Asymptomatic AS: should we treat them all?

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Disclosures

- Proctor for Medtronic & Edwards Lifesciences

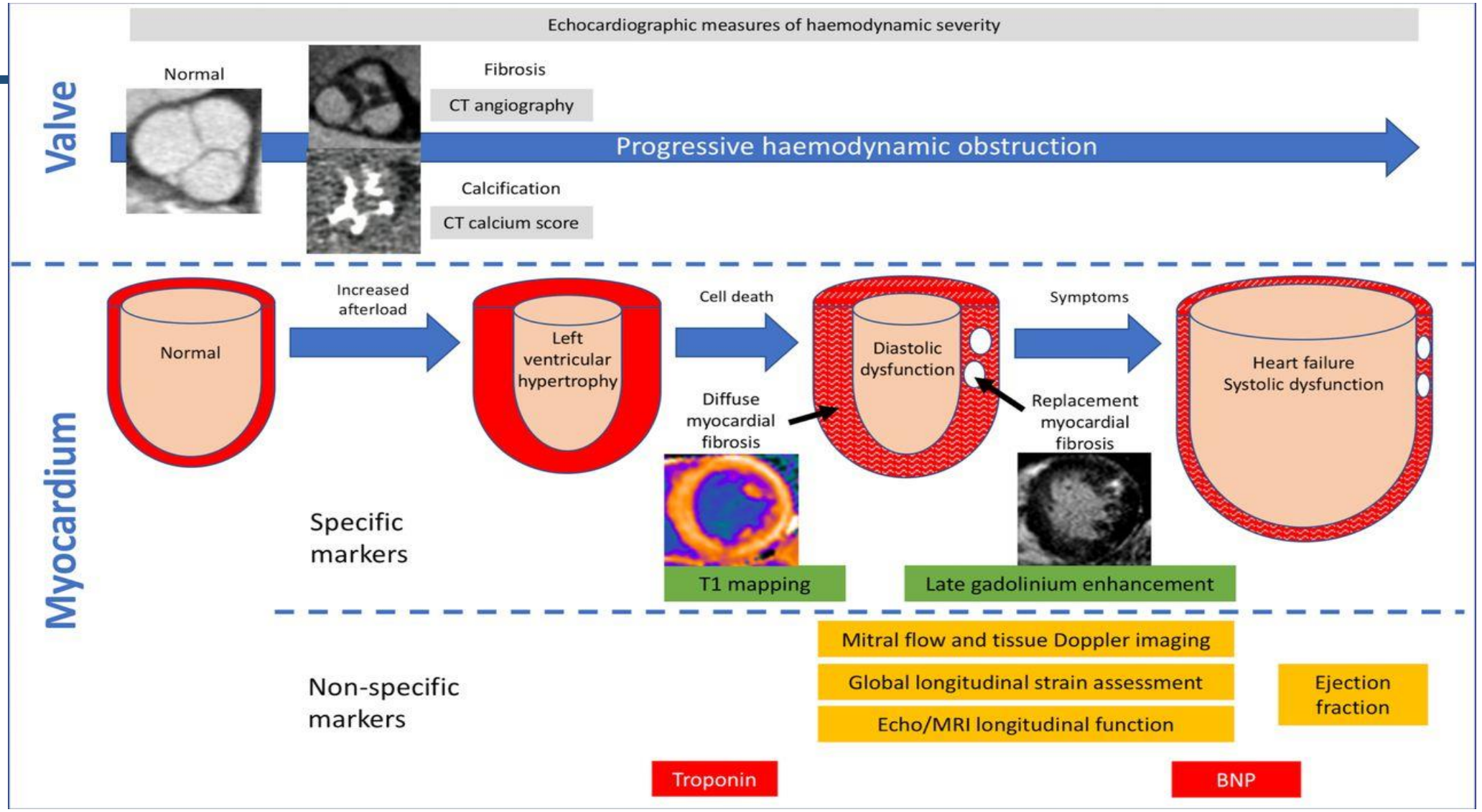
How to Stop ALL OR NOTHING THINKING: Step-by-Step

Treat an Asymptomatic disease??? What an absurd…

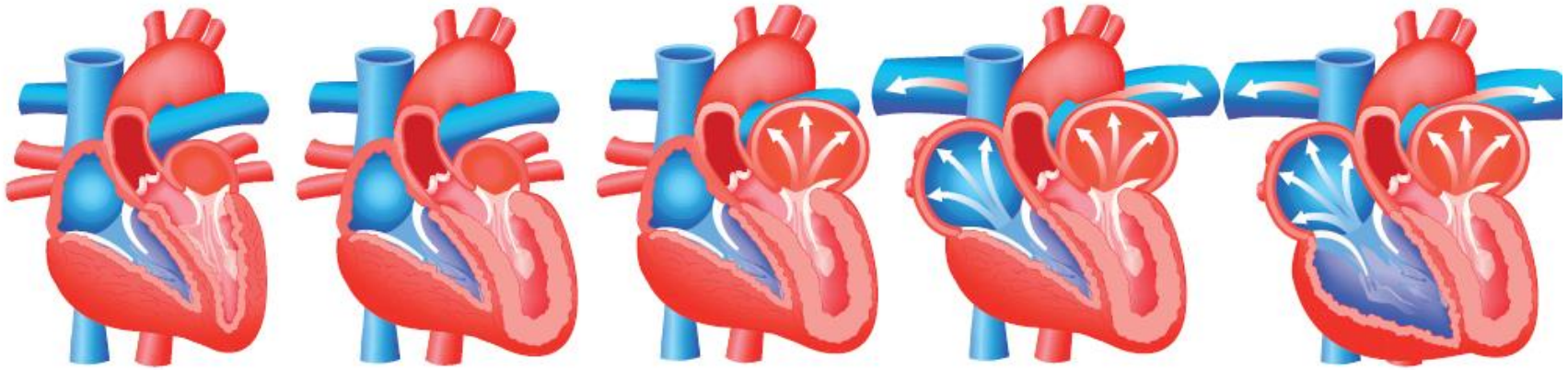
- Hypertension..
- Dyslipidemia..
- Aortic aneurysm..
- Aortic Valve Insufficiency..
- Carotid stenosis..
- ICD / MADIT II..

להקדים תרופה למכה..

AS disease progression



AS progression and staging



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Genereaux, et al. Eur Heart J 2017;38:3351–8. Strange et al., JACC 2019;74:1851-63

מה מקור האמונה העממית שמטפלים רק ב AS סימפטומטי?

Aortic Stenosis

By John Ross, Jr., M.D. and Eugene Braunwald, M.D.

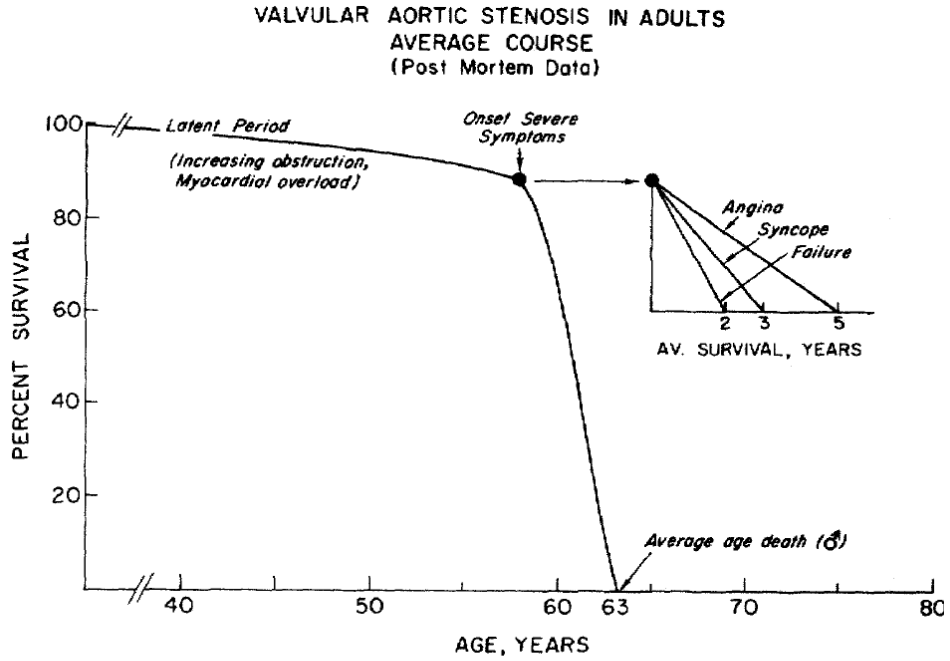


Figure 1

Average course of valvular aortic stenosis in adults. Data assembled from postmortem studies.

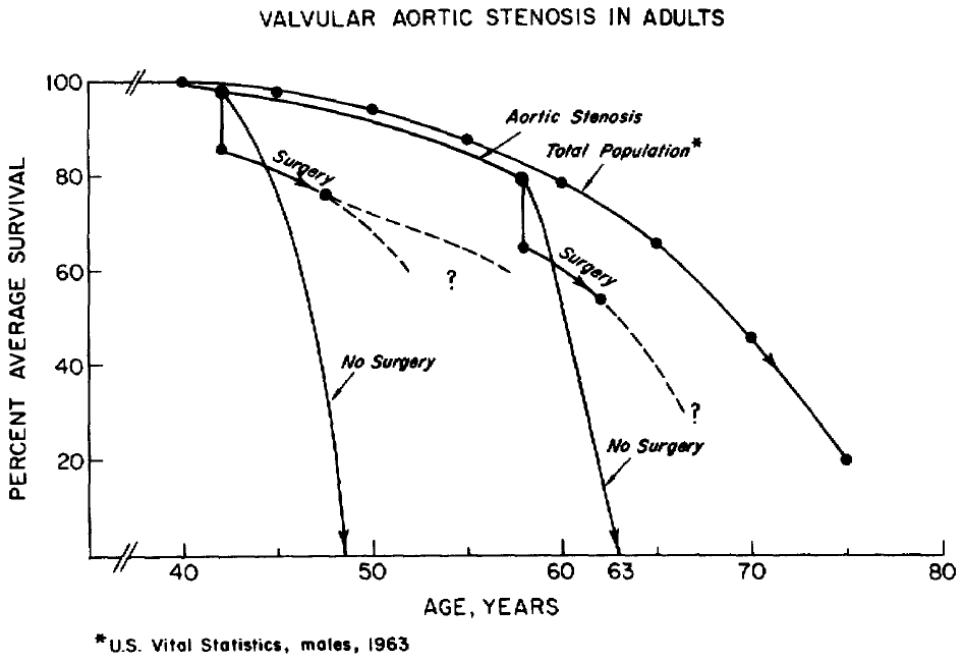


Figure 2

Comparison of the average per cent survival in the total male population after age 40 with that of adult patients with aortic stenosis, with and without operative treatment.

British Heart Journal, 1973, **35**, 41–46.

Natural history of valvular aortic stenosis[1]

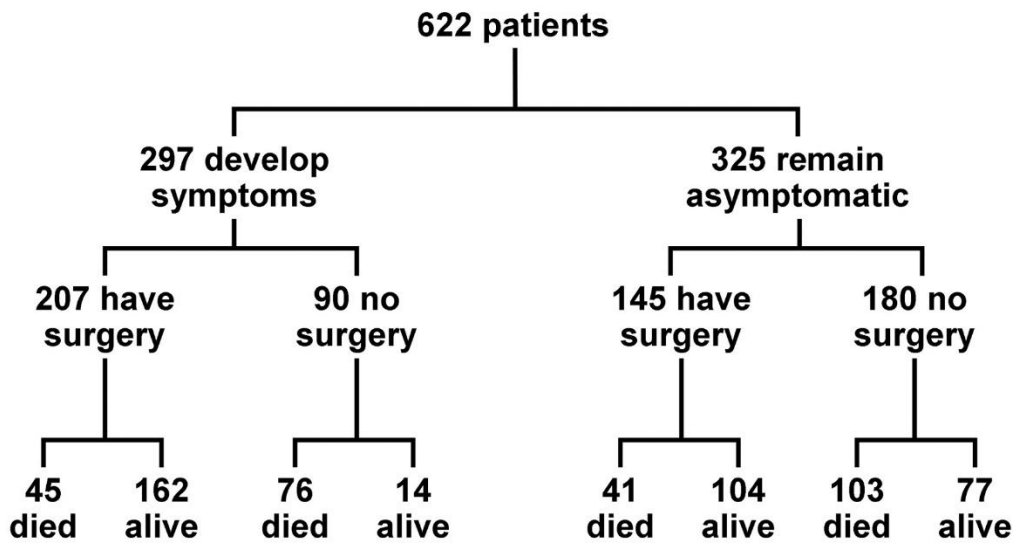
Stuart Frank,[2] Allen Johnson, and John Ross, Jr.

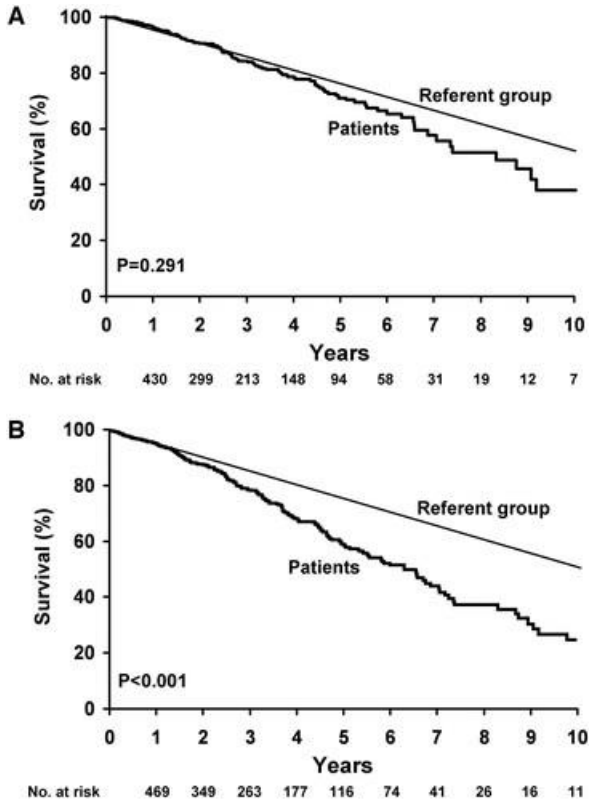
From Cardiology Branch, National Heart Institute, Bethesda, Maryland; and Department of Medicine, School of Medicine, University of California, San Diego, La Jolla, California, U.S.A.

Fifteen adult patients (ages 32 to 59 years) with significant valvular aortic stenosis in whom the severity of obstruction was documented by haemodynamic measurement and in whom the natural history was not interrupted by operation were followed for up to 11·7 years, or until death. The overall prognosis was poor, two-thirds of the group being dead at last follow-up. The percentage mortality, corrected for the number of patients followed, was 36 per cent at 3 years, and 52 per cent at 5 years; of those who were followed for 10 years, 90 per cent had died. The age at the onset of symptoms was not related to duration of survival, there was no clear relation between the type of symptom and survival, and haemodynamic parameters could not be correlated with symptoms or survival. Patients with a combination of symptoms tended to have the worst prognosis. Three patients were asymptomatic, one of whom died suddenly. These data provide a basis for predicting the natural history of isolated valvular aortic stenosis in adult patients, and indicate that significant obstruction together with symptoms portends an extremely poor prognosis.

Follow-up				
Age at onset of symptoms	*Age at study*	*Age at last follow-up*	*Duration of history or follow-up*	*Status*
56	57	61	5 7/12	Alive
51	51	56	5 11/12	Alive
40	41	45	5 9/12	Alive
39	43	47	8	Alive
49	49	51	2 1/11	Alive
56	57	58	2 2/12	Dead
47	47	47	6/12	Dead
29	32	32	3 1/12	Dead
52	53	56	4 2/12	Dead
45	45	46	1 7/12	Dead
58	59	62	3 2/12	Dead
47	57	11	11	Dead
54	55	56	2 8/12	Dead
43	53	54	10 6/12	Dead
44	46	52	6 6/12	Dead

Outcome of Asymptomatic Aortic Stenosis

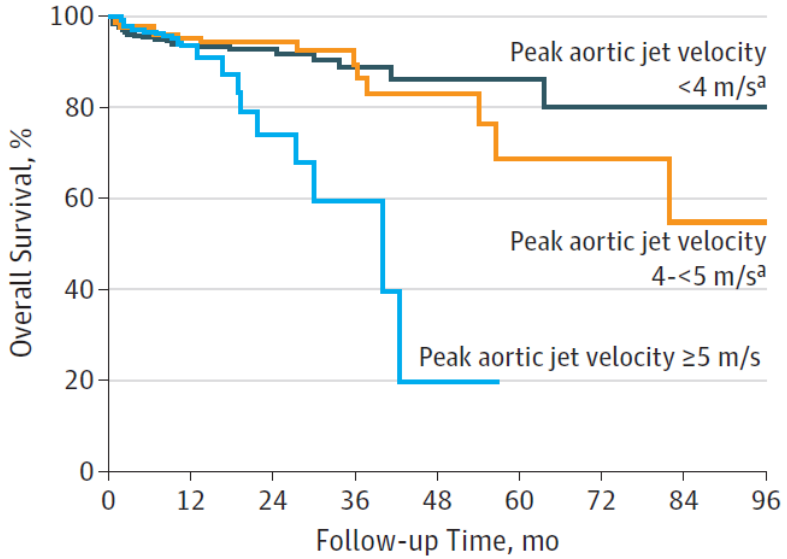




Sudden death occurs in approximately 1%/y

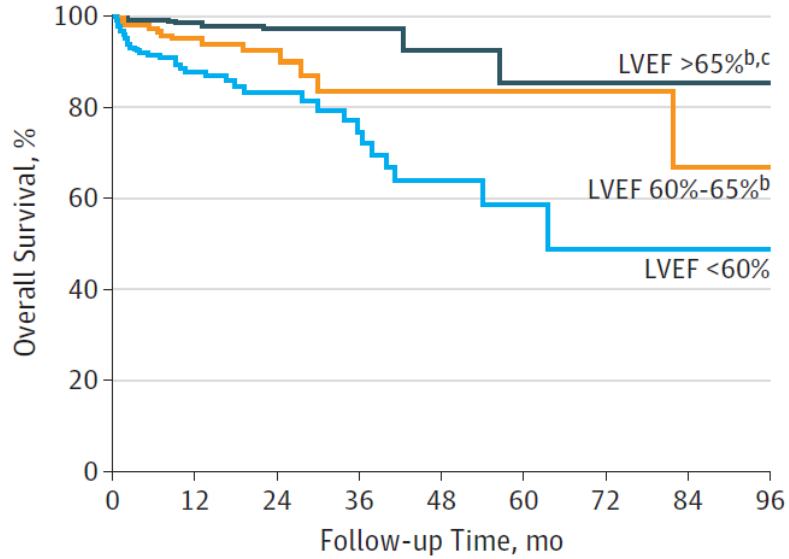
Outcome of Asymptomatic Aortic Stenosis: Effect of LVEF and AV Gradient

A Overall survival by peak aortic jet velocity



No. at risk					
Peak aortic jet velocity <4 m/s	388	161	33	8	4
Peak aortic jet velocity 4-<5 m/s	370	145	25	6	1
Peak aortic jet velocity ≥5 m/s	103	15	1	0	0

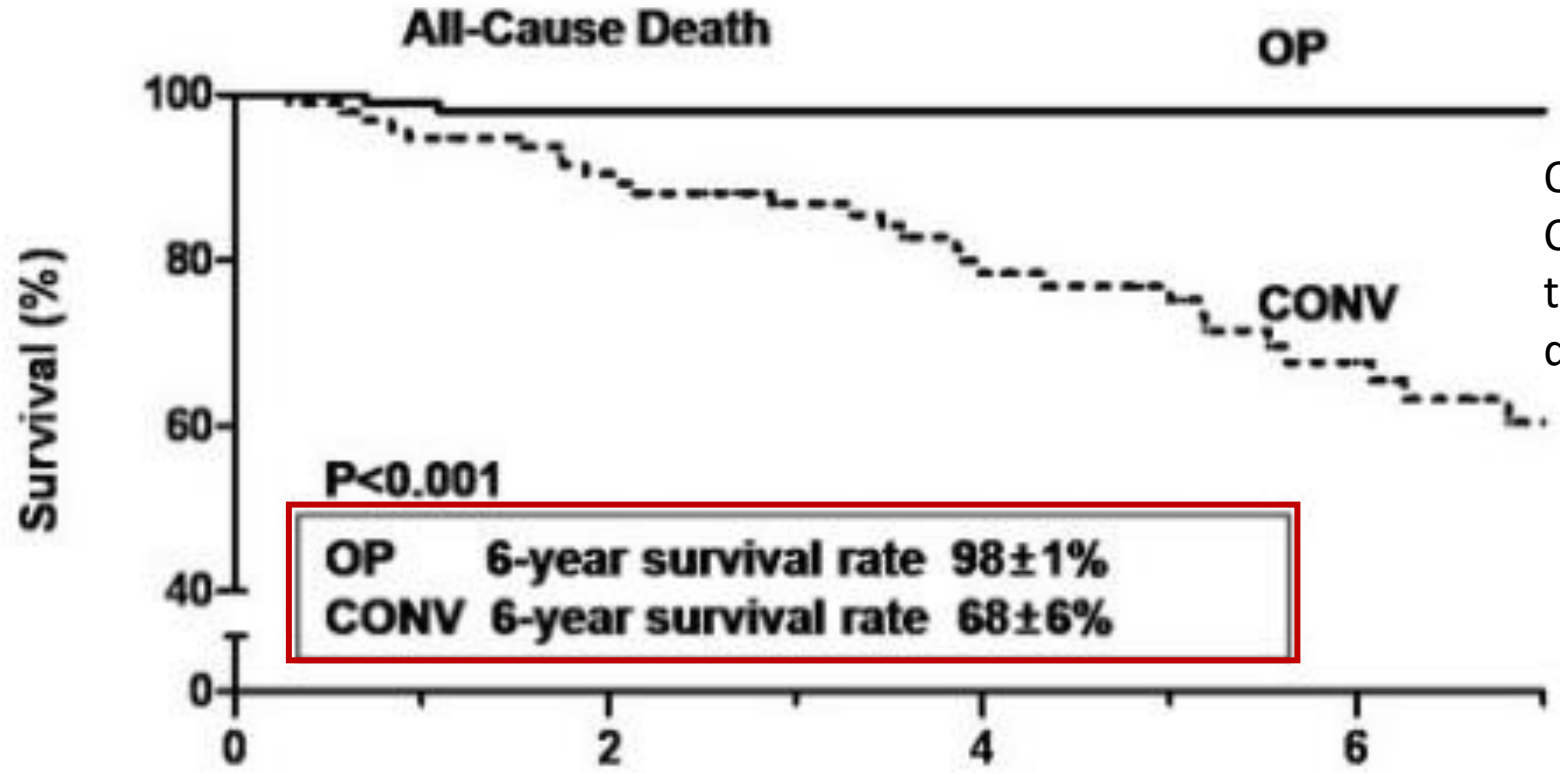
B Overall survival by LVEF



No. at risk					
LVEF >65%	396	118	19	3	1
LVEF 60%-65%	198	66	24	7	3
LVEF <60%	267	64	15	4	1

מישהו בדק אי פעם אם כדאי לטפל ב AS אסימפטומטי?

AVR for Asymptomatic Aortic Stenosis

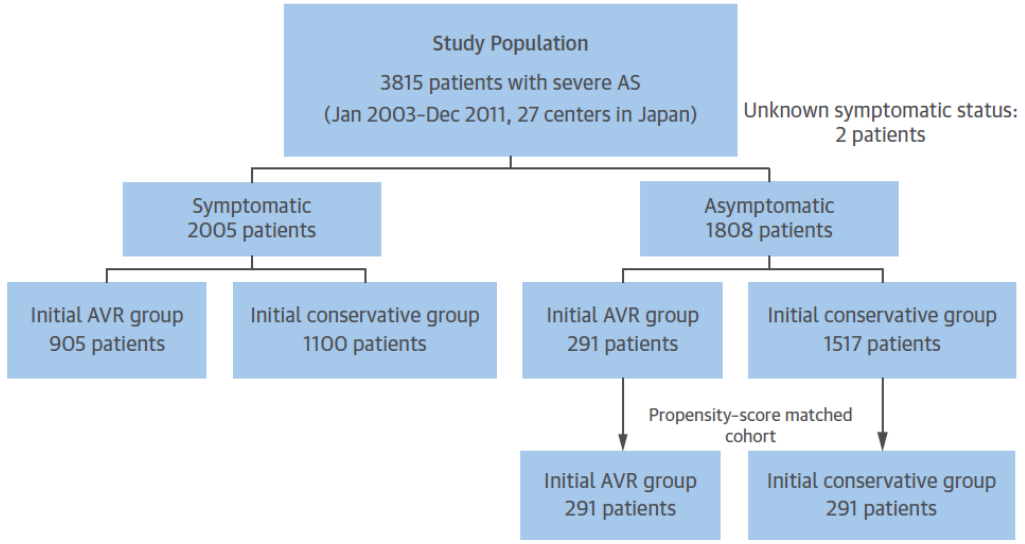


No at Risk

OP	102	96	48	29
CONV	95	82	54	32

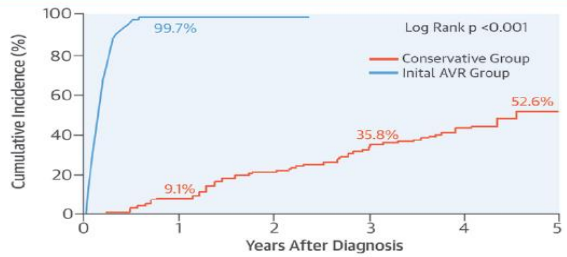
OP = early surgery
CONV = conventional treatment (symptom driven)

AVR for Asymptomatic Aortic Stenosis



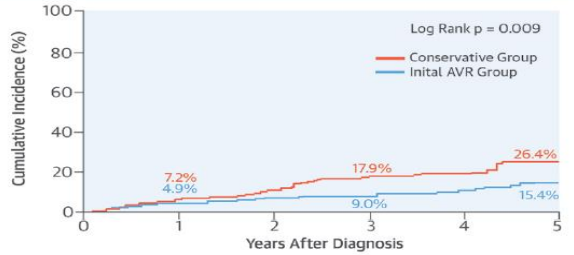
	Entire Cohort			Propensity Score-Matched Cohort		
	Initial AVR Group (n = 291)	Conservative Group (n = 1,517)	p Value	Initial AVR Group (n = 291)	Conservative Group (n = 291)	p Value
Echocardiographic variables						
V_{max}, m/s	4.8 ± 0.8	3.8 ± 0.7	<0.001	4.8 ± 0.8	4.4 ± 0.9	<0.001
V_{max} ≥5 m/s†	114 (39)	93 (6)	<0.001	114 (39)	111 (38)	0.80
V_{max} ≥4 m/s*	245 (84)	619 (41)	<0.001	245 (84)	182 (63)	<0.001
Peak aortic PG, mm Hg	93 ± 32	59 ± 23	<0.001	93 ± 32	79 ± 32	<0.001
Mean aortic PG, mm Hg	54 ± 20	33 ± 14	<0.001	54 ± 20	45 ± 20	<0.001

Surgical AVR or TAVI



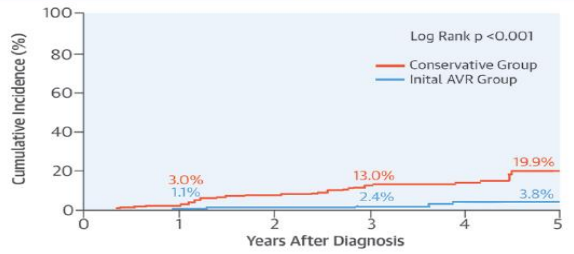
Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Conservative Group					
Patients with at Least One Event		0	24	84	106
Patients at Risk	291	279	229	117	38
Inital AVR Group					
Patients with at Least One Event		87	287		
Patients at Risk	291	204	1		

All-cause Death



Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Conservative Group					
Patients with at Least One Event		3	20	48	60
Patients at Risk	291	279	252	178	72
Inital AVR Group					
Patients with at Least One Event		1	14	25	33
Patients at Risk	291	286	266	188	75

Heart Failure Hospitalization



Interval	0 Day	30 Days	1 Year	3 Years	5 Years
Conservative Group					
Patients with at Least One Event		0	8	31	39
Patients at Risk	291	279	246	161	63
Inital AVR Group					
Patients with at Least One Event		0	3	6	8
Patients at Risk	291	286	264	185	75

Taniguchi T et al. JACC 2015

Conservative care or AVR for asymptomatic AS: Meta-analysis (1)

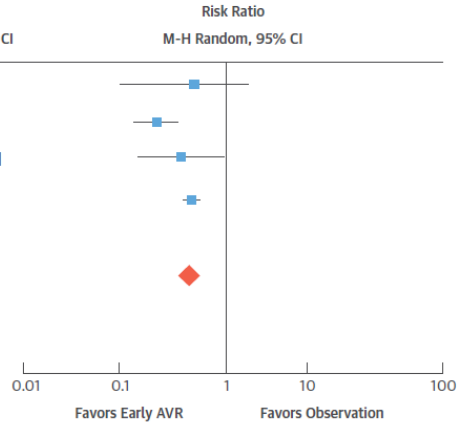
FIGURE 1 Study-Level Meta-Analysis

A

Study	Early AVR Events	Early AVR Total	Observation Events	Observation Total	Weight	Risk Ratio M-H Random, 95% CI
Pellikka et al. (17)	2	30	14	113	11.5%	0.54 [0.13, 2.24]
Pai et al. (19)	10	99	147	239	31.4%	0.16 [0.09, 0.30]
Kang et al. (25)	3	102	10	95	13.9%	0.28 [0.08, 0.98]
Taniguchi et al. (26)	40	291	542	1517	43.2%	0.38 [0.29, 0.52]
Total (95% CI)		**522**		**1964**	**100%**	**0.29 [0.17, 0.51]**
Total events	55		713			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 6.91$, df = 3 (P=0.07); $I^2 = 57\%$

Test for overall effect: Z = 4.35 (P<0.0001)

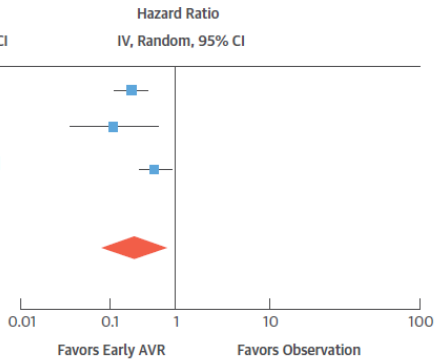


B

Study	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Pai et al. (19)	-1.772	0.2707	38.2%	0.17 [0.10, 0.29]
Kang et al. (25)	-1.9661	0.786	22.1%	0.14 [0.03, 0.65]
Taniguchi et al. (26)	-0.5108	0.2069	39.8%	0.60 [0.40, 0.99]
Total (95% CI)			**100%**	**0.27 [0.09, 0.77]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 15.22$, df = 2 (P=0.005); $I^2 = 87\%$

Test for overall effect: Z = 2.46 (P=0.01)



All-cause mortality with surgical aortic valve replacement versus conservative medical therapy for patients with asymptomatic severe aortic stenosis. **(A)** Unadjusted; **(B)** adjusted. AVR = aortic valve replacement; CI = confidence interval; IV = inverse variance; M-H = Mantel-Haenszel test (fixed effects).

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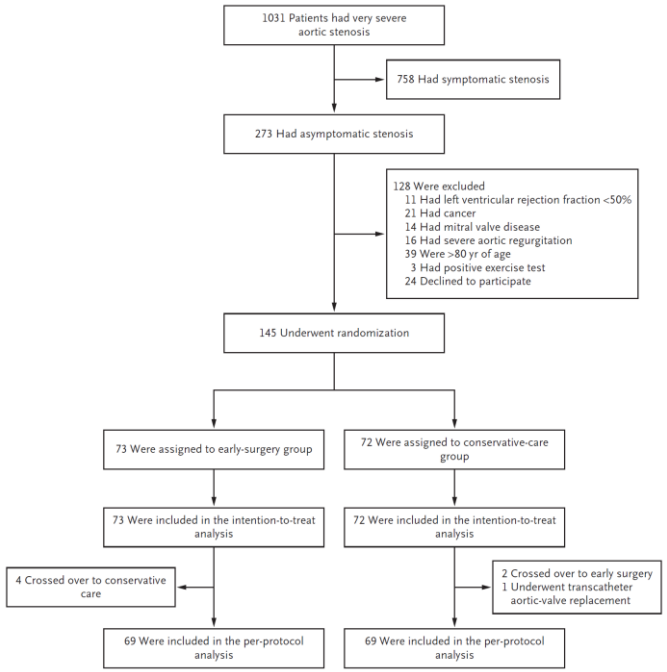
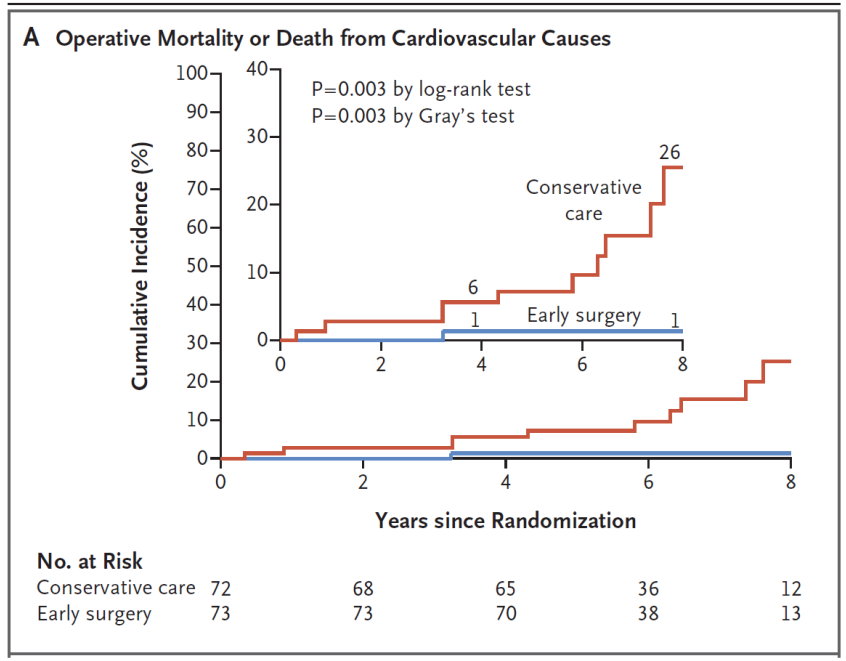
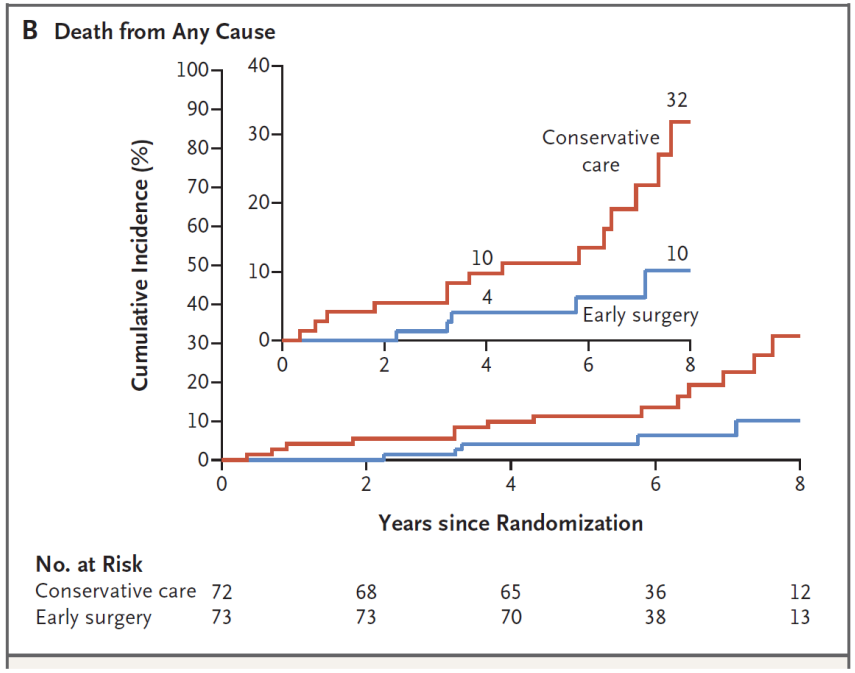
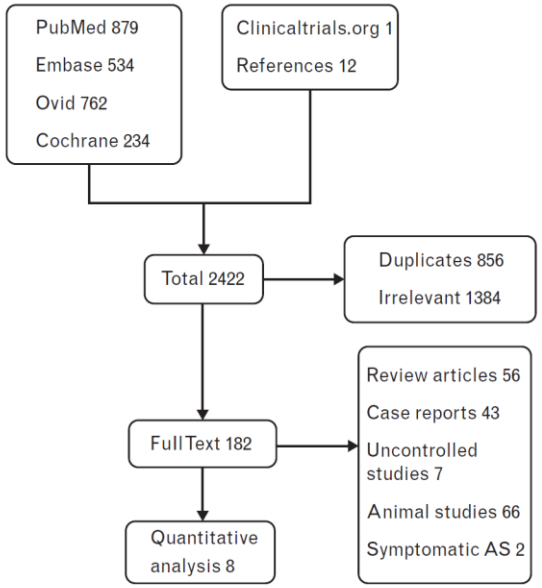
Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis







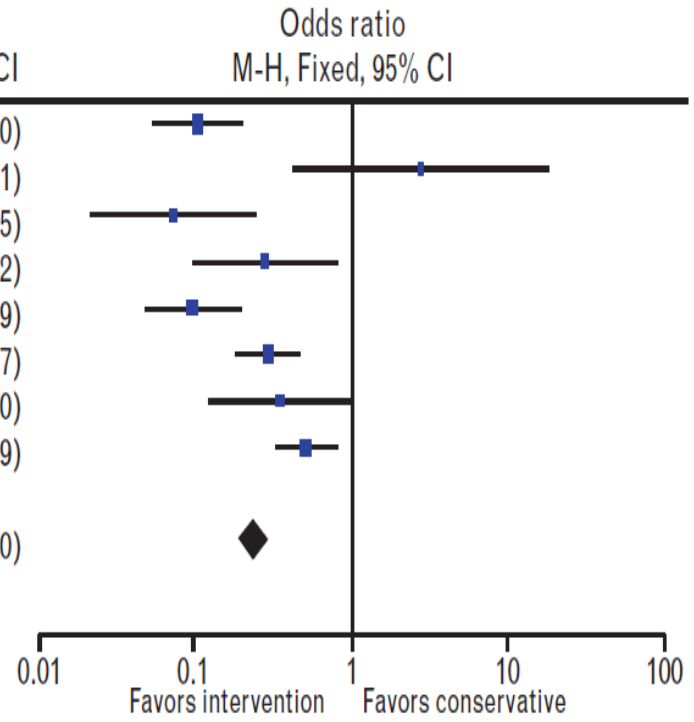
Conservative or AVR for asymptomatic AS: Meta-analysis (2)



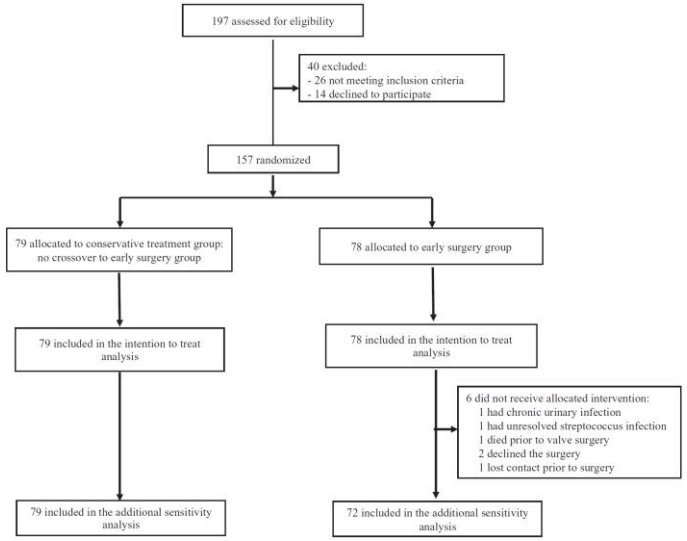
Study or Subgroup	Intervention Events	Total	Conservative Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
Bohbot 2018	11	192	91	247	23.2%	0.10 (0.05, 0.20)
Heuvelman 2012	3	22	2	37	0.4%	2.76 (0.42, 18.01)
Kang 2010	3	102	28	95	8.7%	0.07 (0.02, 0.25)
Kang 2020	5	73	15	72	4.4%	0.28 (0.10, 0.82)
Pal 2006	10	99	129	239	21.0%	0.10 (0.05, 0.19)
Pellikka 2005	41	145	103	180	20.4%	0.29 (0.18, 0.47)
Rosenhek 2009	8	79	9	37	3.4%	0.35 (0.12, 1.00)
Taniguchi 2015	40	291	69	291	18.4%	0.51 (0.33, 0.79)
Total (95% CI)		1003		1198	100.0%	0.24 (0.19, 0.30)
Total events	121		446			

Heterogeneity $Chi^2 = 36.17$; $df = 7$ ($P < 0.00001$); $I^2 = 81\%$

Test for overall effect: $Z = 12.06$ ($P < 0.00001$)

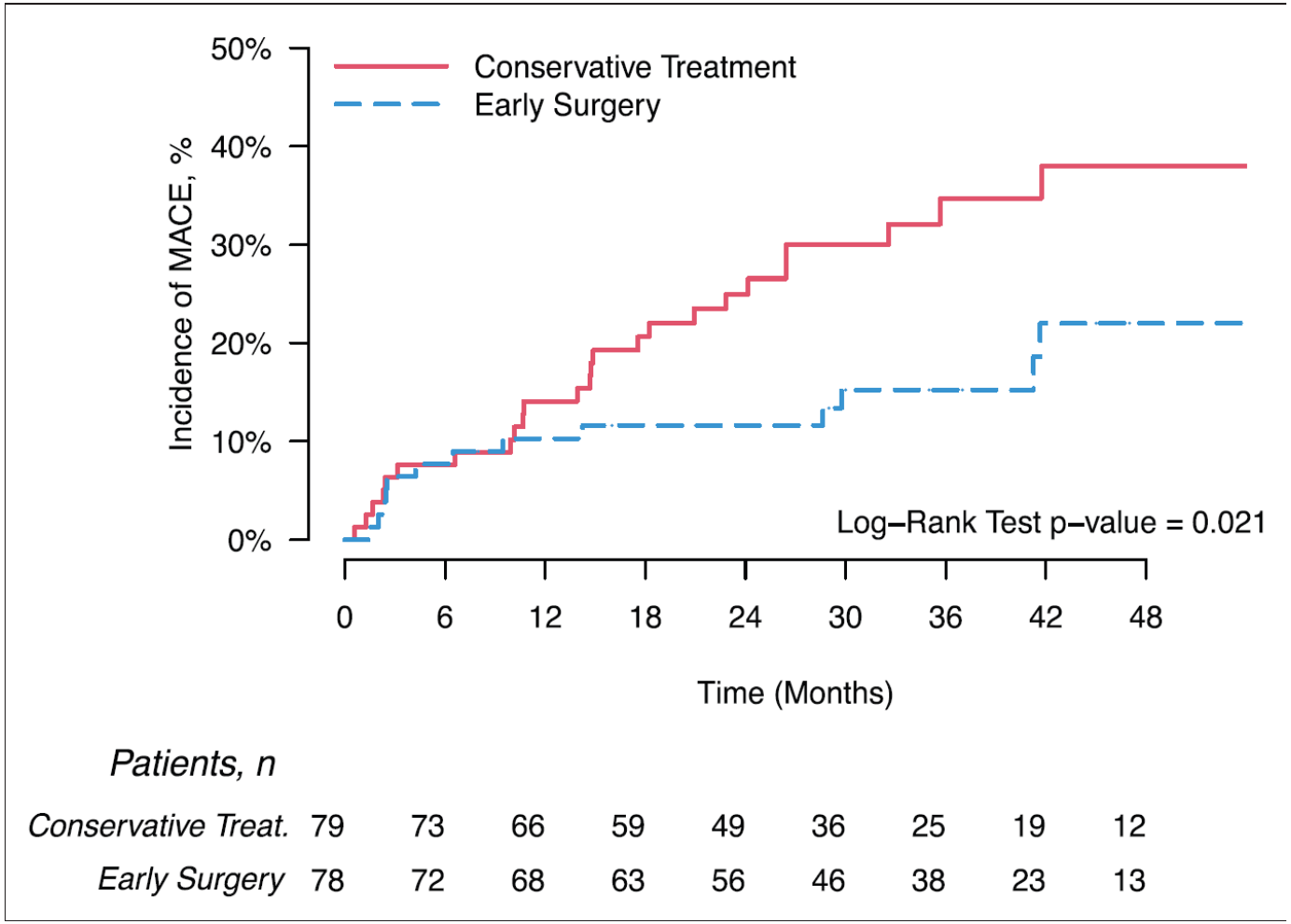


AVATAR: AVR Vs. conservative care for asymptomatic AS



Negative GXT Vmax 4.5 m/s (4-5.5)

All-cause death	16	9
Heart Failure	10	3
AMI	4	1
Stroke	3	3
Total	33	16



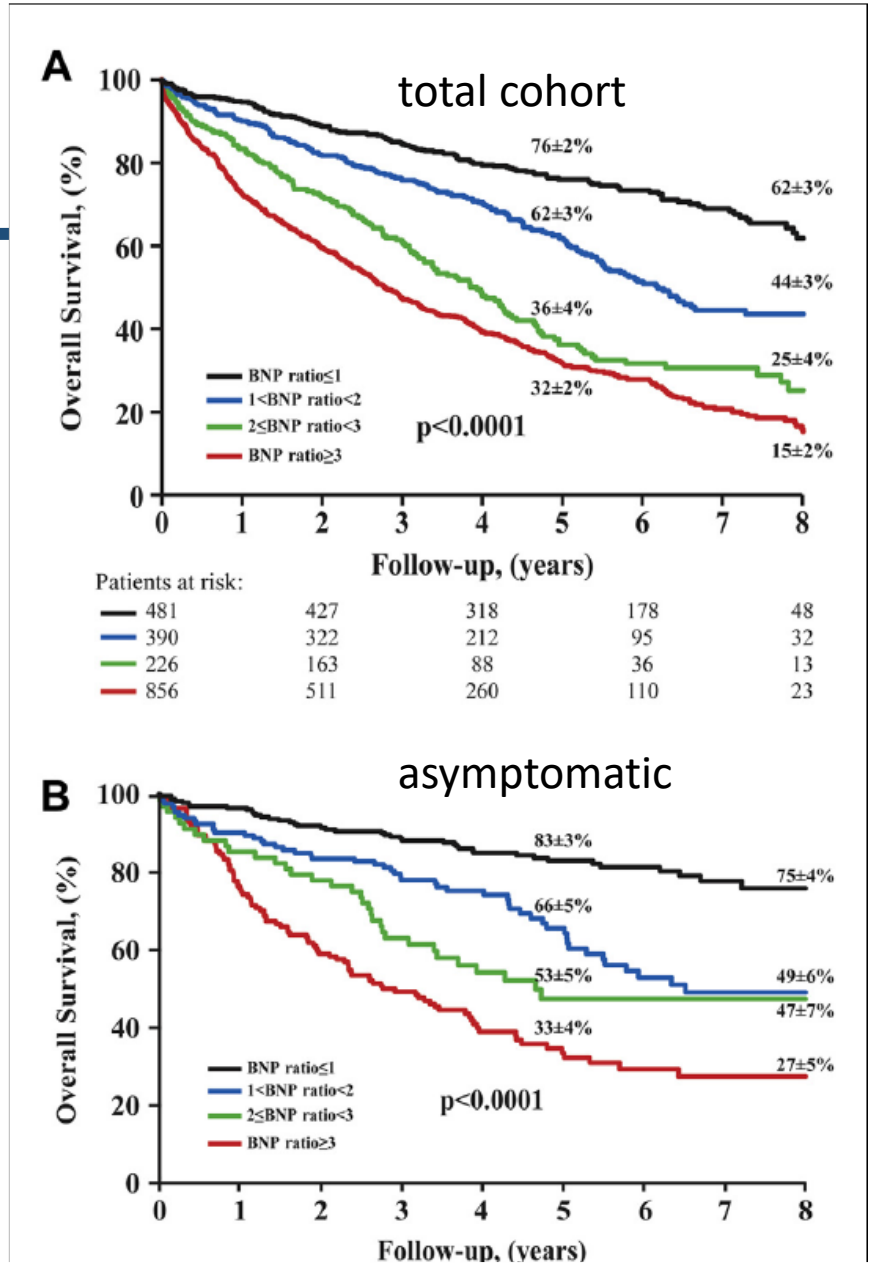
האם ניתן לחזות מי מהמטופלים ייהנה מהחלפת מסתם מוקדמת?

האם יש סמנים פרוגנוסטיים בסובלים מהיצרות אסימפטומטית?

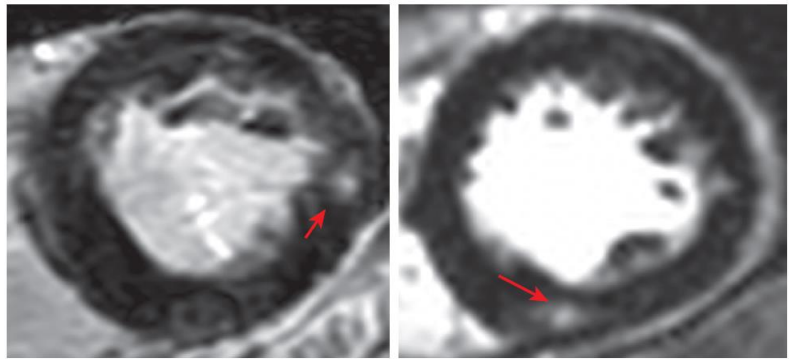
BNP and AS survival

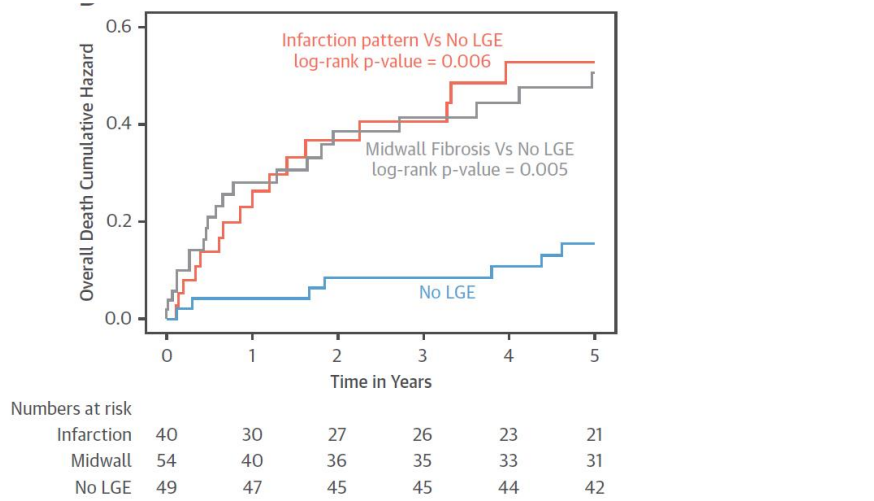
1,953 consecutive patients with at least moderate AS
40% asymptomatic

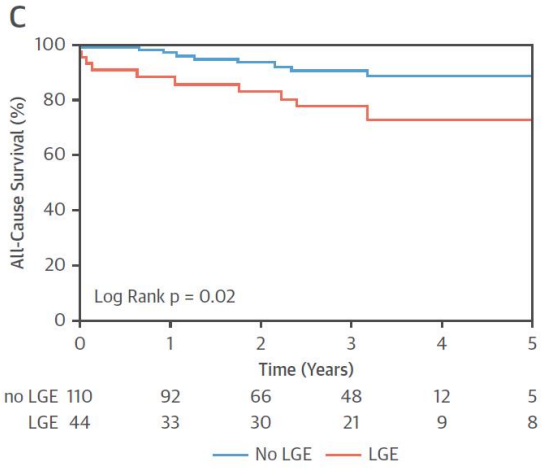
Echocardiographic data	All	Asymptomatic
LV end-diastolic diameter, mm	49.9 ± 7.2	47.7 ± 5.4
LV end-systolic diameter, mm	33.2 ± 9.1	29.3 ± 4.9
Peak aortic jet velocity, m/s	3.78 ± 0.95	3.94 ± 0.95
Mean gradient, mm Hg	36 ± 19	39 ± 19
AVA, cm^2	1.03 ± 0.26	1.04 ± 0.26
AVAi, cm^2/m^2	0.55 ± 0.15	0.55 ± 0.14
LV ejection fraction, %	57 ± 15	65 ± 7
LV ejection fraction <50%	414 (22)	0

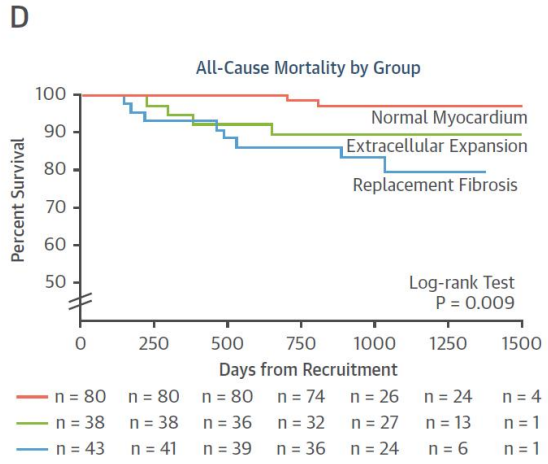


Myocardial fibrosis and AS survival





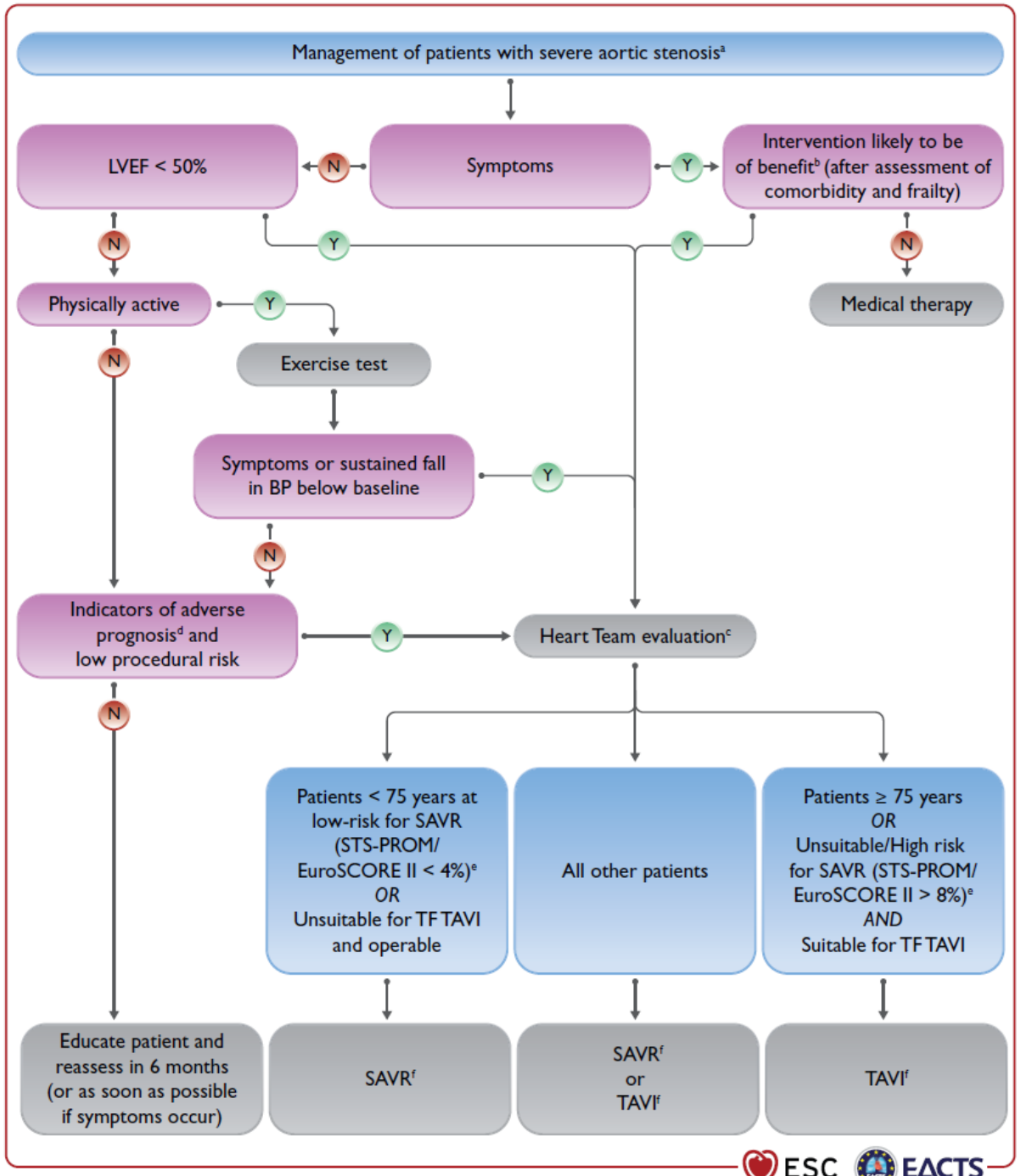




ומה אומרות ההנחיות?

Severe AS: ESC therapy guidelines

The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I	C



Vahanian et al. ESC/EACTS guidelines, EHJ 2021

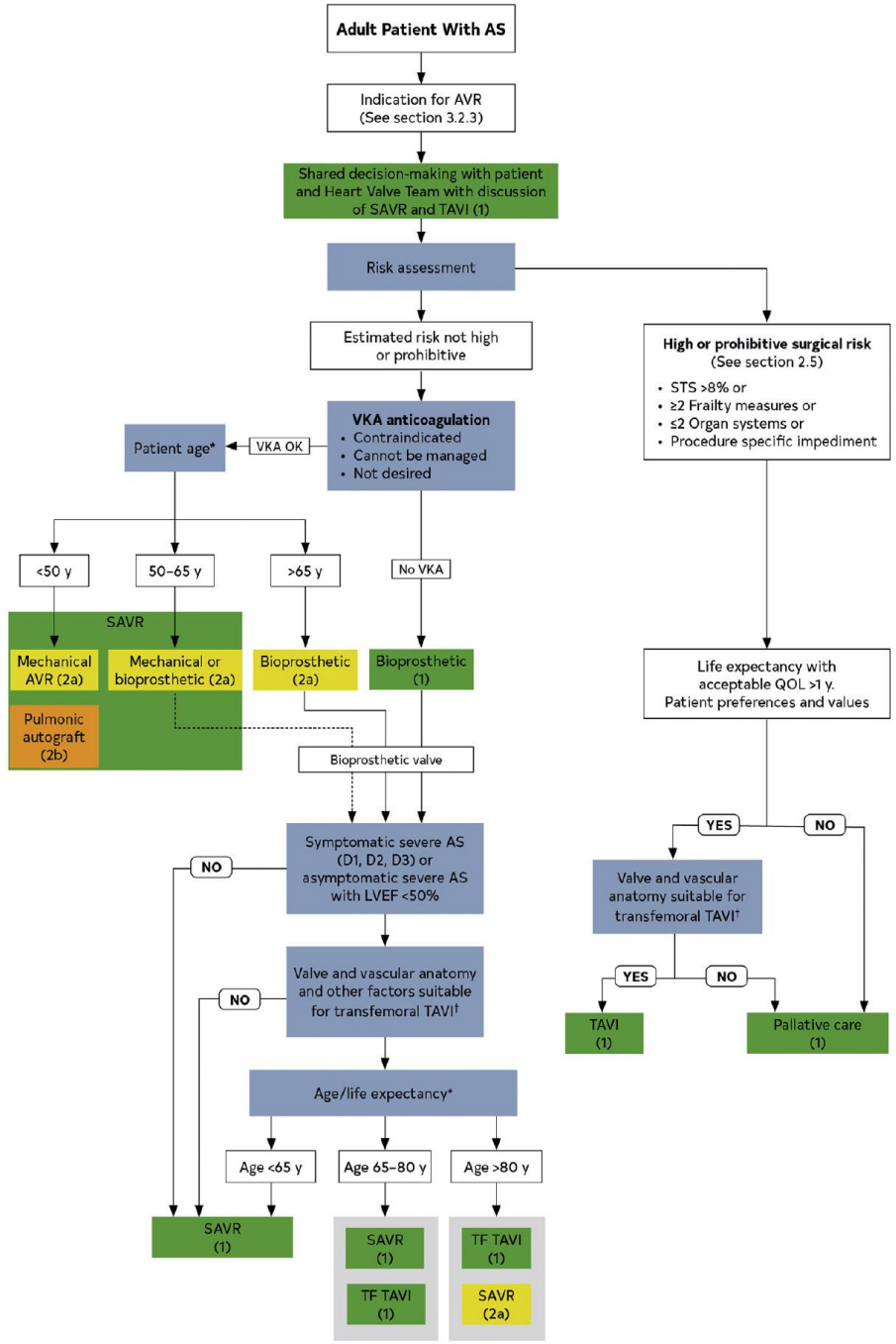
Asymptomatic Aortic Stenosis

Guidelines

Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.[9,238,239]	I	B
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	I	C
Intervention should be considered in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <55%) without another cause.[9,240,241]	IIa	B
Intervention should be considered in asymptomatic patients with severe aortic stenosis and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
Intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe aortic stenosis (mean gradient ≥60 mmHg or V_{max} >5 m/s).[9,242] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[164,189,243] • Markedly elevated BNP levels (>3× age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.[163,171]	IIa	B

Predictors of symptom development and adverse outcomes in asymptomatic patients include clinical characteristics (older age, atherosclerotic risk factors), echocardiographic parameters (valve calcification, peak jet velocity[189,190]), LVEF, rate of haemodynamic progression,[189] increase in mean gradient >20 mmHg with exercise,[172] severe LV hypertrophy,[191] indexed stroke volume,[158] LA volume,[192] LV global longitudinal strain,[26,168,193] and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A).[170,171,194,195] Early intervention may be considered in asymptomatic patients with severe aortic stenosis and one or more of these predictors if procedural risk is low (although application of TAVI in this setting has yet to be formally evaluated) (*Table 6* and *Figure 4*). Otherwise, watchful waiting is a safer and more appropriate strategy.

Severe AS: AHA/ACC therapy guidelines

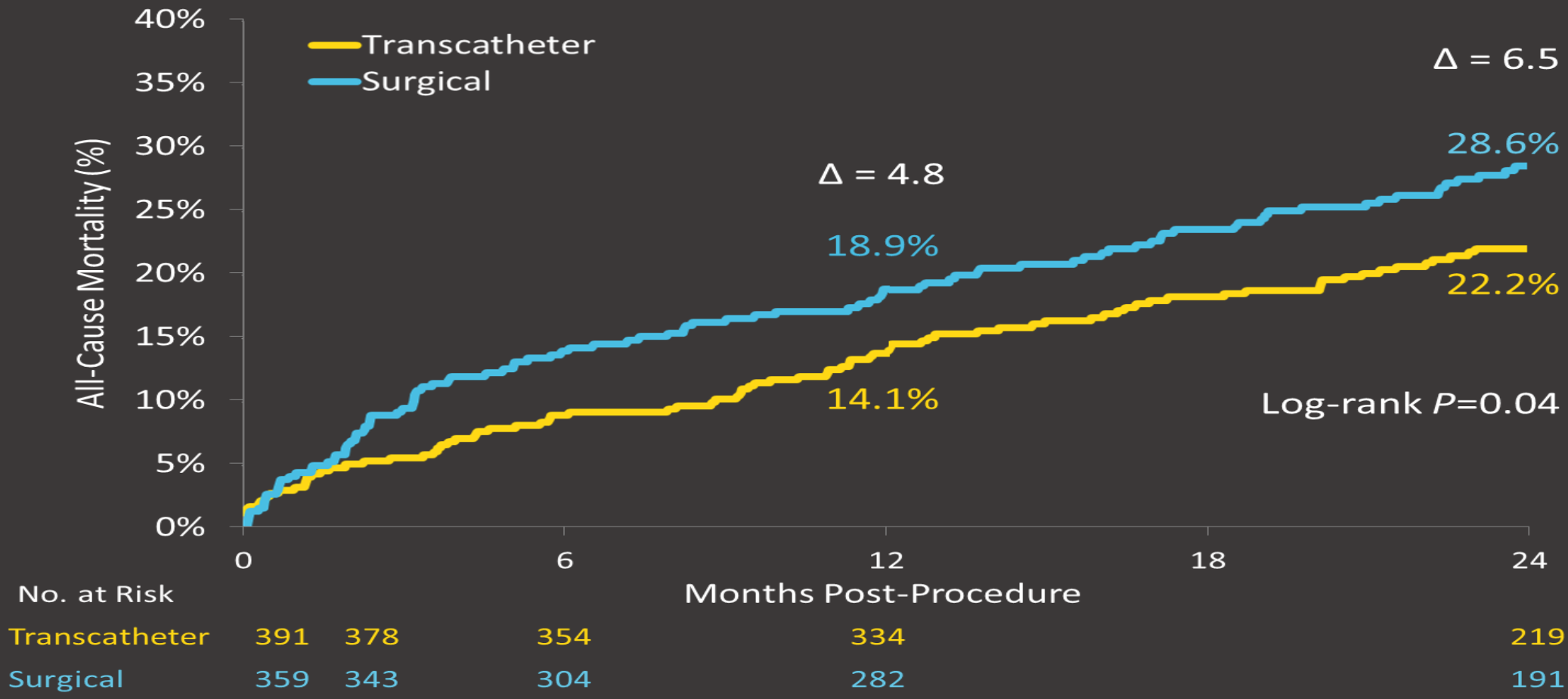


Recommendations for Timing of Intervention of AS
Referenced studies that support the recommendations are summarized in Online Data Supplements 4 and 6 to 10.

COR	LOE	RECOMMENDATIONS
1	A	1. In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated (1–7).
1	B-NR	2. In asymptomatic patients with severe AS and an LVEF <50% (Stage C2), AVR is indicated (8–11).
1	B-NR	3. In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated (12–16).
1	B-NR	4. In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (Stage D2), AVR is recommended (17–24).
1	B-NR	5. In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (Stage D3), AVR is recommended if AS is the most likely cause of symptoms (25–27).
2a	B-NR	6. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mm Hg from baseline to peak exercise (13,28–30).
2a	B-R	7. In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable (15,31–35).
2a	B-NR	8. In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide (BNP) level is >3 times normal (32,36–38).
2a	B-NR	9. In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year (39,40).
2b	B-NR	10. In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in LVEF on at least 3 serial imaging studies to <60%, AVR may be considered (8–11,33).
2b	C-EO	11. In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.

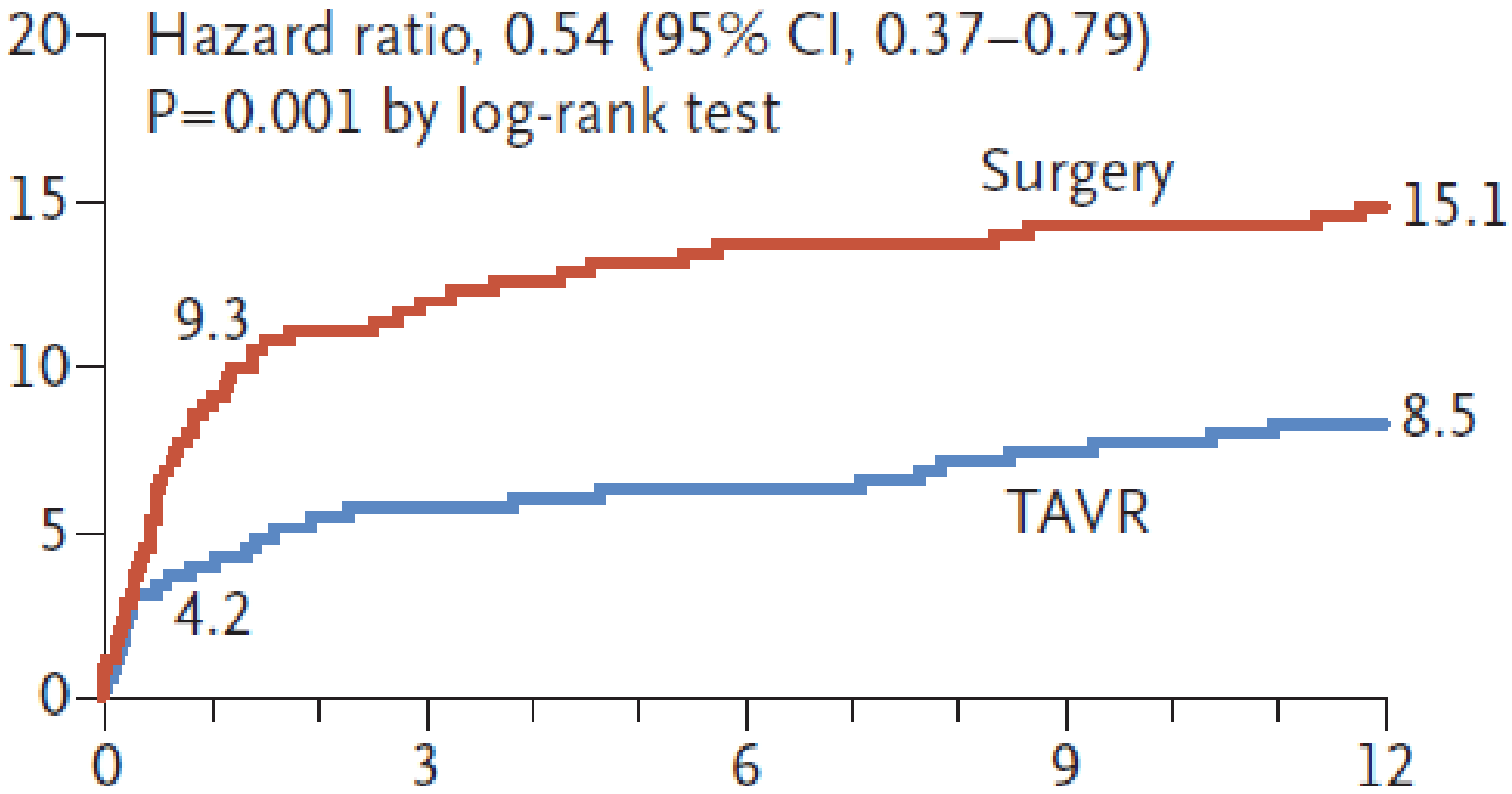
סבבה, השתכנעתם שצריך להחליף את המסתם גם בהיצרות קשה וא-תסמינית של המסתם האאורטלי,
מה עוד אני רוצה?

COREVALVE US High Risk Trial: Mortality

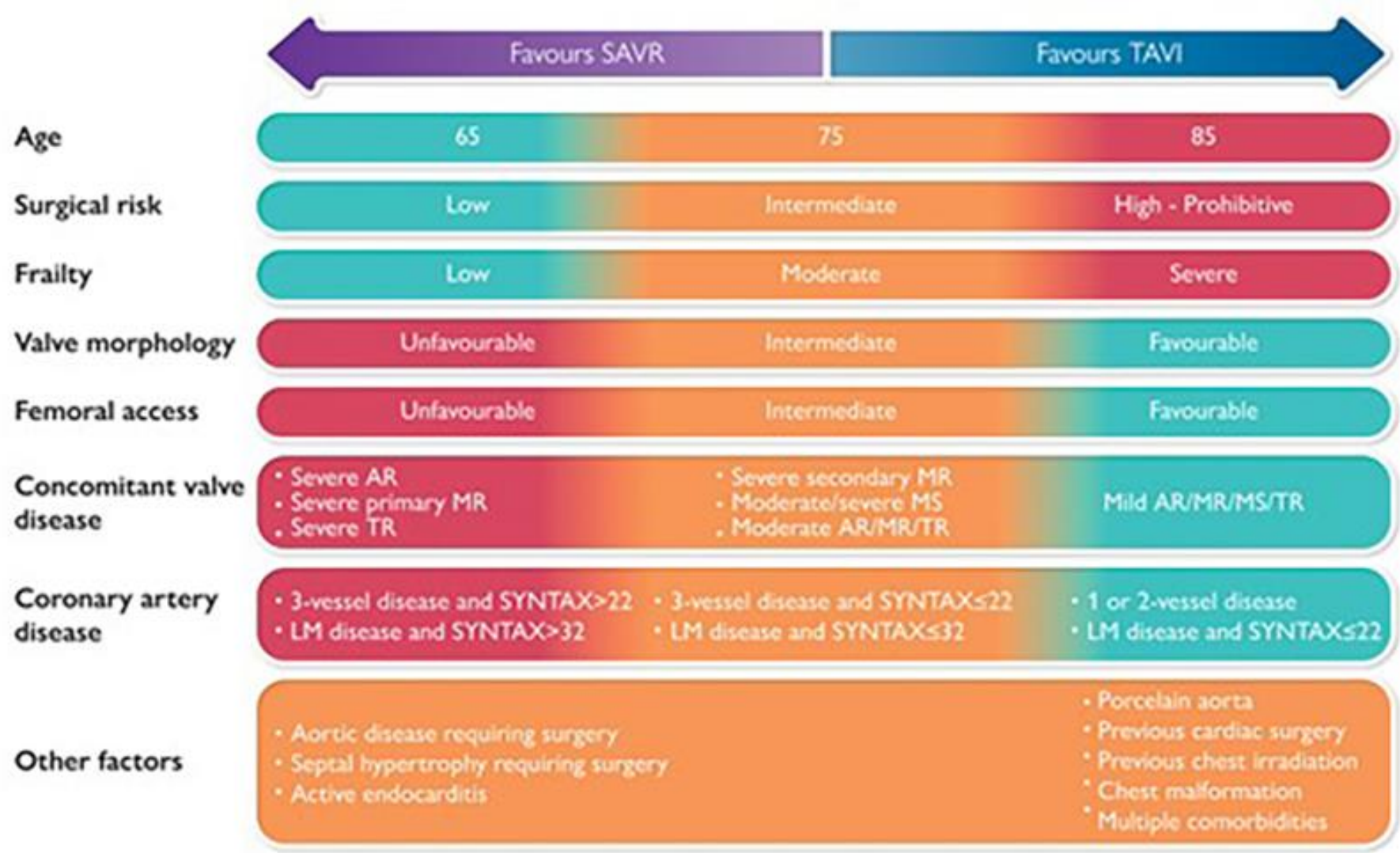


SAVR Vs. TAVI in low risk AS

All cause mortality, all strokes, cardiovascular rehosp.

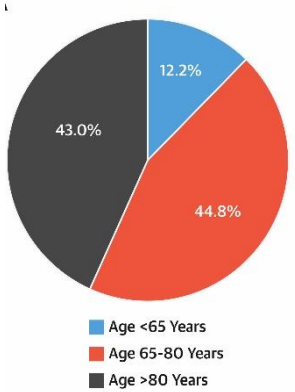


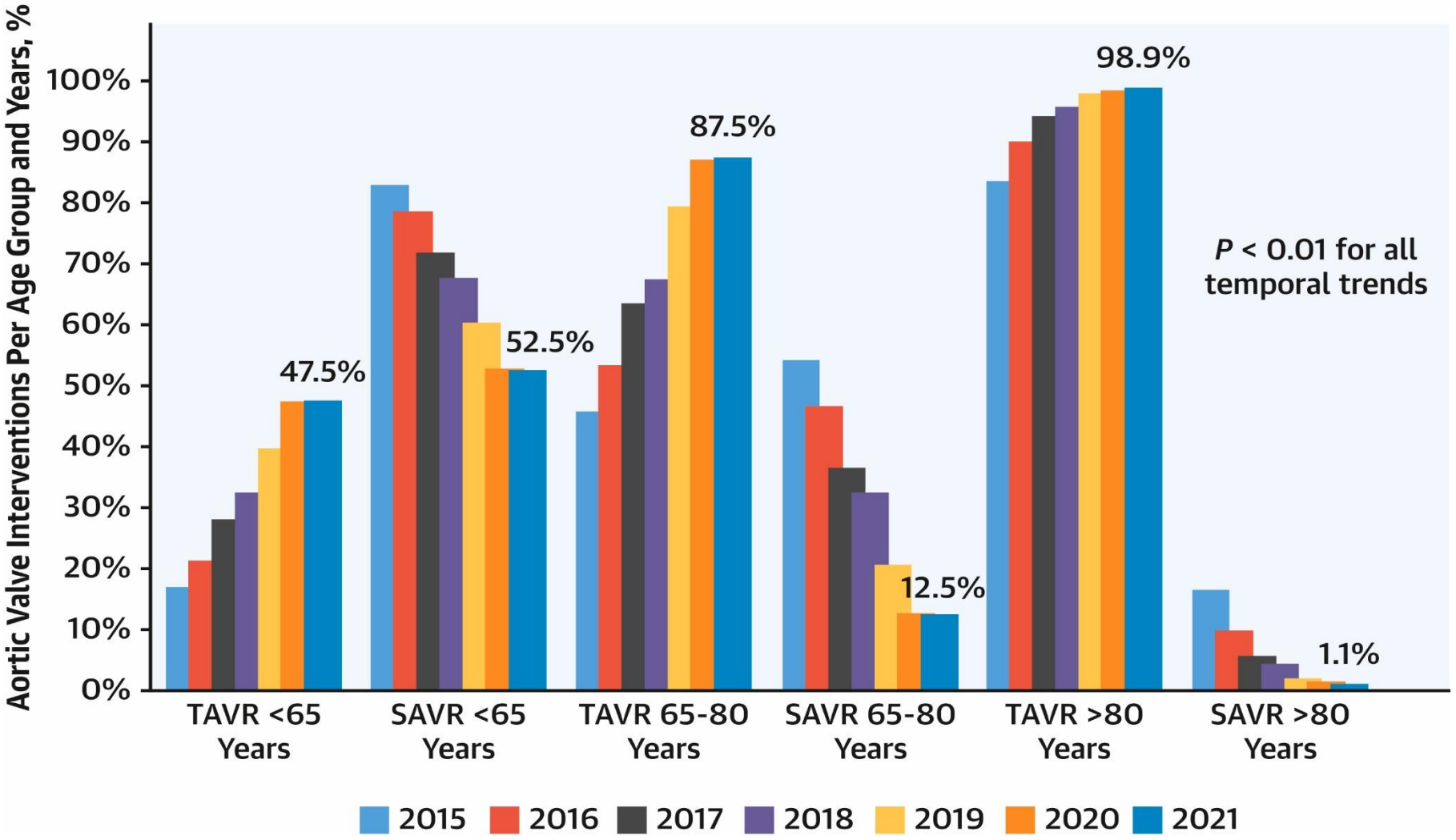
SAVR Vs. TAVI



Windecker et al. EHJ 2022

US national trend in SAVR/TAVI for isolated severe AS





Sharma et al. JACC 2022

TAVI Vs. SAVR for Asymptomatic AS

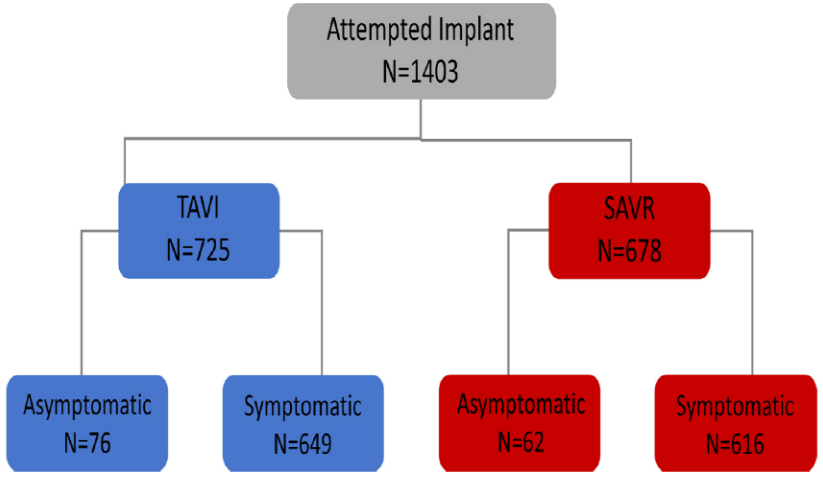
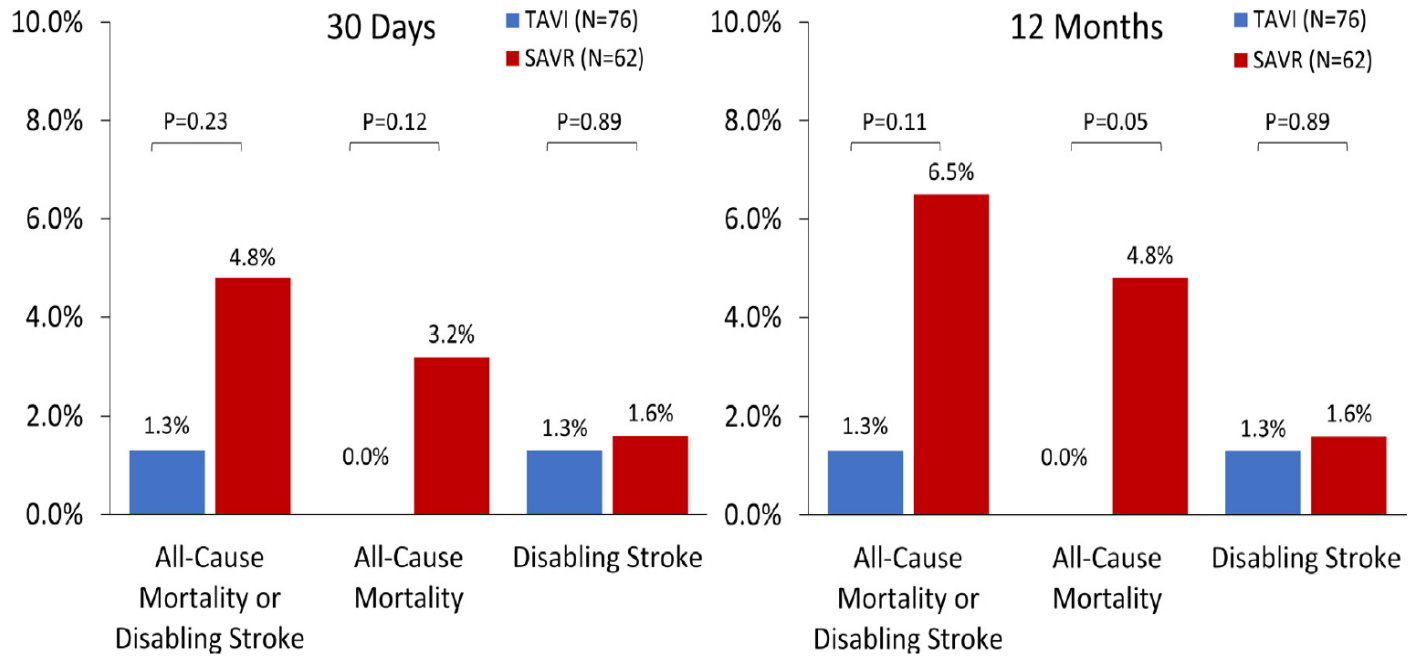
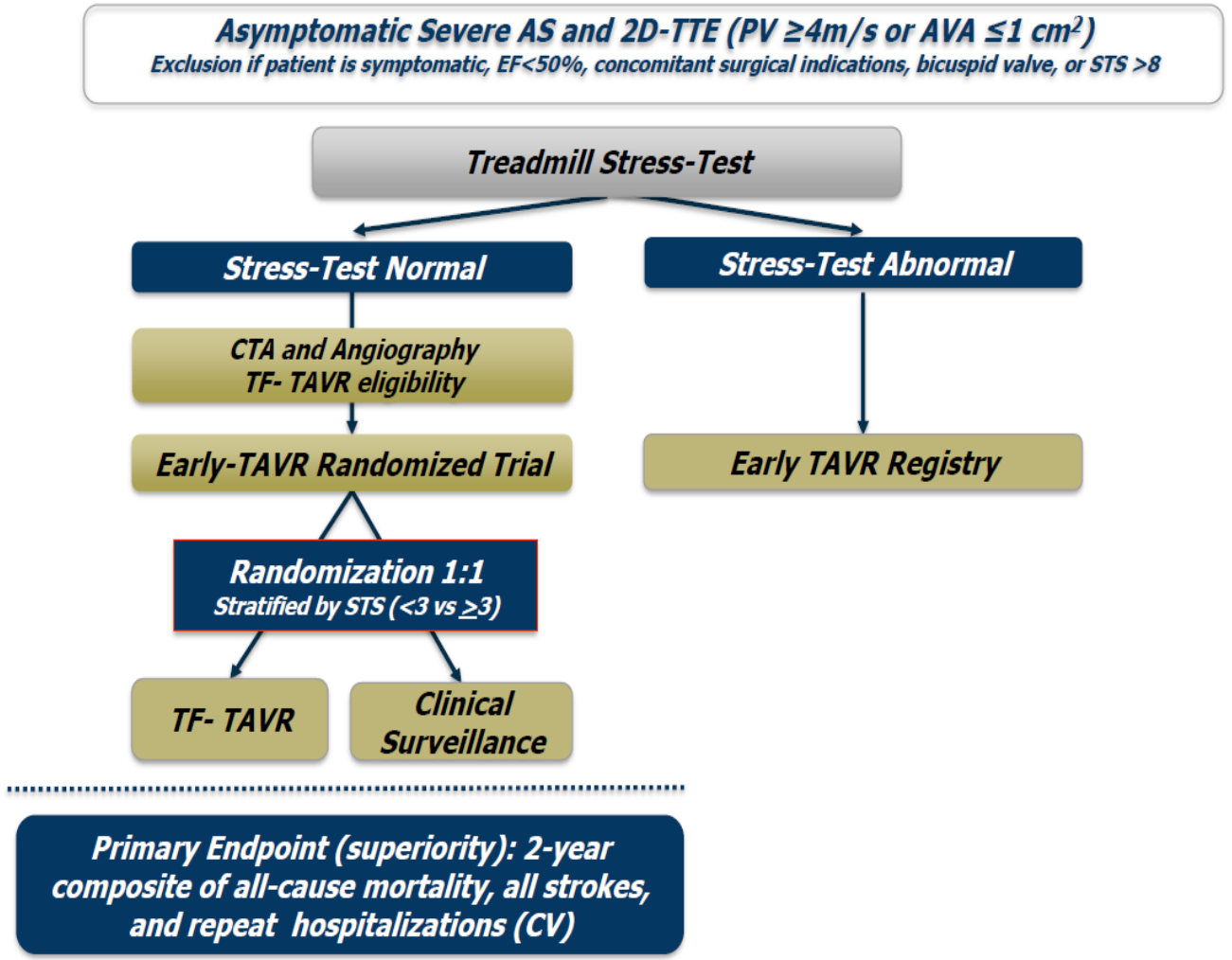


Figure 1. Patient flow for Evolut Low Risk trial protocol.

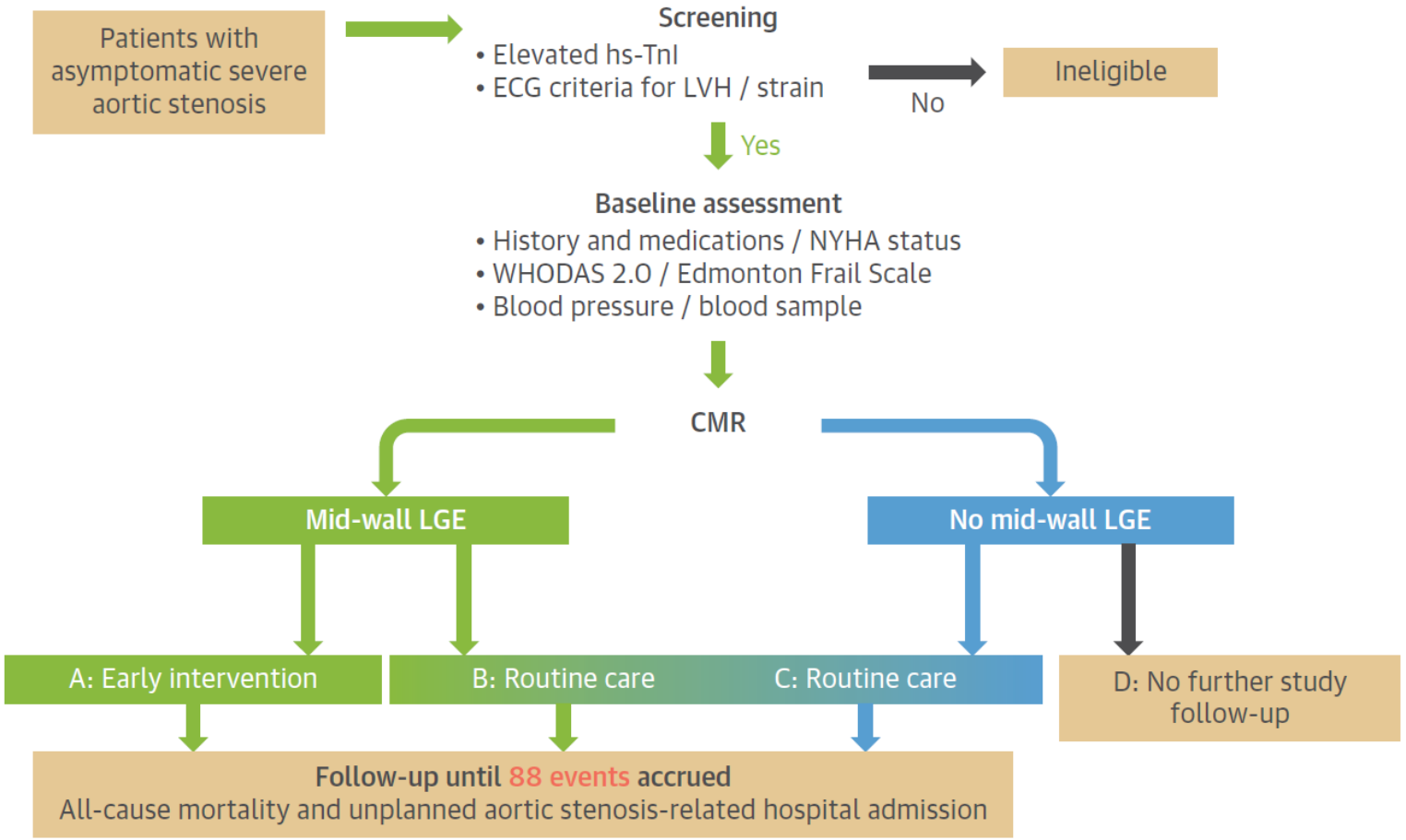


Asymptomatic AS: *Early TAVR Trial (ongoing)*



Van Mieghem et al, presented at TCT 2017

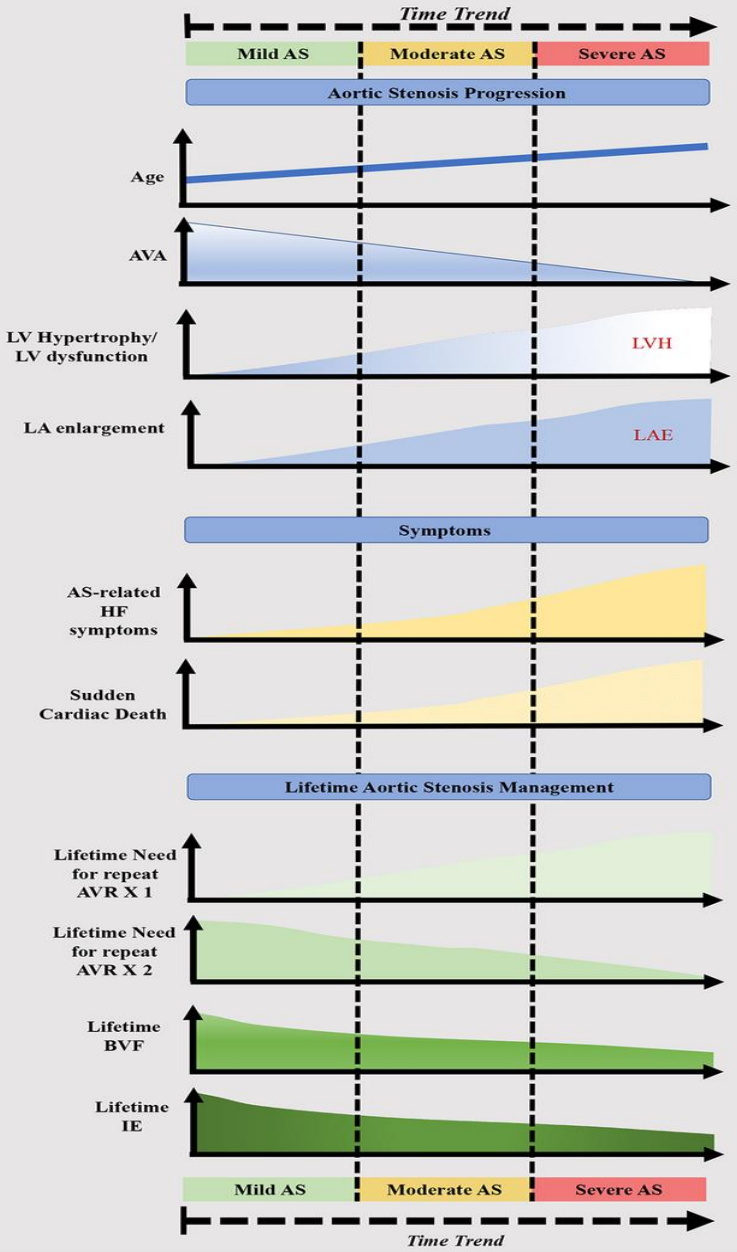
Asymptomatic AS: *EVOLVED Trial (ongoing)*



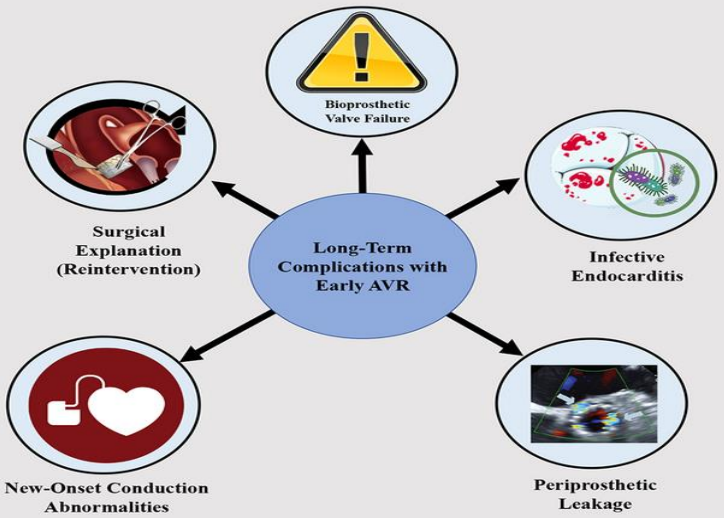
Bing et al. Am Heart J 2019

Perspective of Early Intervention in Aortic Stenosis

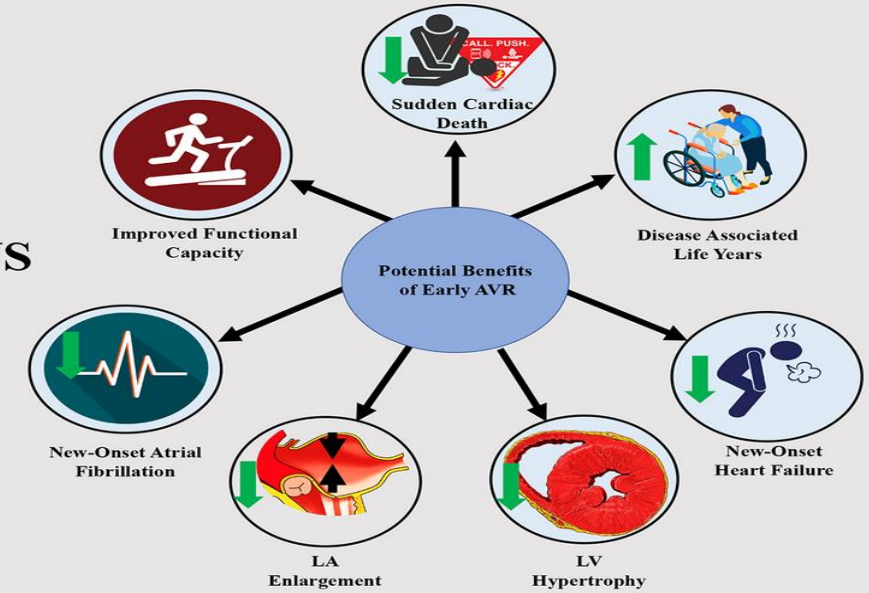
A **Transition of AS Management Perspective with Time**



B **Potential Benefits VS Complications with Early AVR intervention in Asymptomatic Moderate/Severe Aortic Stenosis**



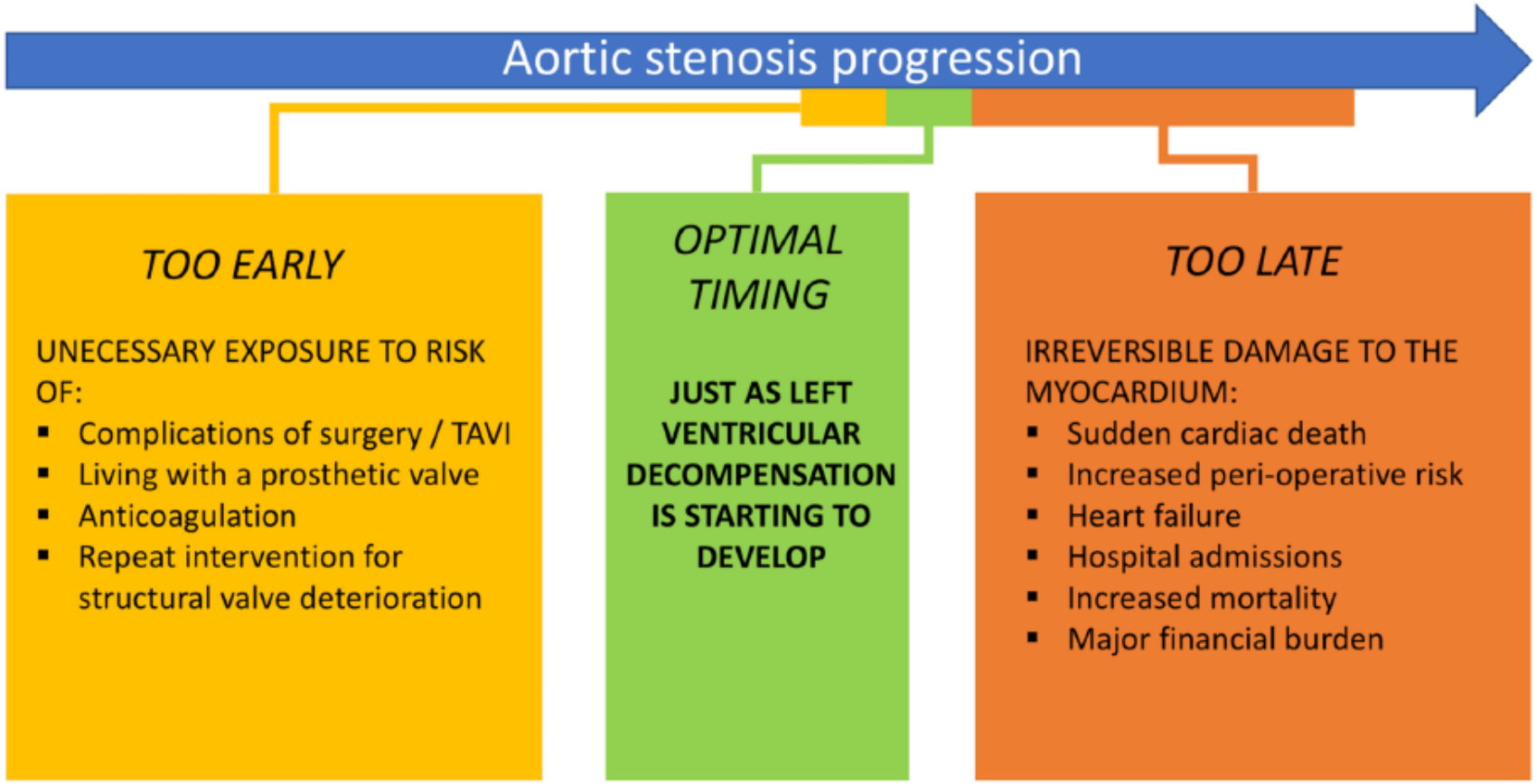
VS



Earlier Intervention| Challenges in Timing

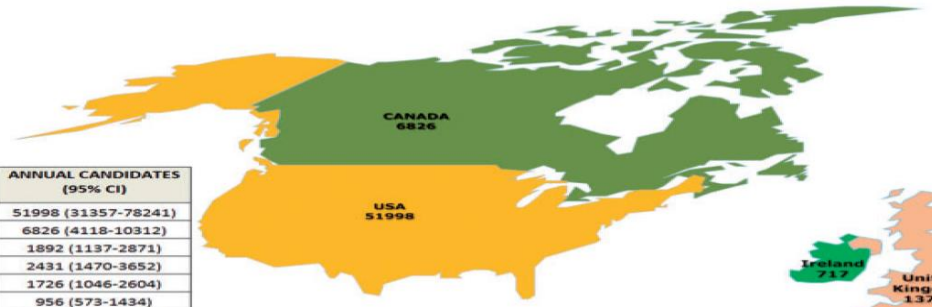
Defining cardiac markers for timing AS intervention is an enduring question for earlier treatment.

When should we offer valve intervention?



Can we make it?

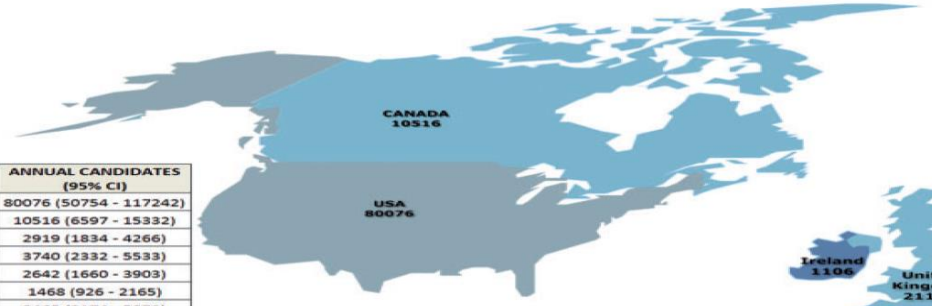
A



COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	51998 (31357-78241)
Canada	6826 (4118-10312)
Austria	1892 (1137-2871)
Belgium	2431 (1470-3652)
Bulgaria	1726 (1046-2604)
Croatia	956 (573-1434)
Czech Republic	2259 (1367-3393)
Denmark	1261 (764-1910)
Estonia	293 (179-441)
Finland	1314 (792-1983)
France	14632 (8886-22012)
Germany	20466 (12237-31180)
Greece	2718 (1656-4089)
Hungary	2108 (1276-3179)
Ireland	717 (435-1073)
Italy	15784 (9538-23700)
Latvia	460 (279-693)
Lithuania	655 (393-992)
Netherlands	3614 (2185-5481)
Norway	998 (597-1503)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	7008 (4195-10581)
Portugal	2516 (1535-3776)
Romania	4035 (2451-6065)
Slovakia	906 (549-1372)
Slovenia	444 (267-664)
Spain	10274 (6153-15470)
Sweden	2279 (1377-3448)
Switzerland	1756 (1059-2650)
United Kingdom	13787 (8293-20807)
European Union	**114757 (69380-172799)**
Northern America	**58556 (35631-87738)**

B



COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	80076 (50754 - 117242)
Canada	10516 (6597 - 15332)
Austria	2919 (1834 - 4266)
Belgium	3740 (2332 - 5533)
Bulgaria	2642 (1660 - 3903)
Croatia	1468 (926 - 2165)
Czech Republic	3465 (2174 - 5078)
Denmark	1938 (1215 - 2850)
Estonia	456 (286 - 673)
Finland	2006 (1253 - 2953)
France	22607 (14305 - 33372)
Germany	31596 (19915 - 46723)
Greece	4190 (2649 - 6144)
Hungary	3262 (2038 - 4807)
Ireland	1106 (701 - 1610)
Italy	24368 (15255 - 35894)
Latvia	709 (442 - 1040)
Lithuania	1009 (639 - 1494)
Netherlands	5524 (3467 - 8126)
Norway	1537 (957 - 2236)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	10797 (6732 - 15971)
Portugal	3892 (2423 - 5802)
Romania	6224 (3872 - 9189)
Slovakia	1391 (879 - 2050)
Slovenia	681 (428 -1004)
Spain	15783 (9919 - 23317)
Sweden	3526 (2230 - 5166)
Switzerland	2696 (1715 - 3949)
United Kingdom	21133 (13305 - 30852)
European Union	**177462 (110059 - 260576)**
Northern America	**90135 (56740 - 131605)**

TAVI for Asymptomatic AS: conclusions

- Severe AS (symptomatic and asymptomatic) is associated with increased morbidity and mortality
- AVR is an effective therapy for severe AS: reducing morbidity and mortality
- AVR has been proven effective in asymptomatic Severe AS
- TAVI appears safer and more effective than SAVR in symptomatic and asymptomatic AS patients

- **TAVI is the right therapy for most asymptomatic severe AS patients**

TAVI for asymptomatic AS

There are risks and costs to a program of action, but they are far less than the long-range risks and costs of comfortable inaction.

John F. Kennedy

Get ready for the next debate: TAVI for moderate AS..

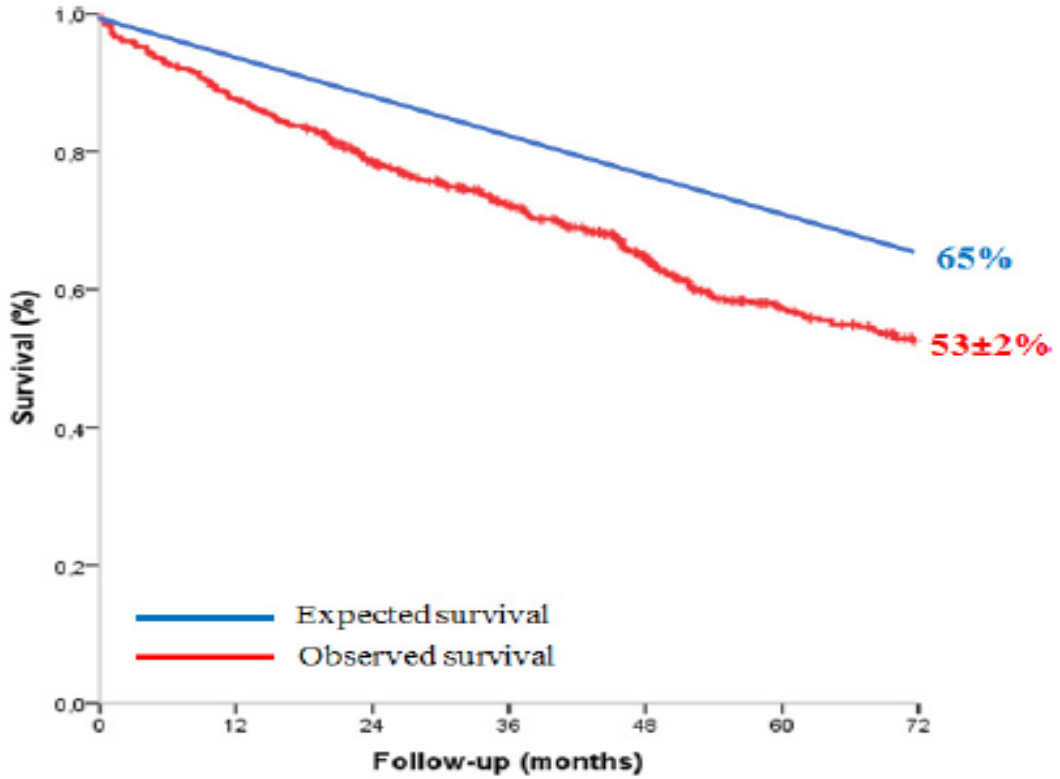
508 patients

Preserved LVEF

mean AVA: 1 – 1.5 cm^2

Matched population to assess expected survival

תודה רבה!



	12 months	24 months	36 months	48 months	60 months	72 months
Expected survival (%)	94	88	82	76	70	65
Observed survival (%)	87	78	72	64	57	53
Relative survival (%)	92.5	88.6	87.8	84.2	81.4	81.5

Delesalle et al. JAHA 2019