The Importance of Sex Differences in Left Ventricular Remodeling for Risk Stratification of Patients with Aortic Regurgitation

P. Lopez Santi, F. Fortuni, J. Bernard, C. Sarrazyn, A.P. Chua, S.C. Butcher, M.C. Meucci, Z.H.U Ching-Yan, R. Enache, E. Tay, A. Bergeron, Yiu K.H, M.A. Clavel, P. Pibarot, J.J Bax, **N. Ajmone-Marsan**

Leiden University Medical Center, The Netherlands

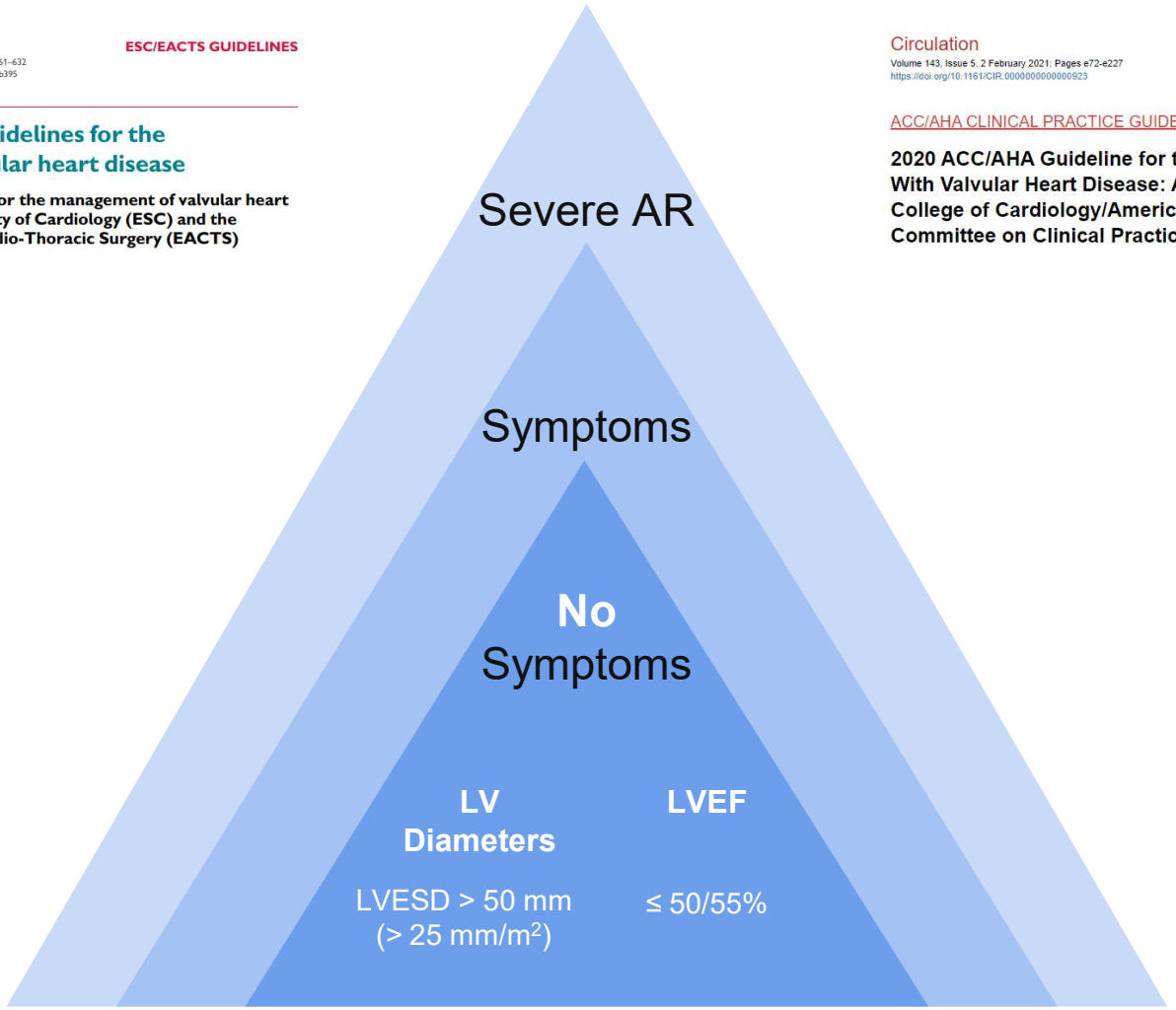
What do we know so far?

ESC European Society of Cardiology
European Heart Journal (2022) 43, 561–632
https://doi.org/10.1093/eurheartj/ehab395

ESC/EACTS GUIDELINES

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)



Circulation
Volume 143, Issue 5, 2 February 2021; Pages e72-e227
https://doi.org/10.1161/CIR.0000000000000923

ACC/AHA CLINICAL PRACTICE GUIDELINE

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

2019
n = 356

JACC: CARDIOVASCULAR IMAGING
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VOL. 12, NO. 11, 2019

ORIGINAL RESEARCH

Do Guideline-Based Indications Result in an Outcome Penalty for Patients With Severe Aortic Regurgitation?

Christophe de Meester, PsD, Bernhard L. Gerber, MD, PsD, David Vancraeynest, MD, PsD, Anne-Catherine Pouleur, MD, PsD, Philippe Noirhomme, MD, Agnès Pasquet, MD, PsD, Laurent de Kerchove, MD, Gébrine El Khoury, MD, Jean-Louis Vanoverschelde, MD, PsD

2015
n = 177

Long Term Results and Predictors of Left Ventricular Function Recovery after Aortic Valve Replacement for Chronic Aortic Regurgitation

Hiroyuki Saisho, MD,[1] Koichi Arinaga, MD, PhD,[1] Satoshi Kikusaki, MD,[1] Yuichiro Hirata, MD,[1] Kumiko Wada, MD,[1] Tatsuyuki Kakuma, PhD,[2] and Hiroyuki Tanaka, MD, PhD,[1]

2007
n = 724
IP 1972-1999

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Published by Elsevier Inc.
Vol. 49, No. 13, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.026

Cardiac Surgery

Improved Outcomes After Aortic Valve Surgery for Chronic Aortic Regurgitation With Severe Left Ventricular Dysfunction

Sunil K. Bhudia, MD,* Patrick M. McCarthy, MD,* Ganesh S. Kumpati, MD,* Joe Helou, MD,* Katherine J. Hoercher, RN,* Jeevanantham Rajeswaran, MSC,† Eugene H. Blackstone, MD*†
Cleveland, Ohio

2006
n = 170

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doi:10.1016/j.jacc.2005.10.049

Valvular Heart Disease

Long-Term Outcome of Surgically Treated Aortic Regurgitation

Influence of Guideline Adherence Toward Early Surgery

Pilar Tornos, MD, Antonia Sambola, MD, Gaietà Permanyer-Miralda, MD, Arturo Evangelista, MD, FESC, Zamira Gomez, MD, Jordi Soler-Soler, MD, FESC, FACC

1996
n = 219

Aortic Regurgitation Complicated by Extreme Left Ventricular Dilation: Long-Term Outcome After Surgical Correction

ELIZABETH KLODAS, MD, MAURICE ENRIQUEZ-SARANO, MD, FACC, A. JAMIL TAJIK, MD, FACC, CHARLES J. MULLANY, MD, KENT R. BAILEY, PhD, JAMES B. SEWARD, MD, FACC
Rochester, Minnesota

1991
n = 104

Serial Long-term Assessment of the Natural History of Asymptomatic Patients With Chronic Aortic Regurgitation and Normal Left Ventricular Systolic Function

Robert O. Bonow, MD; Edward Lakatos, PhD; Barry J. Maron, MD; and Stephen E. Epstein, MD

1985
n = 96

Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function

Robert O. Bonow, M.D., Anthony L. Picone, M.D., Charles L. McIntosh, M.D., Ph.D., Michael Jones, M.D., Douglas R. Rosing, M.D., Barry J. Maron, M.D., Edward Lakatos, Ph.D., Richard E. Clark, M.D., and Stephen E. Epstein, M.D.

1984
n = 113

CLINICAL STUDIES

Determinants of Prognosis of Patients With Aortic Regurgitation Who Undergo Aortic Valve Replacement

PETER H. STONE, MD,* RALPH D. CLARK, MD, NORA GOLDSCHLAGER, MD, ARTHUR SELZER, MD, FACC, KEITH COHN, MD, FACC
San Francisco, California

1981
n = 45

Preoperative criteria predictive of late survival following valve replacement for severe aortic regurgitation

John Greves, M.D., Shahbudin H. Rahimtoola, M.D., John H. McAnulty, M.D., Henry DeMots, M.D., David G. Clark, M.D., Barry Greenberg, M.D., and Albert Starr, M.D. *Portland, Ore.*

1980
n = 229

Prognostic Significance of Preoperative Left Ventricular Ejection Fraction and Valve Lesion in Patients With Aortic Valve Replacement

ROBERT FORMAN, FCP (SA), FACC*
BRIAN G. FIRTH, MRCP (UK), DPHIL (OXON)
MARIUS S. BARNARD, MCH
Cape Town, South Africa

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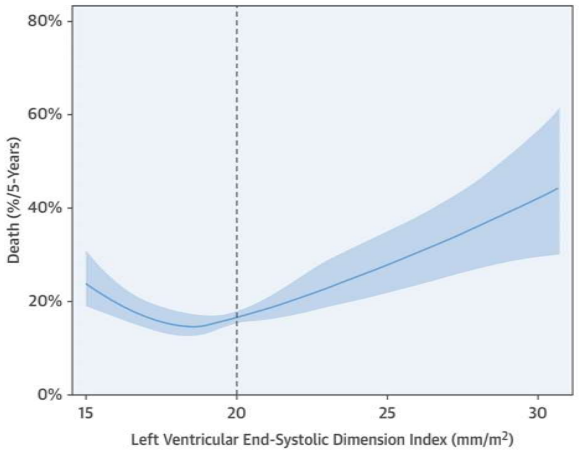
ORIGINAL INVESTIGATIONS

Outcomes in Chronic Hemodynamically Significant Aortic Regurgitation and Limitations of Current Guidelines

Li-Tan Yang, MD,[a] Hector I. Michelena, MD,[a] Christopher G. Scott, MS,[b] Maurice Enriquez-Sarano, MD,[a] Sorin V. Pislaru, MD,[c] Hartzell V. Schaff, MD,[c] Patricia A. Pellikka, MD[a]

CENTRAL ILLUSTRATION **Overall Survival by Left Ventricular End-Systolic Dimension Indexed for Body Surface Area in the Whole Cohort (Operated and Nonoperated Patients)**



Yang, L.-T. et al. J Am Coll Cardiol. 2019;73(14):1741-52.

The spline model shows that 5-year survival started to deteriorate in patients with left ventricular end-systolic dimension index >20 mm/m².

CLINICAL INVESTIGATIONS
AORTIC REGURGITATION

Association of Left Ventricular Volume in Predicting Clinical Outcomes in Patients with Aortic Regurgitation

Vidhu Anand, MBBS, Litan Yang, MD, Sushil Allen Luis, MBBS, Ratnasari Padang, MBBS, PhD, Hector I. Michelena, MD, Julie L. Tsay, MD, Ramila A. Mehta, MS, Christopher G. Scott, MS, Sorin V. Pislaru, MD, PhD, Rick A. Nishimura, MD, and Patricia A. Pellikka, MD, *Rochester, Minnesota*

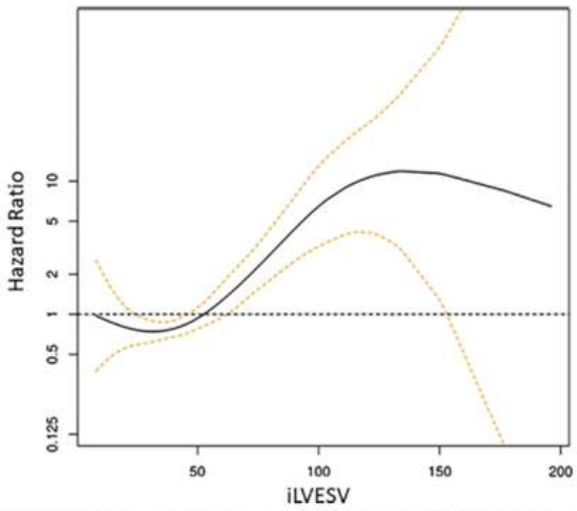
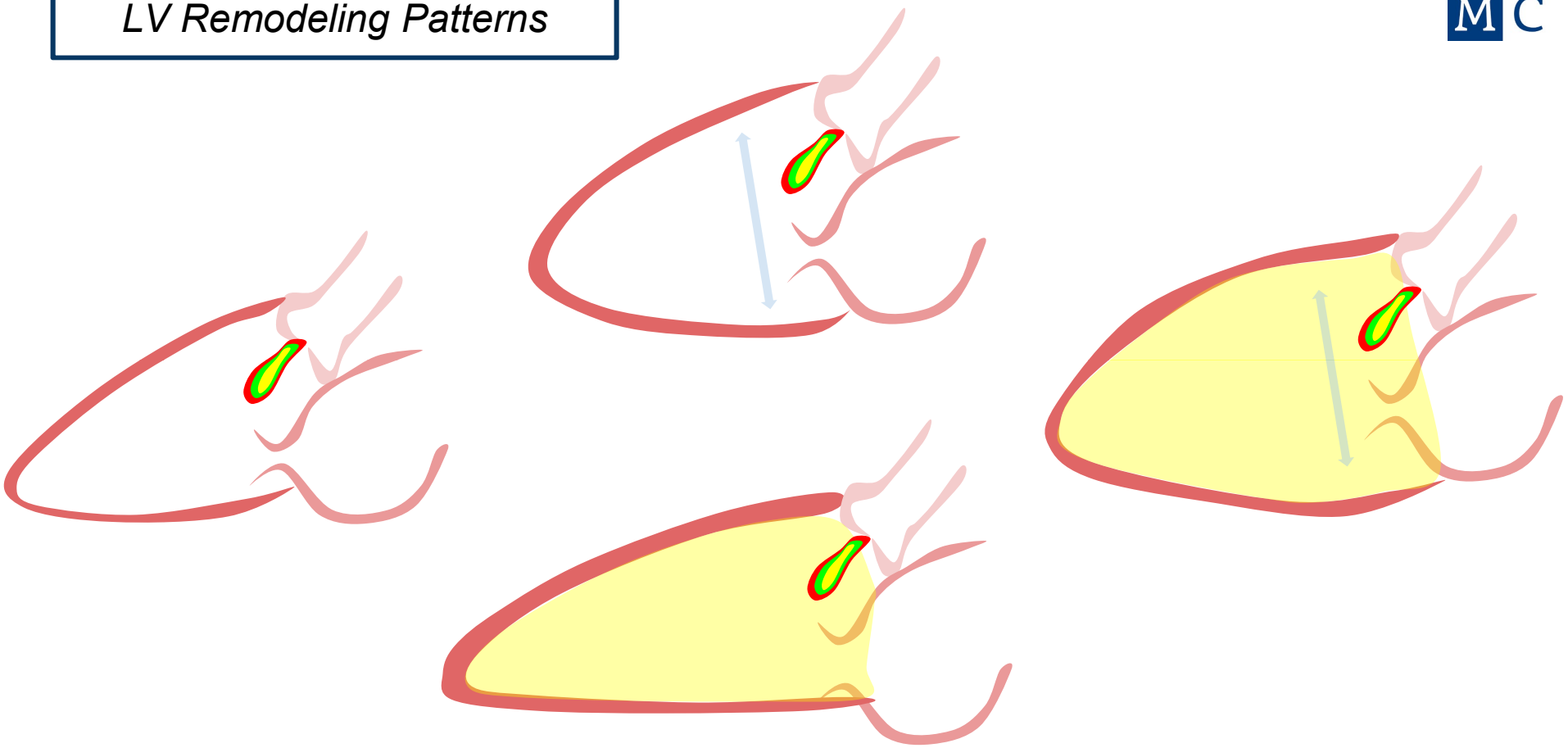
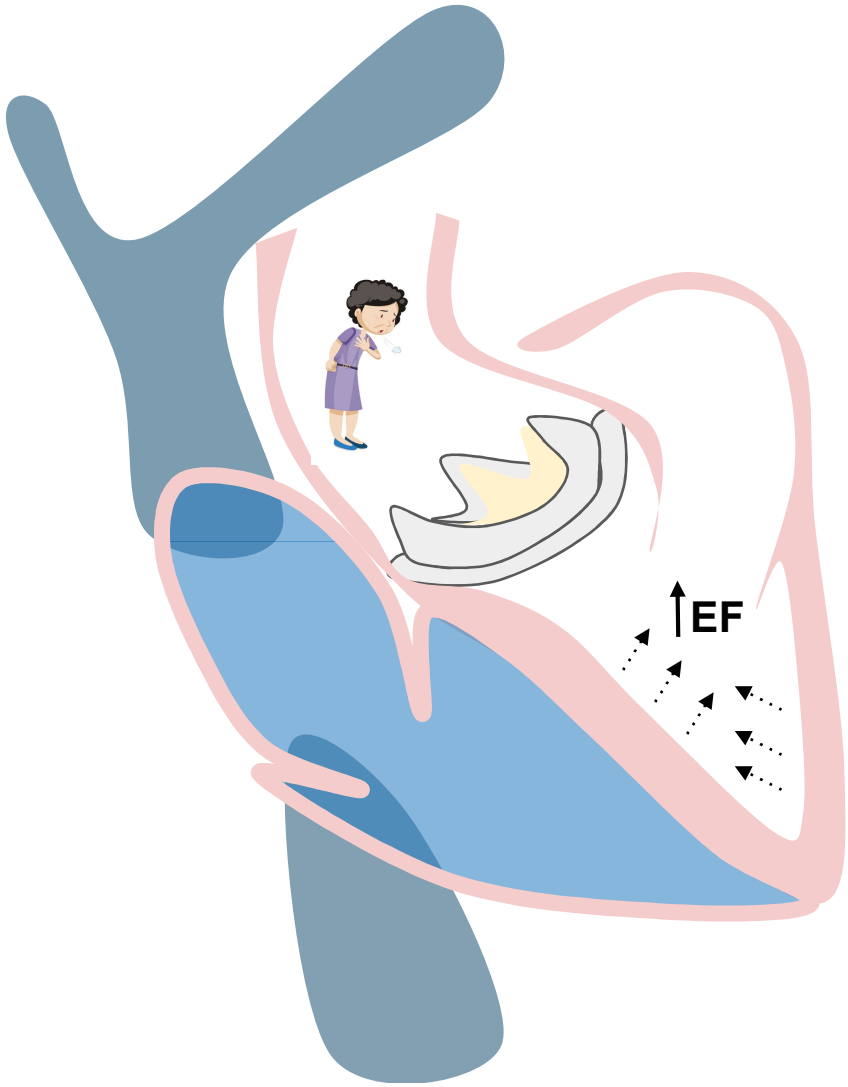


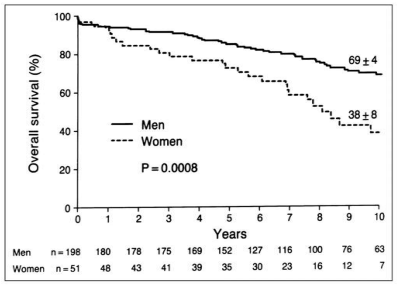
Figure 2 Spline curves demonstrate mortality risk under medical surveillance across the range of measured iLVESV values. The risk increased for iLVESV ≥ 45 mL/m².

LV Remodeling Patterns

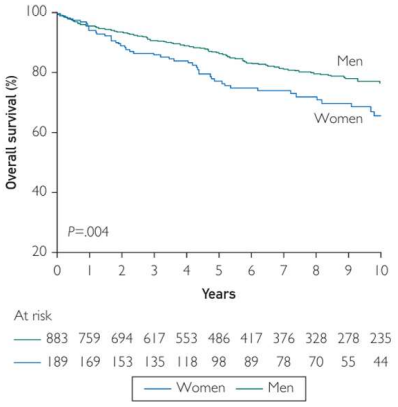


P. Lopez Santi, F. Fortuni, J. Bernard, C. Sarrazyn, A.P. Chua, S.C. Butcher, M.C. Meucci, Z.H.U Ching-Yan, R. Enache, E. Tay, A. Bergeron, Yiu K.H, M.A. Clavel, P. Pibarot, J.J Bax, N. Ajmone-Marsan.





Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Surgery for aortic regurgitation in women. Contrasting indications and outcomes compared with men. Circulation. 1996 Nov 15;94(10):2472–8.



Yang LT, Enriquez-Sarano M, Pellikka PA, Thapa P, Scott CG, Hung JW, et al. Sex Differences in Outcomes of Patients With Chronic Aortic Regurgitation: Closing the Mortality Gap. Mayo Clin Proc. 2021 Aug;96(8):2145–56.

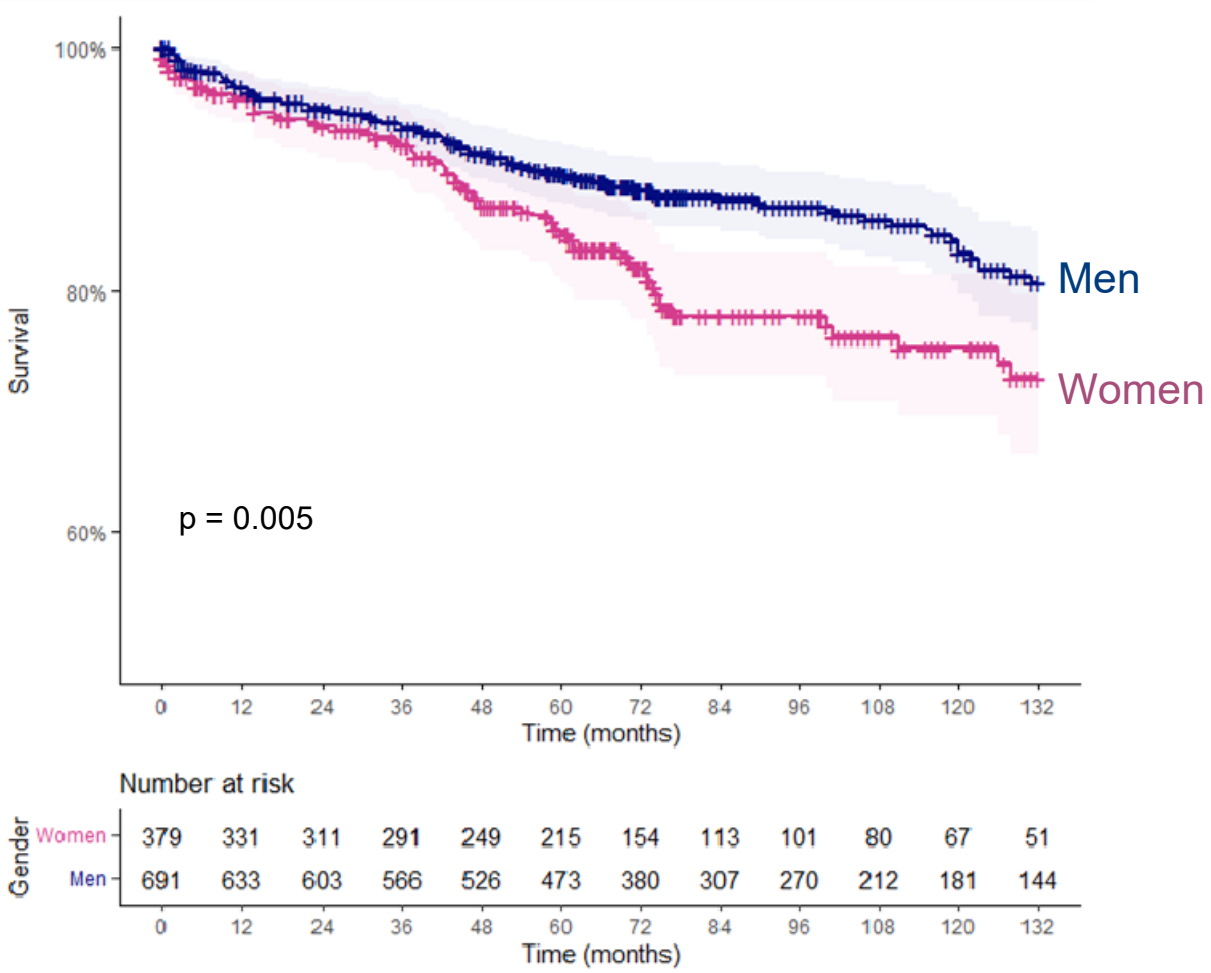
POPULATION	OBJECTIVE	OUTCOME	FOLLOW-UP
Multicentric retrospective study on *1070* patients with moderate-severe Aortic Regurgitation	To assess sex-differences in LV remodeling using **linear** and **volumetric** dimensions in patients with moderate-severe AR and to determine their association with outcome	All-cause mortality	7.4 (IQR 4.5-11) years

Baseline Clinical Characteristics

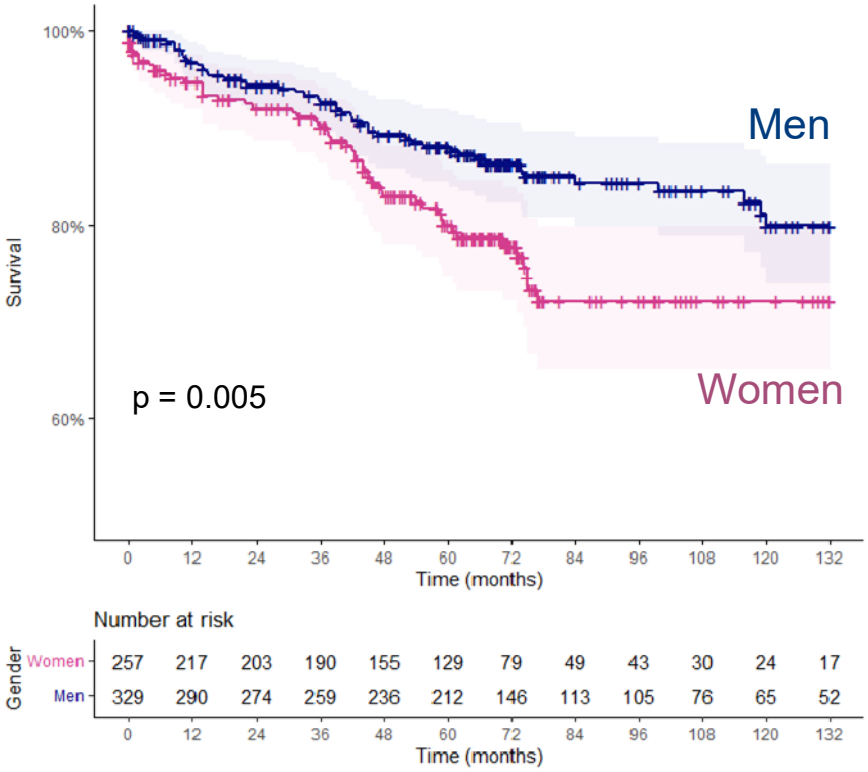
Variables	Total Population (n=1070)	Women (n=379)	Men (n=691)	P-value
Age (years)	56 ± 18	58 ± 19	55 ± 17	0.023
Coronary artery disease (%)	167 (16)	55 (15)	112 (16)	0.487
Arterial Hypertension (%)	489 (47)	180 (48)	309 (45)	0.351
Hyperlipidemia (%)	276 (26)	101 (27)	175 (25)	0.717
Diabetes Mellitus (%)	83 (8)	29 (8)	54 (8)	0.881
NYHA Class (%)				
I-II	791 (88)	332 (88)	630 (91)	0.017
III-IV	108 (12)	47 (12)	61 (9)	
Body Surface Area (m^2)	1.87 ± 0.25	1.74 ± 0.23	1.94 ± 0.23	<0.001
Bicuspid Aortic Valve (%)	454 (42)	134 (35)	320 (46)	<0.001

Baseline Echocardiographic Characteristics

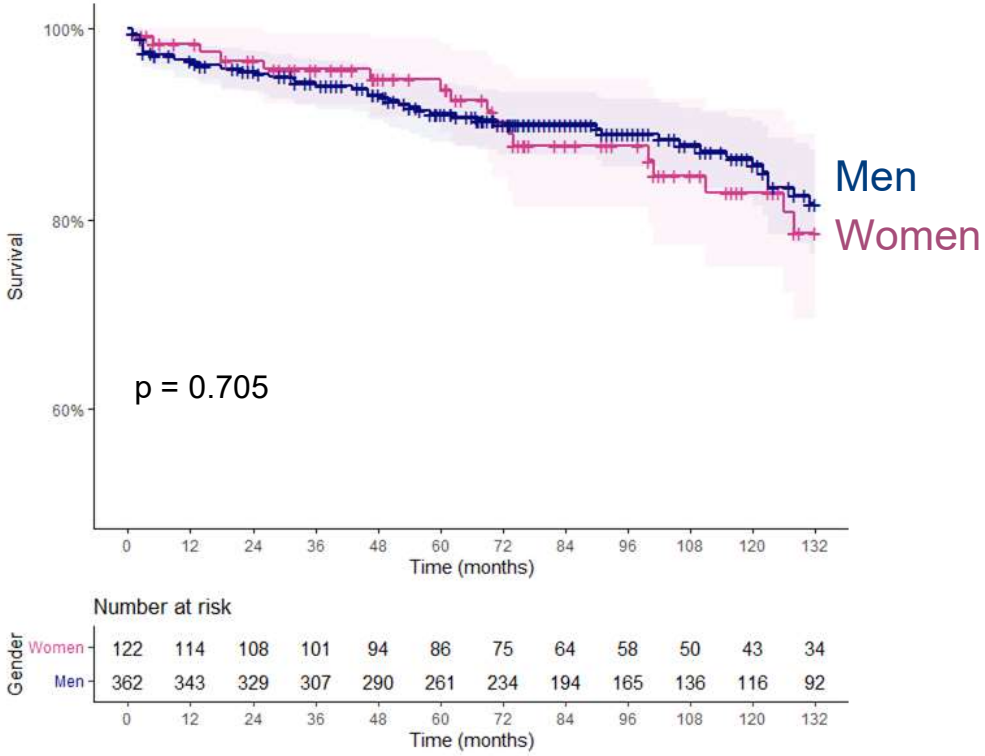
Variables	Total Population (n=1070)	Women (n=379)	Men (n=691)	P-value
Left Ventricular End-Systolic Diameter (mm)	38 ± 10	35 ± 9	40 ± 9	<0.001
Left Ventricular End-Systolic Diameter Index (mm/m^2)	21 ± 5	20 ± 5	21 ± 5	0.013
Left Ventricular End-Systolic Diameter Index > 20 mm/m^2	527 (49)	165 (44)	362 (52)	0.006
Left Ventricular End-Systolic Volume (ml)	60 ± 51	47 ± 31	71 ± 55	<0.001
Left Ventricular End-Systolic Volume Index (ml/m^2)	37 ± 26	26 ± 17	37 ± 28	<0.001
Left Ventricular End-Systolic Volume Index > 40 ml/m^2	402 (38)	88 (23)	314 (45)	<0.001
Left Ventricular End-Systolic Volume Index > 45 ml/m^2	352 (33)	66 (17)	286 (41)	<0.001
Left Ventricular End-Diastolic Volume (ml)	143 ± 75	112 ± 57	162 ± 76	<0.001
Left Ventricular End-Diastolic Volume Index (ml/m^2)	75 ± 40	64 ± 33	83 ± 41	<0.001
Left Ventricular Ejection Fraction Biplane (%)	55 ± 10	56 ± 10	54 ± 10	<0.001
Left Atrial Volume Index (ml/m^2)	33 ± 19	28 ± 15	31 ± 19	0.036
Left Ventricular Mass Index (g/m^2)	128 ± 65	105 ± 53	139 ± 63	<0.001
E Velocity (cm/s)	74 ± 32	79 ± 37	73 ± 30	0.145
Ascending Aorta Diameter (mm)	38 ± 8	36 ± 7	39 ± 8	<0.001


100%
80%
60%
Survival
p = 0.005
Men
Women
0
12
24
36
48
60
72
84
96
108
120
132
Time (months)
Number at risk
Gender
Women
379
331
311
291
249
215
154
113
101
80
67
51
Men
691
633
603
566
526
473
380
307
270
212
181
144
0
12
24
36
48
60
72
84
96
108
120
132
Time (months)

Conservative treatment

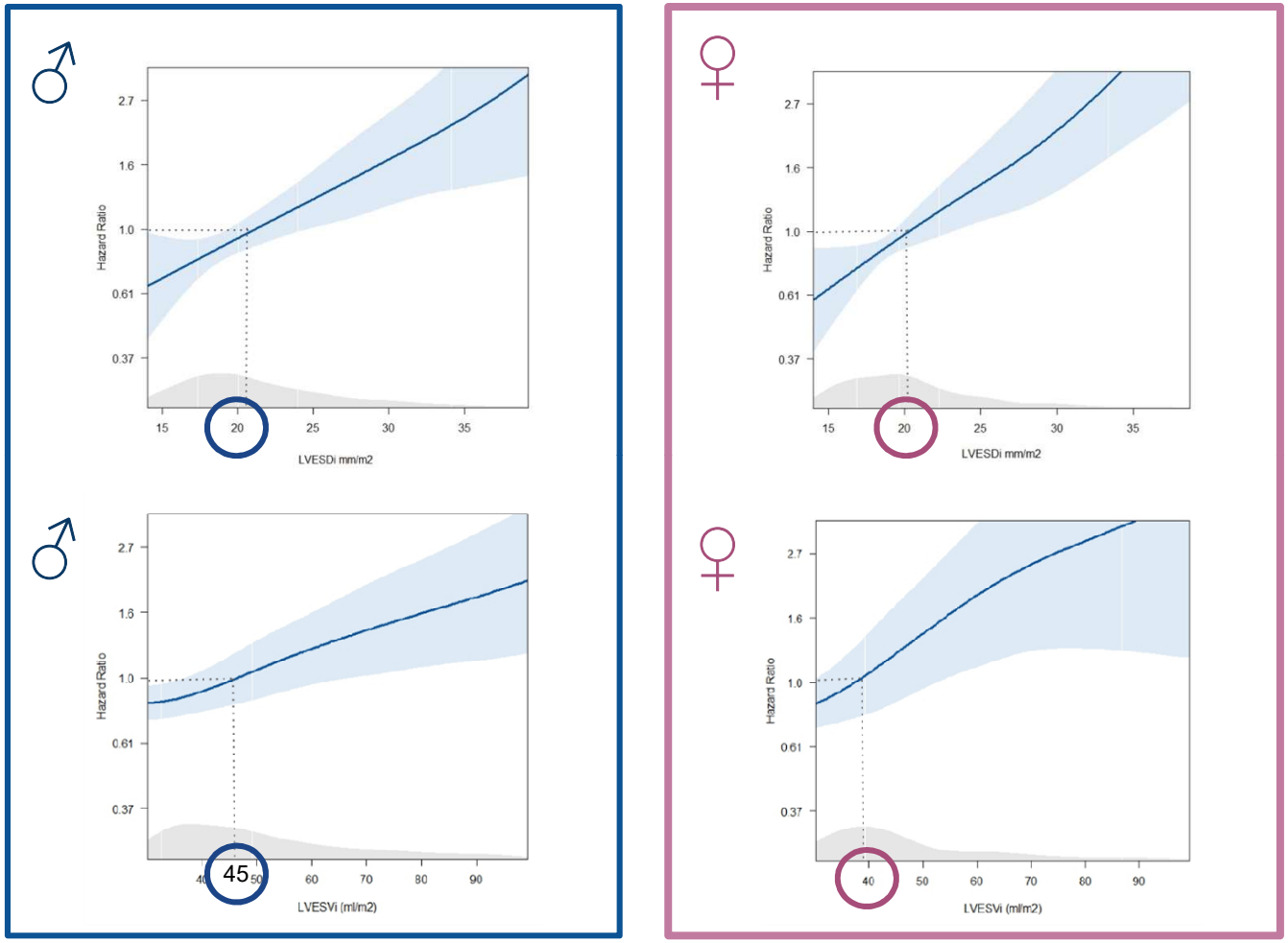


AVS

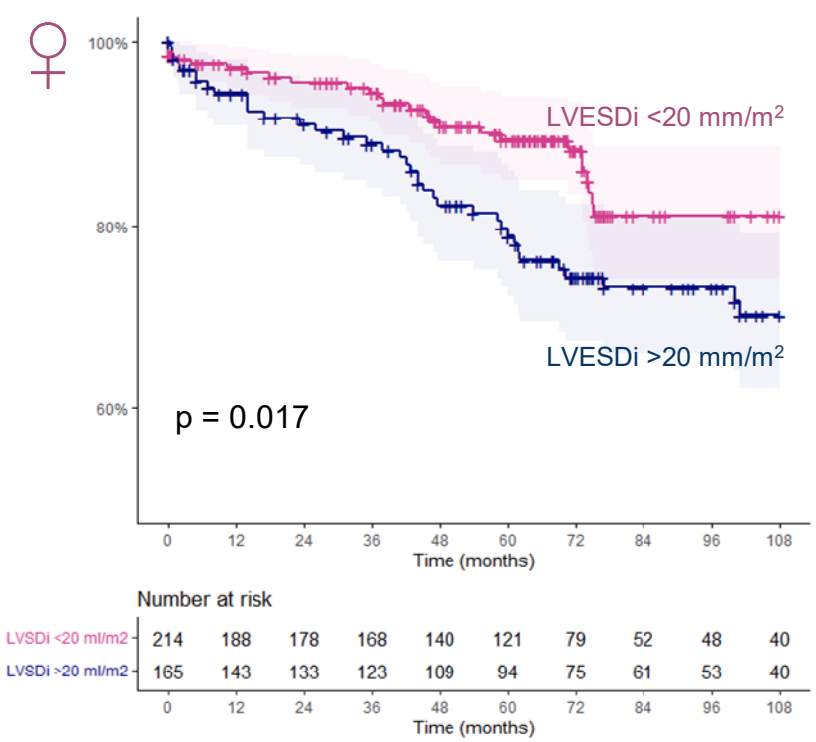


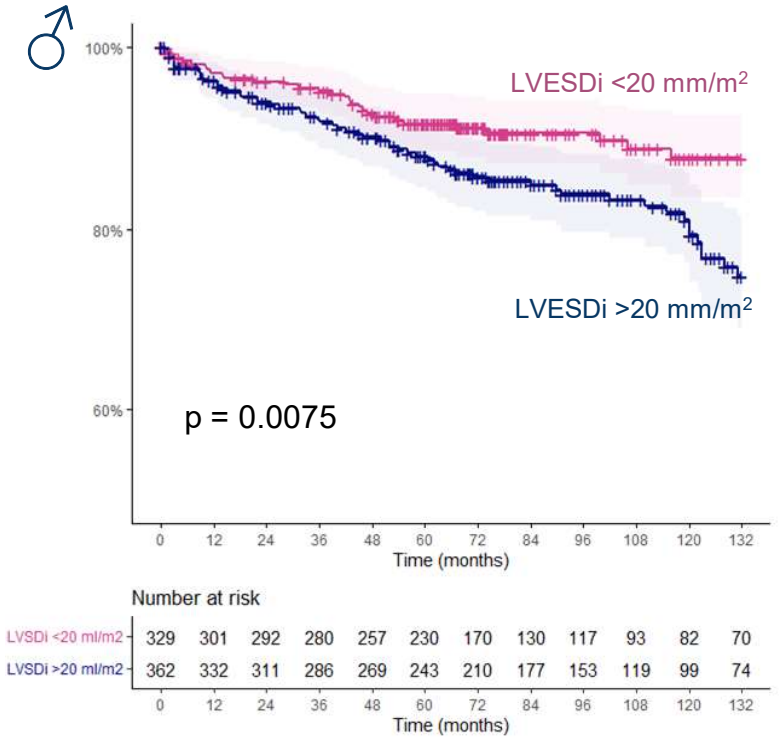
LVESDi
mm/m²

LVESVi
mL/m²

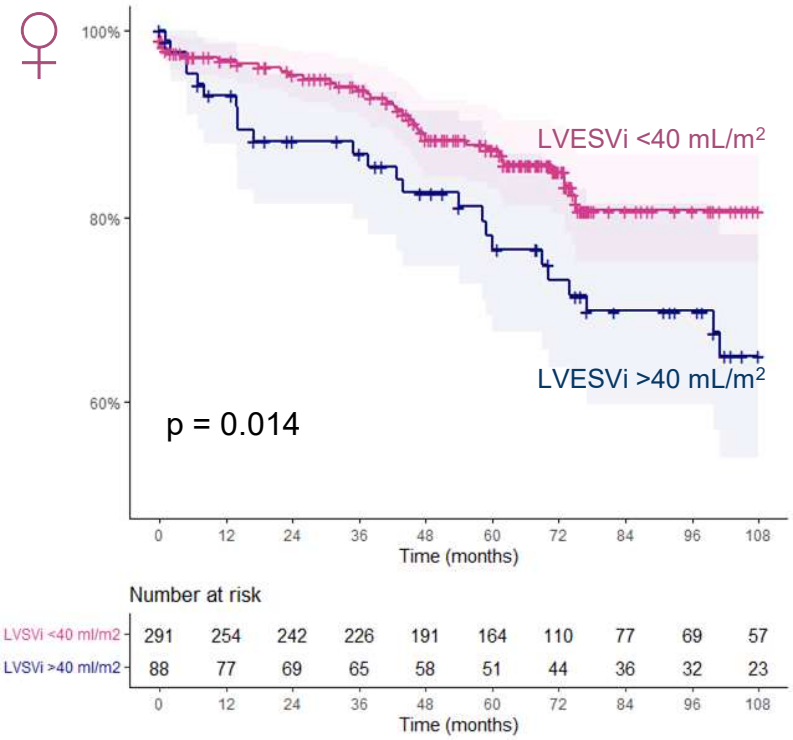


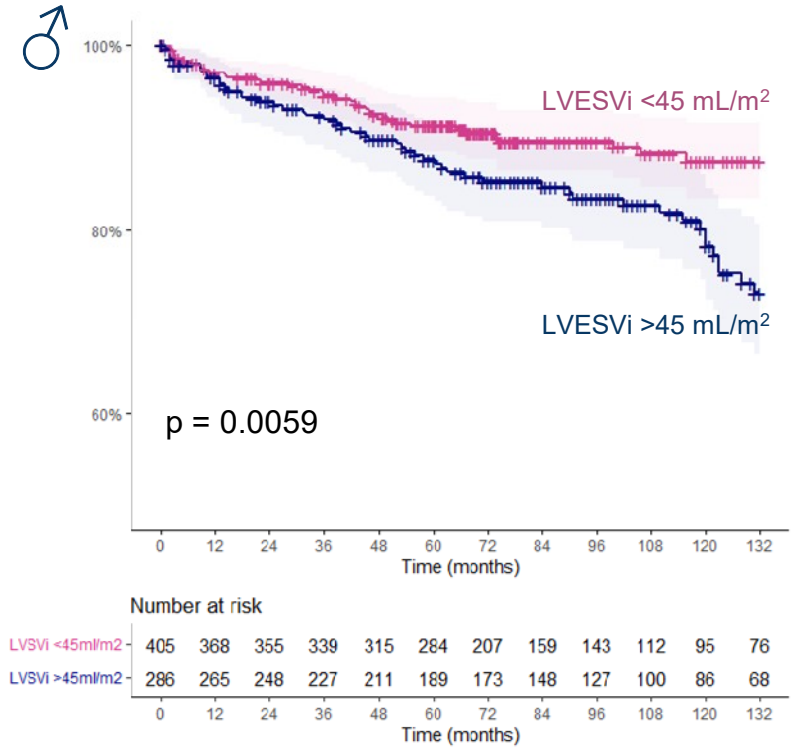
All-cause mortality and LVESDi





All-cause mortality and LVESVi





Uni- and multivariate Cox regression analysis for all-cause mortality in **women**

	Univariate Model		Multivariate Model LVESDi		Multivariate Model LVESVi	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age	1.050 (1.033-1.066)	**<0.001**	1.043 (1.024-1.063)	**<0.001**	1.045 (1.025-1.065)	**<0.001**
Coronary artery disease	2.772 (1.609-4.776)	**<0.001**	1.273 (0.714-2.269)	0.413	1.297 (0.720-2.339)	0.386
Arterial Hypertension	1.604 (1.000-2.565)	0.050				
NYHA Class III-IV	2.742 (1.632-4.608)	**<0.001**	2.137 (1.228-3.720)	**0.007**	2.017 (1.124-3.618)	**0.019**
AVS*	0.540 (0.299-0.976)	**0.041**	0.483 (0.255-0.913)	**0.025**	0.422 (0.212-0.839)	**0.014**
LVEF <55%	2.297 (1.443-3.656)	**<0.001**	1.695 (1.034-2.785)	**0.007**	1.809 (1.065-3.071)	**0.028**
LAVI (ml/m^2)	1.010 (1.000-1.021)	0.058				
LVESDi >20 mm/m^2	**1.661 (1.044-2.643)**	**0.032**	**1.710 (1.003-2.916)**	**0.006**		
LVESVi >40 ml/m^2	**1.758 (1.095-2.825)**	**0.020**			**1.968 (1.119-3.463)**	**0.019**

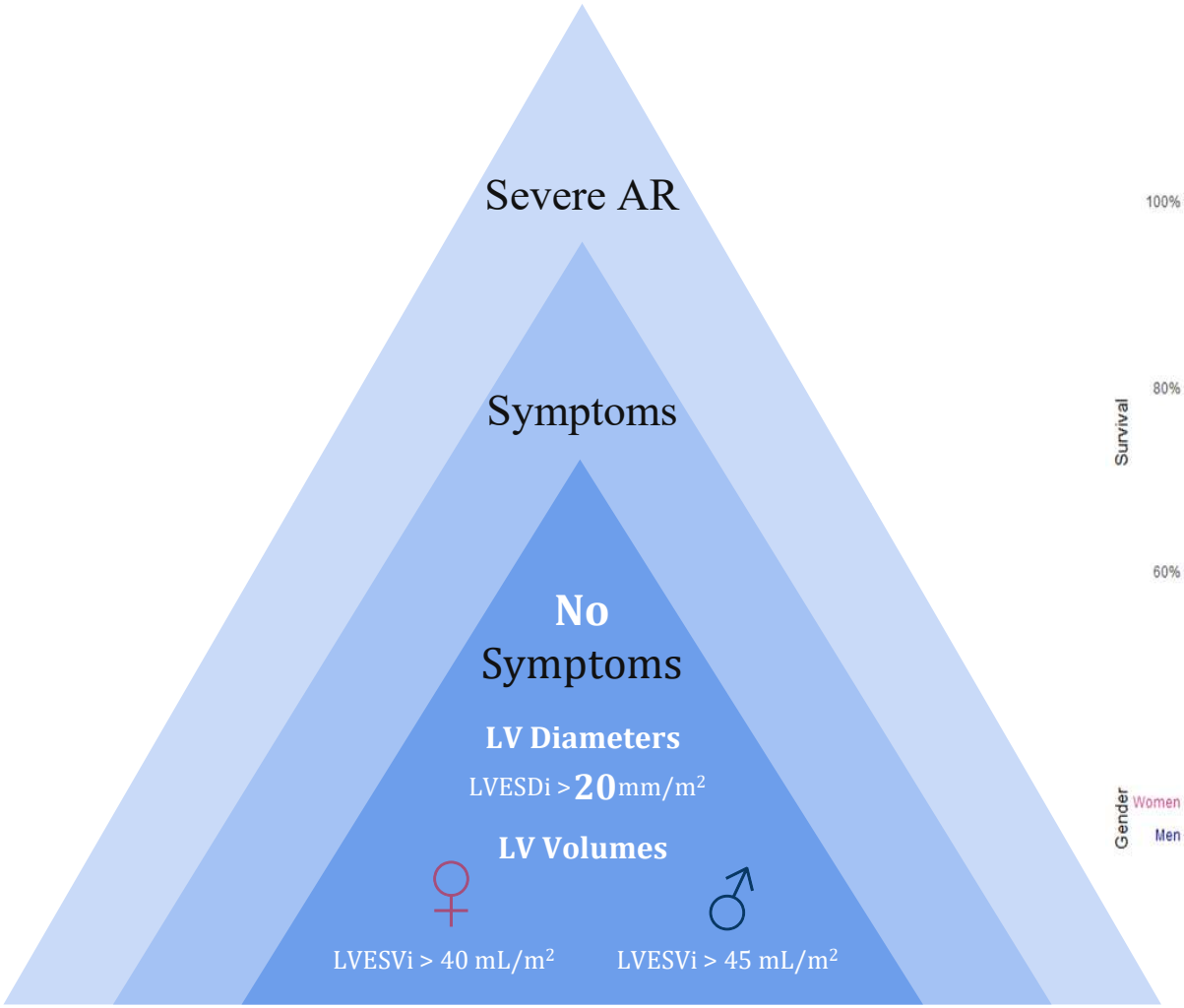
Uni- and multivariate Cox regression analysis for all-cause mortality in **men**

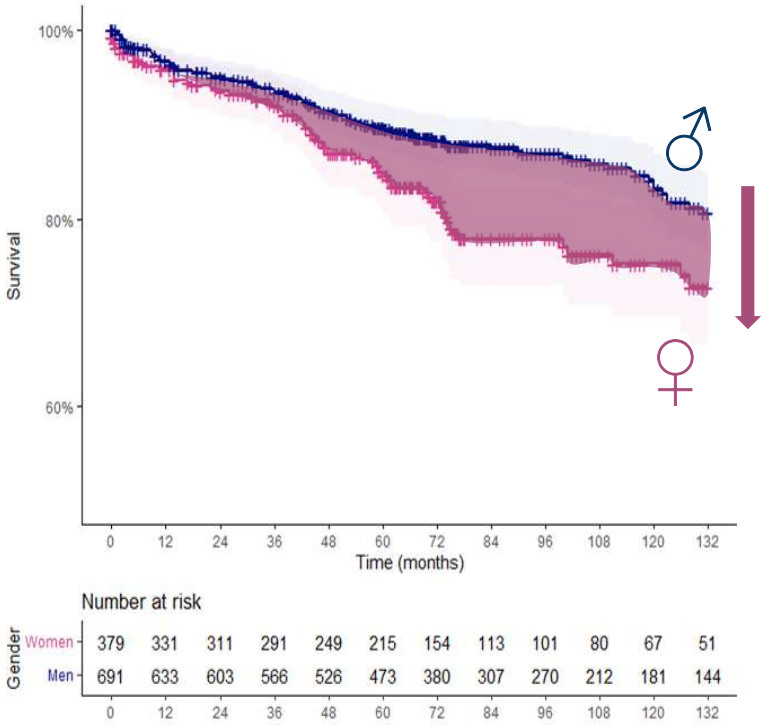
	Univariate Model		Multivariate Model LVESDi		Multivariate Model LVESVi	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age	1.072 (1.055-1.090)	**<0.001**	1.064 (1.045-1.084)	**<0.001**	1.066 (1.047-1.086)	**<0.001**
Coronary artery disease	2.645 (1.704-4.105)	**<0.001**	1.210 (0.752-1.945)	0.432	1.201 (0.750-1.925)	0.446
Arterial Hypertension	1.977 (1.307-2.992)	**0.001**	0.924 (0.585-1.460)	0.735	0.930 (0.591-1.464)	0.754
NYHA Class III-IV	3.108 (1.935-4.992)	**<0.001**	1.876 (1.117-3.152)	**0.017**	1.767 (1.048-2.979)	**0.033**
AVS*	0.561 (0.361-0.871)	**0.010**	0.391 (0.238-0.642)	**<0.001**	0.373 (0.226-0.616)	**<0.001**
LVEF <55%	2.667 (1.703-4.176)	**<0.001**	2.041 (1.232-3.379)	**0.006**	1.871 (1.097-3.191)	**0.021**
LAVI ml/m2	1.007 (1.003-1.011)	**<0.001**	1.029 (1.001-1.058)	**0.042**	1.029 (1.001-1.058)	**0.044**
LVESDi >20 mm/m^2	**1.812 (1.178-2.788)**	**0.007**	**1.638 (1.015-2.643)**	**0.043**		
LVESVi >40 ml/m^2	**1.472 (0.979-2.215)**	**0.063**				
LVESVi >45 ml/m^2	**1.830 (1.106-3.029)**	**0.019**			**1.775 (1.076-2.928)**	**0.025**

- Women with moderate-severe AR have worse survival rates than men (75% vs. 84%, p=0.005).

- No significant difference in mortality between sexes for patients undergoing AVS.

- The optimal threshold for LV linear dimensions associated with higher mortality was >20 mm/m² in both sexes, but differed for volumetric dimensions, with women having lower cut-off values (LVESVi >40 ml/m²) compared to men (LVESVi >45 ml/m²).


Severe AR
Symptoms
No Symptoms
LV Diameters
LVESDi > 20 mm/m²
LV Volumes
LVESVi > 40 mL/m²
LVESVi > 45 mL/m²


100%
80%
60%
Survival
0 12 24 36 48 60 72 84 96 108 120 132
Time (months)
Number at risk
Gender
Women 379 331 311 291 249 215 154 113 101 80 67 51
Men 691 633 603 566 526 473 380 307 270 212 181 144
0 12 24 36 48 60 72 84 96 108 120 132