Impatto clinico della fibrosi miocardica nella stenosi aortica severa

Gianfranco Sinagra, *Trieste*

DISCLOSURE INFORMATION

Prof. Gianfranco Sinagra

Negli ultimi due anni ho avuto i seguenti rapporti con soggetti portatori di interessi commerciali in campo sanitario

Novartis, Bayer, Astrazeneca, Boston Scientific, Vifor Pharma, Menarini, Akcea Therapeutics

Relatore a congressi

Novartis, Impulse Dynamics, Biotronik

Consulenze e Collaborazione scientifica occasionale

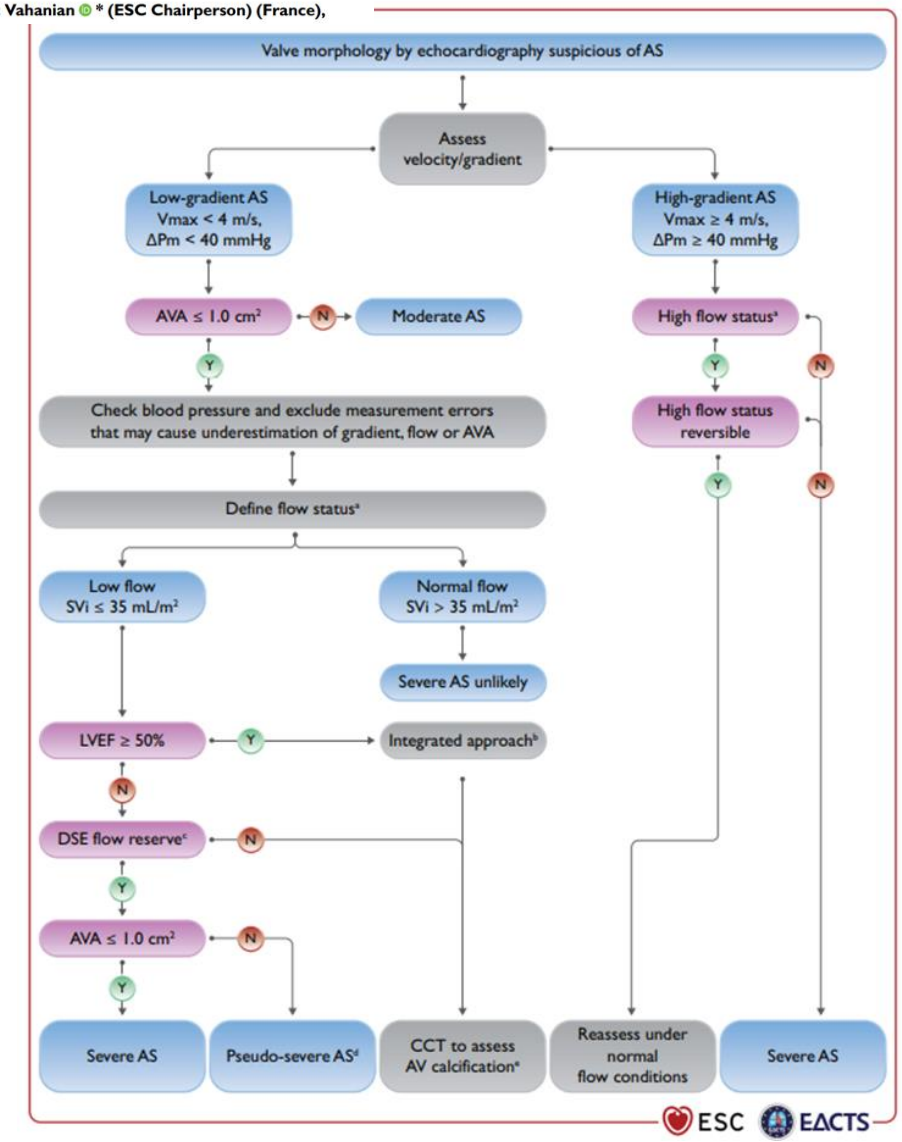
Ai sensi dell'Art. 10 L.675 del 31/12/1996 e dell'Art. 76, comma 4 dell'Accordo Stato-Regioni del 02/02/2017 e del paragrafo 4.5 del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

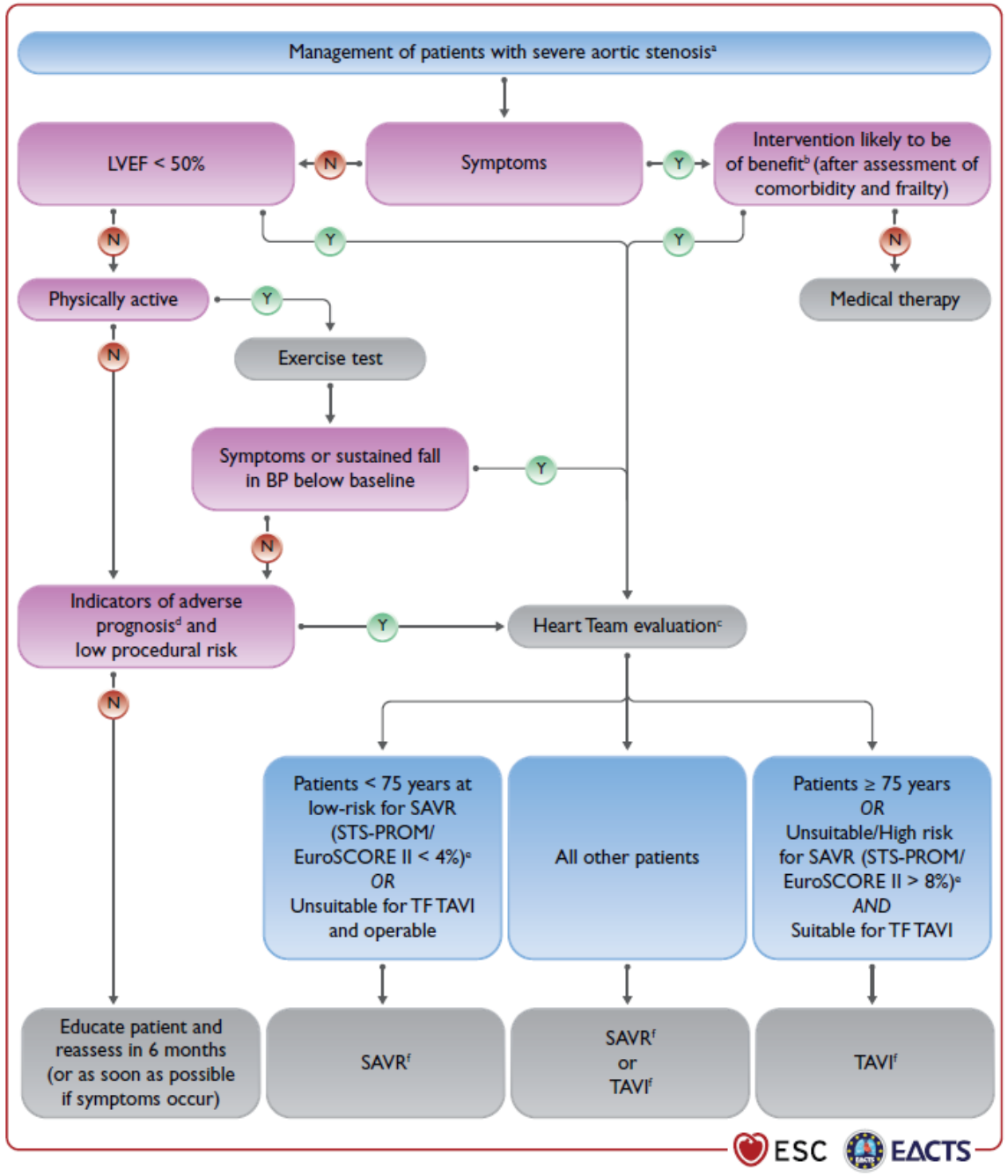
ESC European Society of Cardiology
European Heart Journal (2021) 00, 1–72
doi:10.1093/eurheartj/ehab395

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Alec Vahanian * (ESC Chairperson) (France),





doi:10.1093/eurheartj/ehab395

A) Symptomatic aortic stenosis	Class[b]	Level[c]
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1.0 cm^2 (or ≤0.6 cm^2/m^2)].[235,236]	I	B
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction (<50%), and evidence of flow (contractile) reserve.[32,237]	I	B
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation that the aortic stenosis is severe[d] (*Figure 3*).	IIa	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient severe aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival >1 year.	III	C

B) Asymptomatic patients with severe aortic stenosis		
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

ESC
European Society of Cardiology

ESC European Society of Cardiology European Heart Journal (2021) 00, 1–72 doi:10.1093/eurheartj/ehab395

ESC/EACTS GUIDELINES

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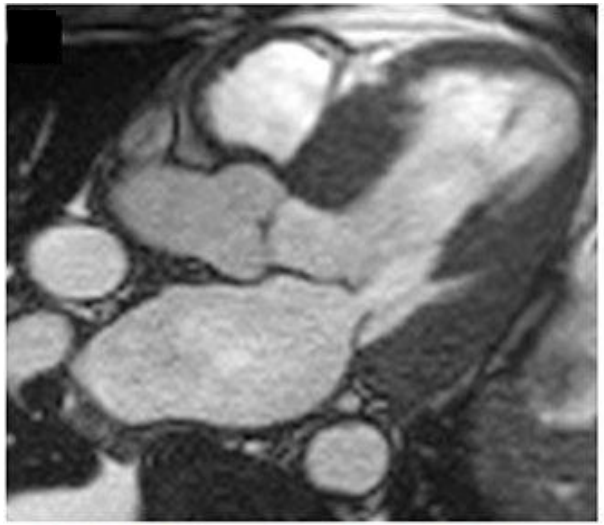
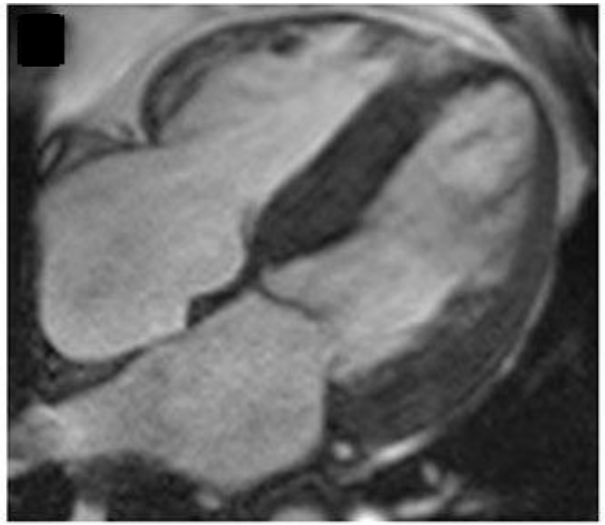
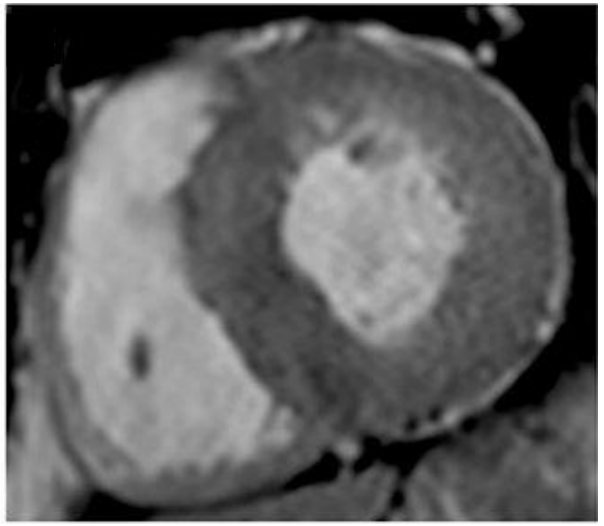
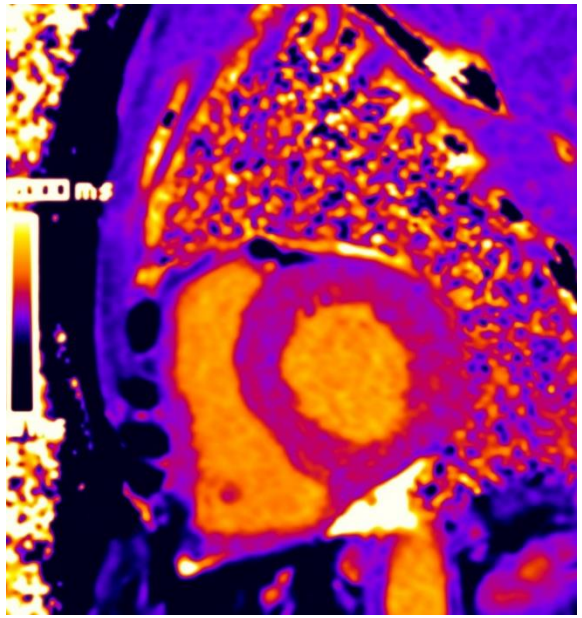
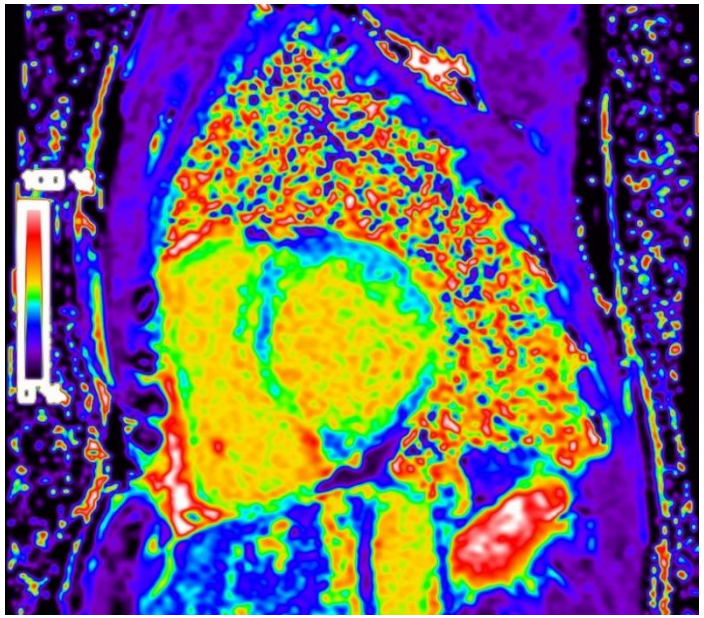
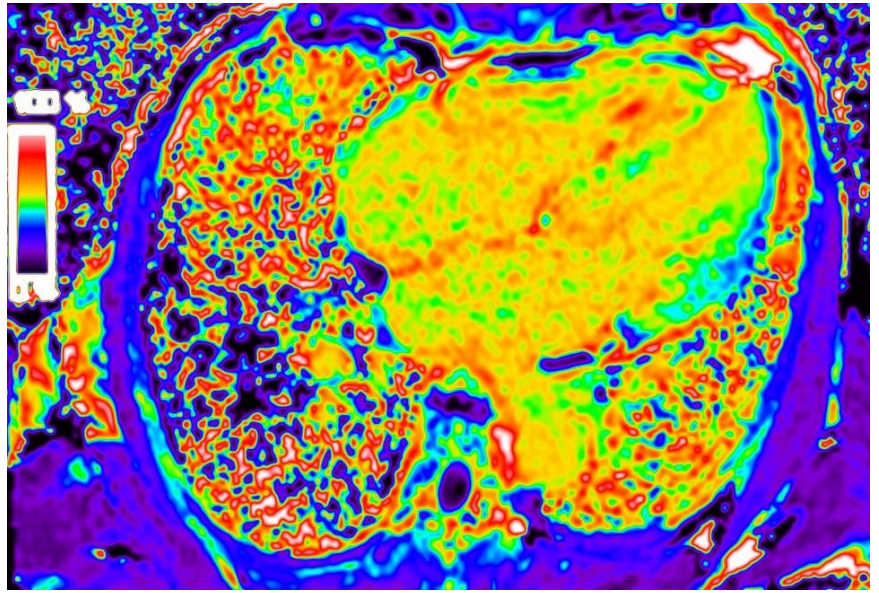




IVS marcata, pareti atriali ben evidenti, e ispessimento apparati valvolari

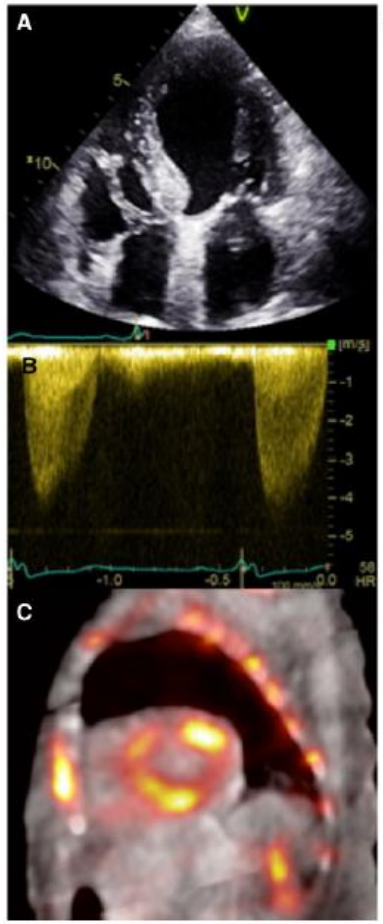


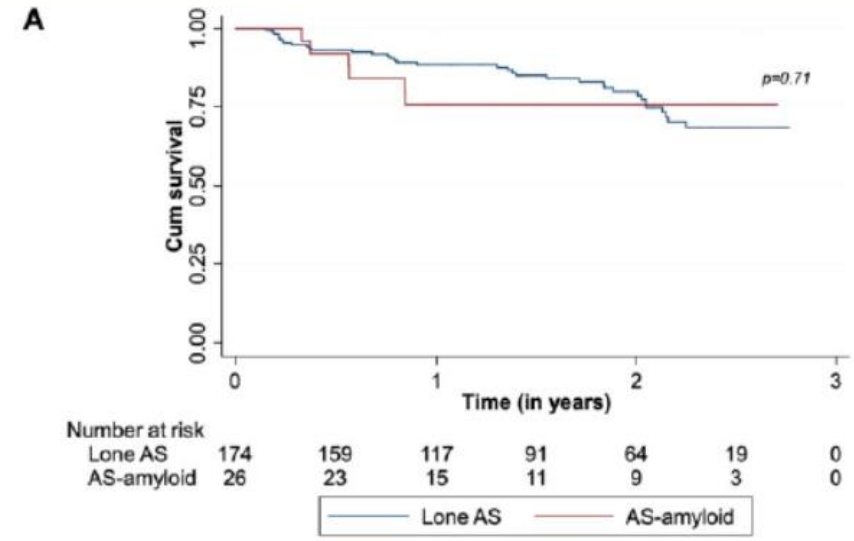



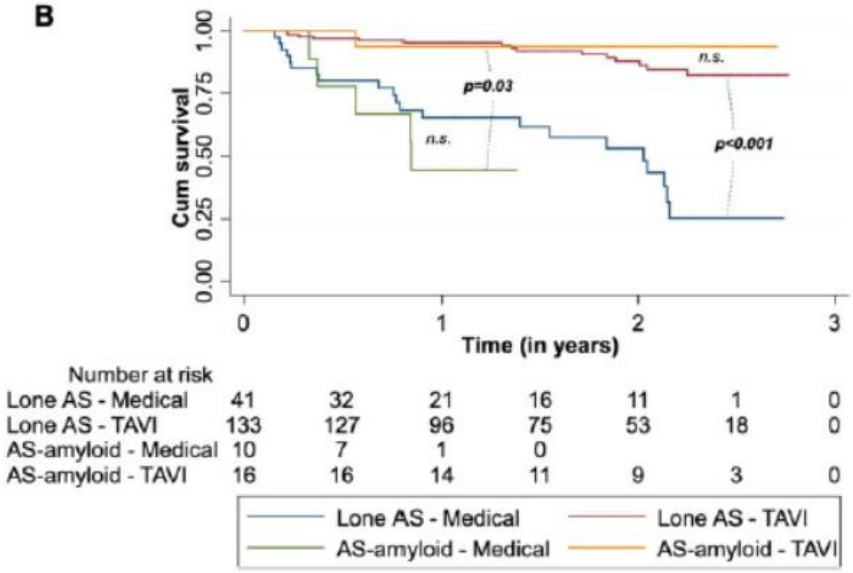
T1 mapping (sin) aumentato diffusamente, consistente con una distorsione della struttura miocardica e della matrice extracellulare. Sequenze (centro e dx) per volume extracellulare (ECV). incremento globale ECV al 50% della massa miocardica (SIV giallo-rosso), non distrettuale nelle aree normalmente piu' alterate nel modello St Ao pura (SIV ant).

ESC European Society of Cardiology
European Heart Journal (2020) 0, 1–10
doi:10.1093/eurheartj/ehaa170

Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation





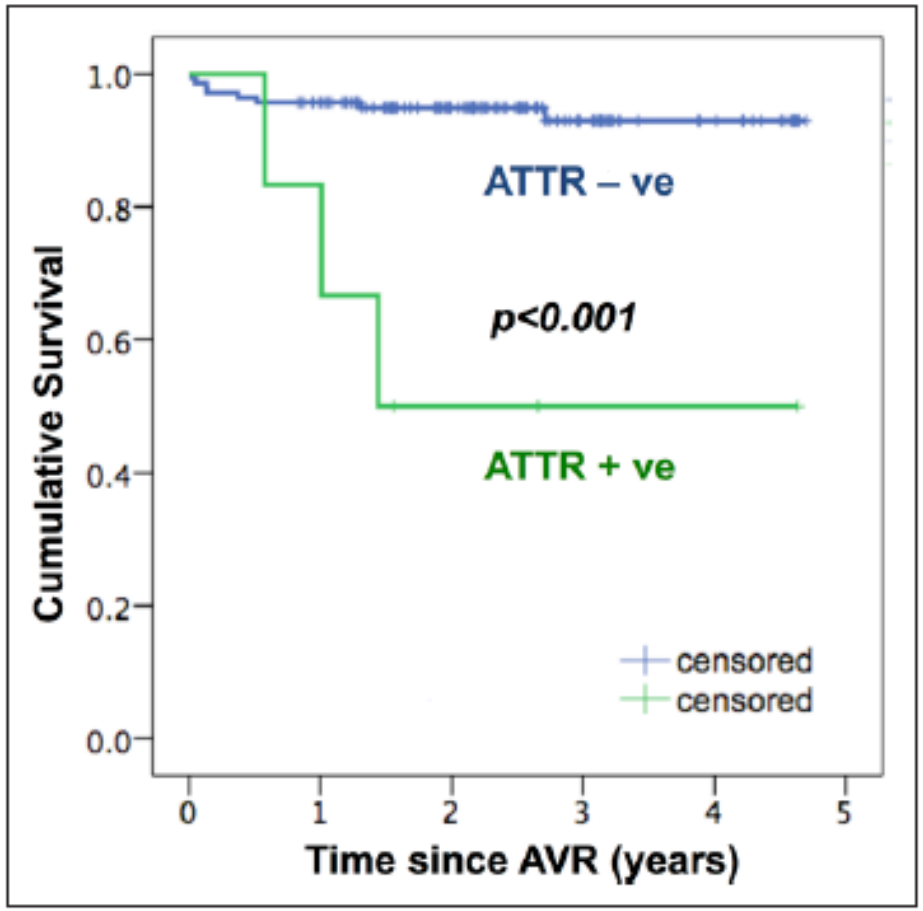


Scully PR et al doi:10.1093/eurheartj/ehaa170

Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis

Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement

Thomas A. Treibel, MBBS; Marianna Fontana, MD; Janet A. Gilbertson, CSci; Silvia Castelletti, MD; Steven K. White, MBChB; Paul R. Scully, MBBS; Neil Roberts, MD; David F. Hutt, BApSc; Dorota M. Rowczenio, PhD; Carol J. Whelan, MD; Michael A. Ashworth, MD; Julian D. Gillmore, MD, PhD; Philip N. Hawkins, FMedSci; James C. Moon, MD



146 pts; Fup 2.3 yrs; deaths 50% (aSA vs 7,5% cSA)

2016 DOI: 10.1161/CIRCIMAGING.116.005066

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European Heart Journal (2021) **00**, 1–72
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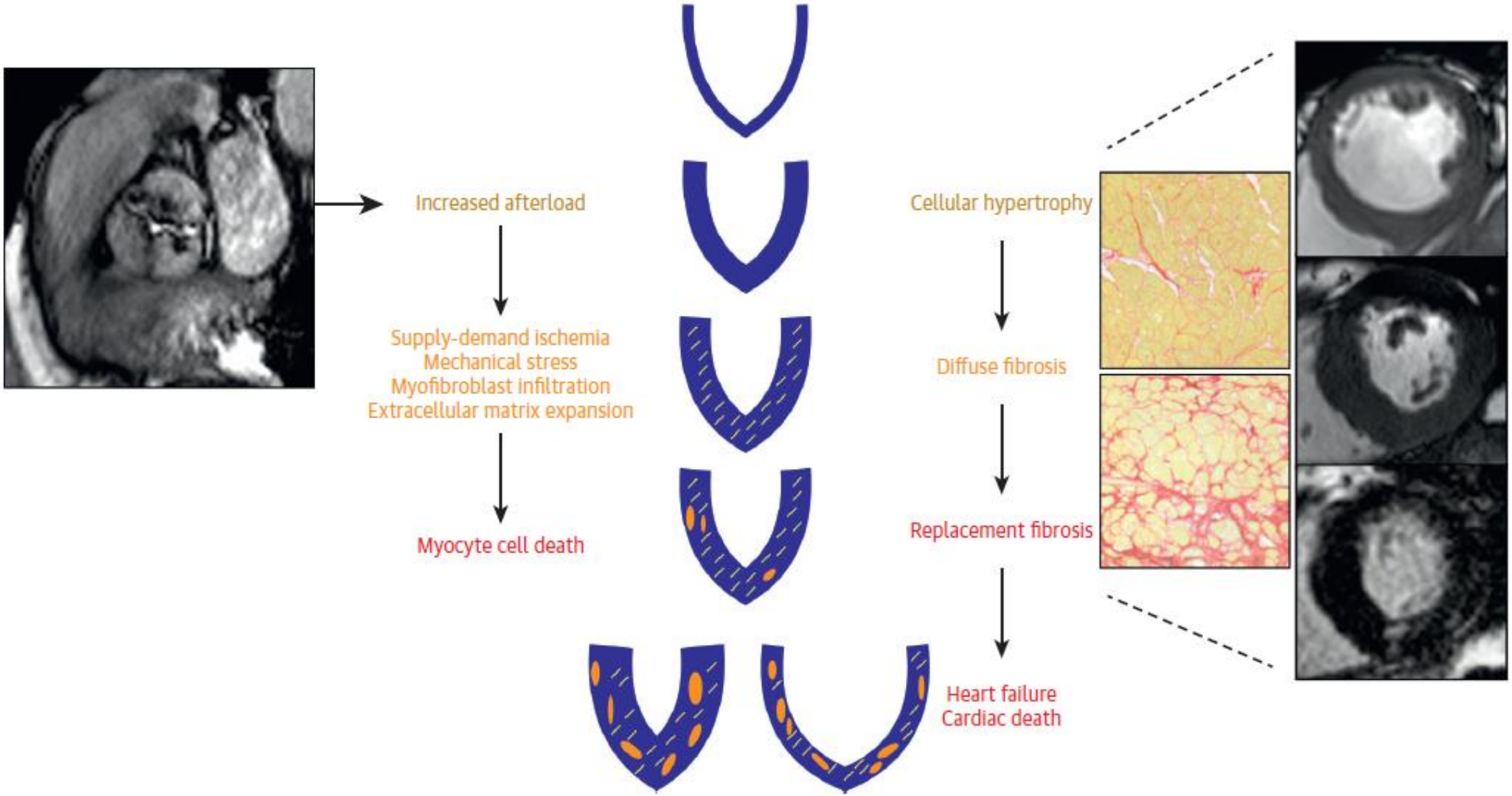
3.2.3.2 Cardiac magnetic resonance

In patients with inadequate echocardiographic quality or discrepant results, CMR should be used to assess the severity of valvular lesions particularly regurgitant lesions, and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis.[33] CMR is the reference method for the evaluation of right ventricular (RV) volumes and function and is therefore particularly useful to evaluate the consequences of tricuspid regurgitation.[34] It also has an incremental value for assessing the severity of aortic and mitral regurgitation.

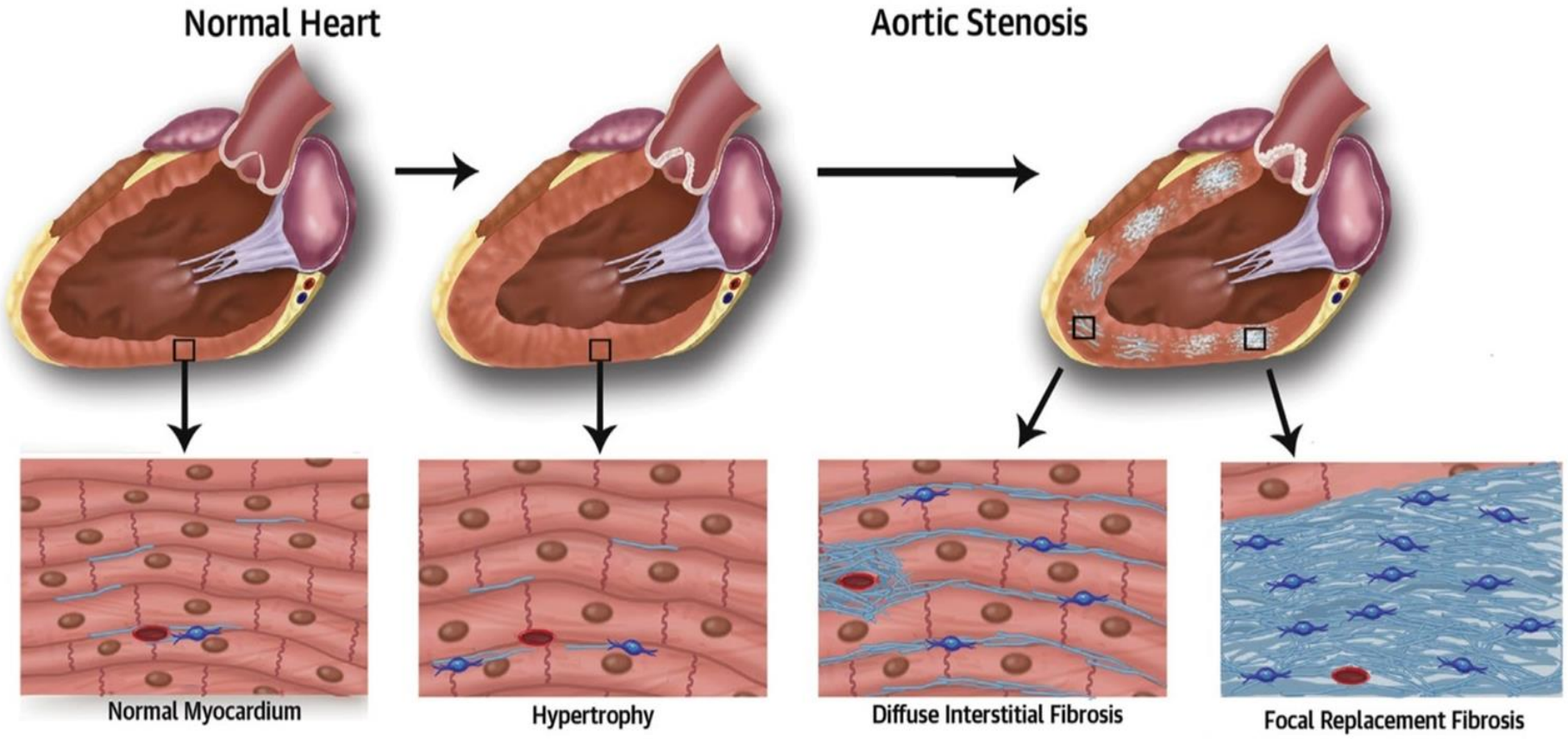
5.1.2 Additional diagnostic and prognostic parameters

Myocardial fibrosis is a major driver of LV decompensation in aortic stenosis (regardless of the presence or absence of CAD), which can be detected and quantified using CMR. Amyloidosis is also frequently associated with aortic stenosis in elderly patients (incidence 9–15%).[175] When cardiac amyloidosis is clinically suspected, based on symptoms (neuropathy and hematologic data), diphosphonate scintigraphy and/or CMR should be considered. Both entities persist following valve intervention and are associated with poor long-term prognosis.[176–179]

doi:10.1093/eurheartj/ehab395



Bing et al - ***Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis (JACC, 2019)***



↑ myocyte volume

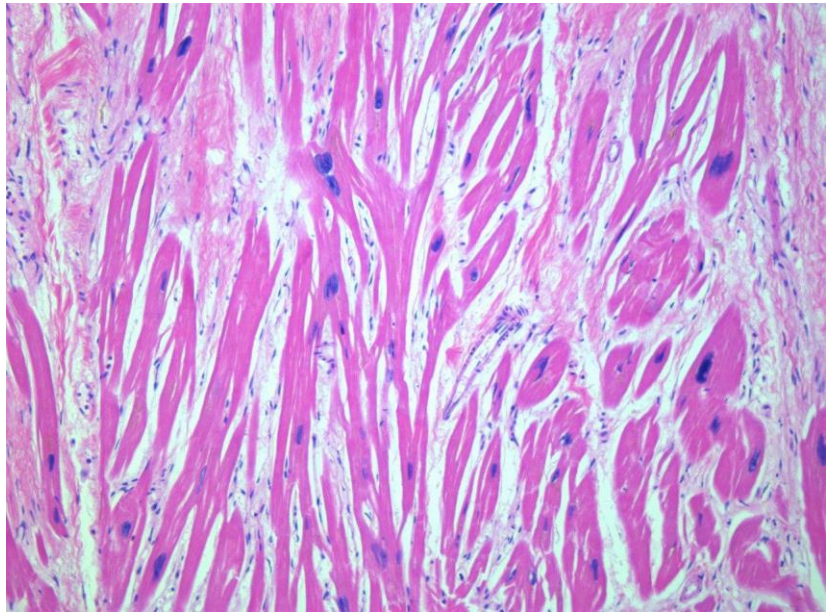
↑ deposition of collagen in interstitial spaces

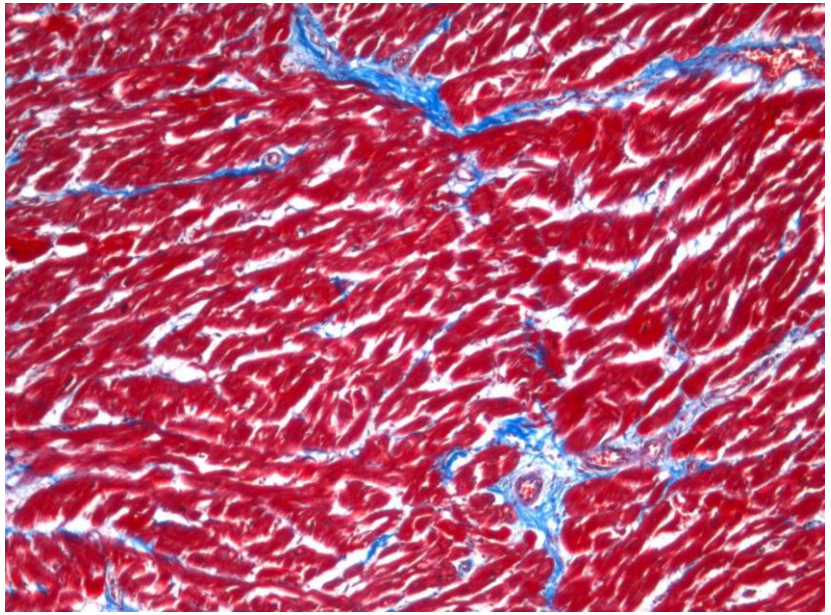
(reversible)

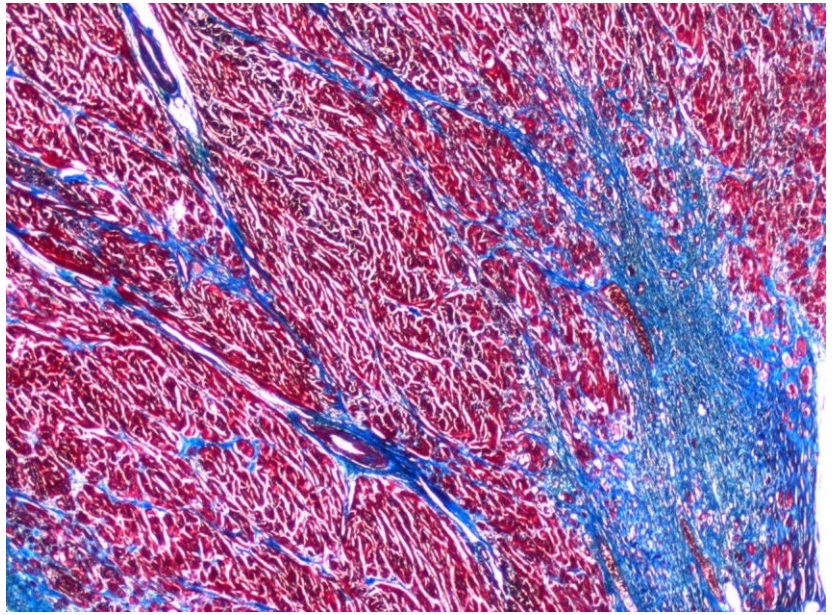
Replacement of myocytes by fibrotic tissue

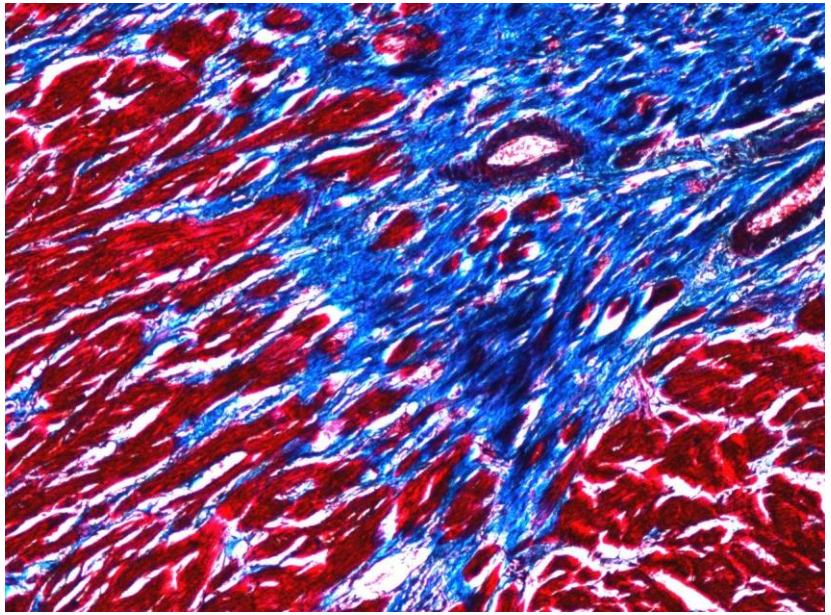
(Irreversible)

Gilles Barone-Rochette et al - ***Prognostic Significance of LGE by CMR in Aortic Stenosis Patients Undergoing Valve Replacement (JACC, 2014)***





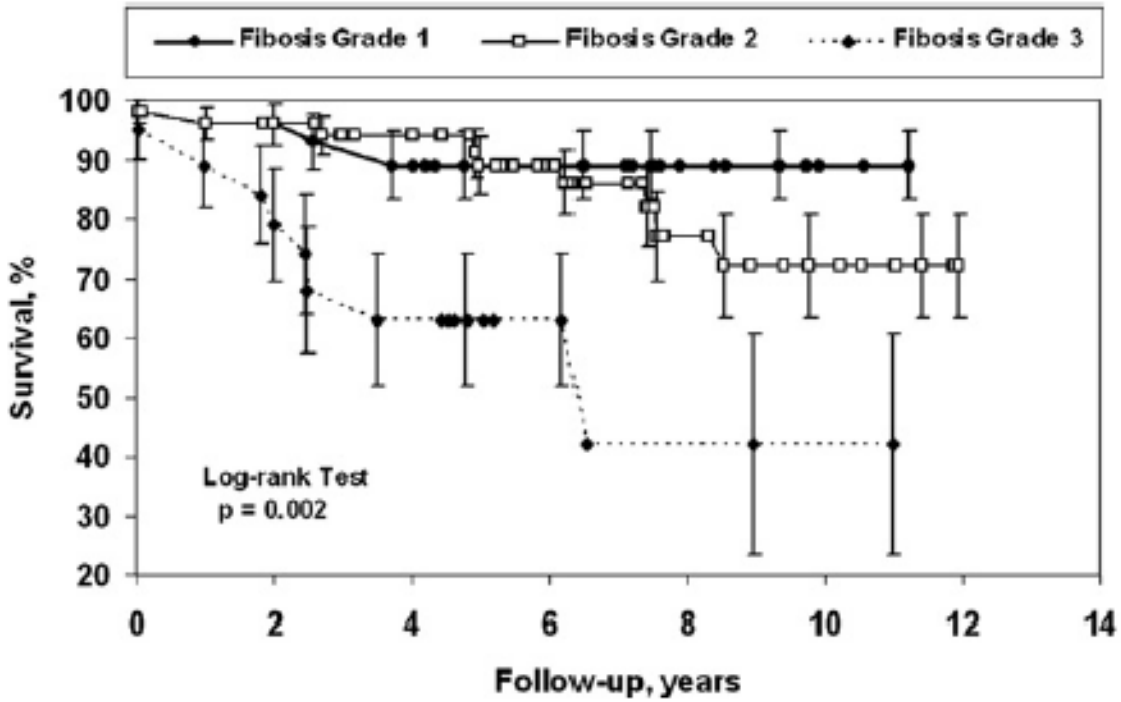




Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis

99 pts; fup 6.2 yrs; IVS specimen

Aldo Domenico Milano, MD, PhD,[a] Giuseppe Faggian, MD,[a] Mikhail Dodonov, MD,[a] Giorgio Golia, MD,[b] Anna Tomezzoli, MD,[c] Uberto Bortolotti, MD,[d] and Alessandro Mazzucco, MD[a]



Conclusions: In patients with severe aortic valve stenosis, the amount of myocardial fibrosis appears to have significant effect on clinical status and long-term survival after aortic valve replacement. From these results, we believe that new strategies for the earlier detection of myocardial fibrosis are needed to achieve a better prognostic outcome. (J Thorac Cardiovasc Surg 2012;144:830-7)

Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis

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TABLE 3. Hemodynamic profile according to myocardial fibrosis grade

	Fibrosis grade I		Fibrosis grade II		Fibrosis grade III	
Variable	Preoperative (n = 28)	Postoperative (n = 28)	Preoperative (n = 52)	Postoperative (n = 50)	Preoperative (n = 19)	Postoperative (n = 18)
Mean NYHA	2.4 ± 0.7	1.9 ± 0.6*	2.5 ± 0.7	2.2 ± 0.8*	3.1 ± 0.6	3.2 ± 0.8
LVEDD (mm)	47 ± 6	46 ± 6*	54 ± 5	53 ± 5*	63 ± 4	63 ± 4
LVESD (mm)	29 ± 6	30 ± 5†	37 ± 5	36 ± 6	47 ± 5	48 ± 5
LVFS (%)	39 ± 6	41 ± 6	33 ± 6	34 ± 7	24 ± 6	24 ± 5
RWT	0.61 ± 0.10	0.49 ± 0.07†	0.44 ± 0.07	0.37 ± 0.07†	0.31 ± 0.04	0.37 ± 0.12*
LVEF (%)	57 ± 7	60 ± 10*	55 ± 8	57 ± 8	42 ± 7	40 ± 5
LVMI (g/m^2)	196 ± 33	118 ± 30†	194 ± 30	134 ± 37†	190 ± 38	173 ± 36†
Aortic MG (mm Hg)	50 ± 11	13 ± 4†	51 ± 14	12 ± 3†	44 ± 12	12 ± 3†
Aortic VAi (cm^2/m^2)	0.39 ± 0.08	0.93 ± 0.19†	0.38 ± 0.09	0.99 ± 0.19†	0.40 ± 0.10	0.93 ± 0.12†
ESWS (kdyne/cm^2)	65 ± 20	68 ± 18	109 ± 30	114 ± 33	206 ± 41	182 ± 36†

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Prognostic Significance of LGE by CMR in Aortic Stenosis Patients Undergoing Valve Replacement

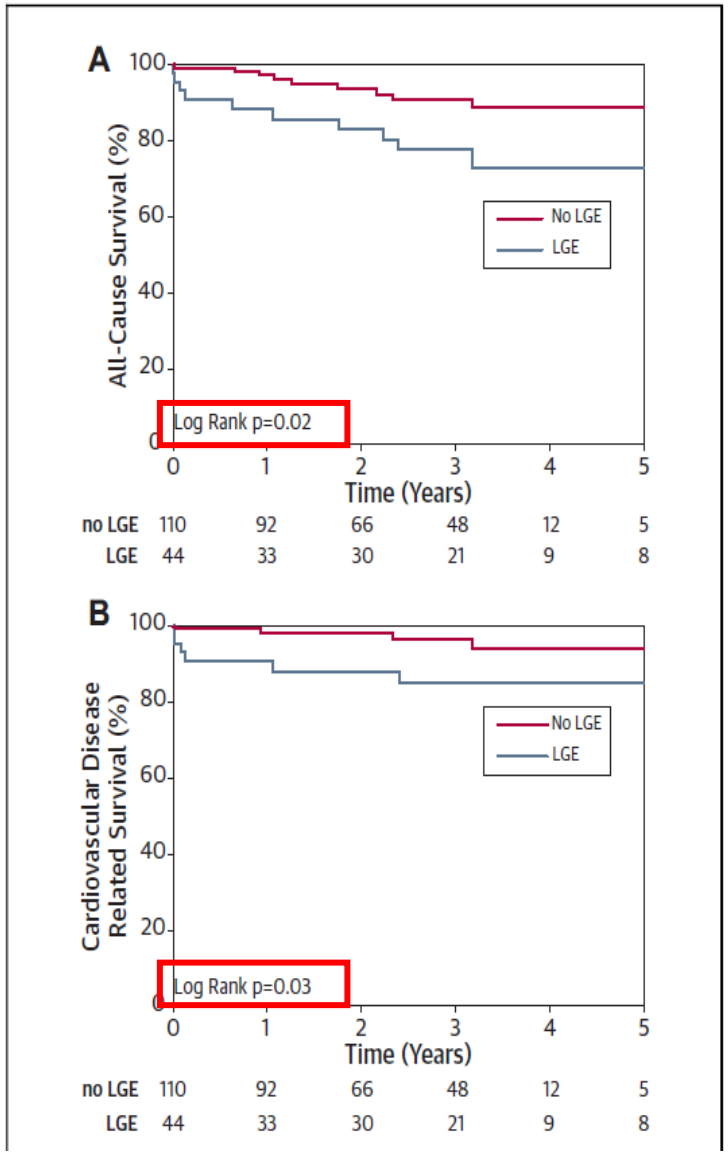
Gilles Barone-Rochette, MD, Sophie Piérard, MD, Christophe De Meester de Ravenstein, MS, Stéphanie Seldrum, MD, Julie Melchior, MD, Frédéric Maes, MD, Anne-Catherine Pouleur, MD, PhD, David Vancraeynest, MD, PhD, Agnes Pasquet, MD, PhD, Jean-Louis Vanoverschelde, MD, PhD, Bernhard L. Gerber, MD, PhD

- 194 pts; age 74 yrs; no previous AMI;
- 154 undergoing SAVR (29% LGE+);
- 40 pts undergoing TAVR (25 transfemoral vs 15 apical TAVR;
- 50% LGE+)
- Fup 2.9 yrs

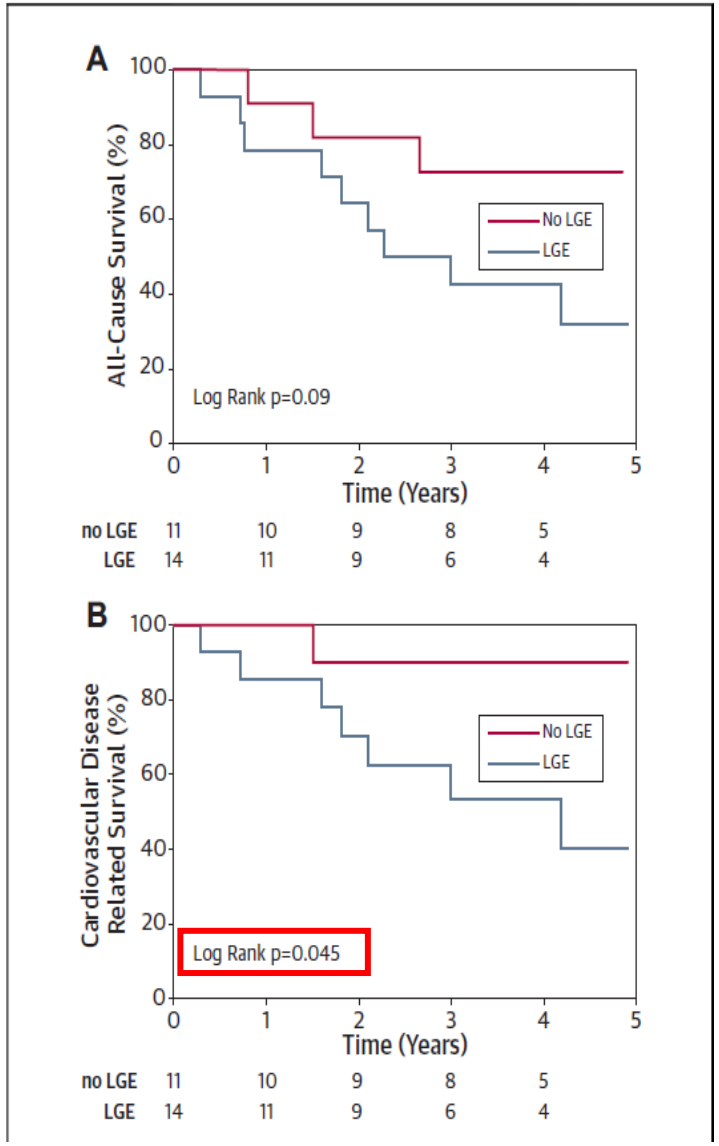
TABLE 4 Predictors of Overall Survival After Surgical AVR on Univariate and Multivariate Cox Analysis

	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Presence of LGE	2.8 (1.1-6.7)	0.02	2.8 (1.1-6.9)	0.025
NYHA functional class III/IV	3.2 (1.3-8.0)	0.007	3.2 (1.1-8.1)	0.01
LBBB	2.8 (0.92-8.3)	0.06	-	-

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.



All-cause (A) and cardiovascular disease related (B) survival in 154 patients undergoing **SAVR**



All-cause (A) and cardiovascular disease related (B) survival in 25 patients undergoing **transfemoral TAVR**

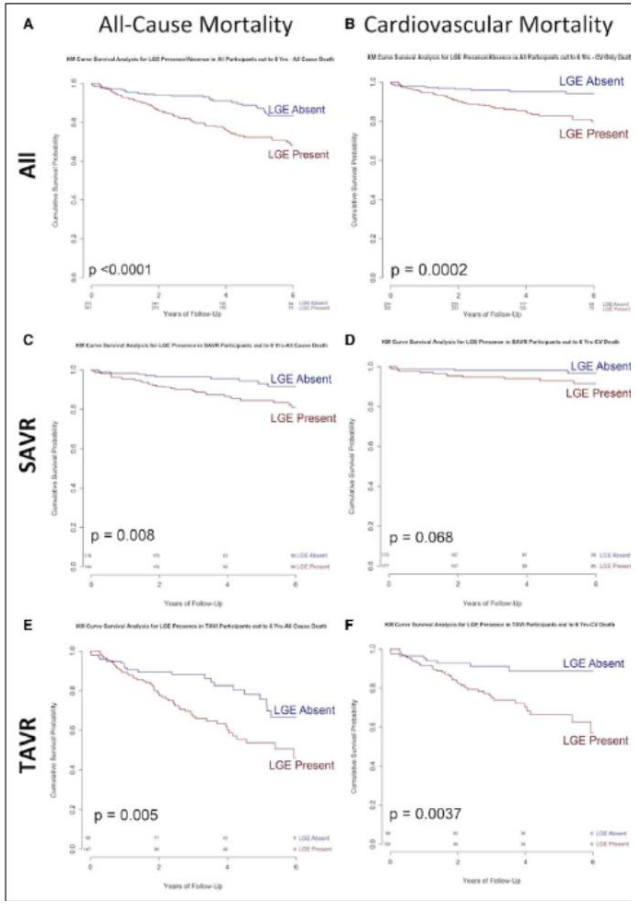
Circulation. 2018;138:1935–1947. DOI: 10.1161/CIRCULATIONAHA.117.032839

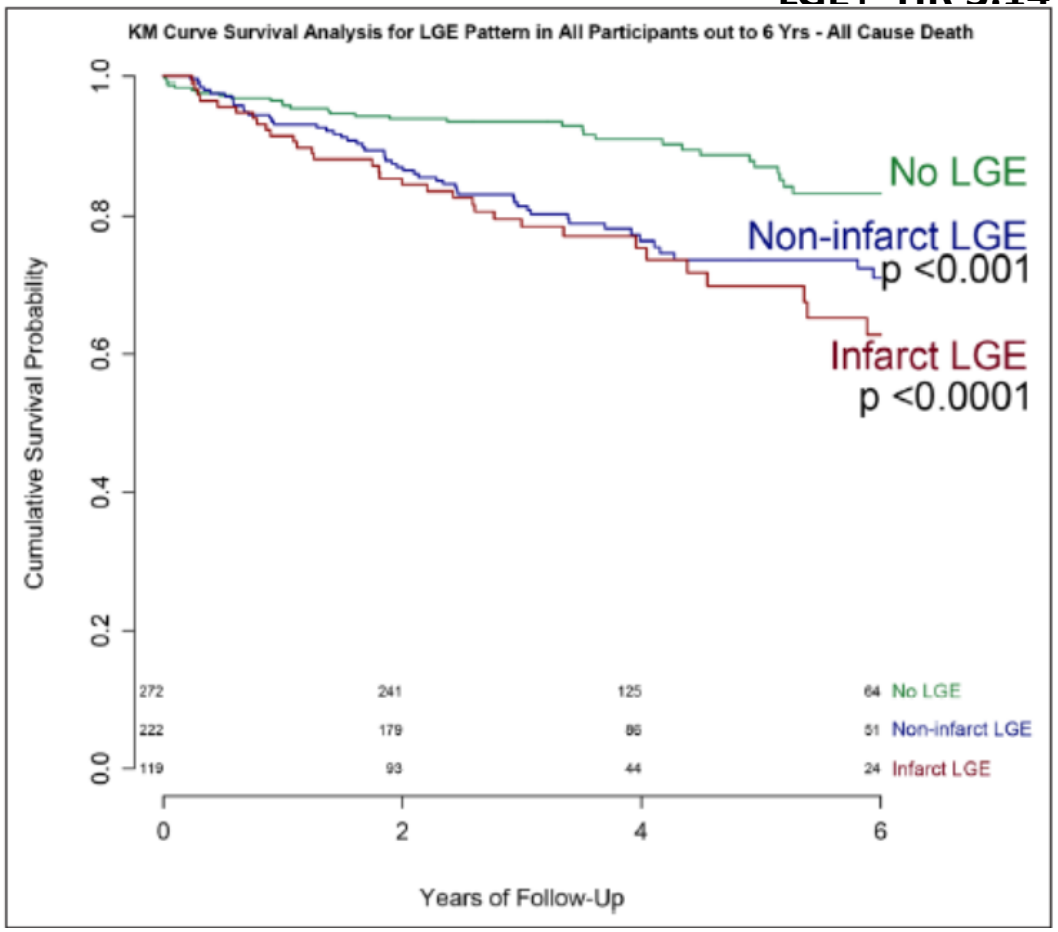
ORIGINAL RESEARCH ARTICLE

Myocardial Scar and Mortality in Severe Aortic Stenosis

Data From the BSCMR Valve Consortium

N 674; 9 UK centers; 2003-2015
74.6 aa; 59% SAVR ; 29% CAD
LGE – (49%): 75 aa; 27% CAD; 50% NYHA I-II (= LGE+)
LV EDVI 73.3 ml/mq (vs 85.4 LGE+)
LVEF 64% (vs 58% LGE+)
RV EDVI 66,8 ml/mq (vs 68,5 LGE+)
Fup 3.6 yrs; 21.5% deaths
LGE+ HR 3.14 regardless scar type





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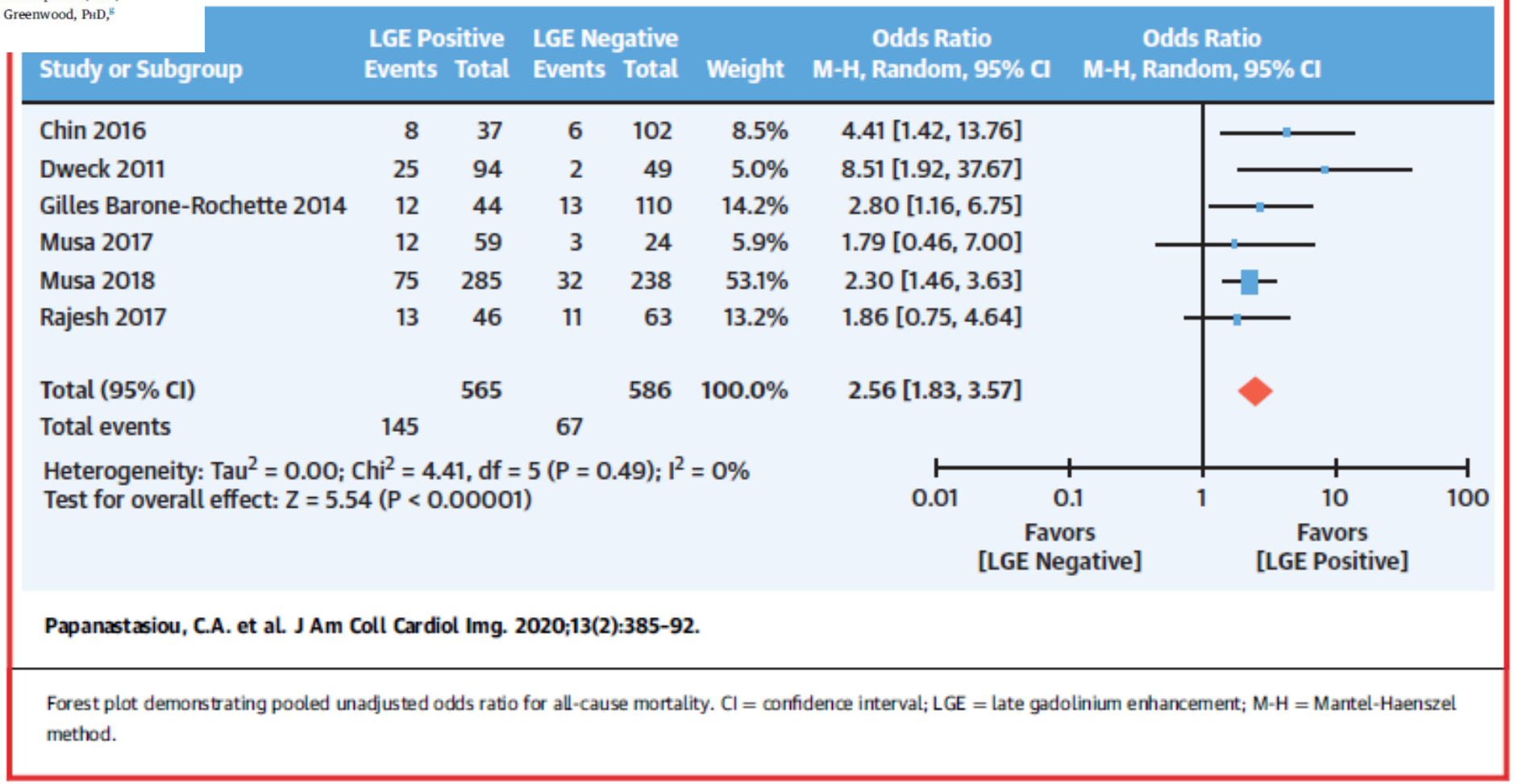
VOL. 13, NO. 2, 2020

ORIGINAL RESEARCH

The Prognostic Role of Late Gadolinium Enhancement in Aortic Stenosis

A Systematic Review and Meta-Analysis

Christos A. Papanastasiou, MD, MSc,[a] Damianos G. Kokkinidis, MD, MSc,[b] Polydoros N. Kampaktsis, MD,[c] Iosif Bikakis, MD,[d,e] Daniela K. Cunha, MD,[f,g] Evangelos K. Oikonomou, MD,[f] John P. Greenwood, PhD,[g] Mario J. Garcia, MD,[h] Theodoros D. Karamitsos, MD, PhD[a]



Papanastasiou, C.A. et al. J Am Coll Cardiol Img. 2020;13(2):385-92.

Forest plot demonstrating pooled unadjusted odds ratio for all-cause mortality. CI = confidence interval; LGE = late gadolinium enhancement; M-H = Mantel-Haenszel method.

Doi:10.1016/j.jcmg.2019.03.029

JACC: CARDIOVASCULAR IMAGING
VOL. 13, NO. 2, 2020

ORIGINAL RESEARCH

The Prognostic Role of Late Gadolinium Enhancement in Aortic Stenosis

A Systematic Review and Meta-Analysis

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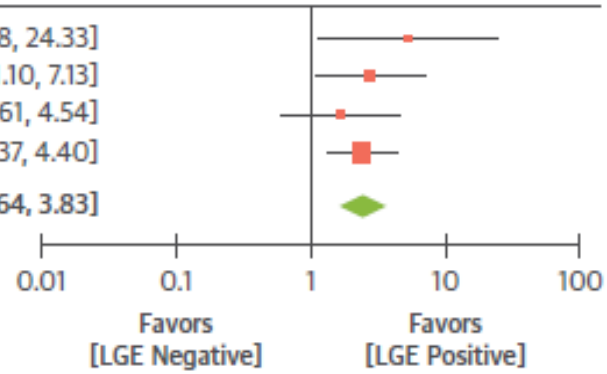
URE 3 Meta-Analysis Results

A

Study or Subgroup	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Dweck (midwall) 2011	1.6771	0.7728	7.9%	5.35 [1.18, 24.33]
Gilles Barone-Rochette 2014	1.0296	0.4767	20.7%	2.80 [1.10, 7.13]
Musa 2017	0.5128	0.5104	18.1%	1.67 [0.61, 4.54]
Musa 2018	0.8993	0.2973	53.3%	2.46 [1.37, 4.40]
Total (95% CI)			100.0%	2.50 [1.64, 3.83]

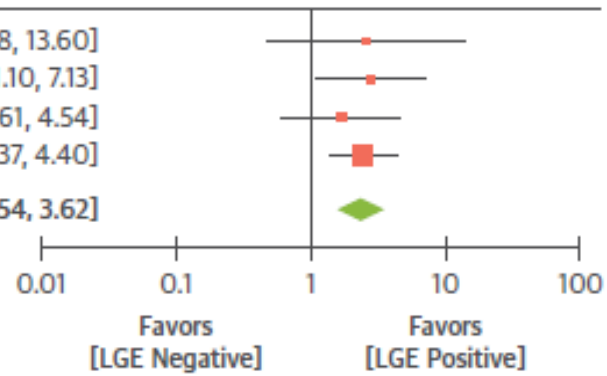
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$, df = 3 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 4.23 (P < 0.0001)



B

Study or Subgroup	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Dweck (infarct) 2011	0.94	0.8522	6.6%	2.56 [0.48, 13.60]
Gilles Barone-Rochette 2014	1.0296	0.4767	21.0%	2.80 [1.10, 7.13]
Musa 2017	0.5128	0.5104	18.3%	1.67 [0.61, 4.54]
Musa 2018	0.8993	0.2973	54.1%	2.46 [1.37, 4.40]
Total (95% CI)			100.0%	2.36 [1.54, 3.62]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.62$, df = 3 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 3.93 (P < 0.0001)



Forest plots demonstrating pooled adjusted hazard ratios for all-cause mortality. Dweck et al. (9) reported results for **(A)** midwall and **(B)** infarct pattern LGE separately. Therefore, separate meta-analyses were conducted for each result. IV = inverse variance; other abbreviations as in Figure 2.

Doi:10.1016/j.jcmg.2019.03.029

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Extracellular Myocardial Volume in Patients With Aortic Stenosis

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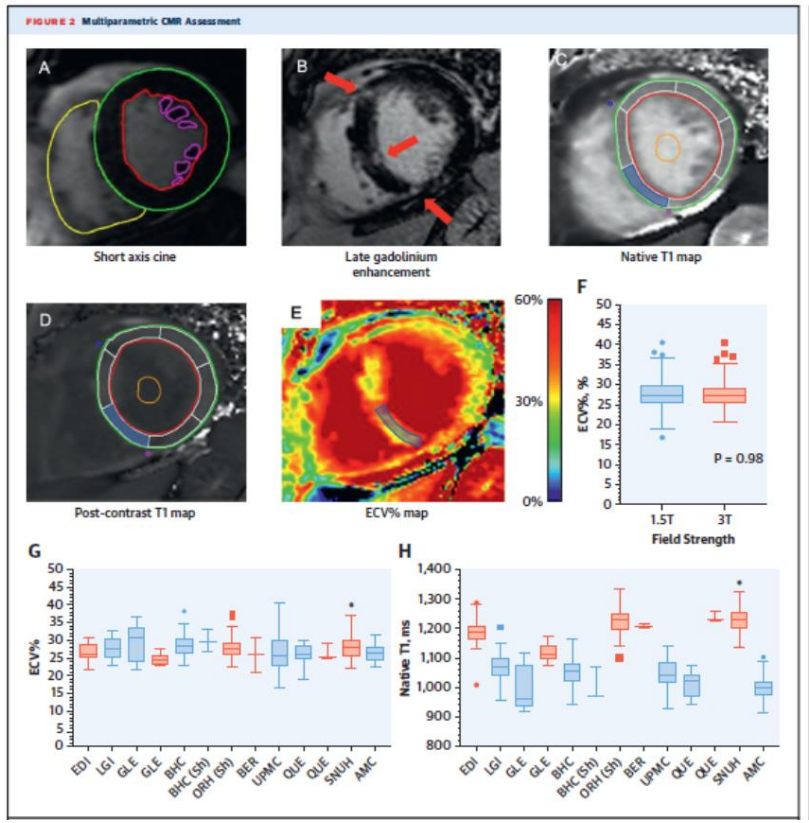

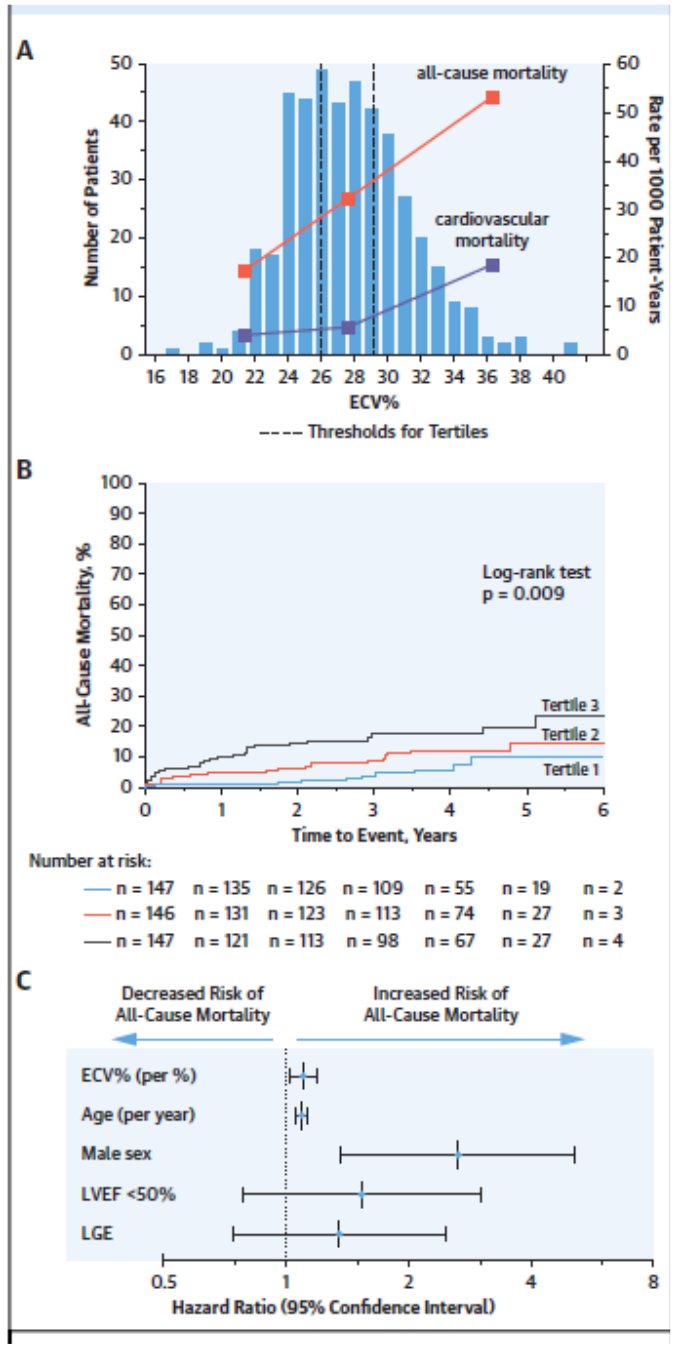

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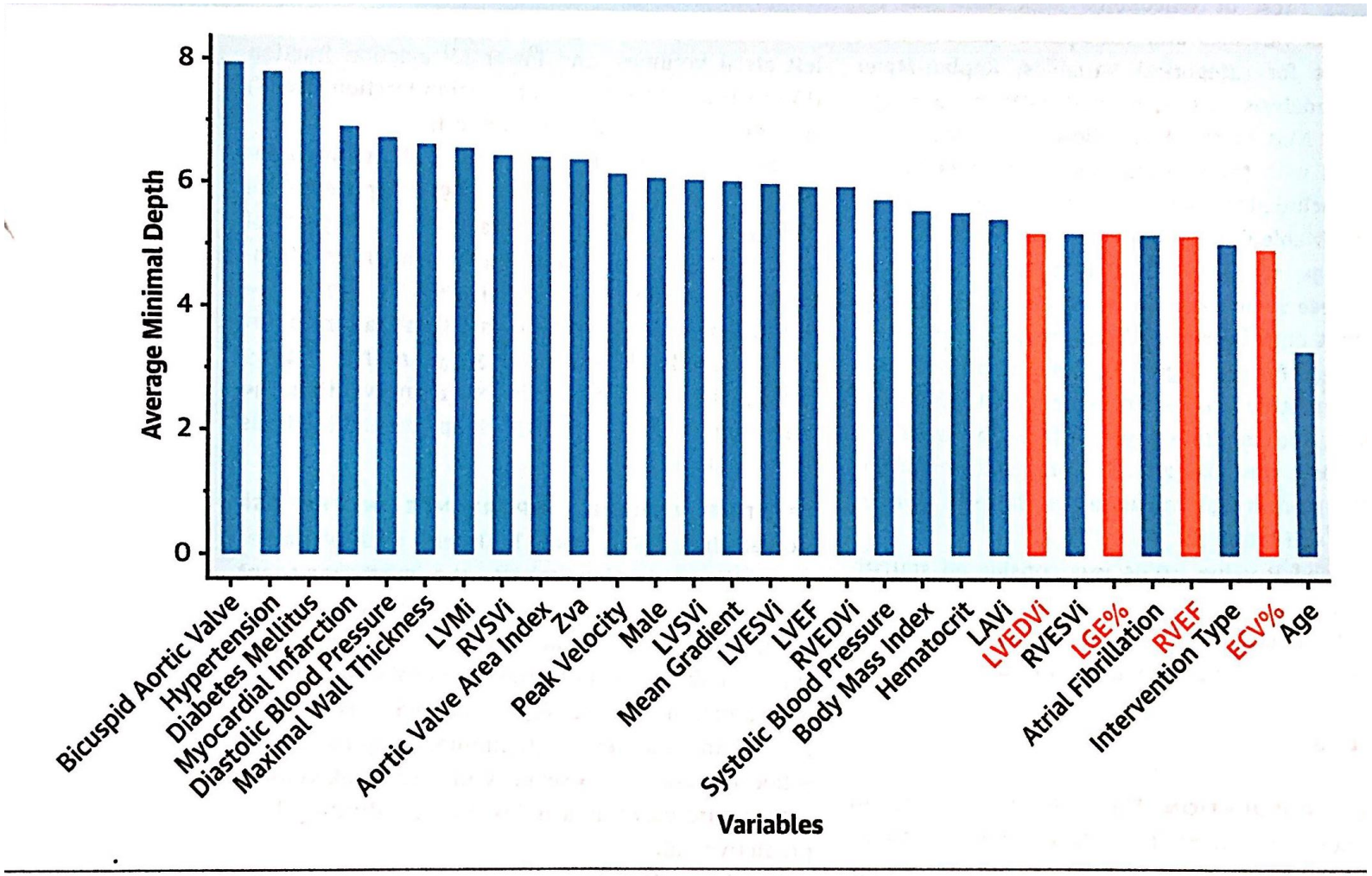
Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis



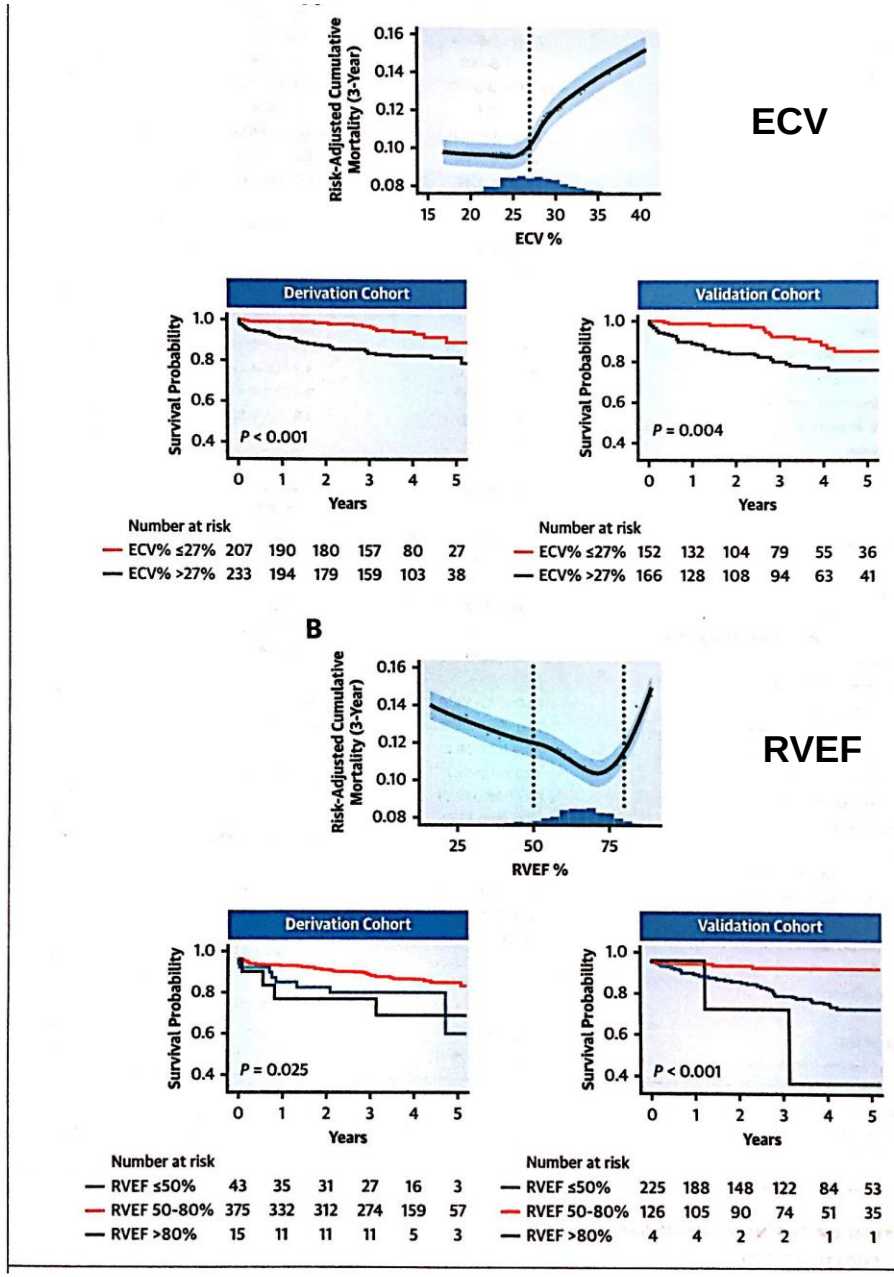
Machine learning study
799 pts; fup 3.8 yrs;
52 deaths
CMR mediana 15 gg prima SAVR/TAVR
6,6% LFLG AS

71% SAVR
14% SAVR+CABG
15% TAVR

STS/ES II <3
LVEF >60%

Doi:10.1016/j.jacc.2021.05.047

Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis



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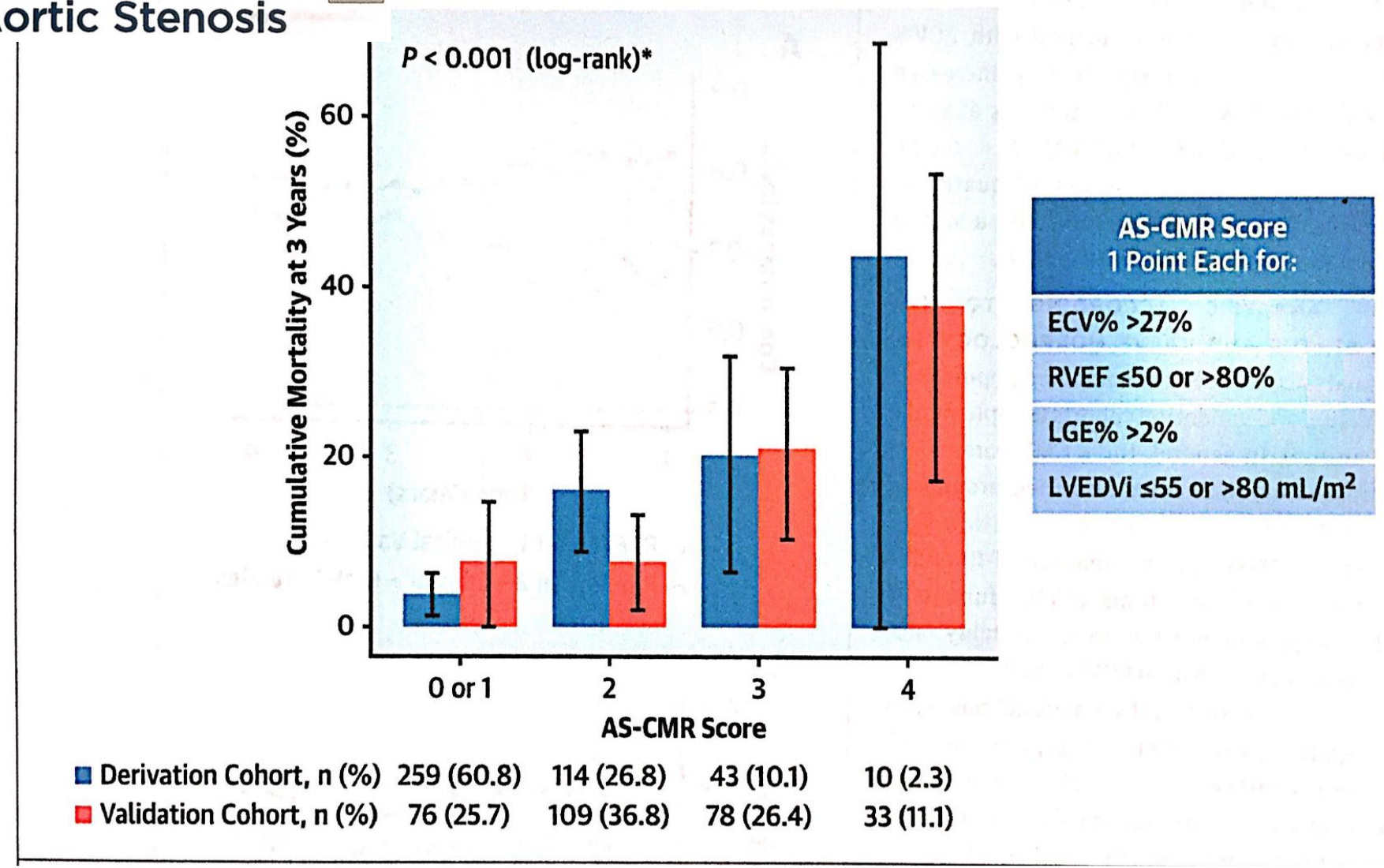

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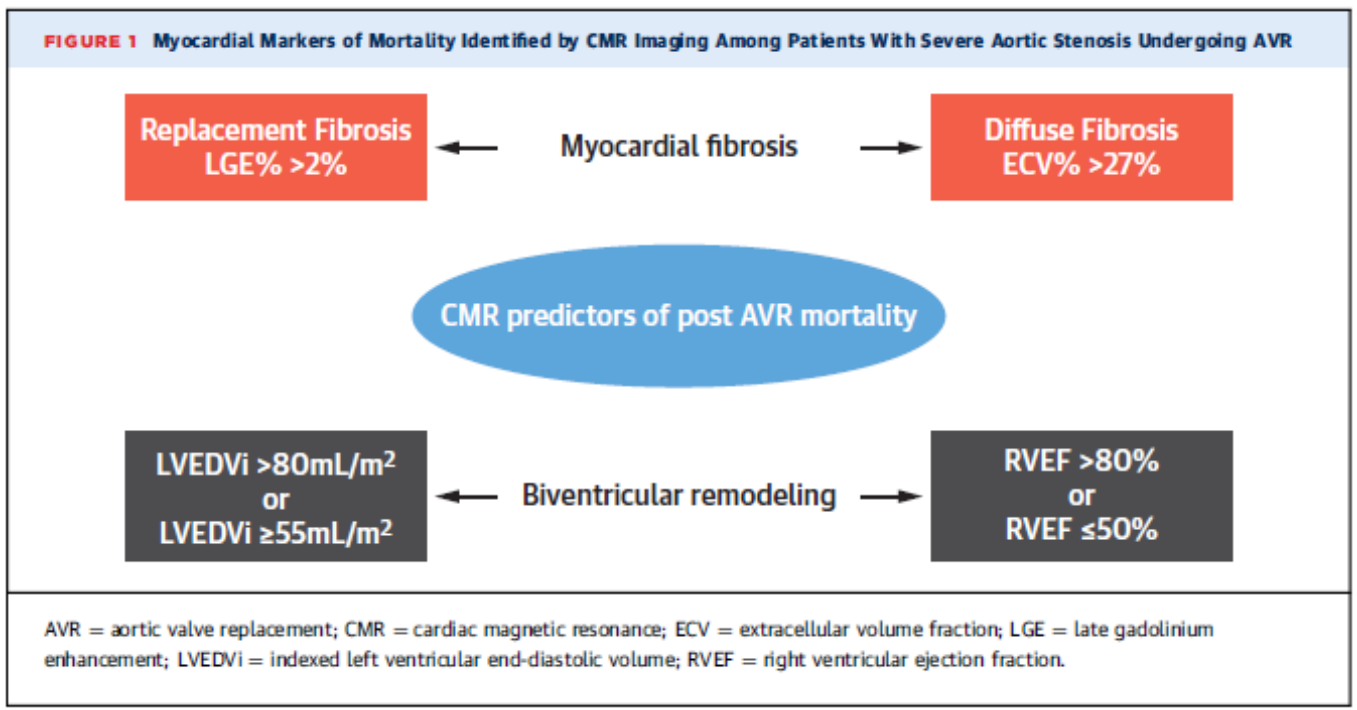
EDITORIAL COMMENT

Myocardial Damage and Severe Aortic Stenosis

Looking Beyond the Left Ventricular Ejection Fraction*

Cróchán J. O'Sullivan, MD, PhD

FIGURE 1 Myocardial Markers of Mortality Identified by CMR Imaging Among Patients With Severe Aortic Stenosis Undergoing AVR



AVR = aortic valve replacement; CMR = cardiac magnetic resonance; ECV = extracellular volume fraction; LGE = late gadolinium enhancement; LVEDVi = indexed left ventricular end-diastolic volume; RVEF = right ventricular ejection fraction.

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JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 2, 2019

FOCUS ISSUE: IMAGING IN AORTIC STENOSIS: PART II

STATE-OF-THE-ART PAPER

Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis

Rong Bing, MBBS, BMedSci,[a] João L. Cavalcante, MD,[b] Russell J. Everett, MD, BSc,[a] Marie-Annick Clavel, DVM, PhD,[c] David E. Newby, DM, PhD, DSc,[a] Marc R. Dweck, MD, PhD[a]

FIGURE 4 Schematic for the Development of Myocardial Fibrosis in Aortic Stenosis and Response to AVR

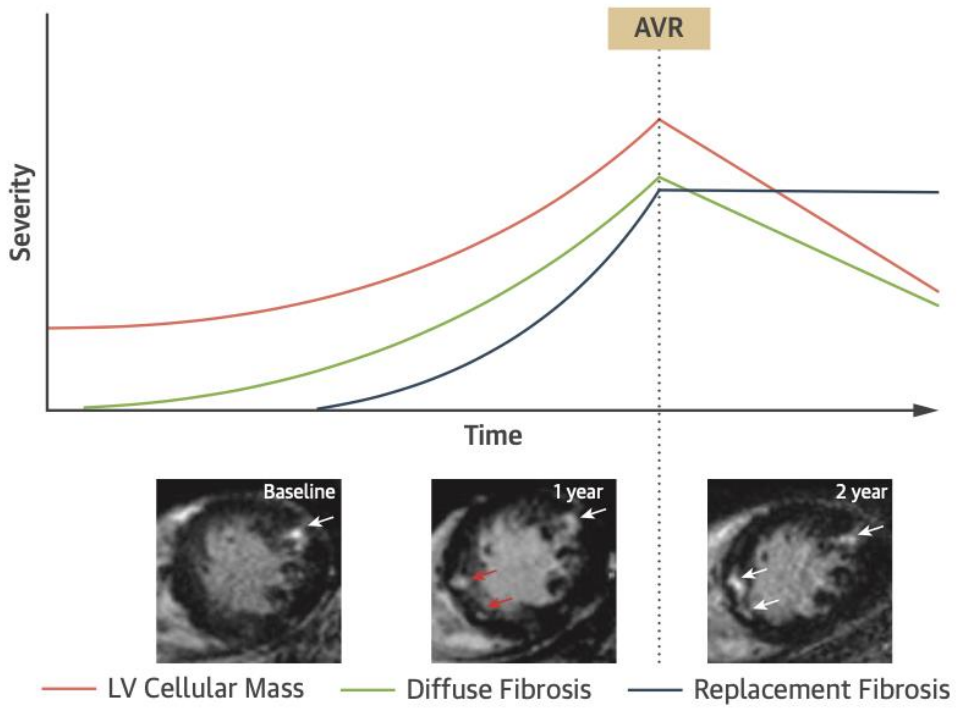
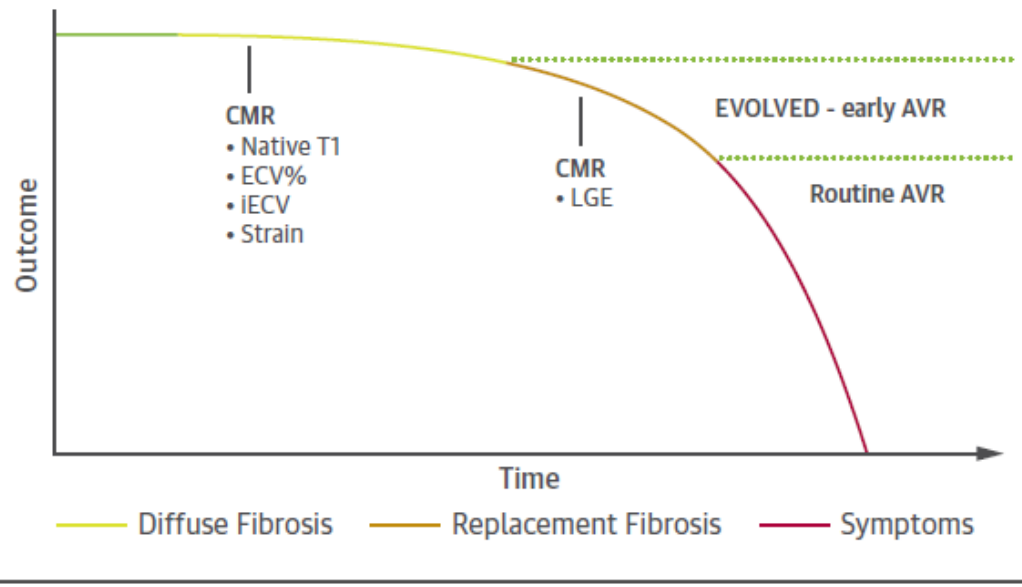


FIGURE 5 Proposed Integration of Myocardial Fibrosis Into the Classical Description of the Natural History of Aortic Stenosis



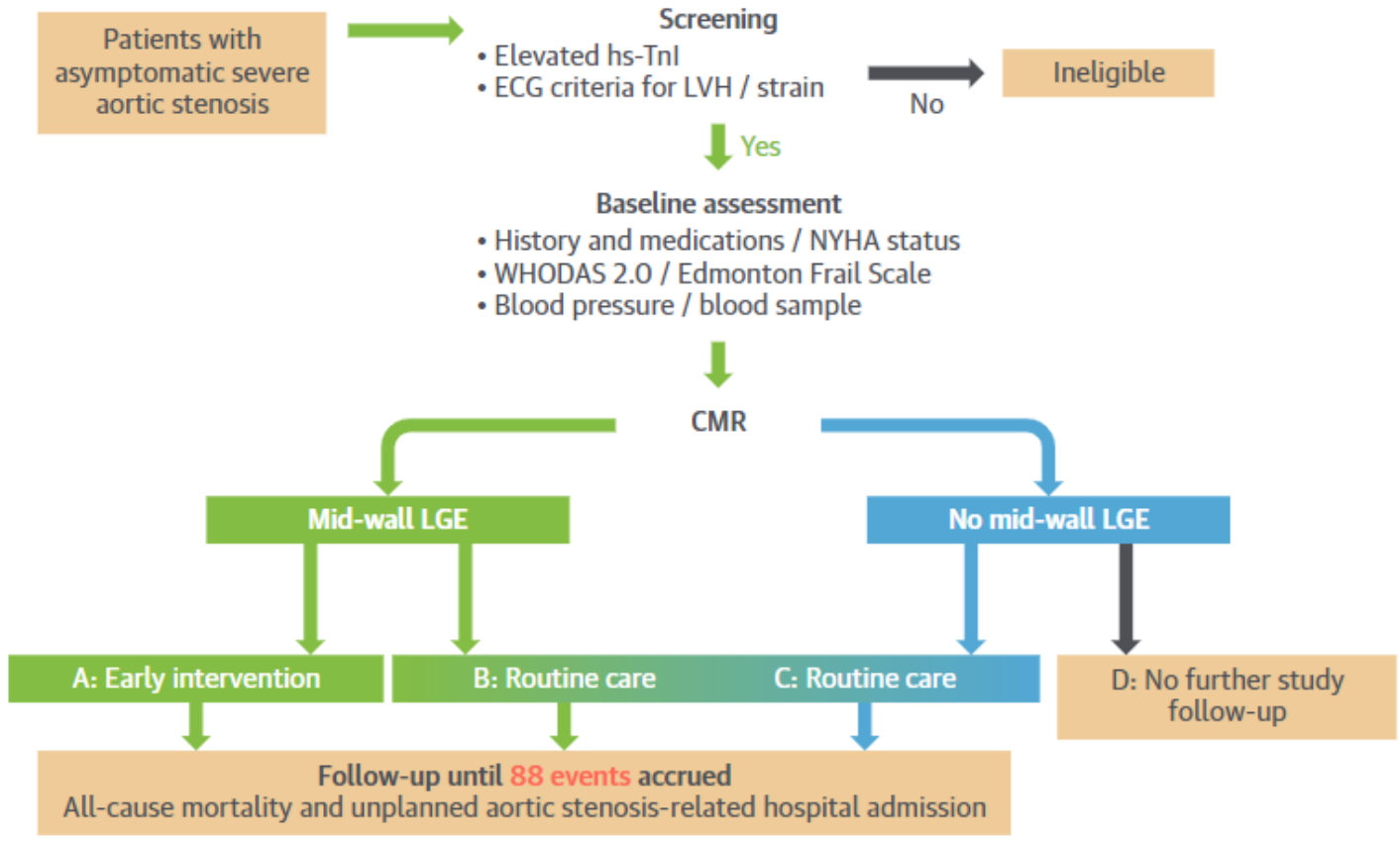
Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS (EVoLVeD)

ClinicalTrials.gov Identifier: NCT03094143

Recruitment Status : Recruiting
First Posted : March 29, 2017
Last Update Posted : April 28, 2021

See Contacts and Locations

FIGURE 5 Summary of Protocol for the EVOLVED Trial



Take Home Messages

- Il sovraccarico pressorio, l'incremento della massa Vsin, l'alterata bioenergetica e perfusione miocardica, contribuiscono alle alterazioni strutturali che dall'ipertrofia, conducono ad apoptosi e fibrosi favorendo la transizione da una risposta compensatoria in geometria e funzione allo SC;
- Nella StAo la fibrosi è un processo dinamico che riflette il sovraccarico pressorio ma anche altre componenti ascrivibili ad età, comorbidità e coesistente eventuale coronaropatia;
- In generale nell'ambito della componente attribuibile alla StAO, distinguiamo una forma interstiziale diffusa (reversibile) ed una forma focale sostitutiva (strutturata ed irreversibile);
- le moderne tecniche di T1 mapping e LGE consentono di caratterizzare queste 2 forme, oltre che valutare il peso di scar postinfartuali o alterazioni suggestive di amiloide;
- La presenza di LGE stratifica il rischio anche in termini di eventi e recupero post-intervento;
- Sintomatologia da sforzo, BNP e valutazione RM (volumi, funzione Vsin e Vdx, caratterizzazione tissutale), possono essere d'ausilio nella caratterizzazione della StAo severa asintomatica (EVOLVED trial);
- Nelle forme più avanzate di StAo con disfunzione Vsin severa, estesa fibrosi e rimodellamento Vsin, assenza di risposta contrattile, impegno del circolo polmonare e funzione Vdx i pattern RM possono caratterizzare la severità strutturale ed orientare le scelte terapeutiche e la gestione perioperatoria più appropriata.