Innate immunity in cardiology: vessel (coronary spasm) and valve (aortic stenosis)

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Immunology
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Disclosure

None

(Heart attack) Myocardial infarction

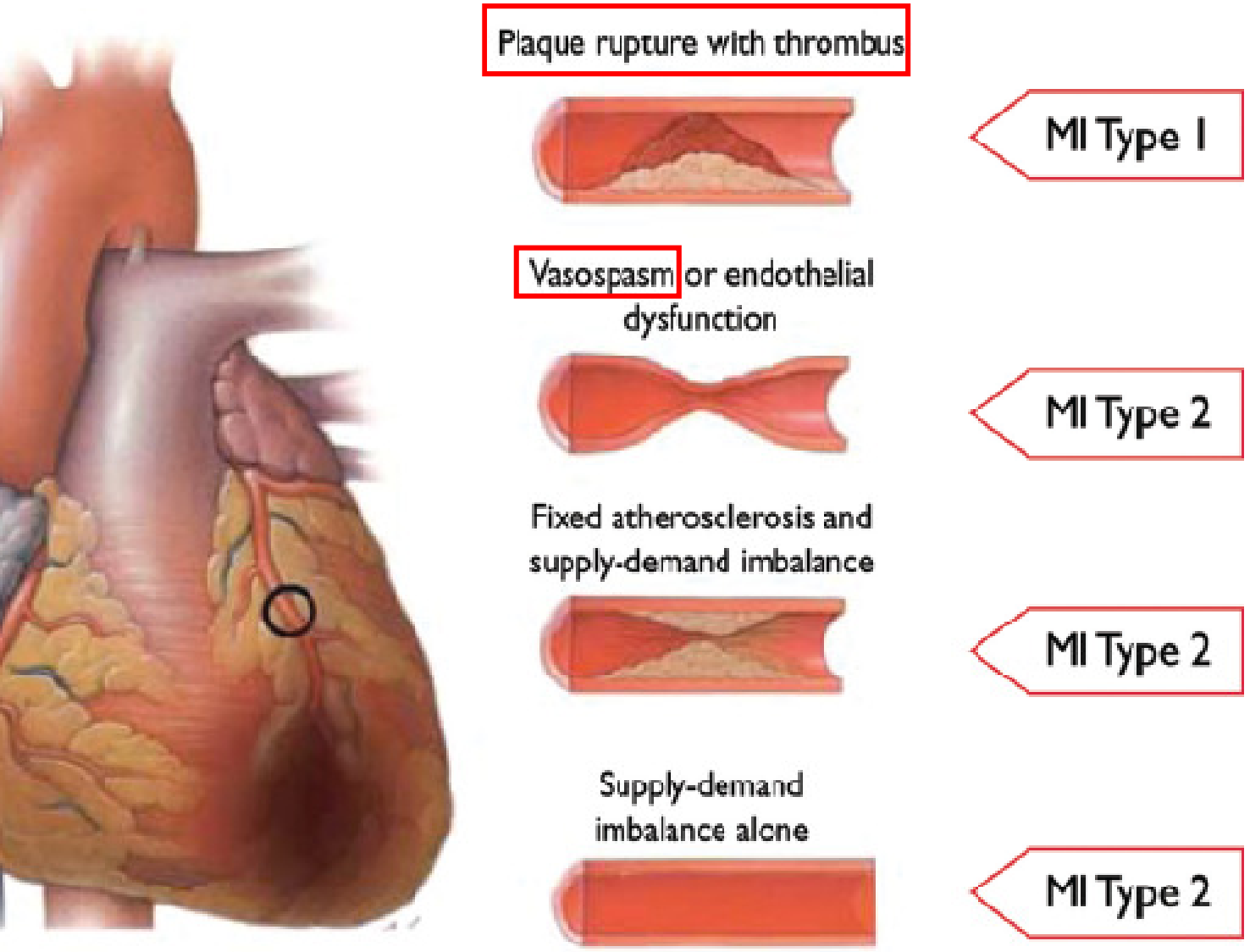
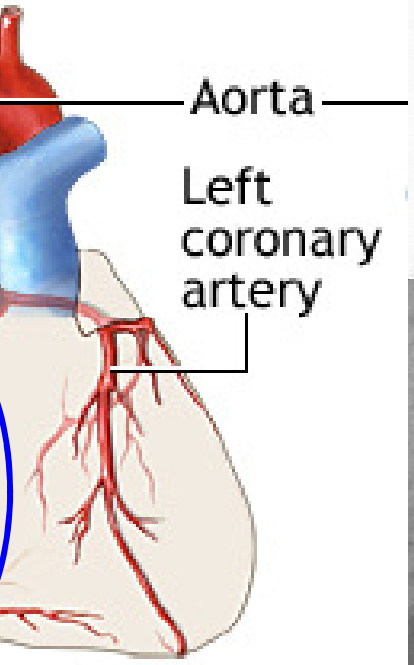


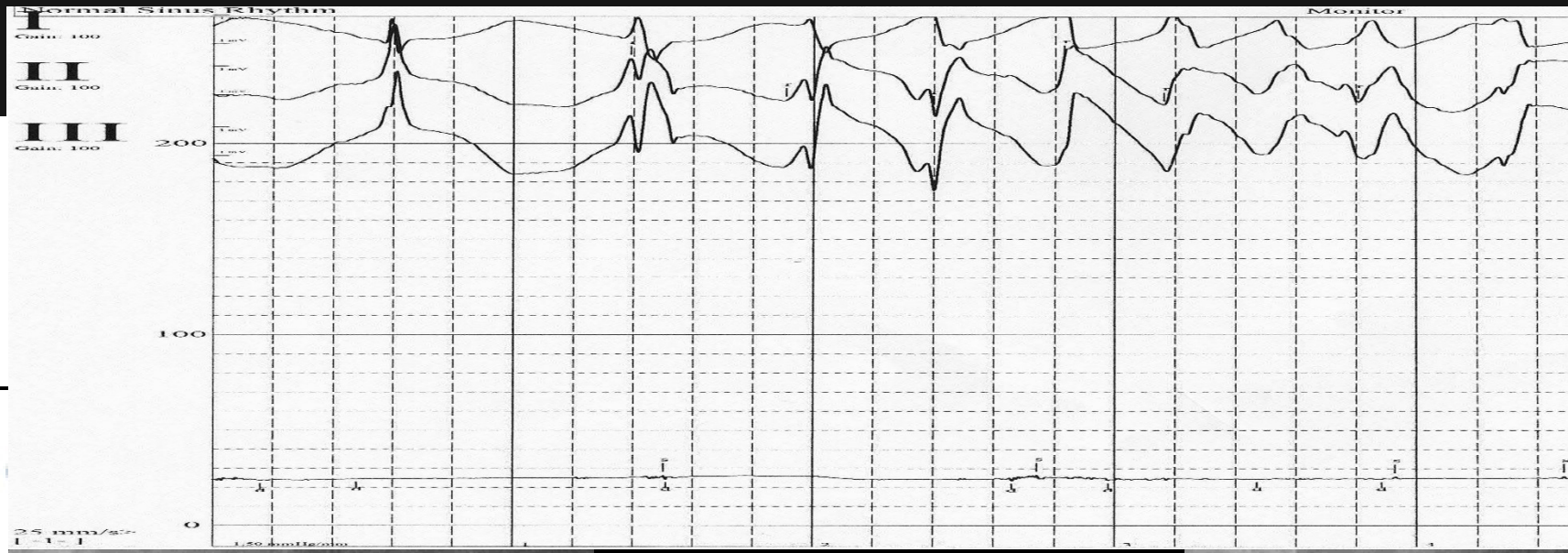
Figure 2. Differentiation betw
cardial infarction (MI) types 1
according to the condition of
nary arteries.

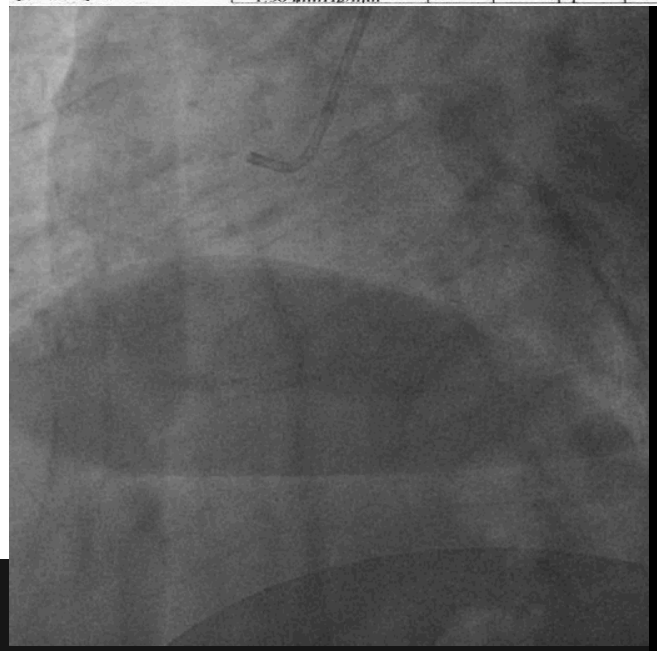
Thygesen K, et al. Third universal definition of myocardial infarction. Circulation. 2012;126

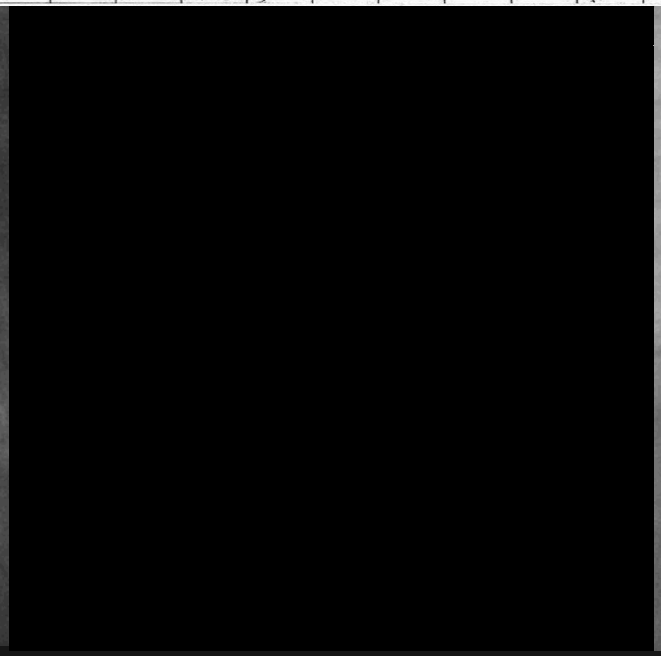
heart

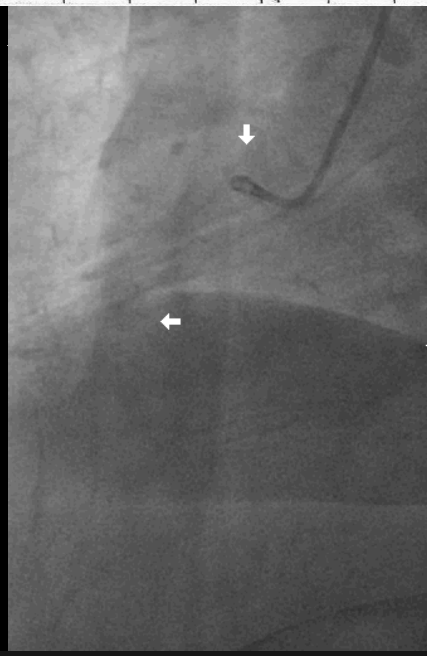


ry artery









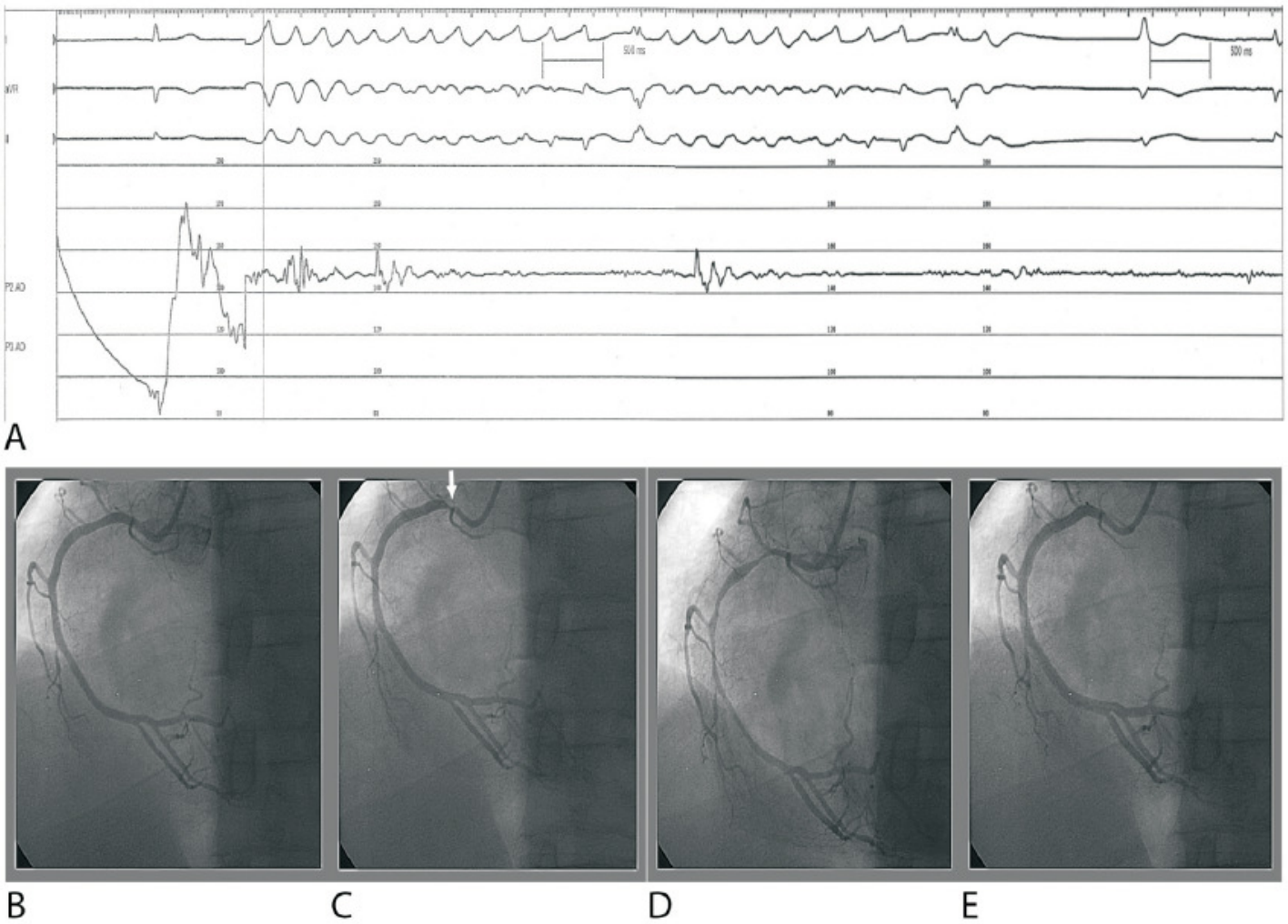


Figure 2. *Electrocardiograms, pressure tracing and right coronary arteriogram in a patient with unstable angina pectoris, presenting after wakening with resting chest tightness at night. (A) simultaneous lead I, II, aVR electrocardiogram and systemic arterial pressure tracing during intracoronary ergonovine testing; (B) baseline angiographically normal right coronary artery with minimal plaquing; (C) ostial spasm (arrow) immediately after intracoronary administration of 15 μg ergonovine; (D) in 10 seconds, the ostial spasm recovered spontaneously, multi-focal spasms appeared in the proximal and middle portion, and ventricular fibrillation occurred at the same time for 10 seconds and recovered spontaneously without intervention; (E) multi-focal spasms were relieved after intracoronary administration of 100 μg nitroglycerin. The patient's consciousness remained clear throughout examination.*

Frequency: Racial Heterogeneity

the US: 2-3% of all patients undergoing diagnostic cardiac catheterization for c
in will subsequently be classified as having variant angina.

ternationally: In **Italy**, where rigorous inpatient electrocardiographic monitorir
equently used, the incidence of variant angina in patients admitted with chest pa
proximately **10%**.

riant angina is particularly common in **Japan** with **20-30%** of patients who und
ronary angiography for chest pain assigned a diagnosis of vasospastic angina
ese patients, 40-80% have angiographically normal coronary arteries. In **Taiw**
5% of unstable angina/myocardial infarction is due to coronary spasm. Among th
tients, 57% is due to coronary spasm.

Andrew P Selwyn, Professor of Medicine, Harvard Medical School. 20

Sex and Age

ne major prognostic studies of patients with variant ang
onfirm that **69-91%** are **male**. Variant angina may be relativ
nore common in *white female* patients (22%) than in Japan
atients (11%).

ge: The mean age of patients with variant angina is **51-57** yea

Andrew P Selwyn, Professor of Medicine, Harvard Medical School. 20

Diagnosis

KG and Exercise Tolerance Test: highly variable.

oronary angiography is the criterion **standard** for the diagno
f variant angina

f the provocative test agents shown to induce coronary arte
pasm in susceptible patients, ergonovine malea
nethylergonovine maleate, acetylcholine, or hyperventilati
re the most useful. Ergonovine maleate for injection is
onger available.

Andrew P Selwyn, Professor of Medicine, Harvard Medical School. 20

Comparison of Peripheral Monocyte Counts in Patients With and Without Coronary Spasm and Without Fixed Coronary Narrowing

TABLE 1 Baseline Characteristics

Characteristics	Insignificant Coronary Artery Disease		p Value
	With Spasm (n = 123)	Without Spasm (n = 57)	
Age (yr)	59 ± 12*	58 ± 12	0.507
Men	66%	44%	0.005
Body mass index (kg/m^2)	26 ± 3	27 ± 5	0.240
Smoker	39%	21%	0.018
Diabetes mellitus	18%	19%	0.820
Systemic hypertension	37%	40%	0.628
Total cholesterol (mg/dl)	203 ± 39	199 ± 48	0.575
Peripheral white blood cell (mm^3)	7,100 ± 1,912	6,752 ± 1,776	0.248
≤5,700	26 (21%)	18 (32%)	0.129
5,701–6,700	35 (29%)	12 (21%)	0.293
6,701–8,200	28 (23%)	15 (26%)	0.603
≥8,201	34 (28%)	12 (21%)	0.346
Peripheral monocytes (mm^3)	497 ± 196	401 ± 162	0.001
≤349	25 (20%)	20 (35%)	0.033
349–428	29 (24%)	16 (28%)	0.517
429–546	31 (25%)	14 (25%)	0.926
≥547	38 (31%)	7 (12%)	0.007
Hematocrit (%)	40 ± 4	37 ± 6	0.002
≤36.7	26 (21%)	20 (35%)	0.046
36.8–39.1	29 (24%)	15 (26%)	0.691
39.2–42.4	31 (25%)	14 (25%)	0.926
≥42.5	37 (30%)	8 (14%)	0.021
Platelets (×10^3/mm^3)	224 ± 68	229 ± 129	0.785
Left ventricular ejection fraction (%)	67 ± 12	70 ± 13	0.098

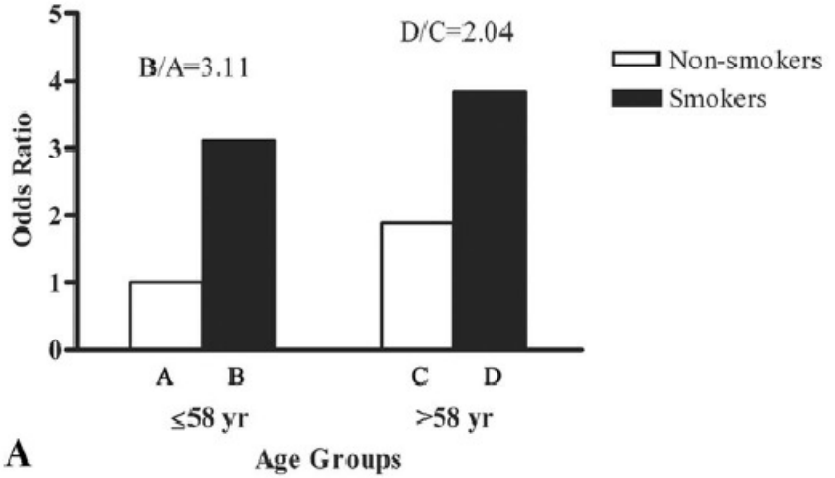
*Data are expressed as mean ± SD or percent.

Hung MJ, et al. Am J Cardiol. 2004;93(5):620-4.

Table 3
Multivariate analysis of variables associated with coronary vasospastic angina pectoris in patients without hemodynamically significant coronary artery disease

	Odds Ratio	95% Confidence Interval	p Value
Men	3.29	1.16–9.34	0.025
Peripheral monocyte count (>546 mm^3)	15.00	2.03–110.85	0.008
hs-CRP (>9.51 mg/L)	68.74	8.03–588.71	<0.001

Hung MJ, et al. Am J Cardiol. 2005;96(11):1484-90.



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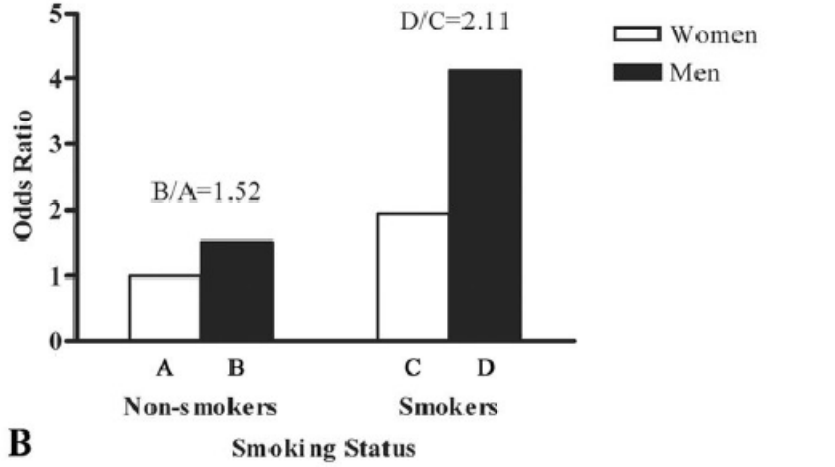

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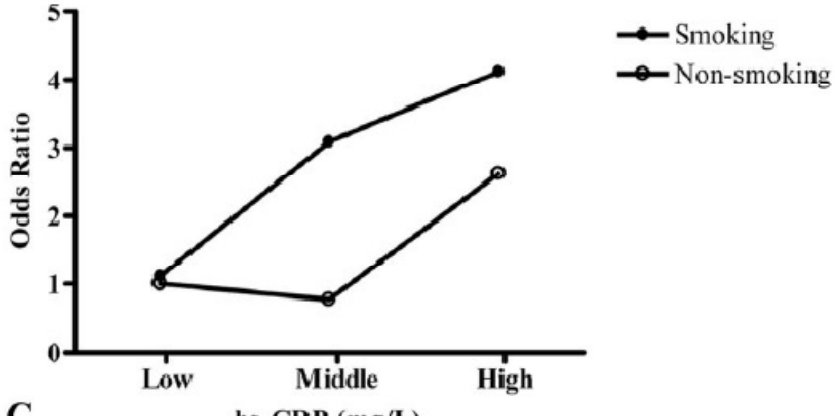
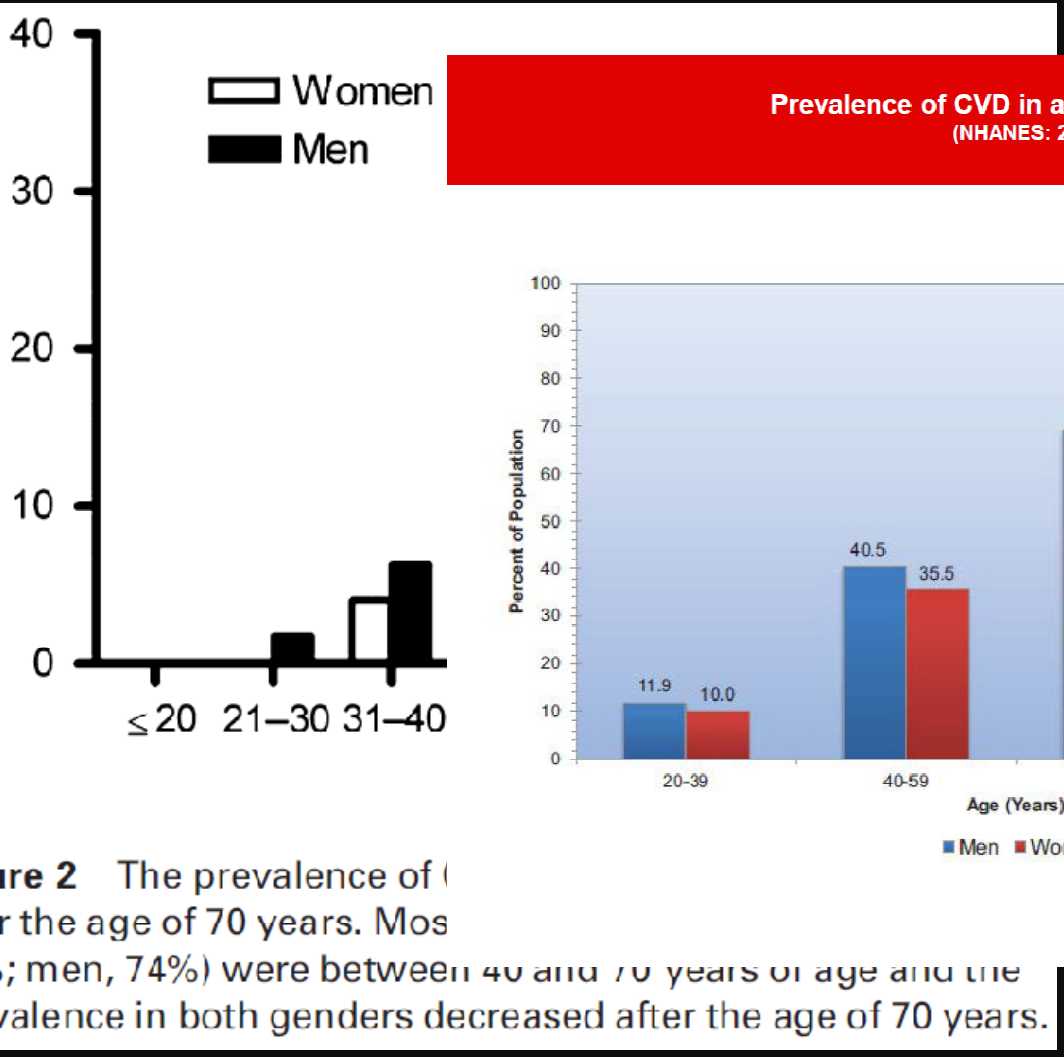


C

Hung MY, et al. Am J Med Sci. 2009 Dec;338(6):440-

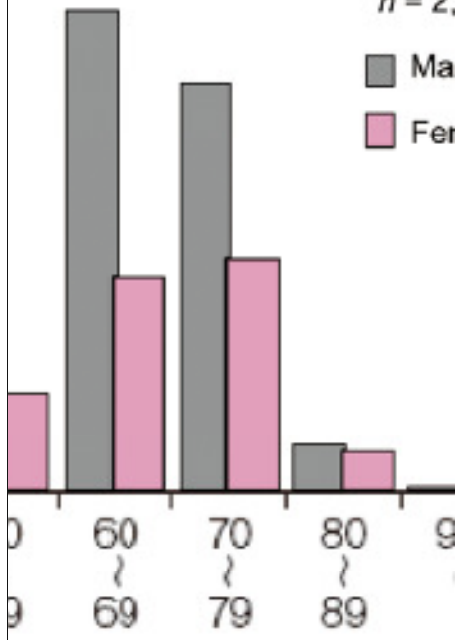


ure 2 The prevalence of (
r the age of 70 years. Mos
; men, 74%) were between 40 and 70 years of age and the
valence in both genders decreased after the age of 70 years.

Hung MY, et al. Eur J Clin Invest. 2010 Dec;40(12):1094-103.

Prevalence of CVD in adults ≥20 years of age
(NHANES: 2009–2012)

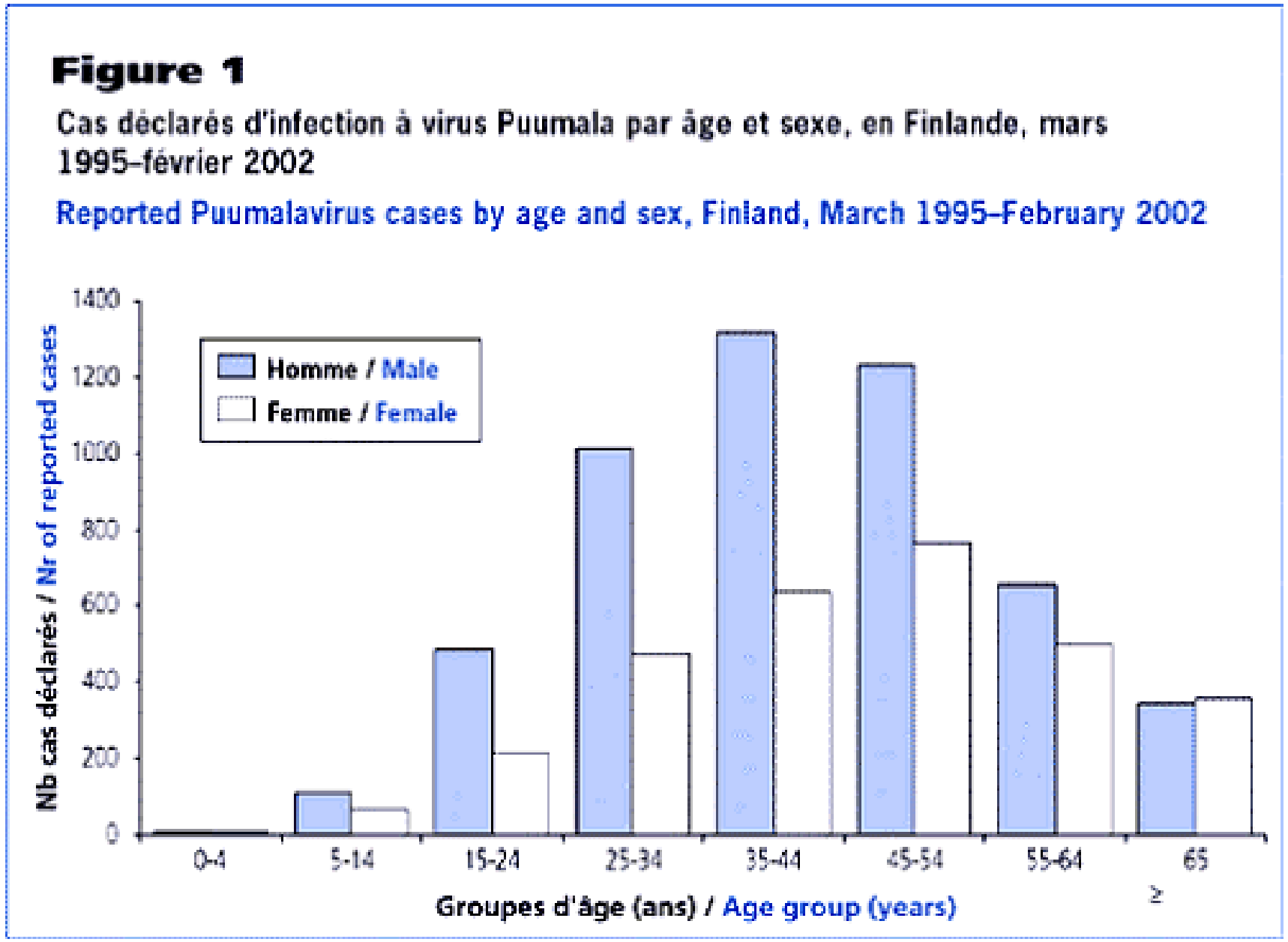
American Heart Association | American Stroke Association
life is why

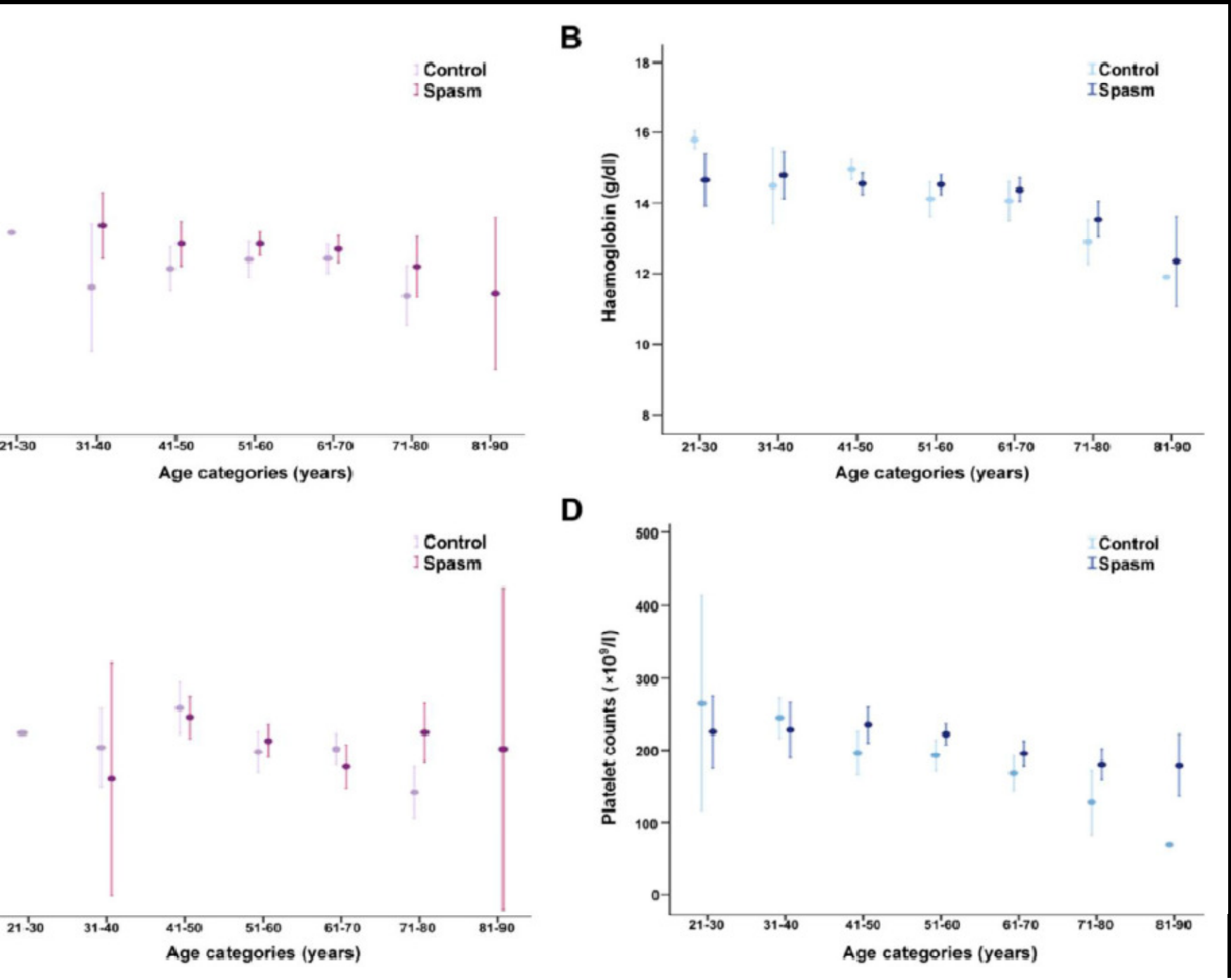


bution of angina in Japa
Adapted from Research report in 2000.[59]

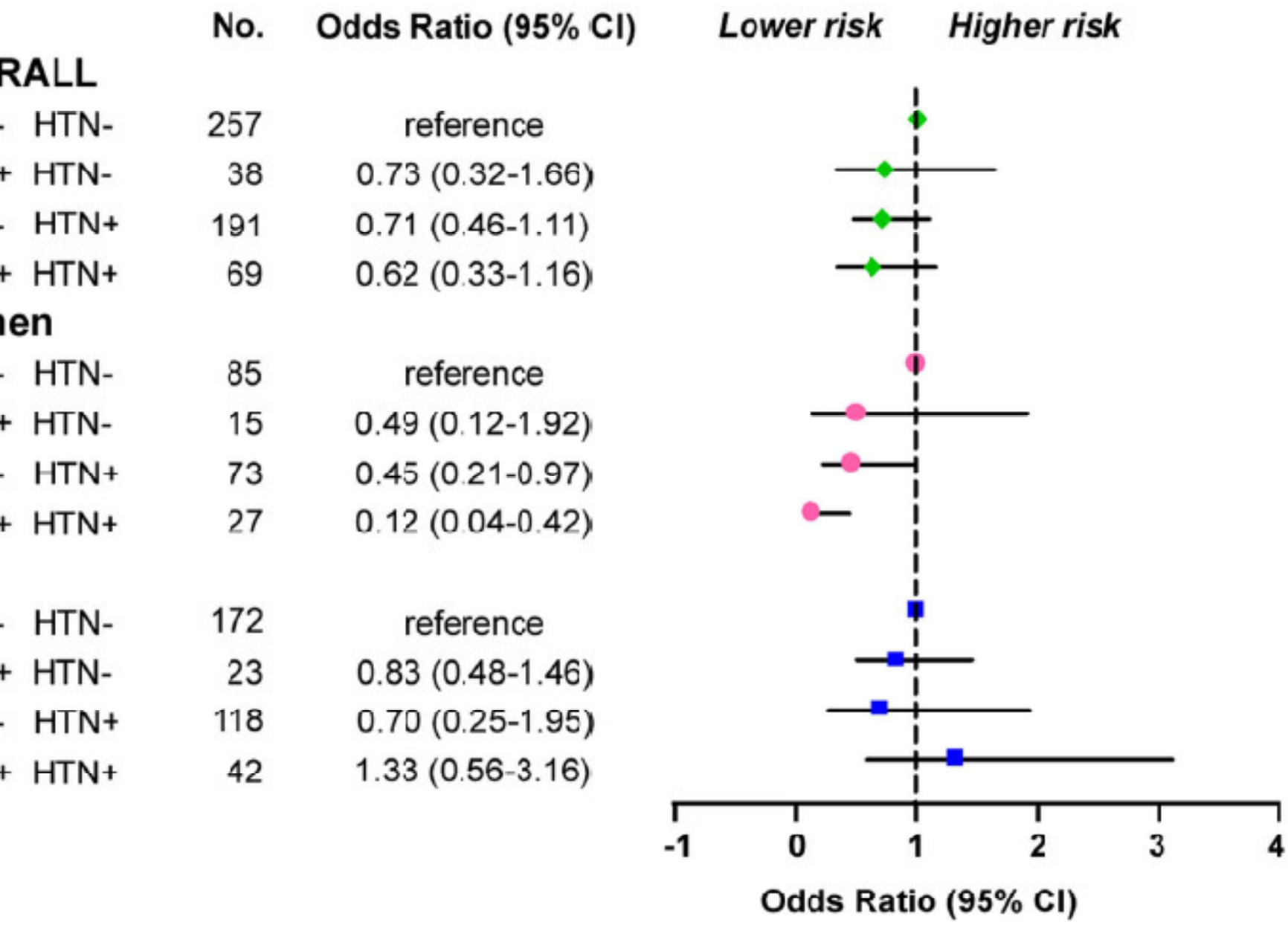
JCS Joint Working Group. Circulation Journal. 2014;78(11): 2

Fig 1. Reported Puumalavirus cases by age and sex, Finland, March 1995-February 2002





Hung MY,et al. Int J Med Sci.



e 2. Multivariate-adjusted association of DM and HTN with risk of CAS according to different m

Hung MJ, Hsu KH, Hu WS, Chang NC, **Hung MY**. PLoS One. 2013;8:e7

Int. J. Med. Sci. 2014, Vol. 11

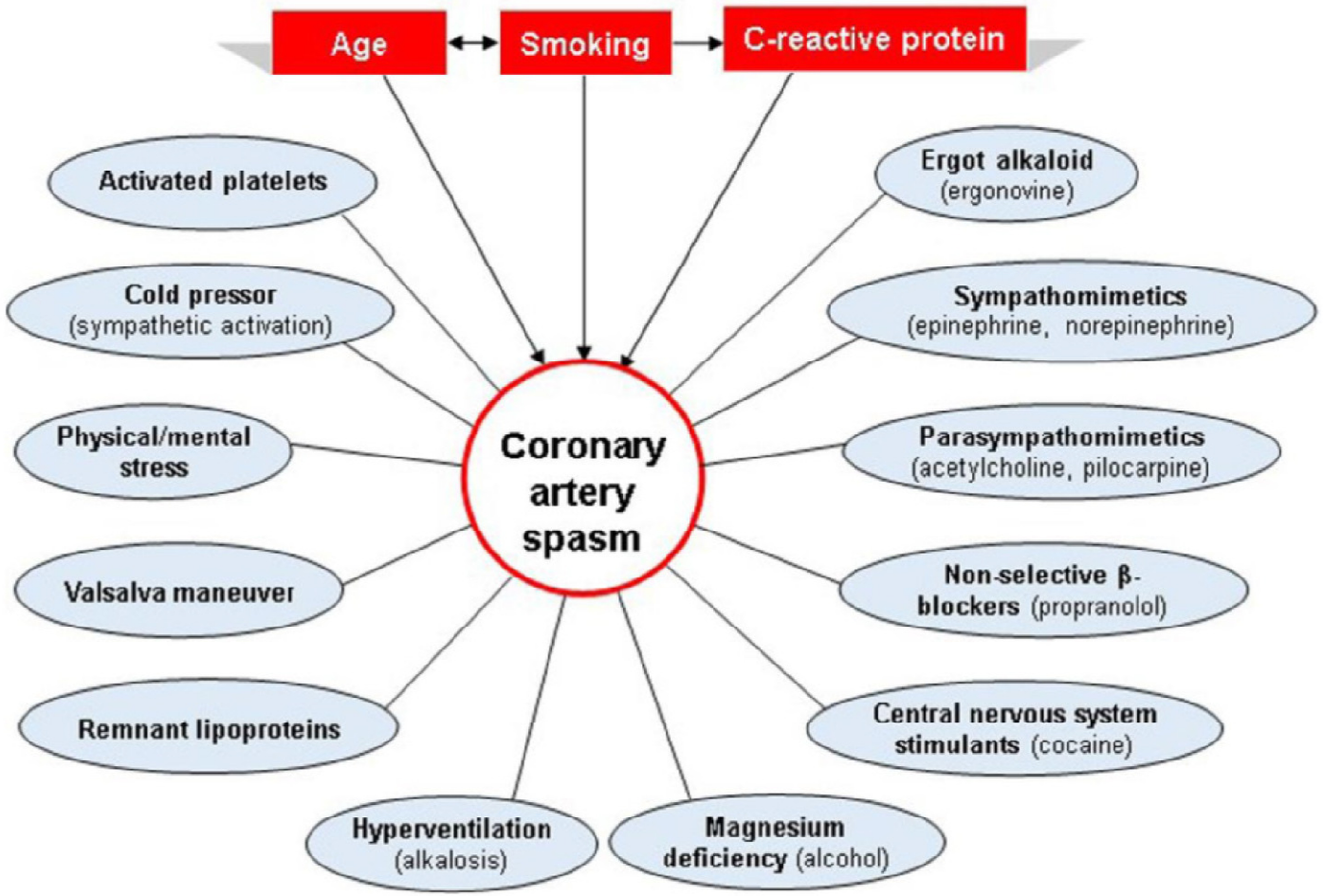
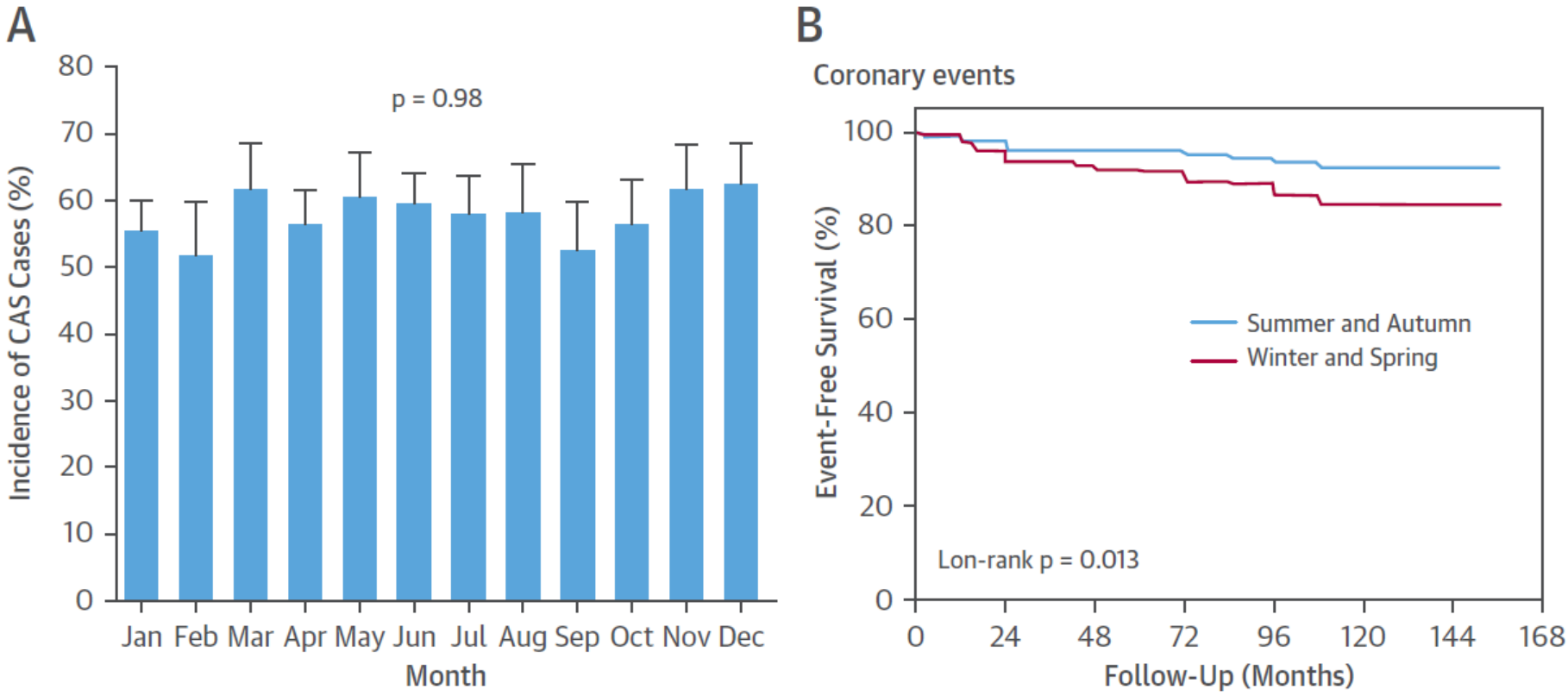


Figure 3. Risk factors and precipitating factors for the development of coronary artery spasm (CAS). While risk factors, which often coexist and interact with one another, increase a person's susceptibility to developing CAS, precipitating factors may contribute to the onset of CAS and act in the same patient to cause angina in different conditions. The risk factors and precipitating factors are represented by rectangles and circles, respectively.

Hung MJ, et al. Int J Med Sci. 2014;11:1161-71.

FIGURE 1 **Numbers of Coronary Events and Prognostic Impact by Season Due to CAS**

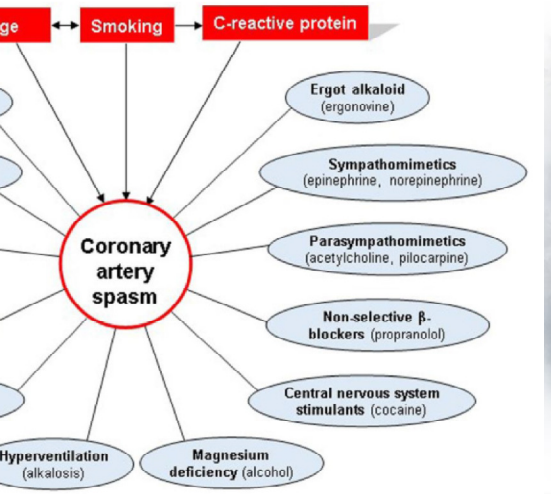


(A) The average incidence of coronary artery spasm (CAS) events per month for each month for each year of the study period. Histograms represent the mean ± SD of the incidence. The incidence of CAS cases is calculated using the following formula: (Number of CAS cases) / (Total number of patients in the CAS and control group). **(B)** Kaplan-Meier survival curves for coronary events showing significantly more events in patients with CAS occurring in winter and spring.

Hung MJ, Hsu KH, Chang NC, **Hung MY**. J Am Coll Cardiol. 2015;65(18):2047-8.

Summary

Vol. 11



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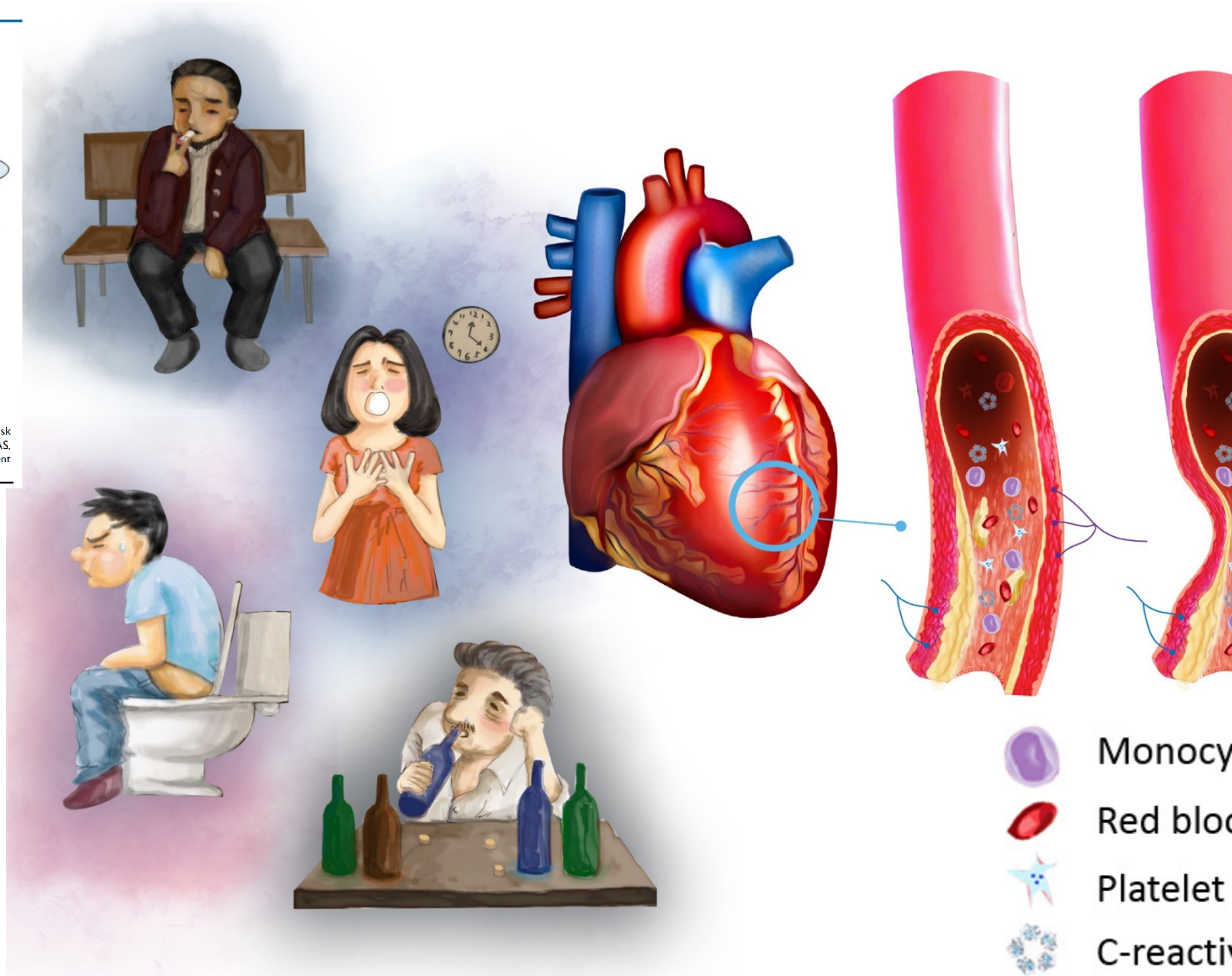
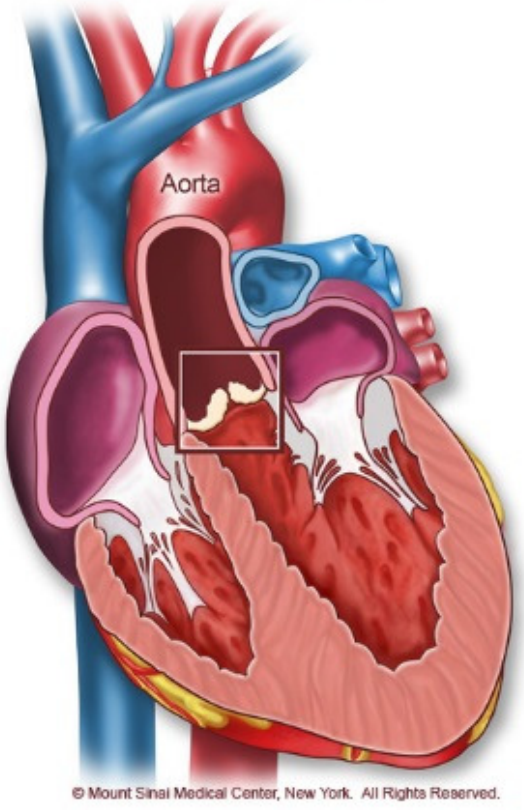
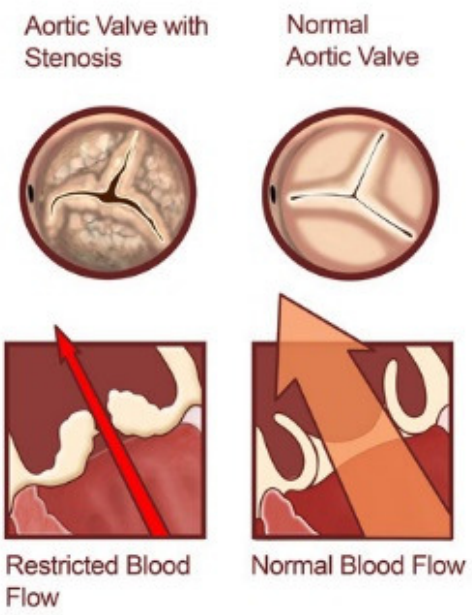


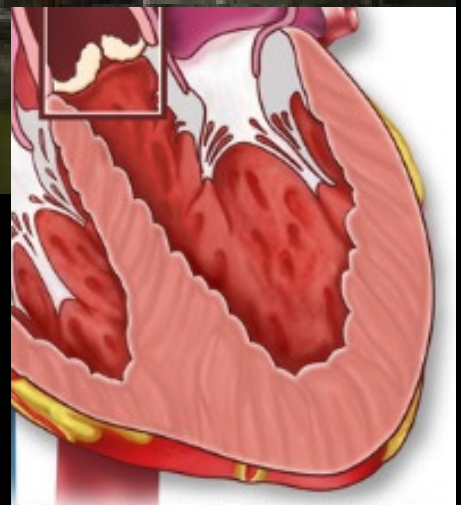
Aortic valve stenosis

Aortic Stenosis





Mount Sinai



Aortic stenosis is the most common valvular heart disease in Western World

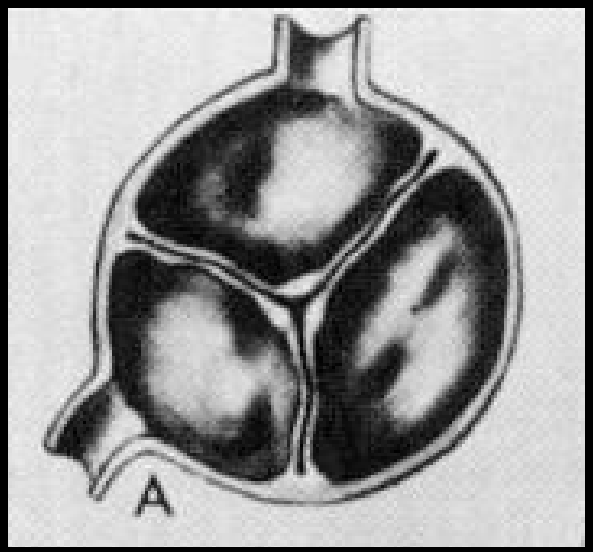
Manning, WJ (October 2013). "Asymptomatic aortic stenosis in the elderly: a clinical review". *JAMA* **310** (14): 1490–1497.

f AS. Wide frequency range generally reflects the age group(s) assessed by individual studies as well as population subgroups
17].

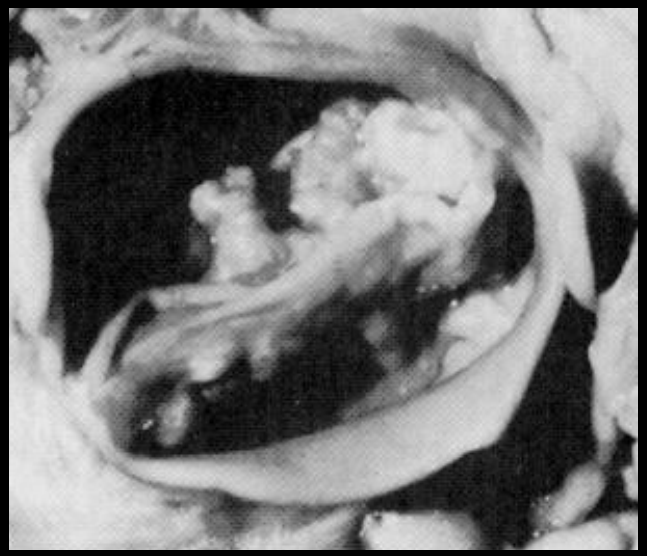
	Approximate frequency (%)	Associated features
ific	50 - 70	Increased risk of coronary events.
ortic valve	6 - 40	Dilatation or dissection of the aorta, involving the aortic root, ascending aorta, or aortic arch.
c	2 - 11	Mitral valve almost always affected as well
aortic valve	<1	Dilatation or dissection of the aorta, involving the aortic root, ascending aorta, or aortic arch.
carditis	<1	Extra-cardiac embolic phenomena.

From: Am J Cardiovasc Dis. 2011; 1(2): 18
Published online Jul 28, 2011.

Aortic Stenosis: Etiology

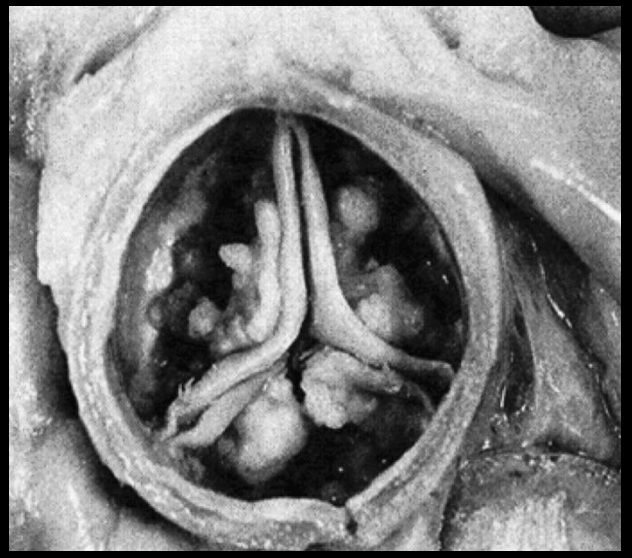


Normal



Bicuspid calcific valve:

- In many cases, it will cause no problems.
- However it may become calcified later in life, leading to varying degrees of severity of aortic stenosis



Degenerattive calcific valve

Calcific Aortic Valve Stenosis (CAVS)

Can cause heart failure and sudden death.

Epidemiology: **2-3% over 75 y**

- however, aortic valve **sclerosis**, not stenosis: **25 % over 65 y**
- The earliest stages of CAVS is aortic sclerosis.

Risk factor: similar to atherosclerosis

– **However**, 50% CAVS don't have clinical sig. atherosclerosis

Hung MY, Witztum JL, Tsimikas S. J Am Coll Cardiol. 2014;63(5):478-80.

Exp. Models: 2 models in **mice**

— Other models develop only valve sclerosis

Interventions to retard progression of CAVS

- Statins:
  - No effect on CAVS progression

Hung MY, Witztum JL, Tsimikas S. J Am Coll Cardiol. 2014 Feb 11;63(5):478-80.

- Oxidative stress
  - **?**
- Angiotensin Converting Enzyme Inhibitor (ACEI)
  - No efftect

Miller JD, et al. Circ Res. 2011 May 27;108(11):1392-412

- Angiotensin receptor-1 blocker (AT1r)
  - Prevents inflammatory cell infiltration.
  - Conflicting results, needs further study

Miller JD, et al. Circ Res. 2011 May 27;108(11):1392-412

- PPARγ
  - prevent differentiation to osteoid cells, slow progression
  - needs further study

Miller JD, et al. Circ Res. 2011 May 27;108(11):1392-412

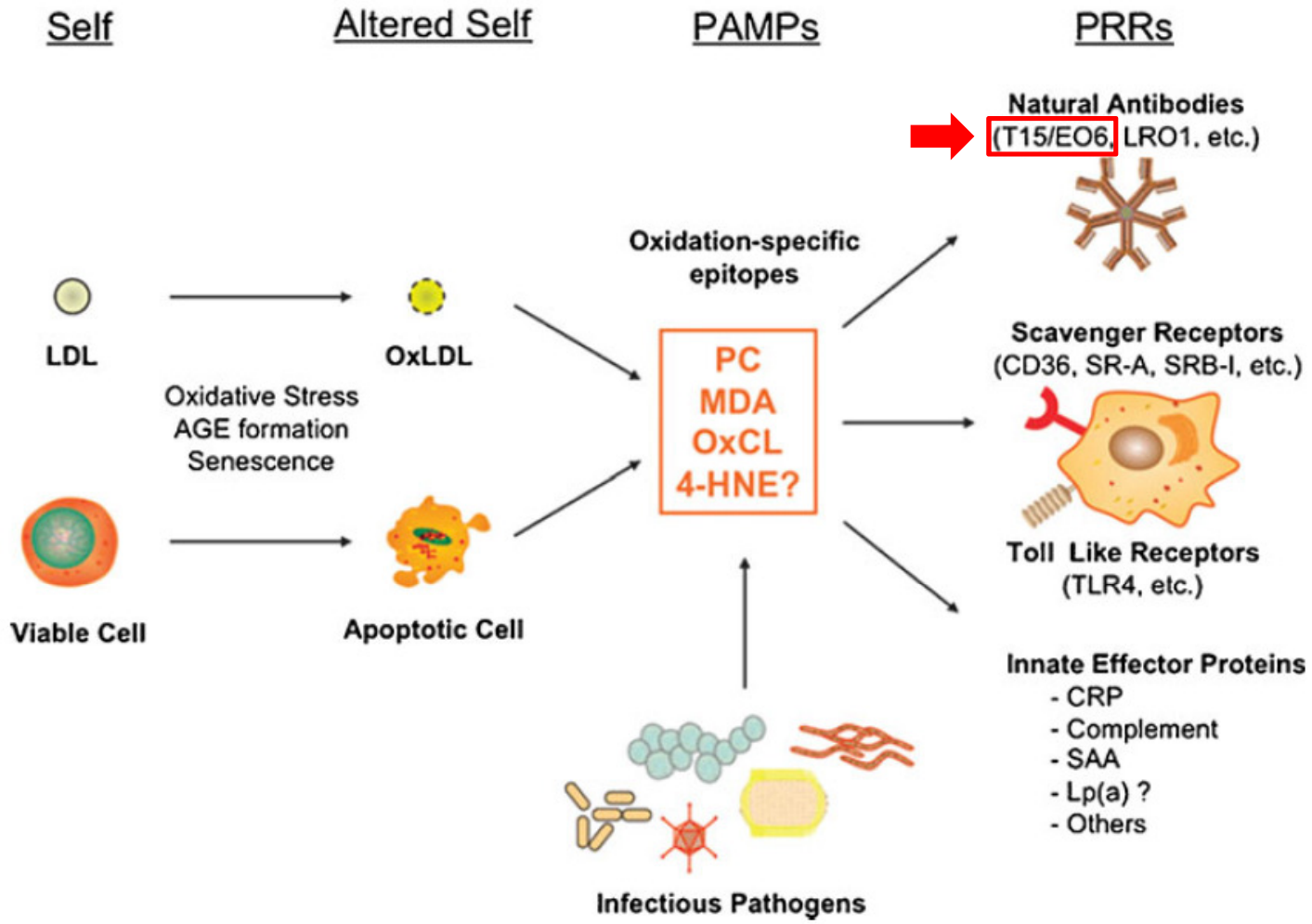
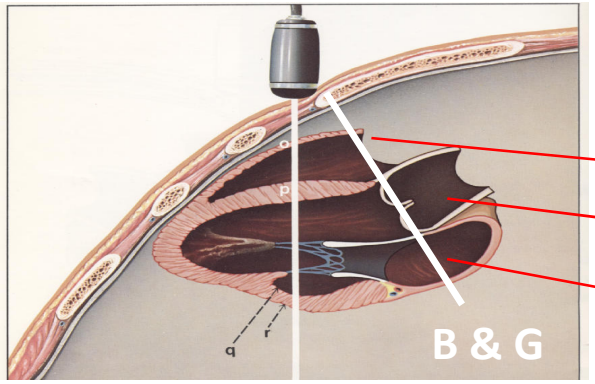
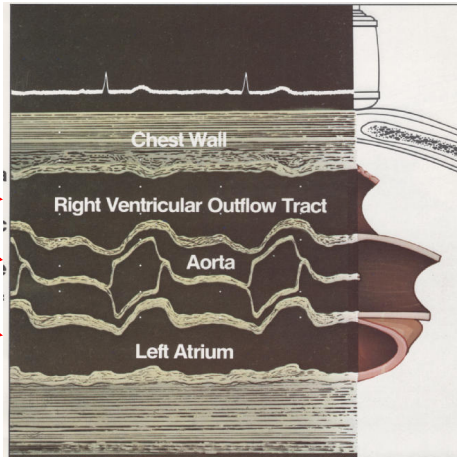
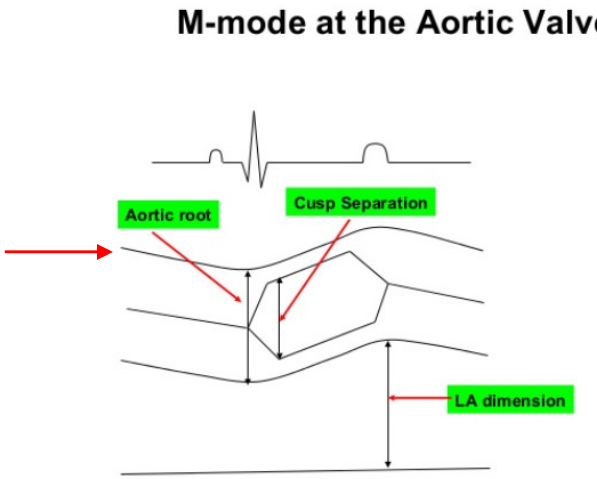


Fig. 1 Oxidation-specific epitopes are a class of pathogen-associated molecular patterns (PAMPs) that are recognized by natural antibodies and other innate immune receptors. Physiological and pathological stress can lead to the generation of oxidation-specific epitopes (altered self) on membranes of lipoproteins as well as cells (self), which are subsequently recognized by natural antibodies, scavenger receptors, and other innate effector proteins via these motifs. In many, if not all, cases, molecular mimicry exists between oxidation-specific epitopes of self-antigens and epitopes of infectious pathogens. 4-HNE, 4-hydroxynonenal; AGE, advanced glycation end product; CRP, C-reactive protein; Lp(a), lipoprotein [a]; MDA, malondialdehyde; OxCL, oxidized cardiolipin; OxLDL, oxidized LDL; PC, phosphorylcholine; SAA, serum amyloid A. (*Reprinted with permission from* Hartvigsen et al. [6••])

Echocardiography

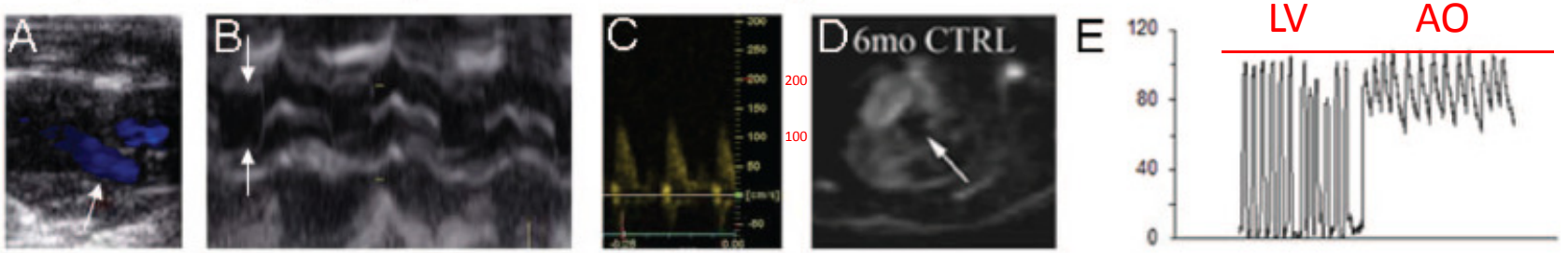




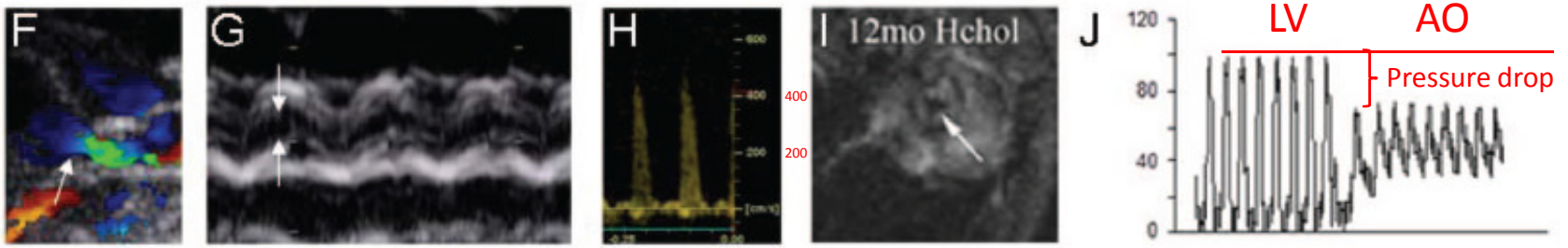


Color Doppler | M-Mode Cusp Sep. Dist. | Doppler Velocimetry | MRI | Direct Pressure Measurement

Normal



CAVS

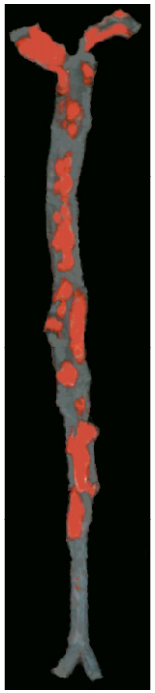


aliasing color flow

Miller JD, et al. Circ Res. 2011 May 27;108(11):1392-412

AS cohort 1

LDLR-KO/EO6-tg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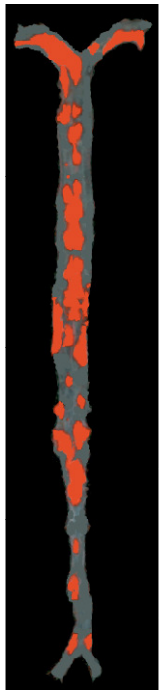
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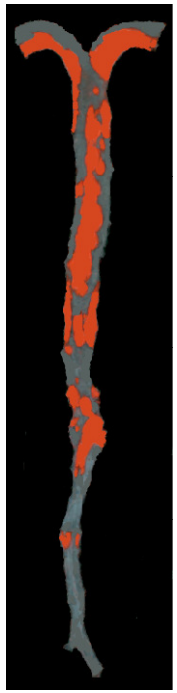
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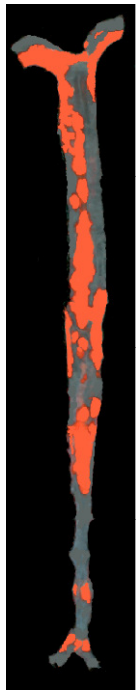
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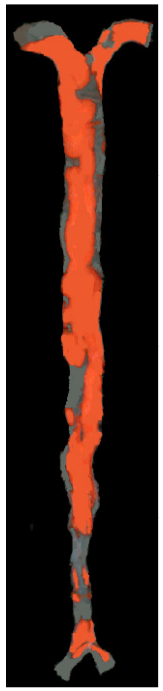
LDLR-KO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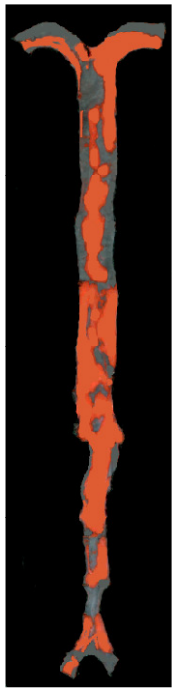
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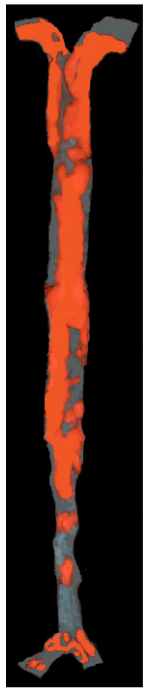
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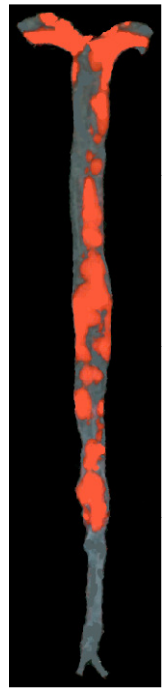
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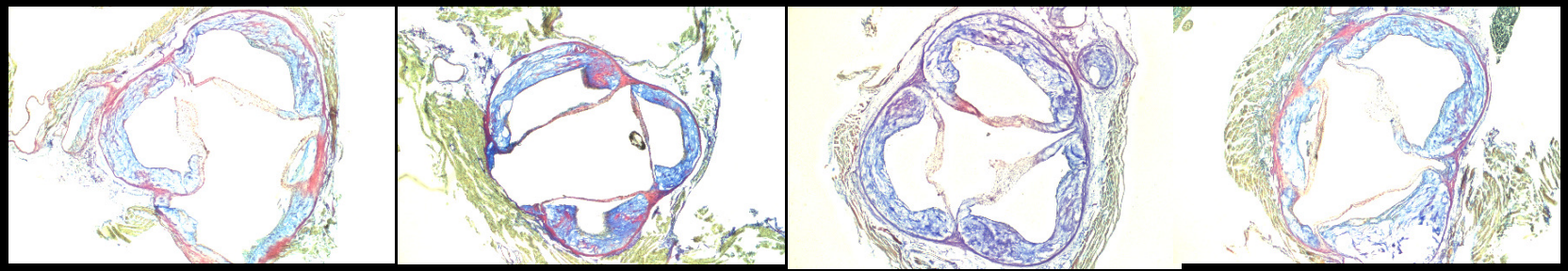

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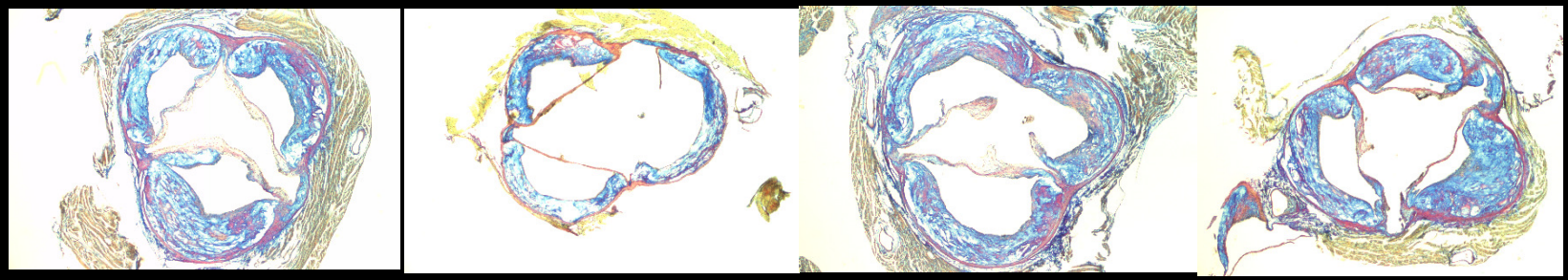

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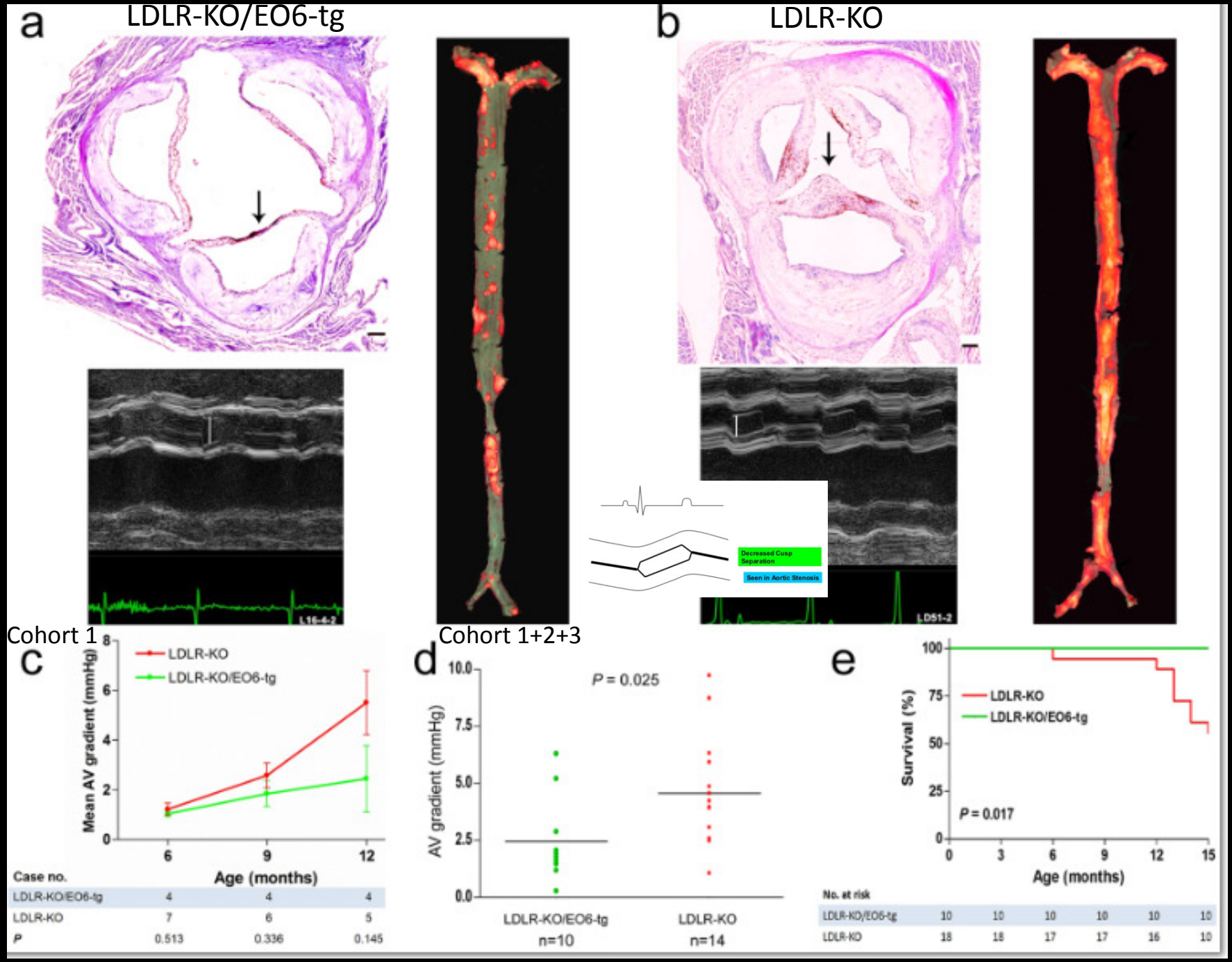

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