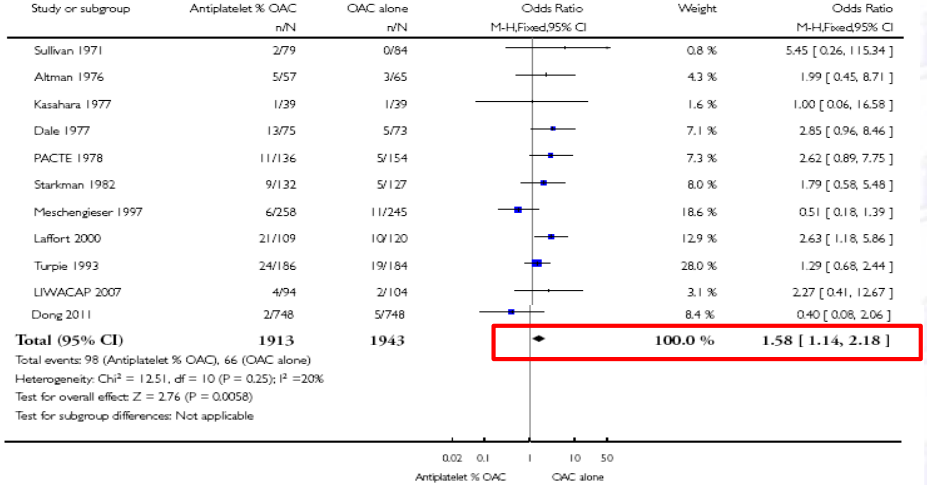
Systematic association of aspririn for mechanical prostheses ?

I	A

Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (178,189,190).

(Nishimura et al. J Am Coll Cardiol 2017;70:252-89)





Thromboembolism

Major Bleeding

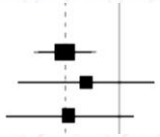
(Massel and Little Cochrane Database Syst Rev 2013:CD003464)

INR self-monitoring

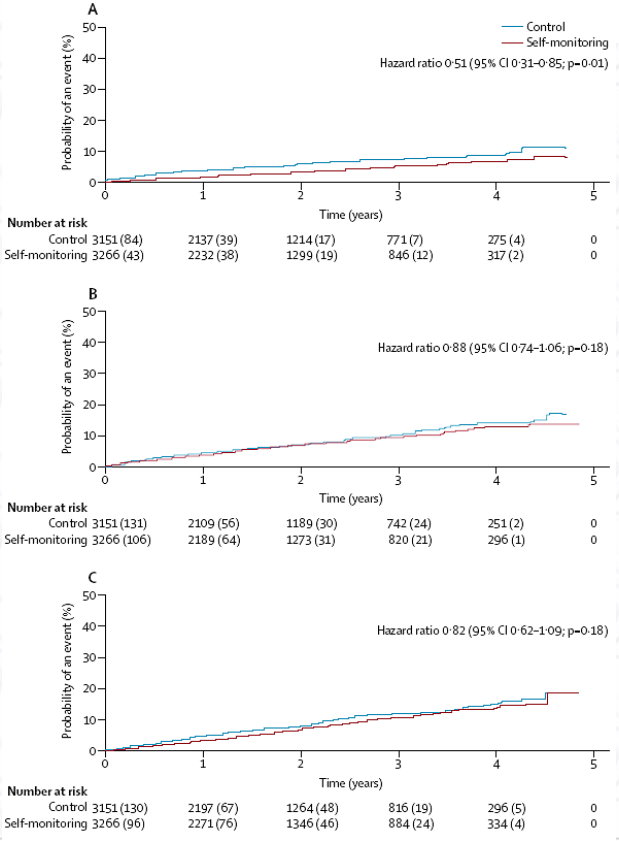
Meta-analysis of 11 randomized trials (6417 pts)

- Significant benefit for the prevention of thromboembolic events
- Particularly marked benefit in patients with mechanical prostheses

Indication				
Mechanical valve	36/1132	63/1040	−16·22	24·58
Atrial fibrillation	70/1629	69/1623	−0·06	34·58
Other	8/261	20/237	−3·87	6·30



(Heneghan et al. Lancet 2012;379:322-34)



Indications for antithrombotic therapy for mechanical prostheses *(continued)*

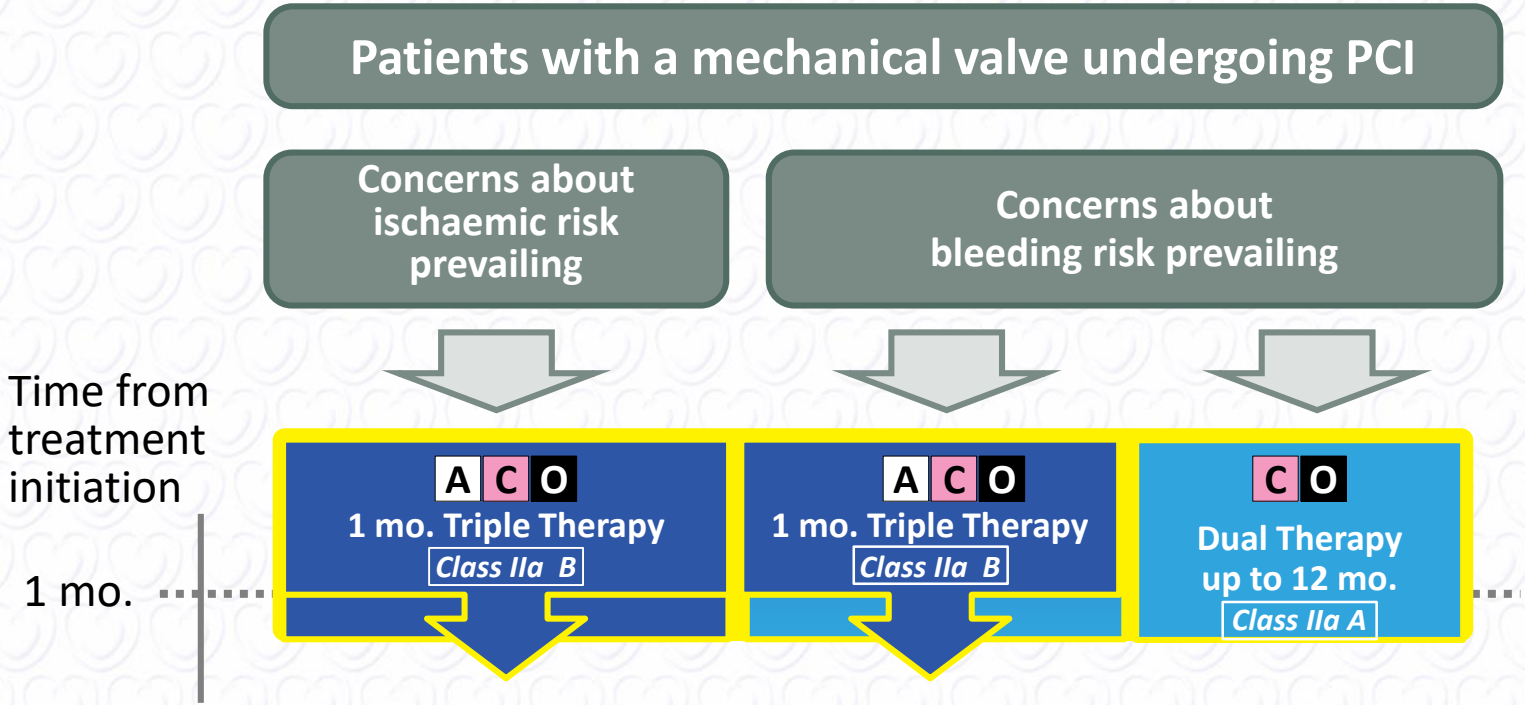
Recommendations	Class	Level	
Mechanical prosthesis			
In patients treated with coronary stent implantation, triple therapy with aspirin (75-100 mg/day), clopidogrel (75 mg/day), and VKA should be considered for 1 month, irrespective of the type of stent used and the clinical presentation (i.e. ACS or stable CAD).	IIa	B	New
Triple therapy comprising aspirin (75-100 mg/day), clopidogrel (75 mg/day), and VKA for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk.	IIa	B	New

Indications for antithrombotic therapy for mechanical prostheses *(continued)*

Recommendations	Class	Level	
Mechanical prosthesis *(continued)*			
Dual therapy comprising VKA and clopidogrel (75 mg/day) should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A	New
In patients who have undergone PCI, discontinuation of antiplatelet treatment should be considered at 12 months.	IIa	B	New
In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in therapeutic range >65-70%.	IIa	B	New
The use of NOACs is contra-indicated.	III	B	New

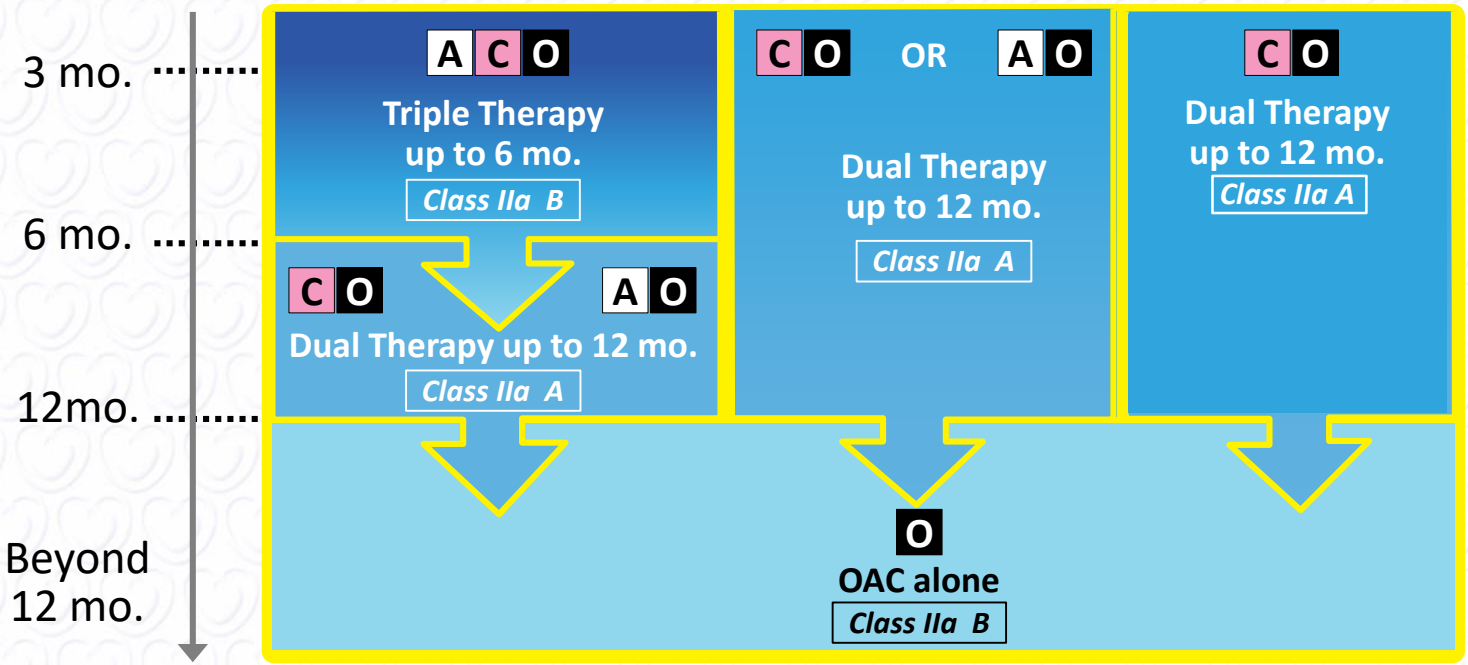
Antithrombotic therapy in patients with mechanical valve prosthesis after undergoing PCI

(Adapted from the 2017 ESC Focused Update on Dual Antiplatelet Therapy)



Antithrombotic therapy in patients with mechanical valve prosthesis after undergoing PCI *(continued)*

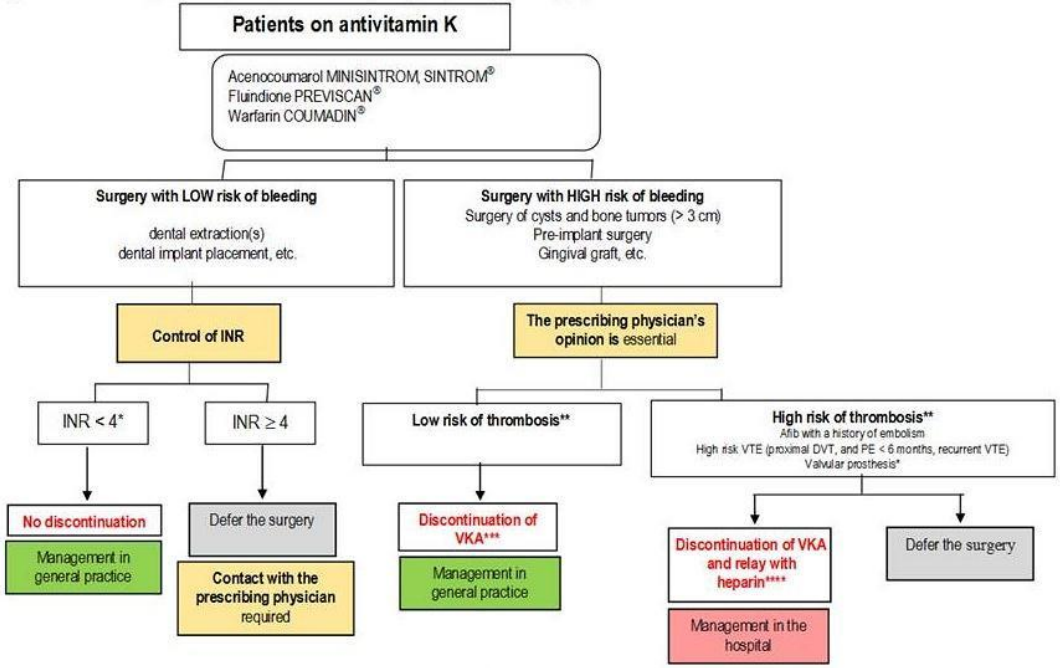
(Adapted from the 2017 ESC Focused Update on Dual Antiplatelet Therapy)



A = Aspirin C = Clopidogrel O = Oral anticoagulation with VKA

Non-cardiac intervention in a patient with a mechanical prosthesis

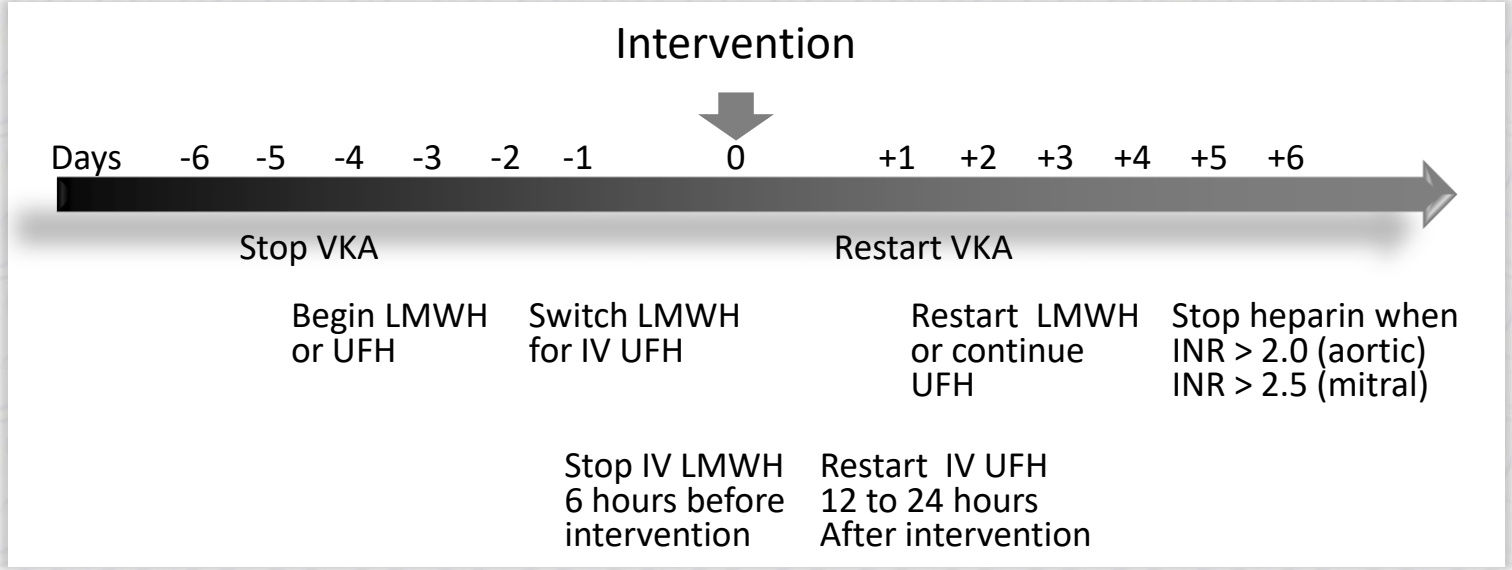
" It is recommended not to interrupt oral anticoagulation for most minor surgical interventions (including dental extraction, cataract removal) "



(www.societechirorale.com /documents/Recommandations/)

Main bridging steps for an intervention requiring interruption of oral anticoagulation in a patient with a mechanical prosthesis

(Reproduced with permission from Iung and Rodes-Cabau)



Timing should be individualized according to patient characteristics, actual INR, and the type of intervention

Indications for antithrombotic therapy for bioprostheses

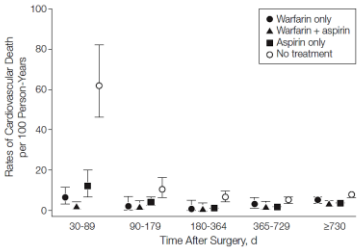
Recommendations	Class	Level
Bioprostheses		
Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprostheses who have other indications for anticoagulation.	I	C
Oral anticoagulation using a VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation using a VKA should be considered for the first 3 months after surgical mitral or tricuspid valve repair.	IIa	C
Low-dose aspirin (75-100 mg/day) should be considered for the first 3 months after surgical implantation of an aortic bioprosthesis or valve-sparing aortic surgery.	IIa	C

Early antithrombotic therapy after AVR using a bioprosthesis

IIa	B-NR	**Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic MVR or AVR in patients at low risk of bleeding (195-197).**	**MODIFIED: LOE updated from C to B-NR.** Anticoagulation for all surgical tissue prostheses was combined into 1 recommendation, with extension of the duration of anticoagulation up to 6 months. Stroke risk and mortality rate are lower in patients who receive anticoagulation for up to 6 months after implantation of a tissue prosthesis than in those who have do not have anticoagulation. Anticoagulation for a tissue prosthesis is also supported by reports of valve thrombosis for patients undergoing bioprosthetic surgical AVR or MVR, a phenomenon that may be warfarin responsive.
See Online Data Supplement 6.			

(Nishimura et al. J Am Coll Cardiol 2017;70:252-89)

4075 patients undergoing AVR (1997-2009).
Of 881 pts without post-op warfarin, 181 received ASA



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

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

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

(1-7)

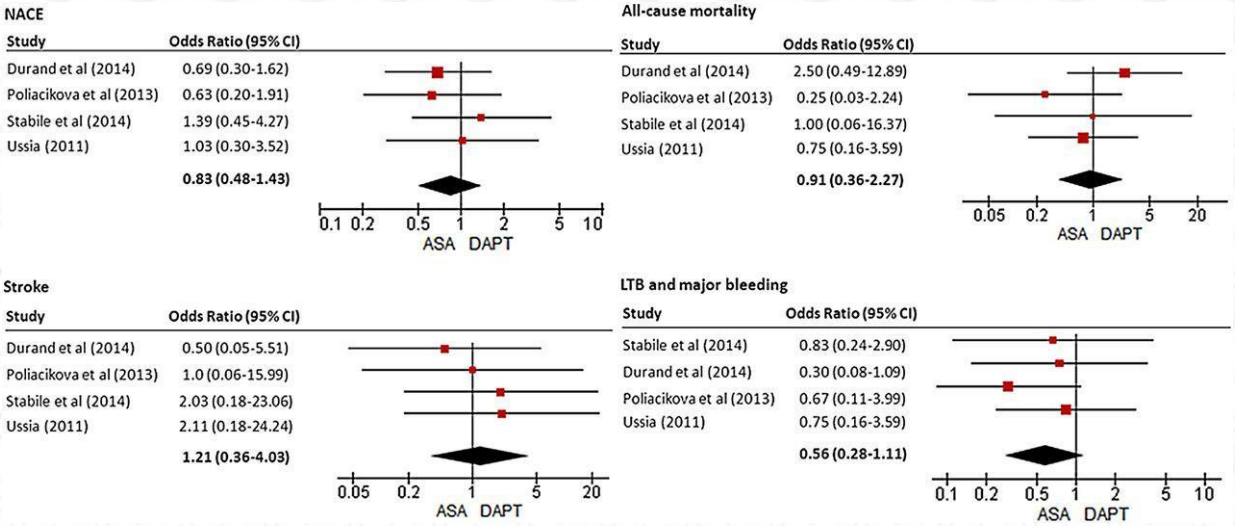
Indications for antithrombotic therapy for bioprostheses *(continued)*

Recommendations	Class	Level	
Bioprostheses *(continued)*			
Dual antiplatelet therapy should be considered for the first 3-6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other reasons.	IIa	C	New
Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk.	IIb	C	New
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	C	

Antithrombotic therapy after TAVI

Aspirin + clopidogrel vs. aspirin alone

(2RCTs and 2 observational series with propensity-matched subgroups totalling 435 pts)



(Hassell et al. Heart 2015;101:1118-25)

TAVI thrombosis diagnosed by CT scan

- 16/156 pts (10%)
  Small but significant increase in gradients
  (Pache et al. Eur Heart J 2016; 37, 2263–71)
- 23/405 pts (7%)
  Increased gradients
  (Hansson et al. J Am Coll Cardiol 2016;68:2059-69)
- 10/752 (13%)
  (4% for surgical bioprosthesis)
  Increased incidence of TIA
  (Chakravarty et al. Lancet 2017;389:2383-92)
- 16/128 (12.5%)
  Increased gradients
  (Vollema et al. Eur Heart J 2017;38:1207-17)

Resolution under anticoagulant therapy in most cases

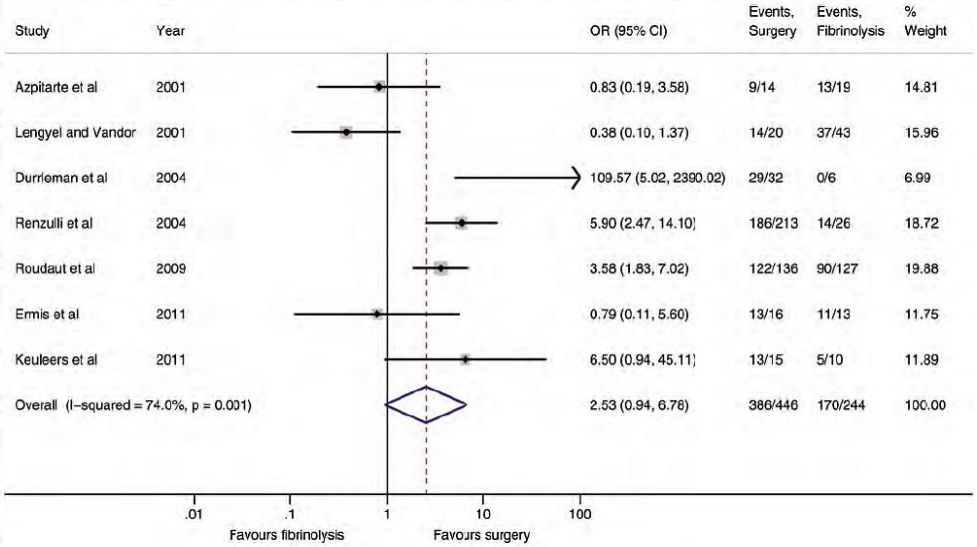
Management of prosthetic valve dysfunction

Recommendations	Class	Level
Mechanical prosthetic thrombosis		
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.	I	C
Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 minutes with UFH, or streptokinase 1,500,000 U in 60 minutes without UFH) should be considered when surgery is not available or is very high-risk, or for thrombosis of right-sided prostheses.	IIa	C
Surgery should be considered for large (>10 mm) non-obstructive prosthetic thrombus complicated by embolism.	IIa	C

Obstructive mechanical prosthetic thrombosis: Fibrinolysis vs. surgery

Meta-anaysis of 7 studies (690 pts with obstructive thrombosis)

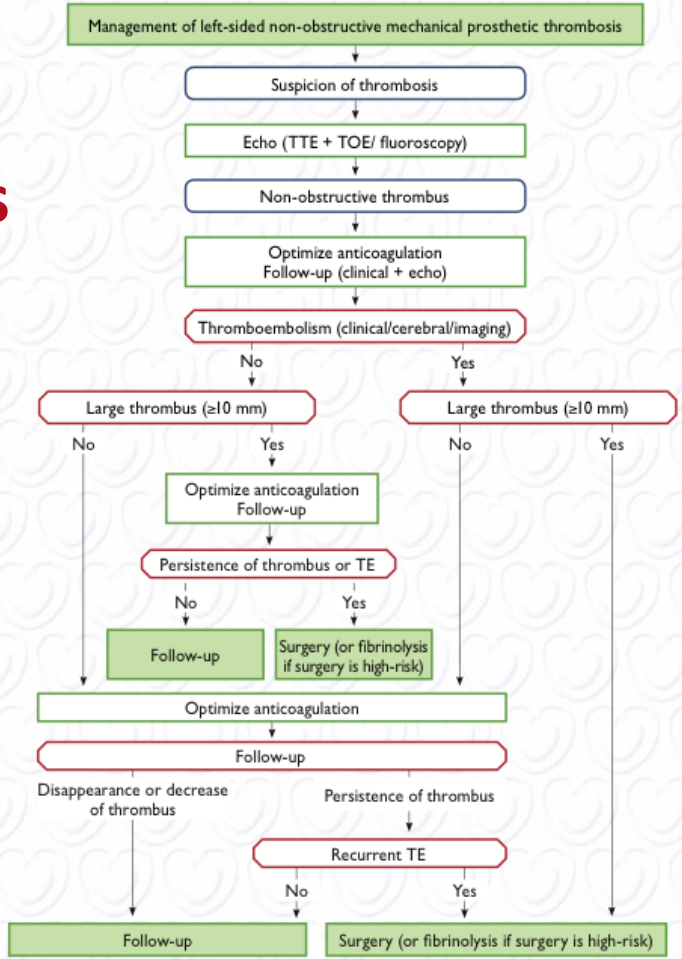
Restoration of normal valve function



(Karthikeyan et al. Eur Heart J 2013;34:1557-66)

Management of mechanical prosthetic thrombosis

Non-Obstructive thrombosis



2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx391)

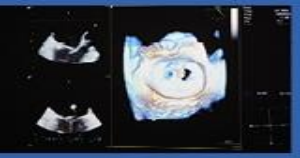
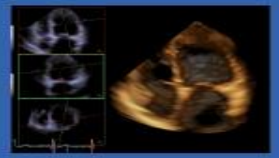
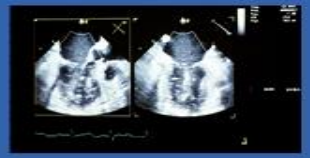
Management of prosthetic valve dysfunction *(continued)*

Recommendations	Class	Level	
Bioprosthetic thrombosis			
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention.	I	C	New
Haemolysis and paravalvular leak			
Reoperation is recommended if paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms.	I	C	
Transcatheter closure may be considered for paravalvular leaks with clinically significant regurgitation in surgical high-risk patients (Heart Team decision).	IIb	C	New

Management of prosthetic valve dysfunction *(continued)*

Recommendations	Class	Level
Bioprosthetic failure		
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction, if reoperation is at low-risk.	IIa	C
Transcatheter valve-in-valve implantation in aortic position should be considered by the Heart Team depending on the risk of reoperation and the type and size of prosthesis.	IIa	C

New

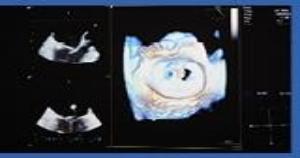
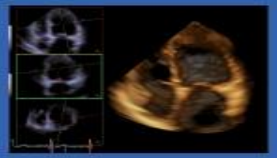
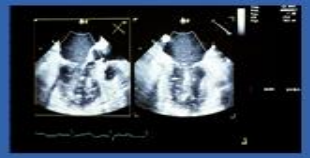




Conclusion

- The choice between a mechanical prosthesis and a bioprosthesis should not overstress age but fully take into account patient's wishes.
- Patients with a mechanical prosthesis require lifelong VKA with a target INR adapted to the prosthesis and patient characteristics.
- The addition of low-dose aspirin to VKA is restricted to selected patients.
- After ACS or PCI in a patient with mechanical prosthesis, antithrombotic therapy should be individualized according to ischaemic and bleeding risks.
- The management of anticoagulant therapy during non-cardiac surgery should be adapted to the type of surgery. Minor surgical procedures generally do not require interruption of anticoagulation.

Gaps in evidence

- Safety and efficacy of very low target INRs (median <2.5) in patients with a mechanical prosthesis in aortic position.
- Safety and efficacy of NOACs in patients with a mechanical prosthesis.
- Safety and efficacy of low-dose aspirin associated with contemporary target INRs in patients with a mechanical prosthesis, according to the presence or absence of atherosclerosis.
- Optimal early antithrombotic therapy after implantation of surgical and transcatheter aortic bioprostheses.
- Long-term outcome data of transcatheter valve-in-valve and valve-in-ring procedures.

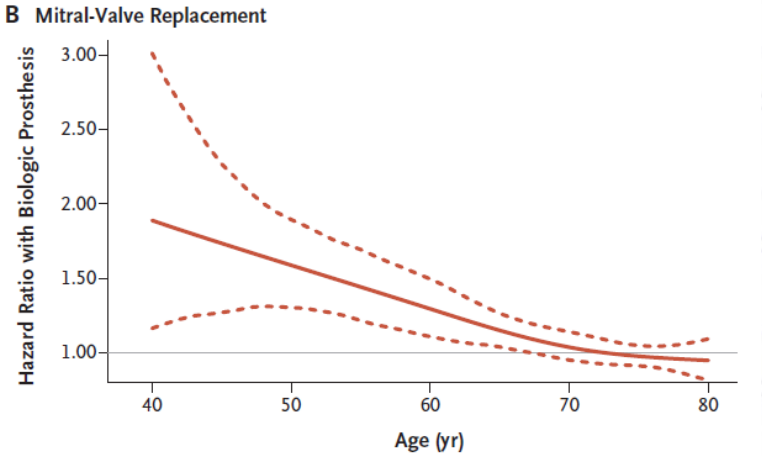




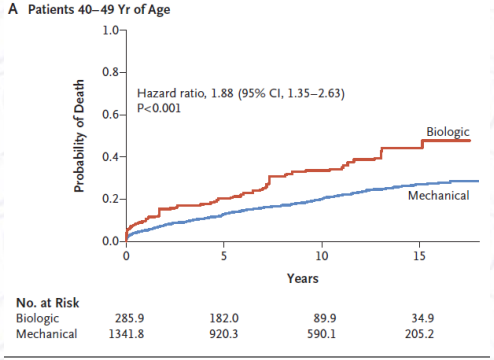

EuroValve

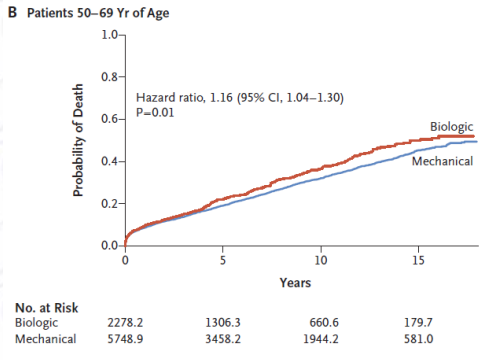
April 26-27, 2018

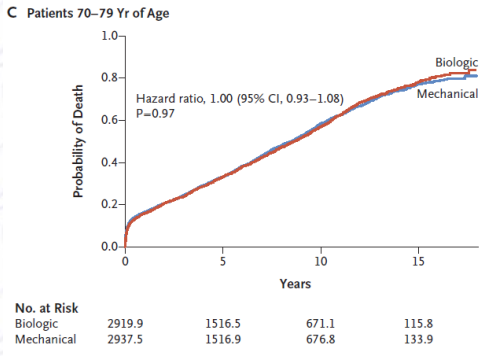
Mechanical or Biologic Prostheses for MVR

Comparison of 9982 patients undergoing MVR using a mechanical prosthesis with 5521 using a bioprosthesis









(Goldstone et al. N Engl J Med 2017;377:1847-57)