Atrial Fibrillation in Hypertension

Korea University Cardiovascular Center

Hong Euy Lim, M.D., Ph.D.

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Contents

- **Epidemiology**
- **Pathophysiology**
  - **Diastolic dysfunction (pressure-induced stretch)**
- **Upstream treatment**
- **New guideline of anticoagulation**

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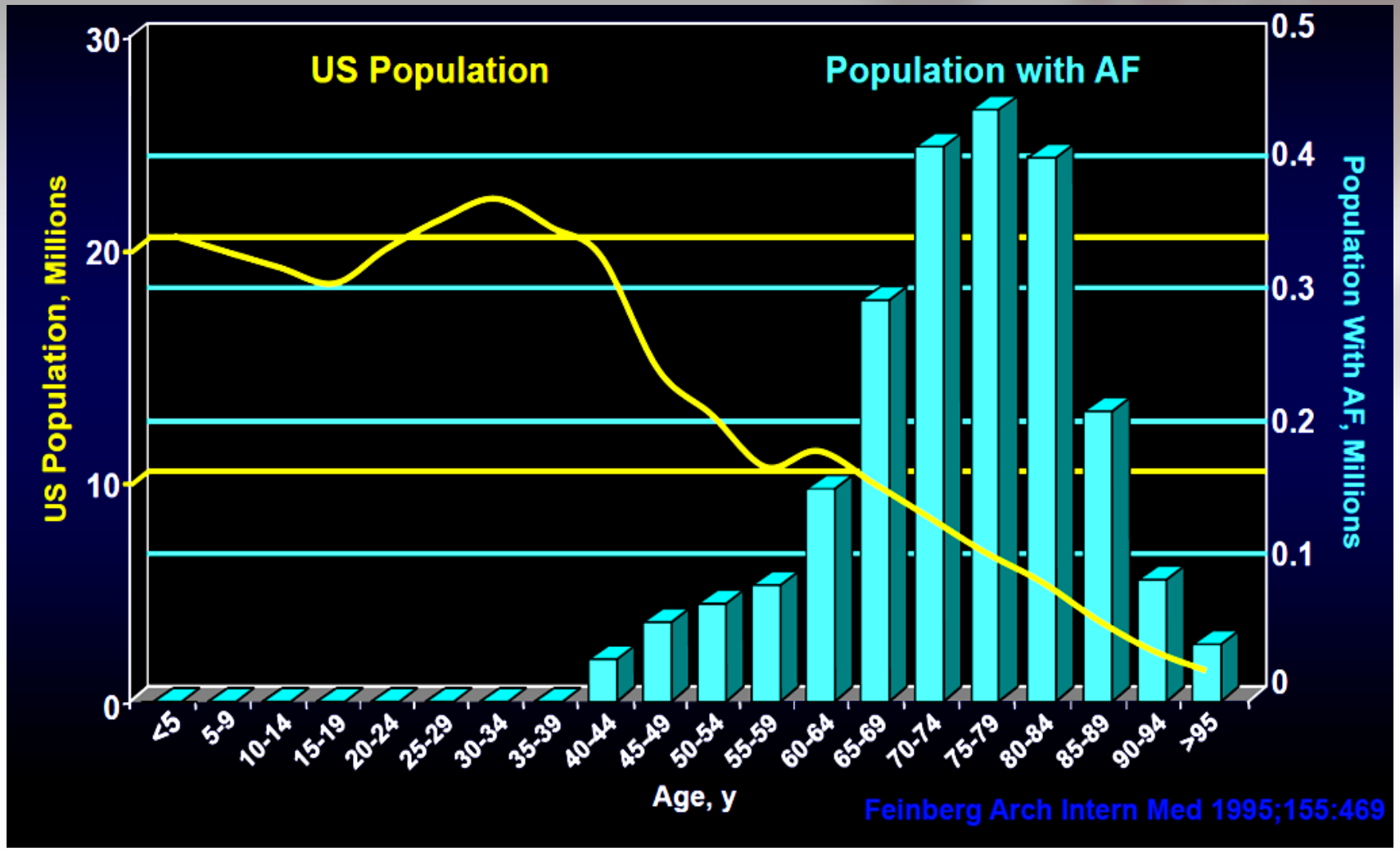
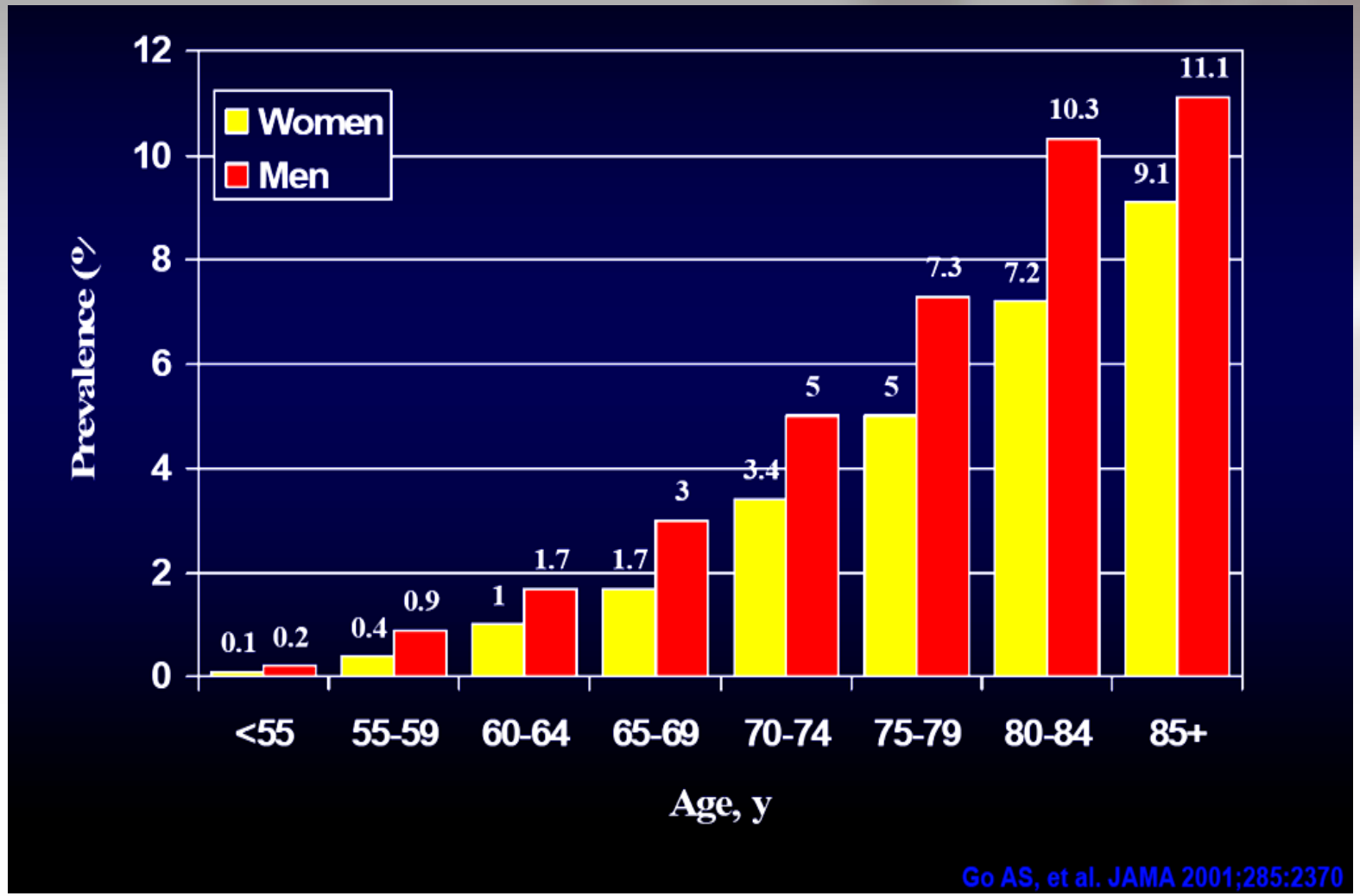
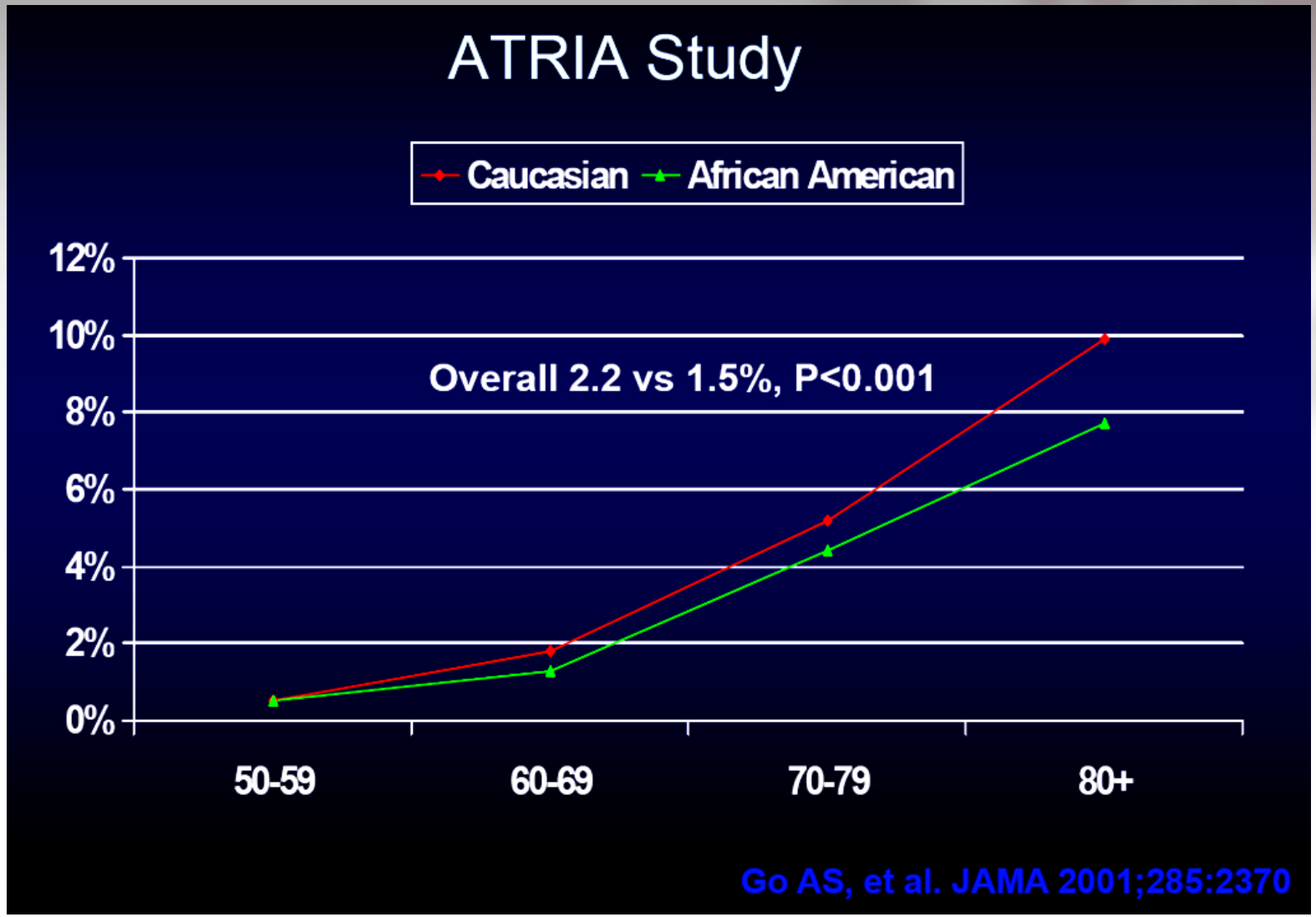
Prevalence of AF



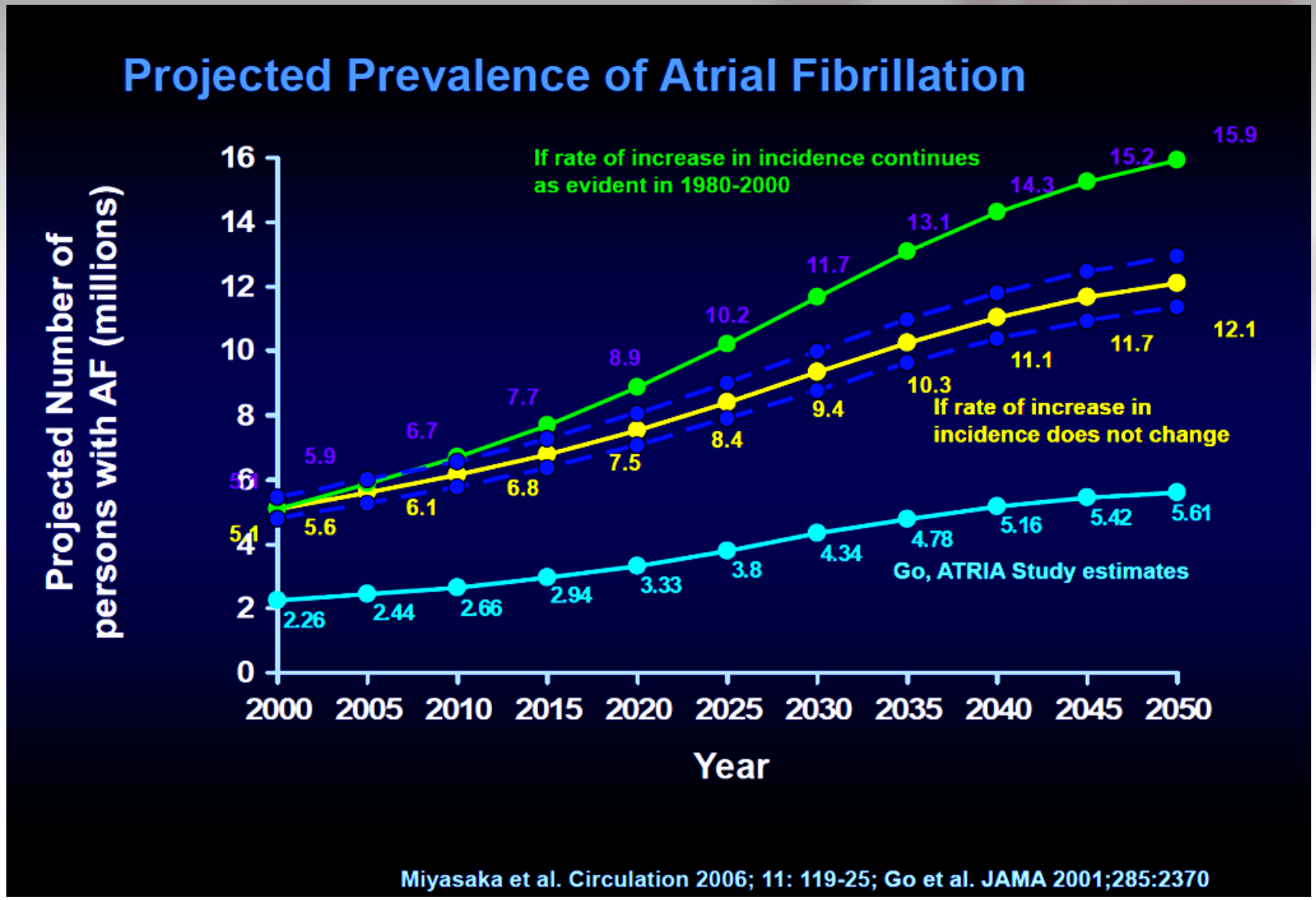
Prevalence of AF



Prevalence of AF



Prevalence of AF



Miyasaka et al. Circulation 2006; 11: 119-25; Go et al. JAMA 2001;285:2370

Risk Factors of AF

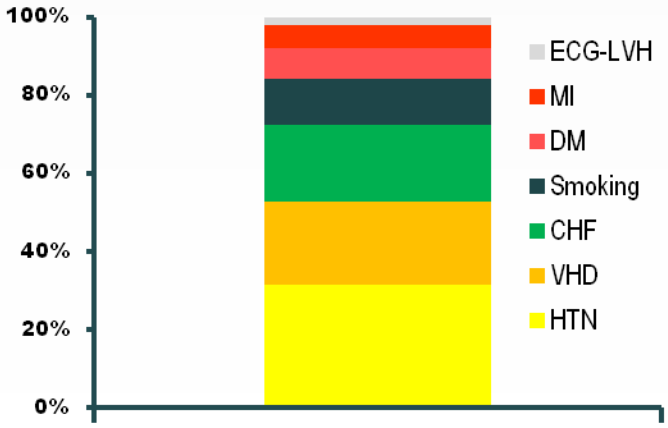
Clinical

Non-modifiable: Age, sex, ethnicity, genetic/familial
Acquired :
Traditional **: HTN, DM, CAD(MI), CHF, VHD, COPD, hyper and hypothyroidism, post-op**
Novel **: obesity, sleep apnea, pulse pressure**

Subclinical/ Biomarkers

LVH
LV systolic / diastolic dysfunction
LA size / function
CRP and BNP

Population-Attributable Risk % for AF



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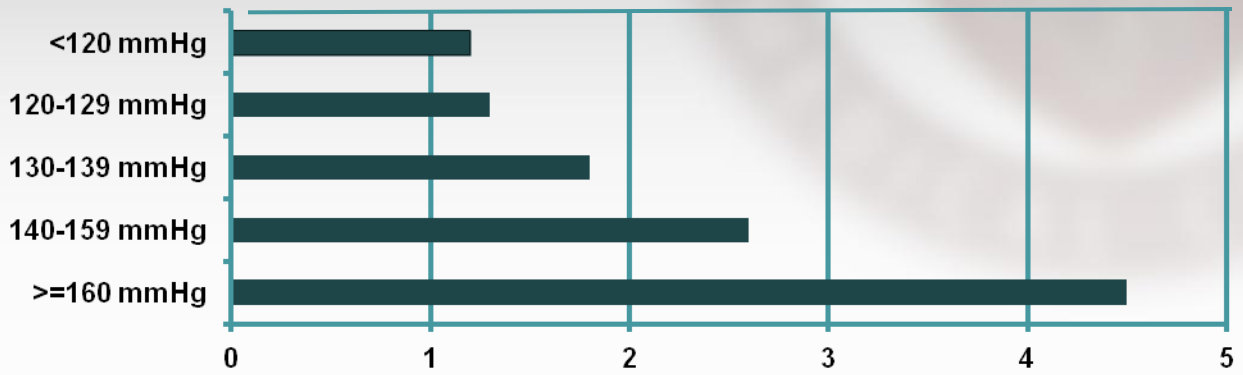
Incidence of AF

Systolic Blood Pressure and Risk of AF among Apparently Healthy Women

Age adjusted AF Incidence by Baseline SBP:



Updated BP Measurements :

Systolic BP	120-129	130-139	140-159	≥160 mmHg
	N=9448	N=6952	N=5304	N=444
Incident AF	136	160	181	27
Multivariable	1.14 (0.89-1.46)	1.37 (1.07-1.76)	1.71 (1.33-2.21)	2.21 (1.45-3.36)
Combined w/ DBP	1.18 (0.91-1.51)	1.43 (1.09-1.87)	1.78 (1.34-2.38)	2.29 (1.45-3.63)

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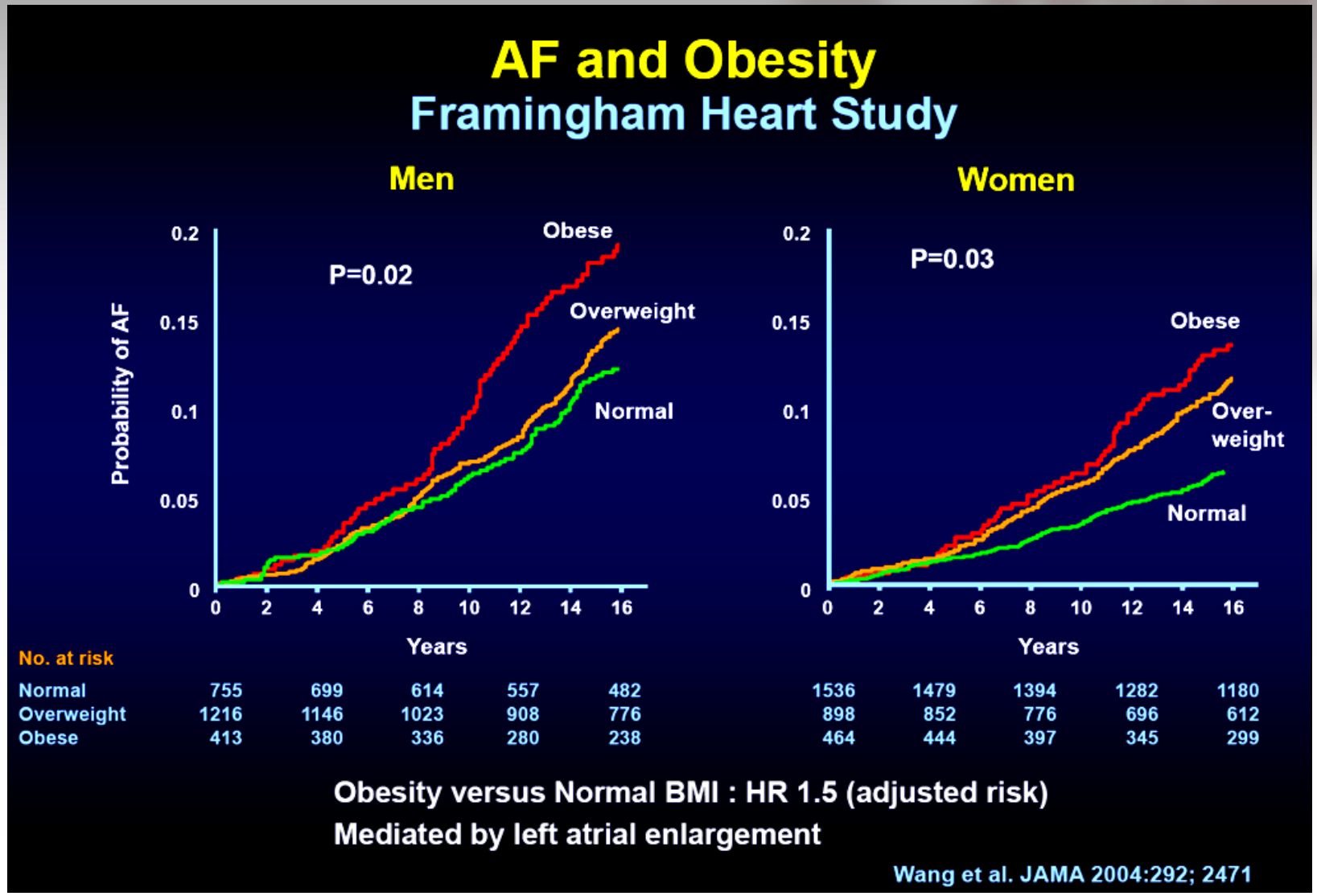
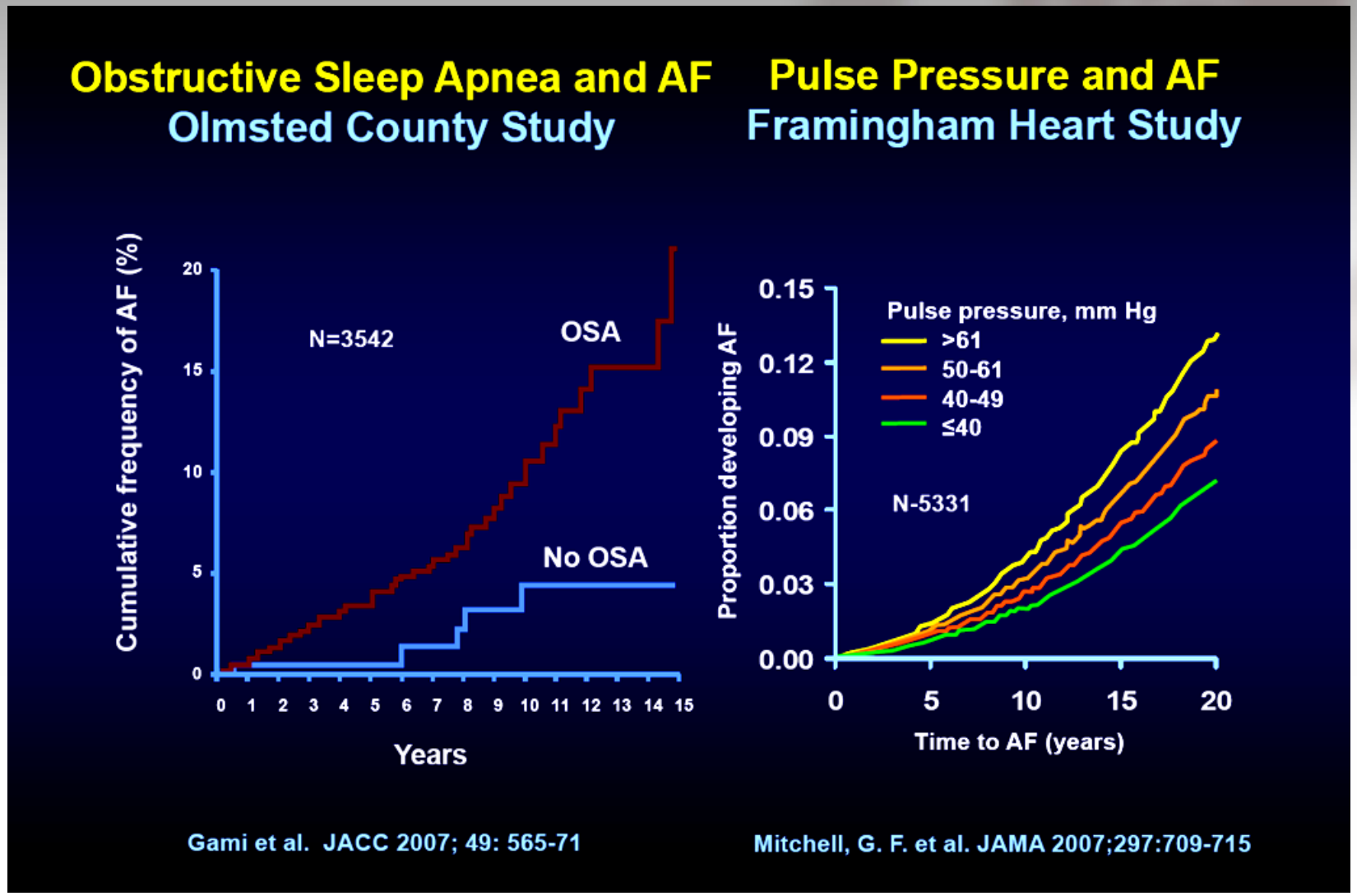
Conen D, et al. Circulation;119:2146-2152

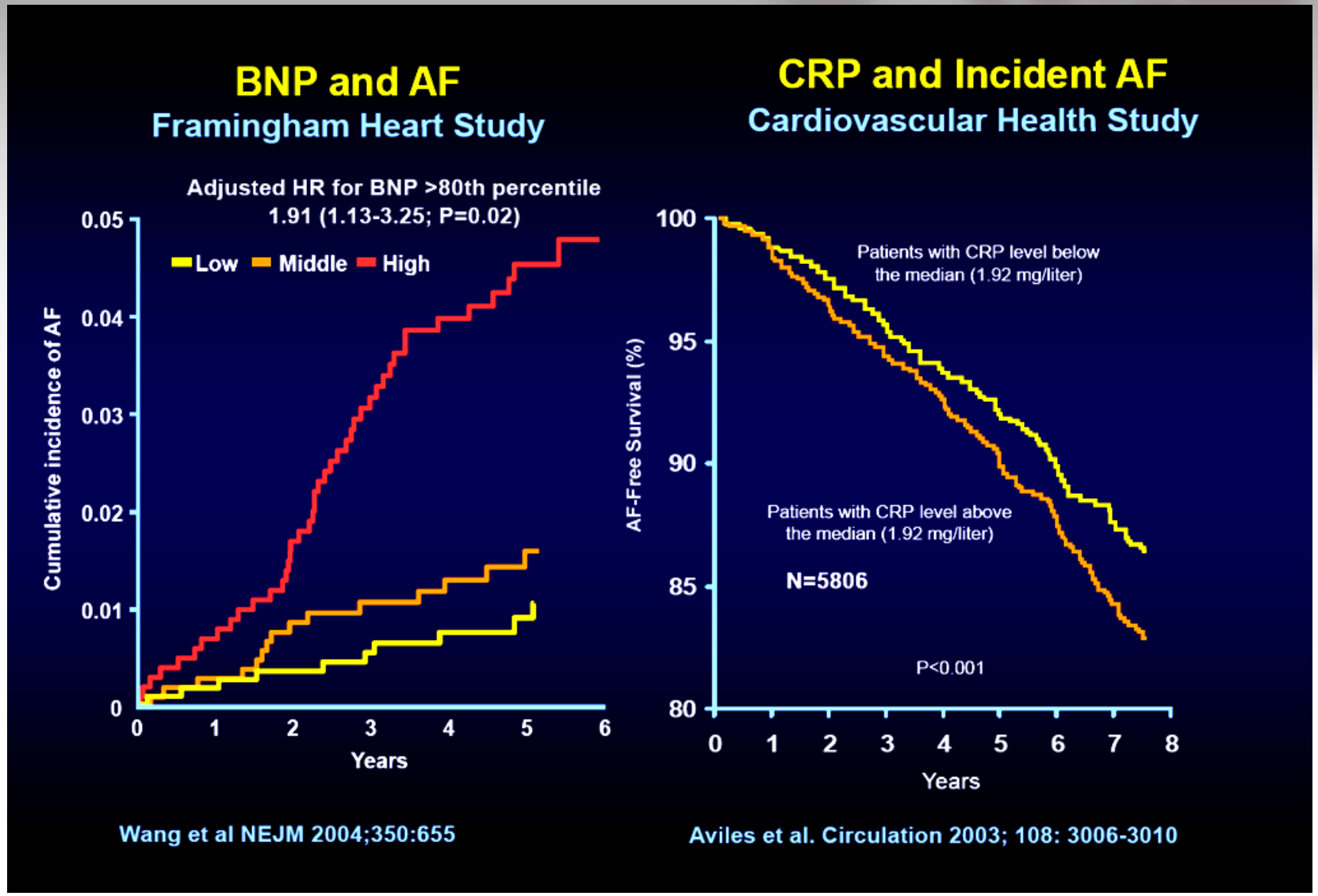
Incidence of AF



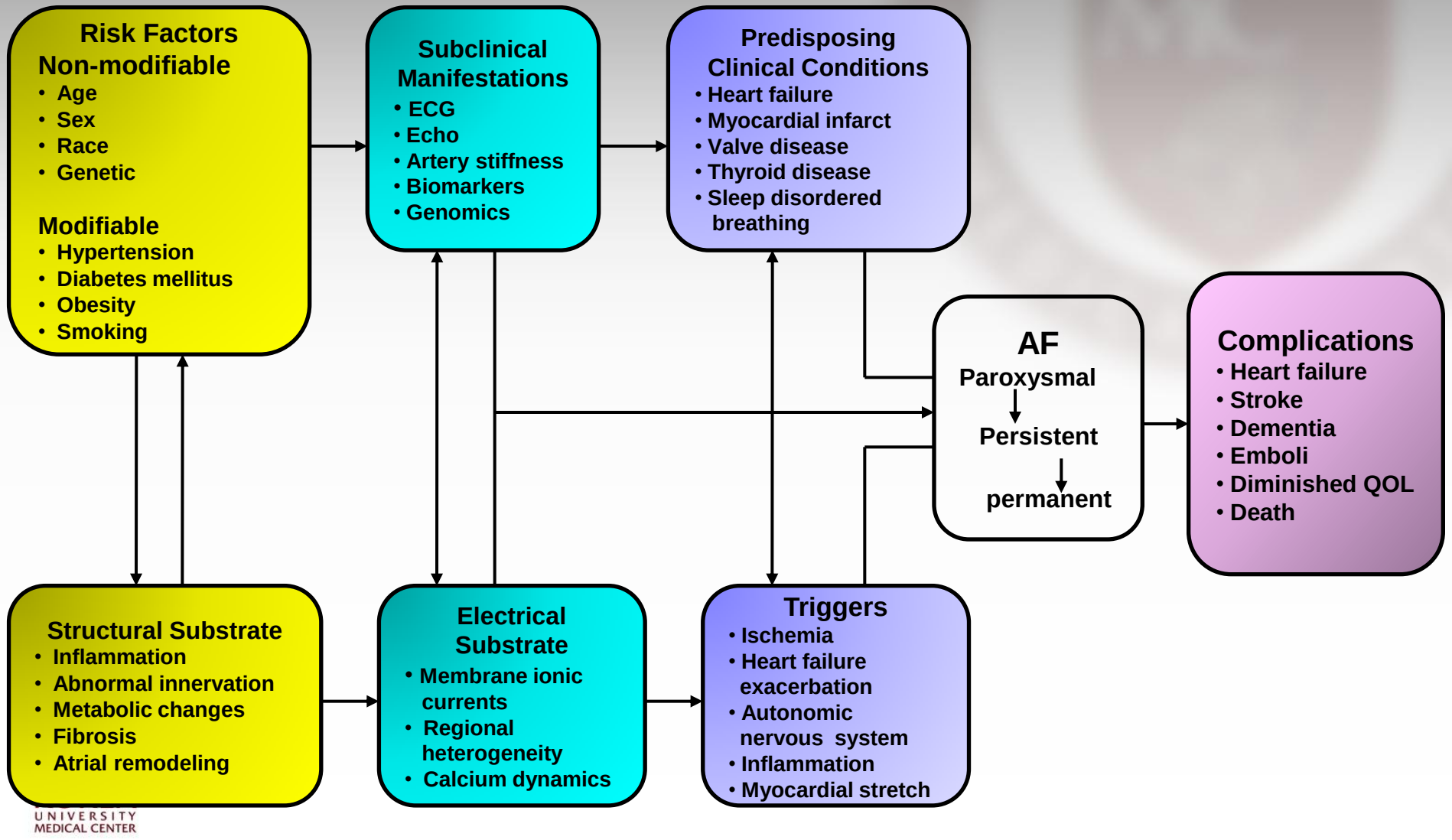
Incidence of AF



Incidence of AF



AF Outcomes



Estimated Risk of AF

AF Risk Prediction		Enter Values Here
Risk Factor	**Units**	
Sex	male or female	f
Age	years	60
Body Mass Index	kg/m^2	29
Systolic Blood Pressure	mmHg	140
PR Interval	milliseconds	200
Treatment for Hypertension	yes (Y) or no (N)	Y
Significant Murmur	yes (Y) or no (N)	N
Prevalent Heart Failure	yes (Y) or no (N)	Y
Your 10-Year Risk		**28.10%**

http://www.framinghamheartstudy.org/risk/index.html
Schnabel *Lancet* 2009;373:739

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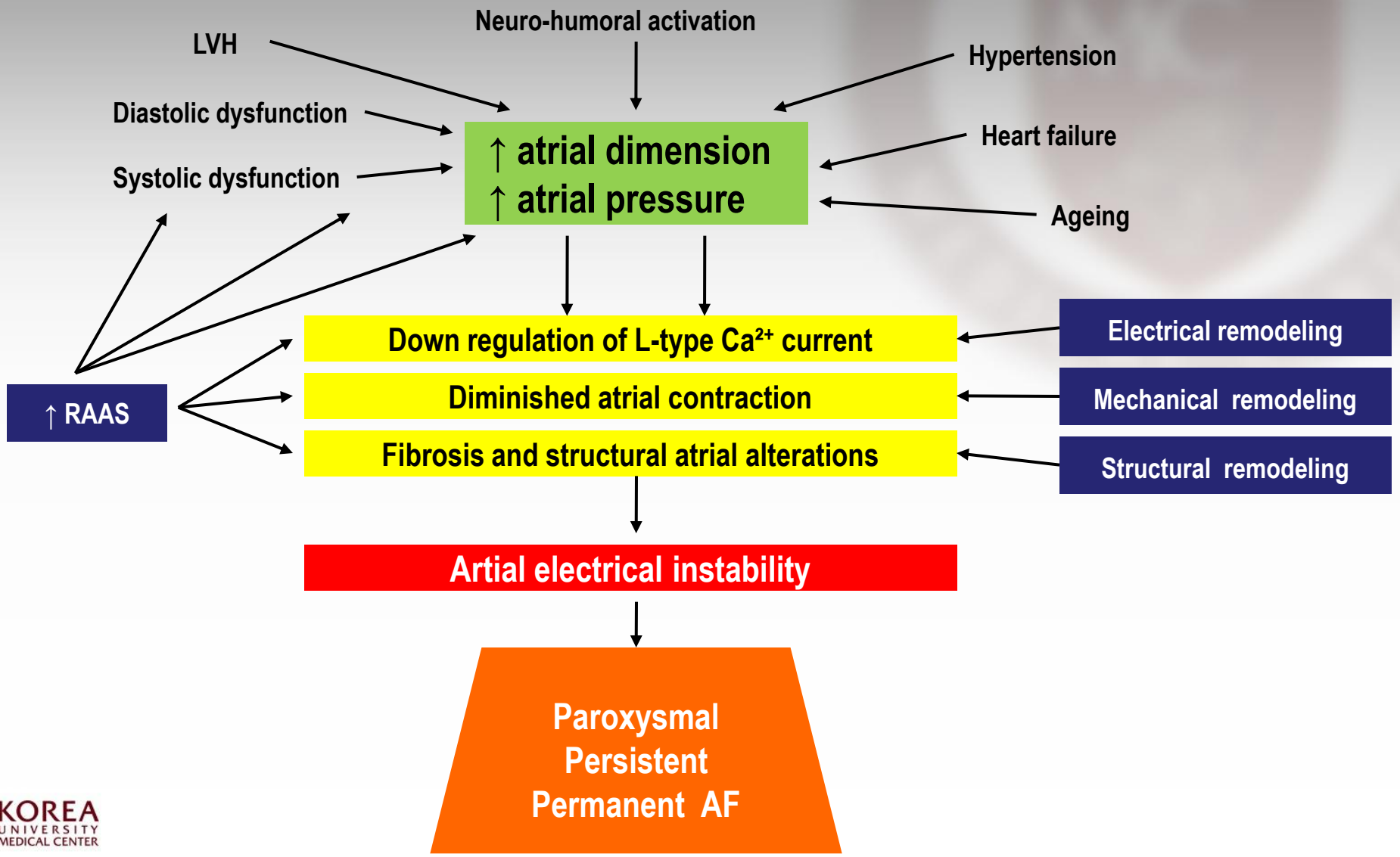
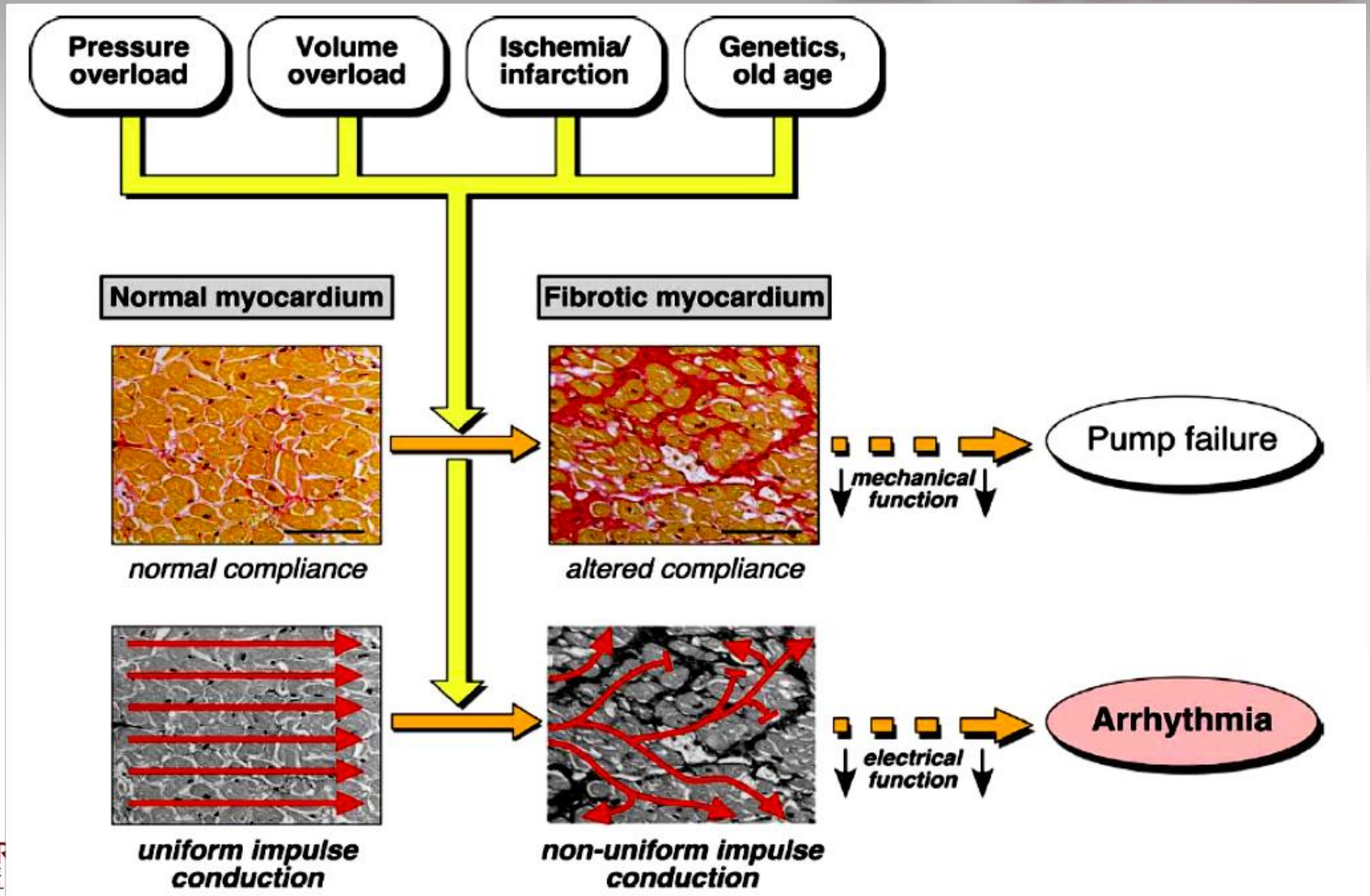
Pathophyiology

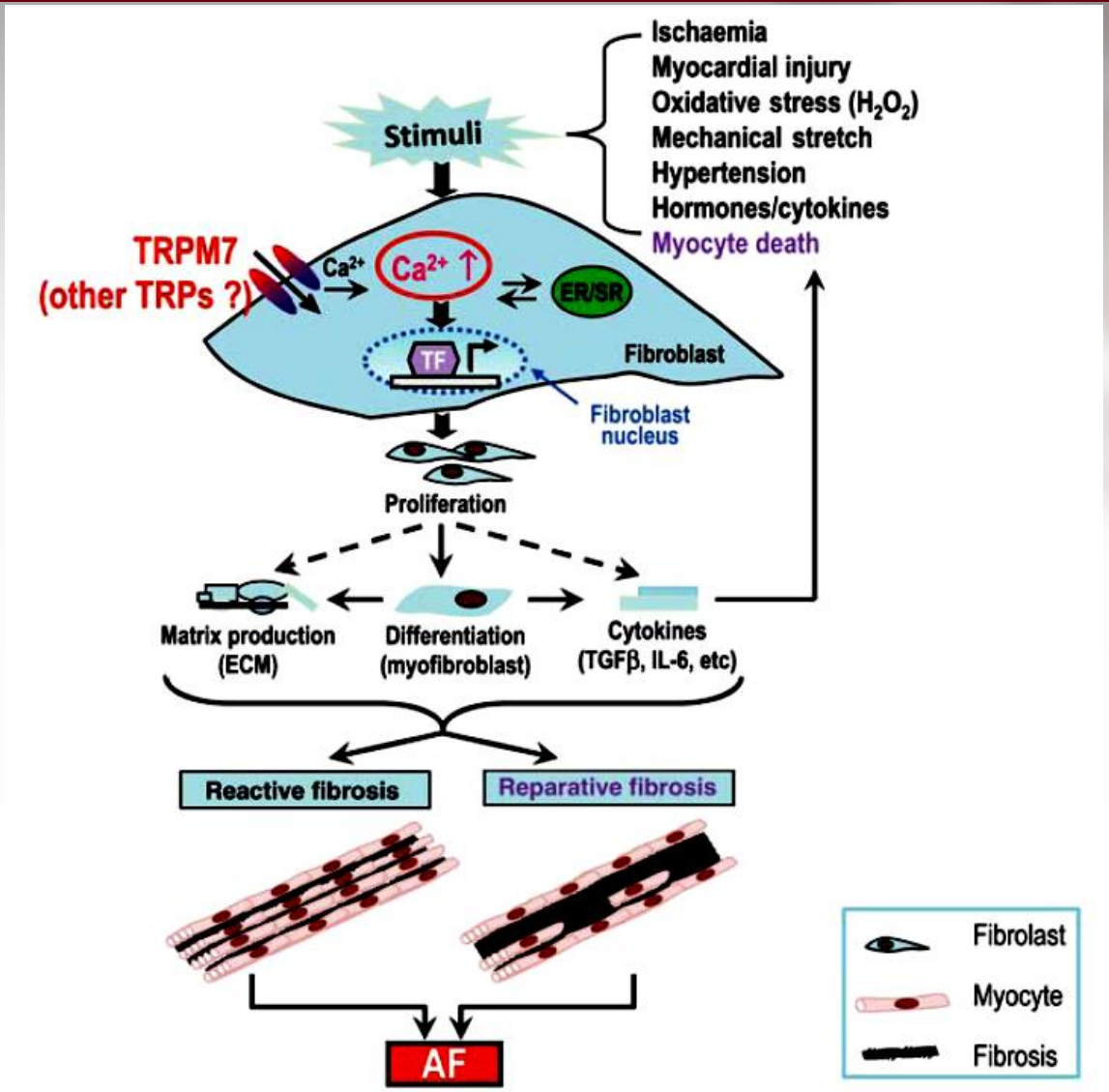


Pathophysiology



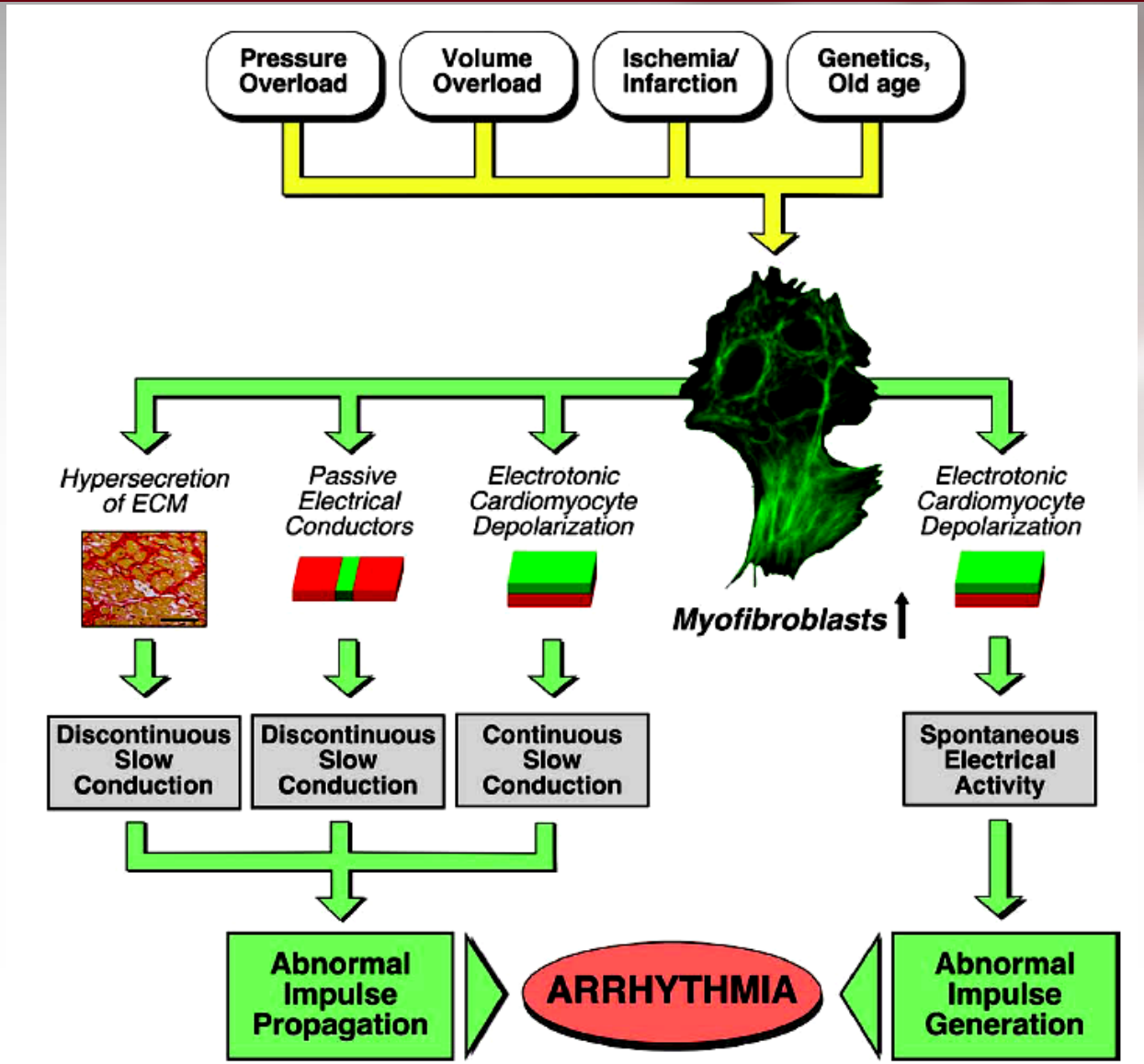
Rohr, et al. HR 2009;6:848-56

Myofibroblast



Yue L, et al. Cardiovasc Res. 2011;89:744–53

Myofibroblast



Mechanical Stretch

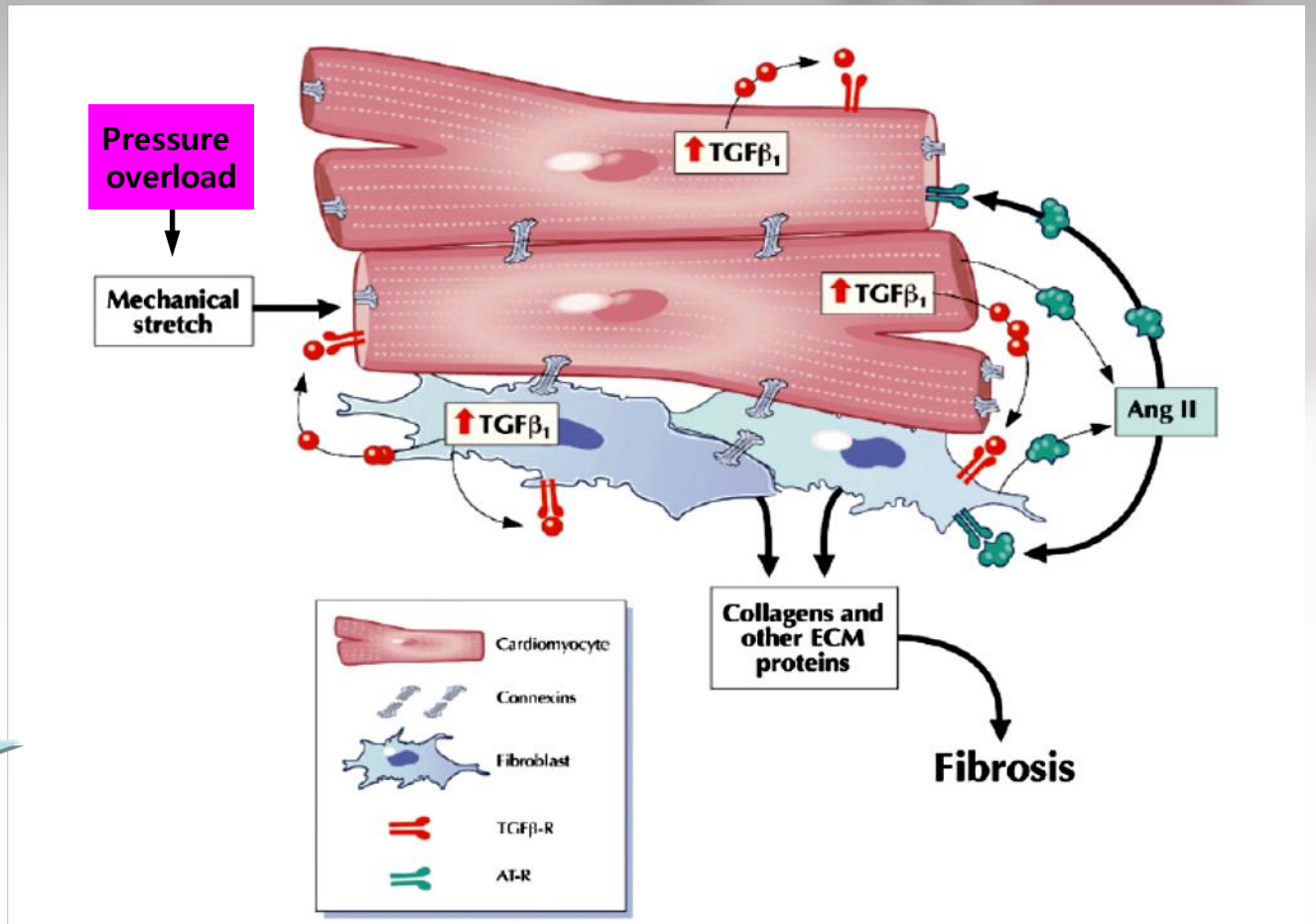
Pathologic Stimuli

Fibroblast

TGF-β1

Differentiate

Myofibroblast



Burnstein B. et al. JACC 2008;51:802–9

Diastolic Dysfunction

Table 2 Hazard ratio for incident atrial fibrillation according to echocardiographic parameters[a]

Parameter	Quantile/group	Adjusted HR	95% CI	P heterogeneity
Peak E velocity	1 (0.16–0.56 m/s)	1.0	–	<0.001
	2 (0.57–0.65 m/s)	0.983	0.807–1.197	
	3 (0.66–0.73 m/s)	1.095	0.900–1.334	
	4 (0.74–0.83 m/s)	1.172	0.961–1.429	
	5 (0.84–1.85 m/s)	1.549	1.275–1.883	
A wave VTI	1 (1–6 cm)	1.0	–	0.005
	2 (7–7 cm)	0.881	0.716–1.085	
	3 (8–9 cm)	0.742	0.622–0.886	
	4 (10–10 cm)	0.803	0.645–1.001	
	5 (11–80 cm)	0.946	0.772–1.160	
Left atrial diameter	1 (1.5–3.3 cm)	1.0	–	<0.001
	2 (3.3–3.7 cm)	1.002	0.818–1.228	
	3 (3.7–4.0 cm)	0.954	0.774–1.177	
	4 (4.0–4.4 cm)	1.176	0.961–1.440	
	5 (4.4–6.5 cm)	1.696	1.386–2.075	
LV systolic function	Normal	1.0	–	0.33
	Mildly depressed	1.227	0.937–1.605	
	Severely depressed	1.077	0.694–1.670	
LV chamber size	Normal	1.0	–	0.55
	Mildly dilated	1.072	0.839–1.368	
	Severely dilated	1.212	0.844–1.741	

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MA Rosenberg, et al. EHJ 2011 (in Press)

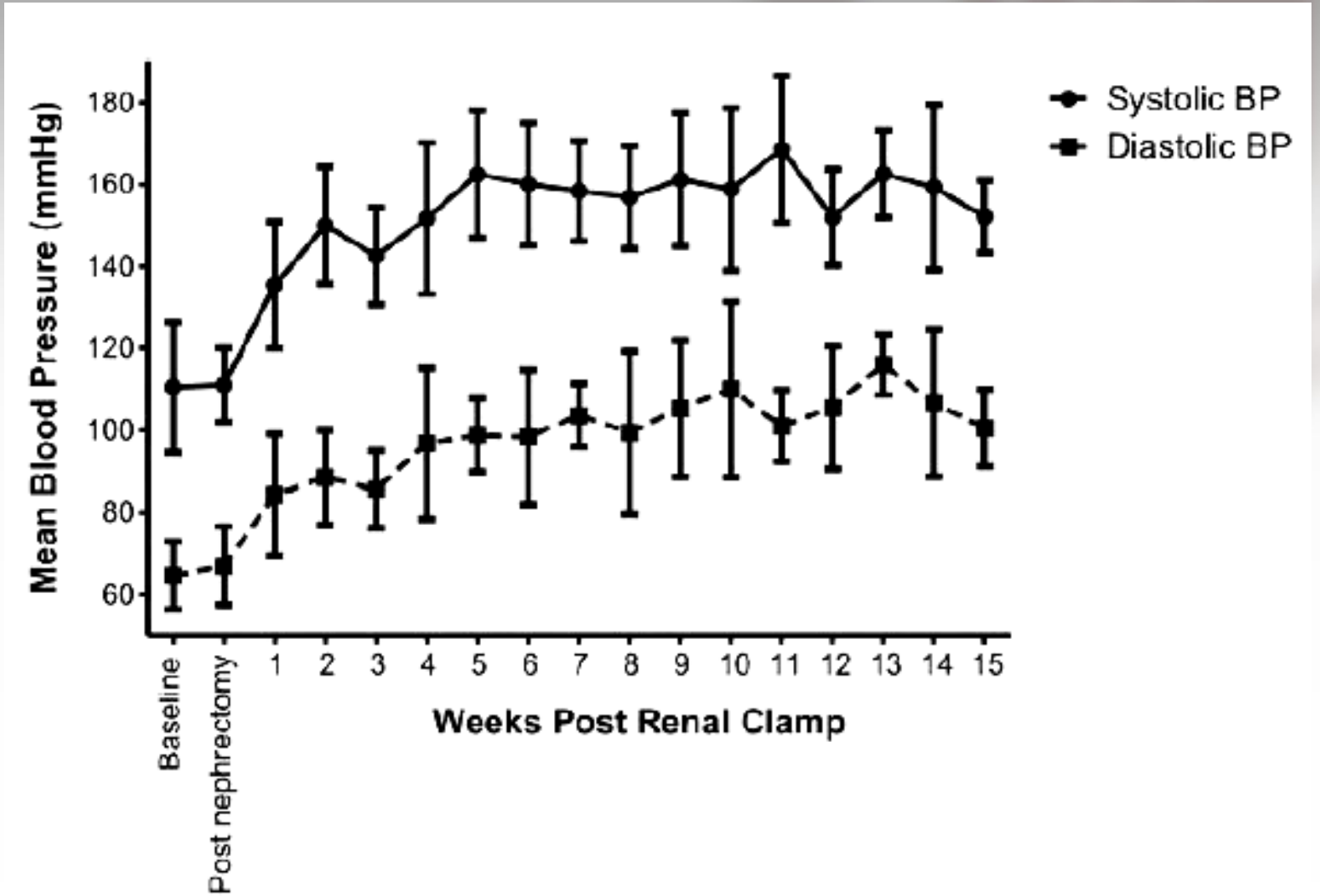
Diastolic Dysfunction

Baseline characteristics and co-morbidities according to left ventricular ejection fraction (LVEF)

Variable	HF-PEF Group (EF ≥45%; n = 1,291)	HF-REF Group (EF <45%; n = 699)	p Value
Age (years)	65 ± 12	62 ± 13	<0.001
Women	648 (50%)	193 (28%)	<0.001
Smoking (current and former)	388 (30%)	322 (46%)	<0.001
Obesity	499 (39%)	184 (27%)	<0.001
Diabetes mellitus	498 (39%)	267 (38%)	0.87
Hypercholesterolemia	622 (48%)	308 (44%)	0.08
Hypertension	1,008 (78%)	370 (53%)	<0.001
Coronary artery disease	587 (46%)	428 (62%)	<0.001
Myocardial infarction	272 (21%)	310 (44%)	<0.001
Valvular heart disease	412 (32%)	181 (26%)	0.005
Atrial fibrillation	372 (29%)	170 (24%)	0.03
Stroke or transient ischemic attack	81 (6%)	53 (8%)	0.27
Peripheral artery disease	101 (8%)	52 (8%)	0.77
Chronic obstructive pulmonary disease	183 (14%)	88 (13%)	0.33
Heart failure duration*			<0.001
<1 year	358 (37%)	177 (30%)	
1–5 years	445 (47%)	305 (51%)	
>5 years	152 (16%)	116 (19%)	
New York Heart Association class III/IV	383 (30%)	275 (39%)	<0.001
Echocardiographic data			
Left ventricular ejection fraction (%)	57 ± 10	32 ± 8	<0.001
Left ventricular end-diastolic diameter (mm)	50 ± 10	62 ± 9	<0.001
Left ventricular end-systolic diameter (mm)	38 ± 11	52 ± 9	<0.001
Posterior wall thickness (mm)	12 ± 3	10 ± 2	<0.001
Interventricular septum thickness (mm)	12 ± 3	10 ± 3	<0.001
Relative wall thickness >0.44†	557 (53%)	62 (11%)	<0.001
Left ventricular hypertrophy‡	588 (58%)	357 (69%)	<0.001
Left atrium diameter (mm)	43 ± 8	45 ± 8	<0.001
Doppler data (E/A ratio)§	1.0 ± 0.6	1.5 ± 0.9	<0.001

Magana-Serrano JA, et al. Am J Cardiol. 2011;108(9):1289-96

One Kidney-One Clip Model



Lau DH, et al. HR 2010;7:1282-1290

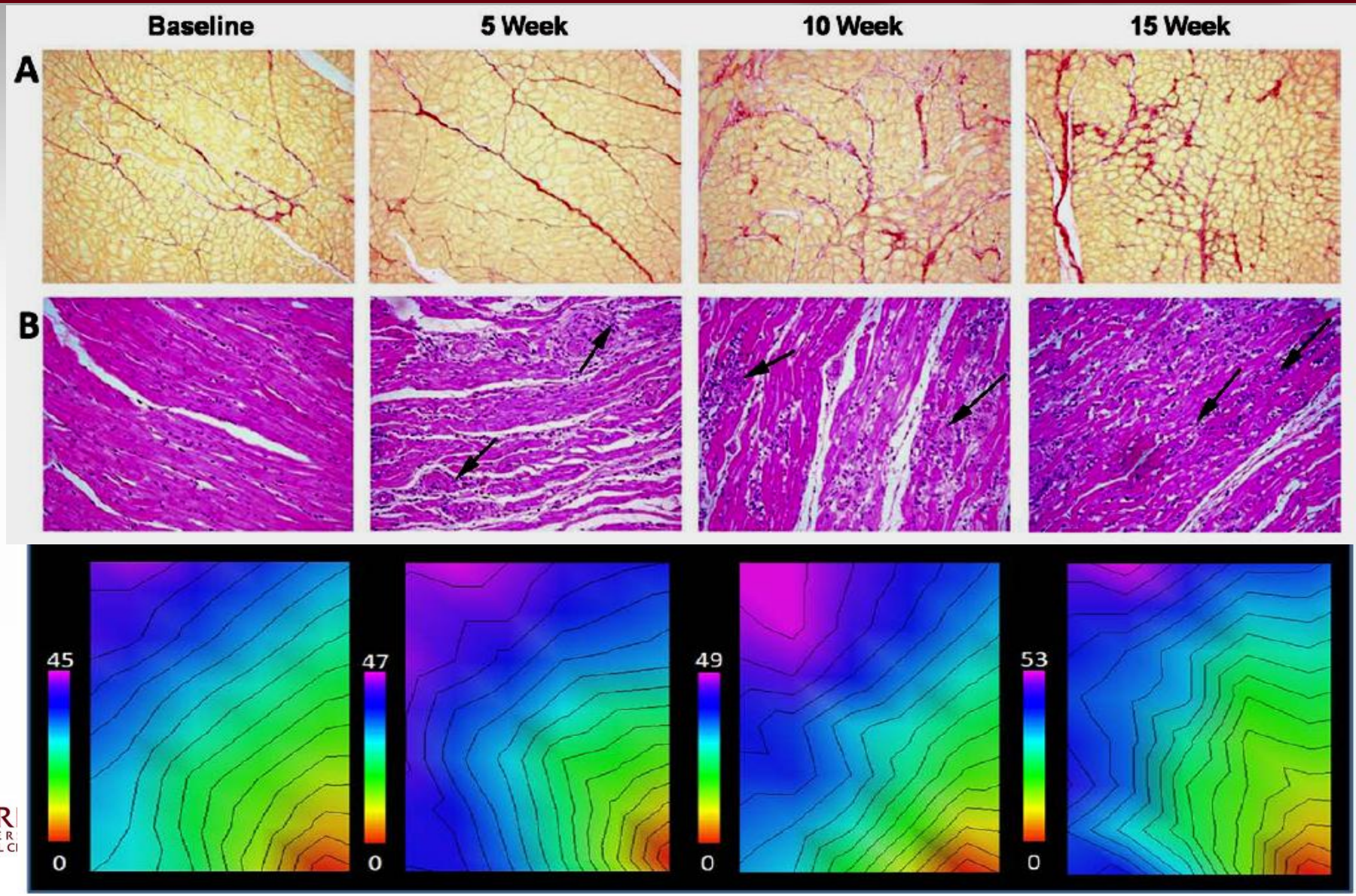
One Kidney-One Clip Model

Table 1 Anatomic and functional characteristics

	Baseline (n = 5)	5 Weeks (n = 5)	10 Weeks (n = 5)	15 Weeks (n = 5)	*P* value
Pathology					
LA weight (g)	21.4 ± 4.3	27.2 ± 7.6	34.9 ± 3.8	29.9 ± 5.2	.003
RA weight (g)	15.7 ± 3.4	18.7 ± 5.1	20.6 ± 4.2	19.5 ± 2.5	.003
IVS weight (g)	42.4 ± 1.2	46.8 ± 3.6	51.0 ± 7.5	56.5 ± 5.4	.03
LV weight (g)	98.1 ± 7.9	101.4 ± 10.5	112.5 ± 20.7	118.2 ± 14.7	.02
IVS (mm)	12.1 ± 0.7	16.2 ± 0.8	15.8 ± 0.3	16.5 ± 1.4	.005
PW (mm)	9.2 ± 1.0	10.7 ± 0.8	12.5 ± 0.5	11.9 ± 1.3	.002
Cardiac Magnetic Resonance Imaging					
LA EDV (mL)	24.9 ± 3.3	35.6 ± 3.9	38.9 ± 11.6	38.9 ± 5.5	.02
LA EF (%)	33.4 ± 2.9	30.9 ± 4.2	29.3 ± 1.6	28.3 ± 0.8	<.05
LV EDV (mL)	84.6 ± 5.6	97.0 ± 16.7	99.5 ± 20.0	96.3 ± 6.8	NS
LV EF (%)	46.3 ± 3.8	43.7 ± 6.6	42.6 ± 4.2	42.9 ± 5.1	NS

EDV = end-diastolic volume; EF = ejection fraction; IVS = interventricular septum; LA = left atrial; LV = left ventricular; PW = posterior left ventricular wall; RA = right atrial.

One Kidney-One Clip Model



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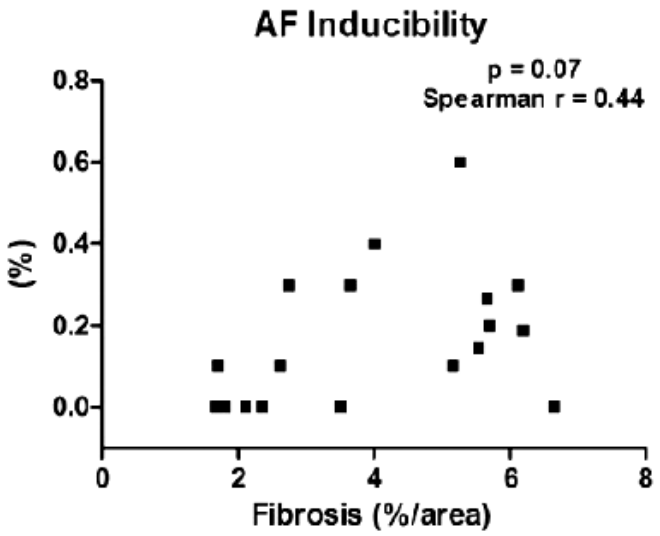
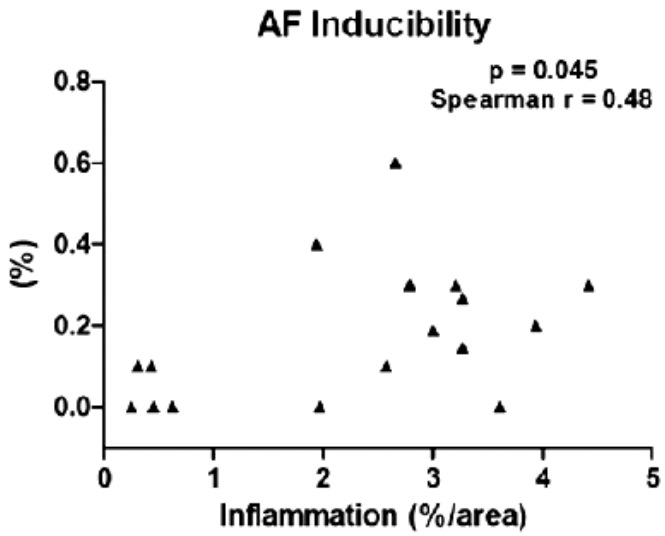
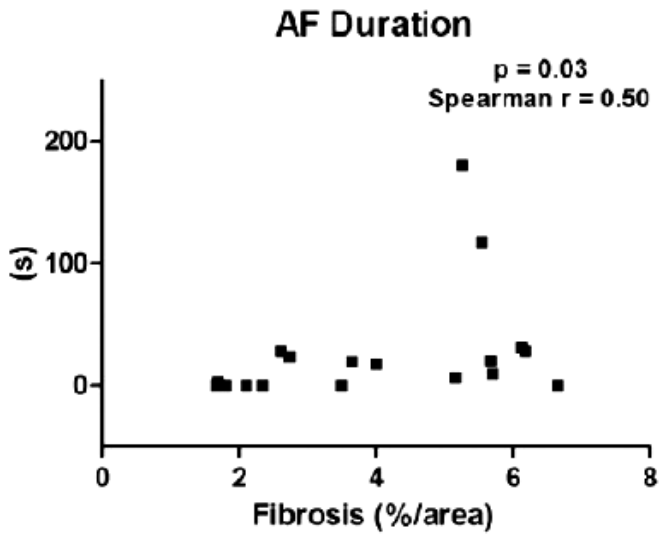
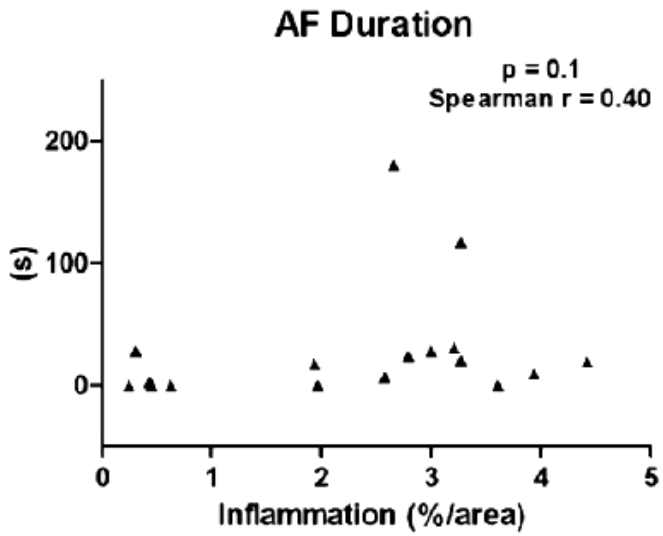






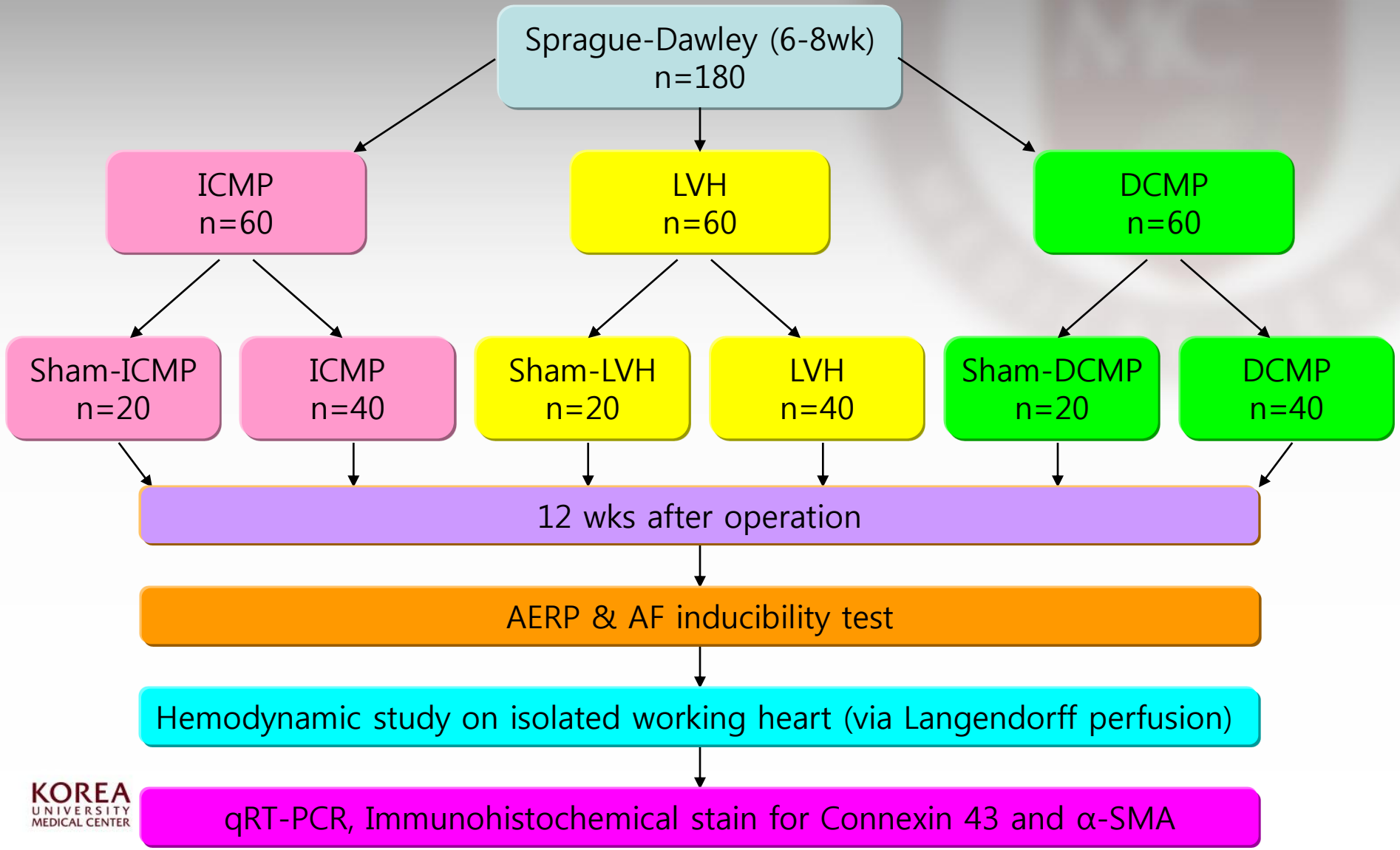


Atrial Remodeling and the Substrate for Atrial Fibrillation in Different Experimental Rat Hearts

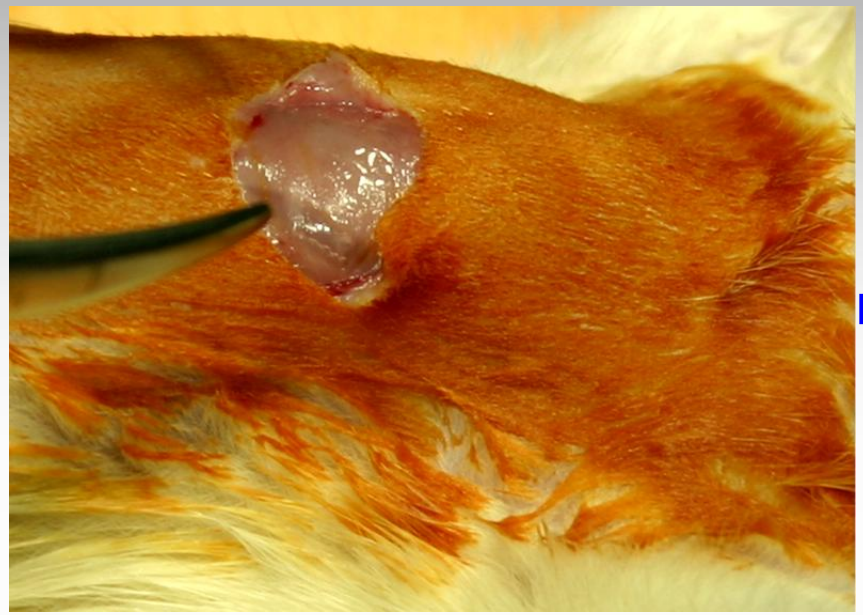
Korea University Cardiovascular Center

Hong Euy Lim / Seung Yong Shin /Young-Hoon Kim, M.D., Ph.D.

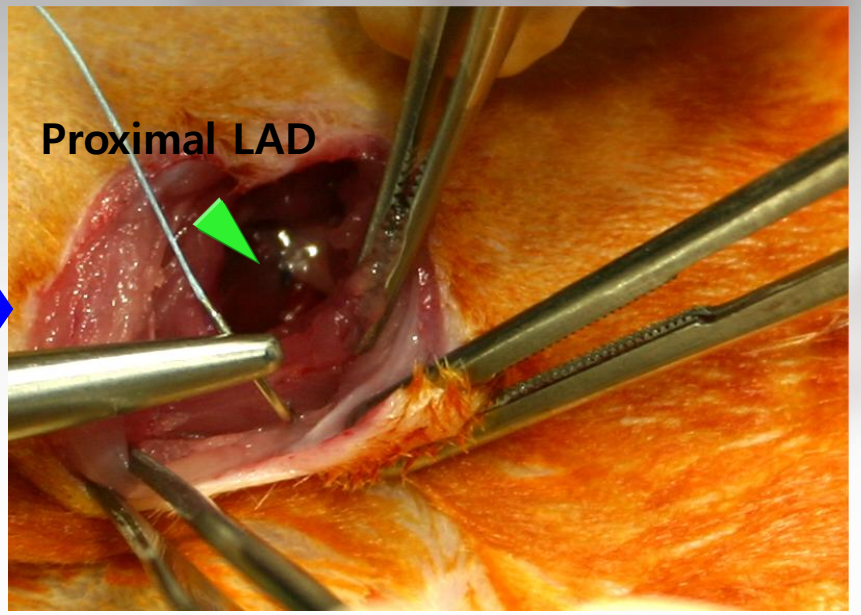
Method


Sprague-Dawley (6-8wk)
n=180
ICMP
n=60
LVH
n=60
DCMP
n=60
Sham-ICMP
n=20
ICMP
n=40
Sham-LVH
n=20
LVH
n=40
Sham-DCMP
n=20
DCMP
n=40
12 wks after operation
AERP & AF inducibility test
Hemodynamic study on isolated working heart (via Langendorff perfusion)
qRT-PCR, Immunohistochemical stain for Connexin 43 and α-SMA

Ischemic Cardiomyopathy (ICMP)

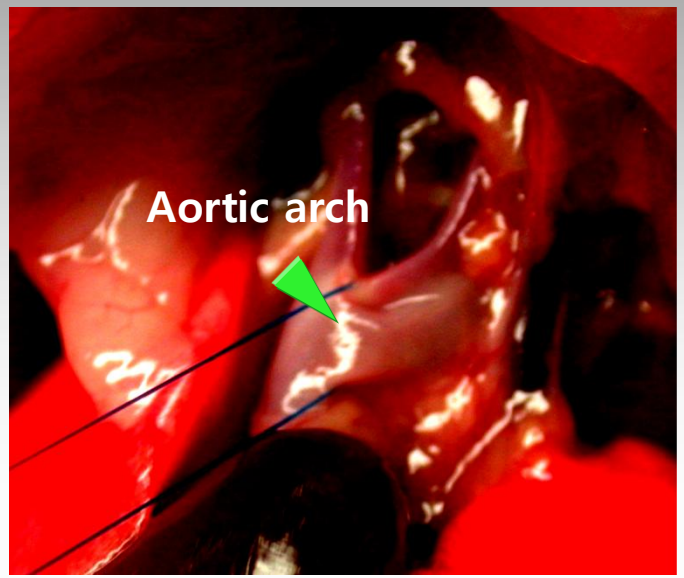


Left anterior thoracotomy

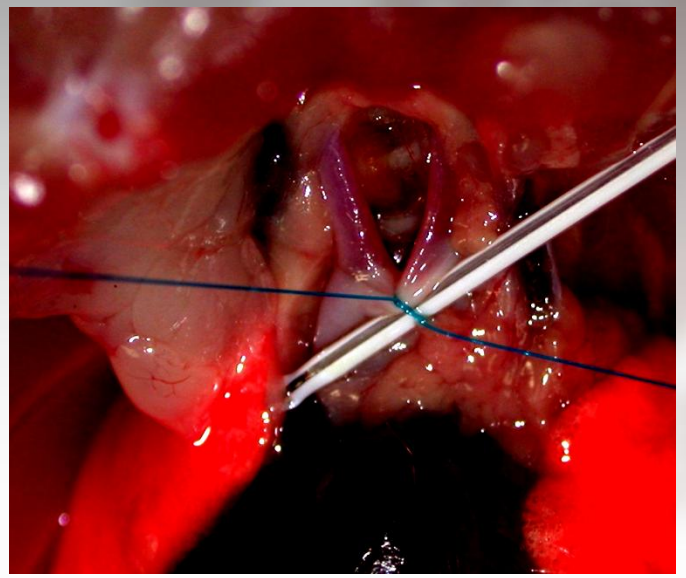


Proximal LAD was ligated

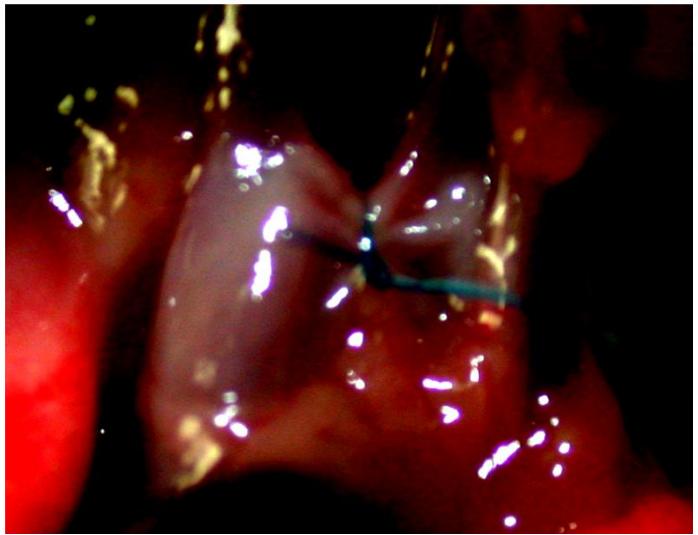
Left Ventricular Hypertrophy (LVH)



Midline cervical incision

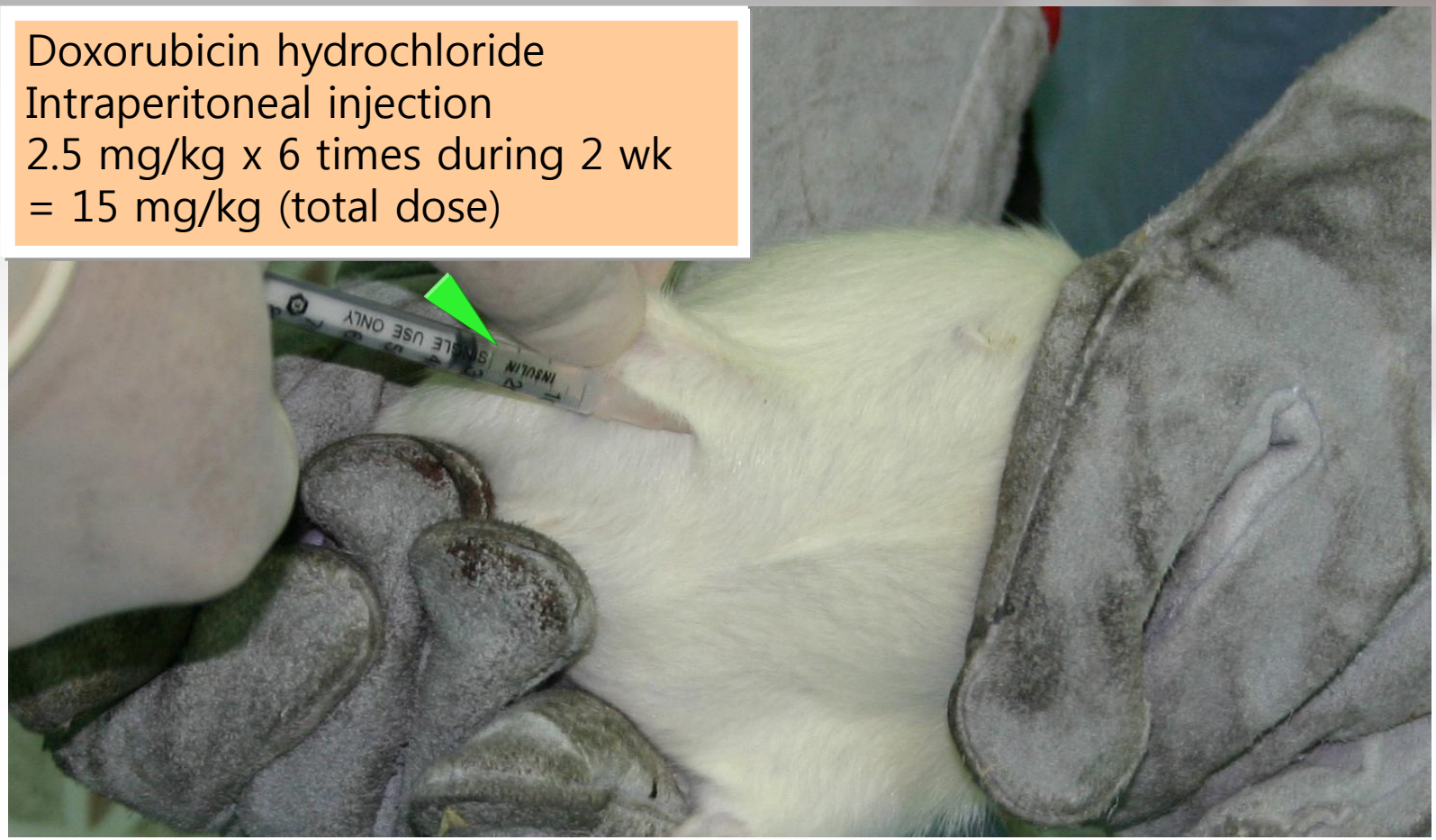


Constriction of aortic arch, (0.8 mm)

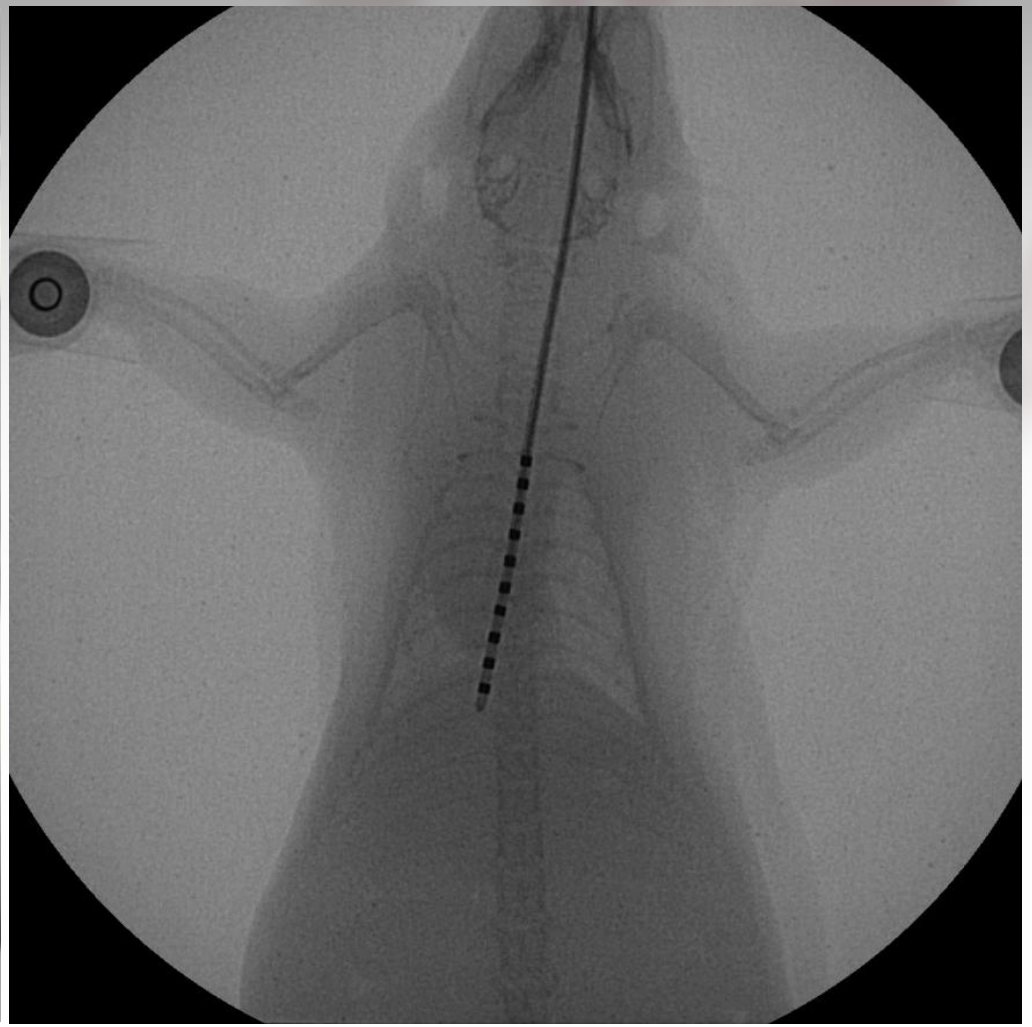


Dilated Cardiomyopathy (DCMP)

Doxorubicin hydrochloride
Intraperitoneal injection
2.5 mg/kg x 6 times during 2 wk
= 15 mg/kg (total dose)

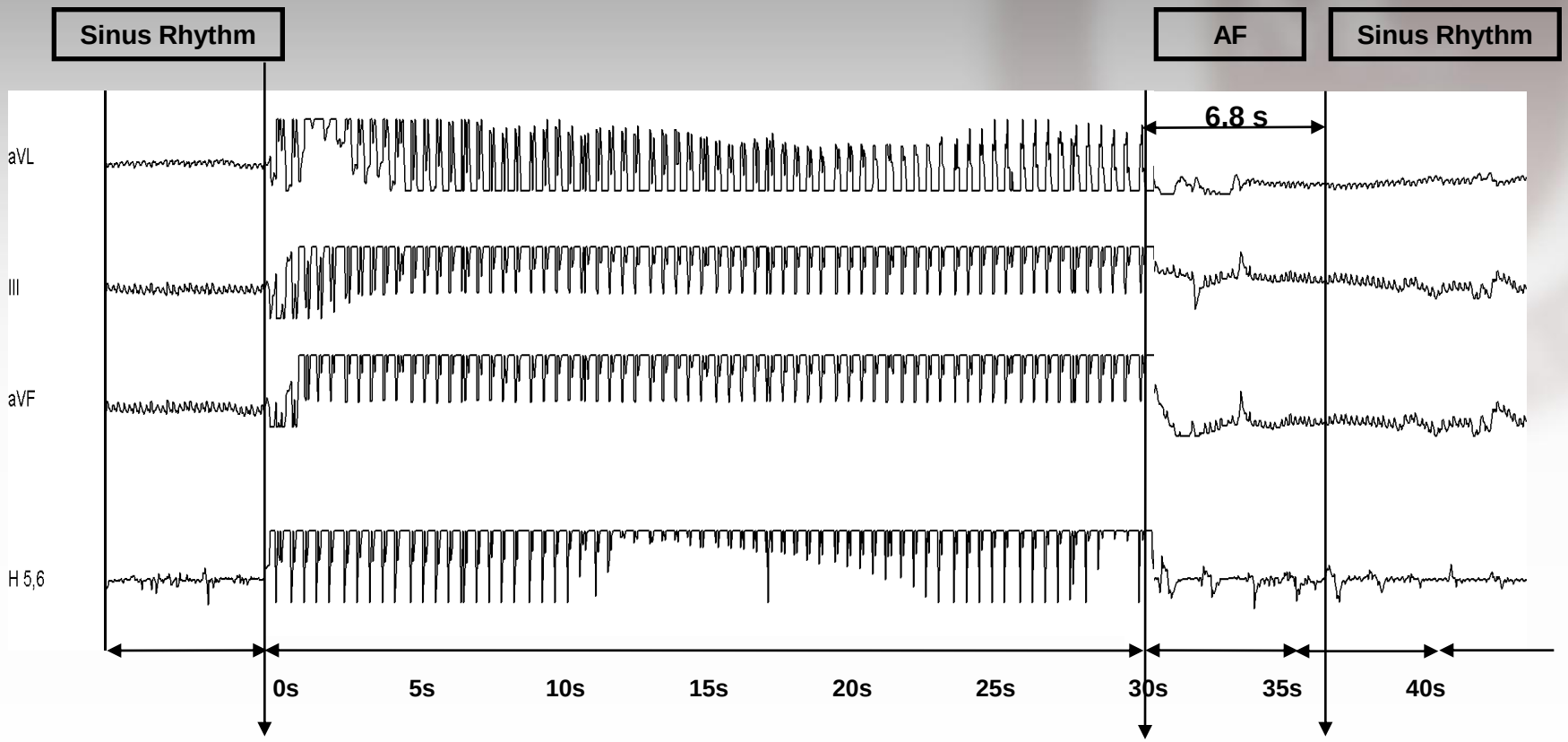


Transesophageal Pacing



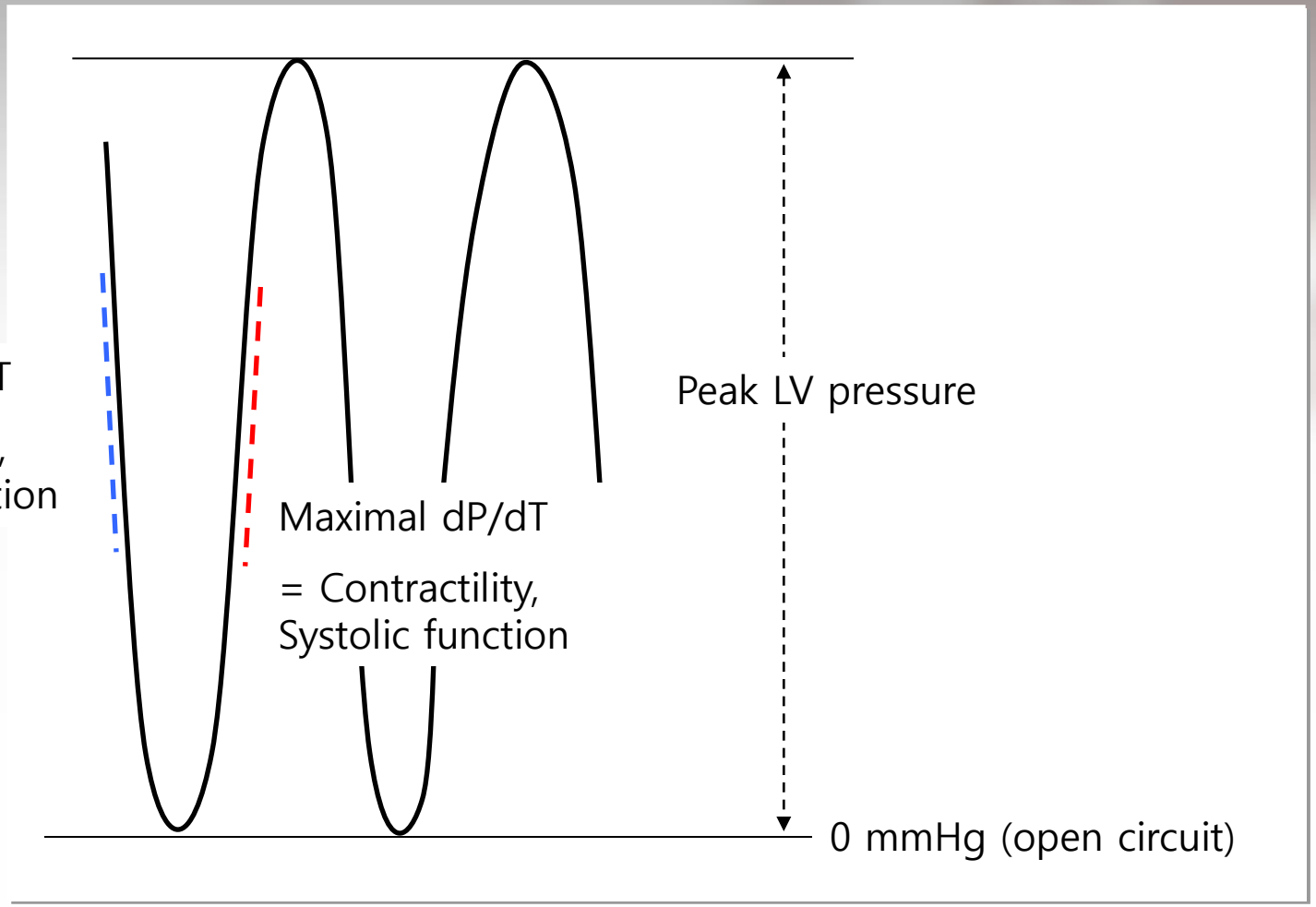
6 Fr. decapolar electrode catheter was inserted into the esophagus

Inducibility of AF



* Repeat 5 times in each rat, AF inducibility and duration were measured.

Hemodynamic Parameters



Quantitative RT-PCR

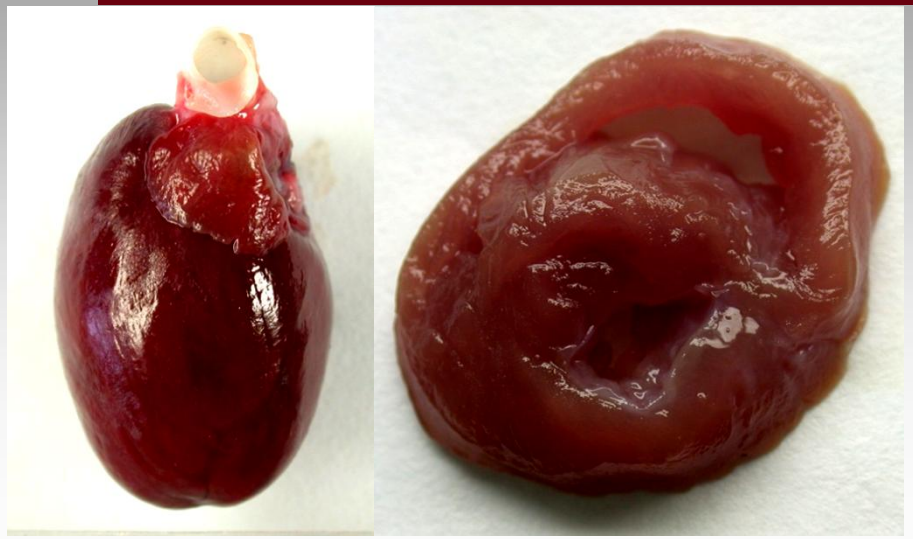
- Machine: LC 480 (Roche® Diagnostics, Germany)
- Material: Atrial tissue homogenates
- Target gene: Cx43, α-SMA (β-Actin for housekeeping gene)

Target	Primer	Length	Position	Sequence
Cx43	Left	23	95-117	agcctgaactctcatttttcctt
	Right	18	183-200	ccatgtctgggcacctct
α-SMA	Left	21	453-473	tgccatgtatgtggctattca
	Right	21	493-513	accagttgtacgtccagaagc
β-Actin	Left	18	398-415	aggcccctctgaacccta
	Right	20	448-467	ggggtgttgaaggtctcaaa

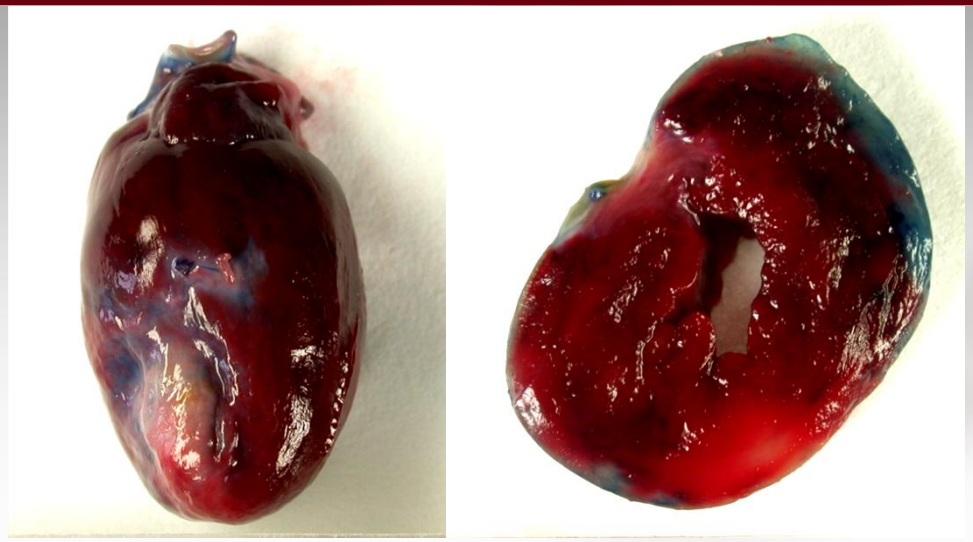
Histology

- Tissue fixation: 4% neutral buffered formalin for 1 hr
- Tissue storage: 70% alcohol
- Paraffin block: cut at 4 μ m thickness
- Masson's trichrome stain for fibrosis
- Antibodies (Ab) for immunohistochemical (IHC) stain
  - α-SMA: Ready-to-Use, clone 1A4, Dako
  - Cx43: 1:1000, polyclone, Abfrontier
  - 2ndary Ab: REAL™EnVision™/HRP, Dako
- Analysis: Image J software (Ver. 1.44p, NIH, USA)

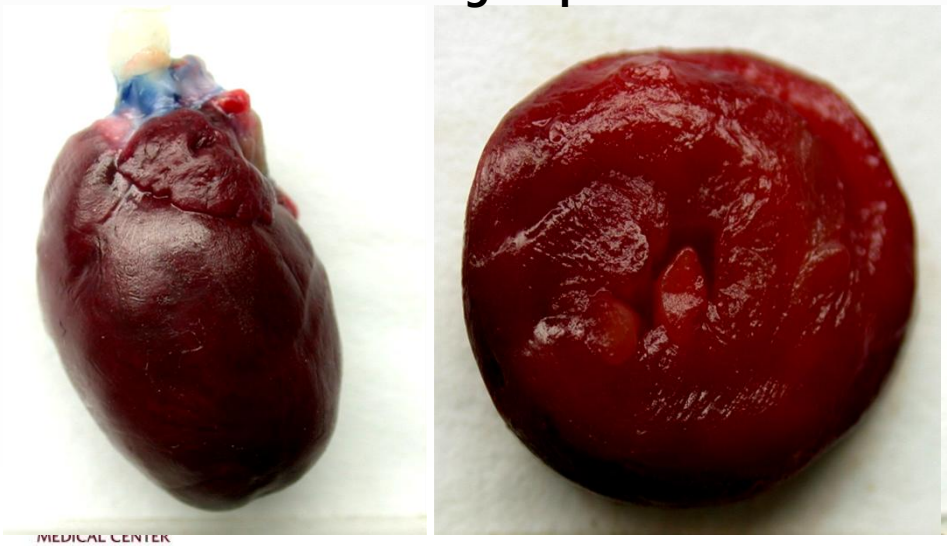
Experimental Models



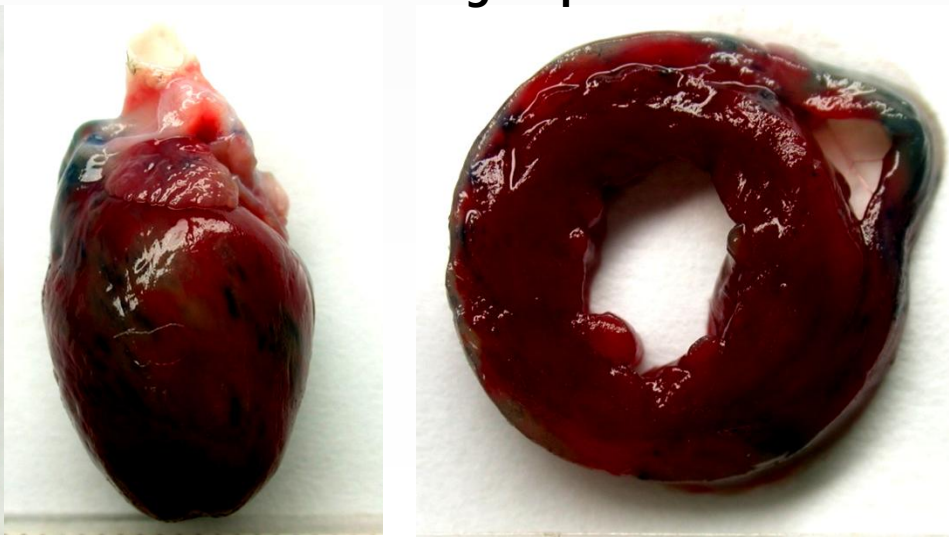
Sham group



ICMP group



LVH group

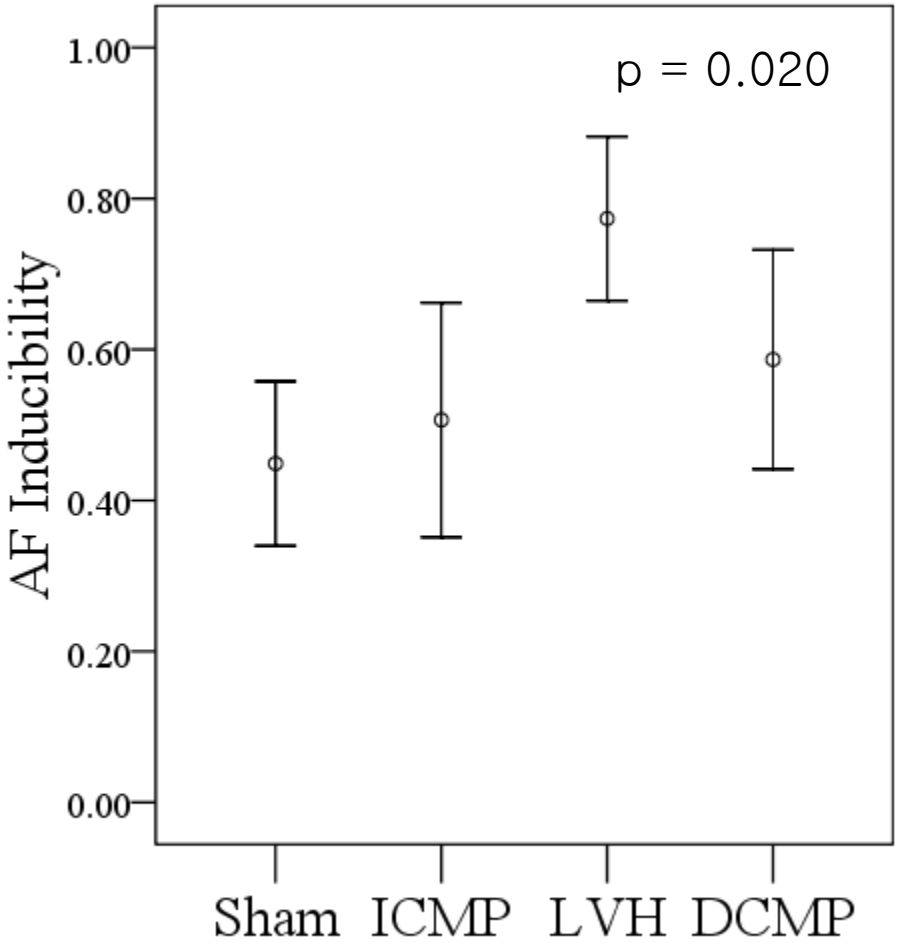


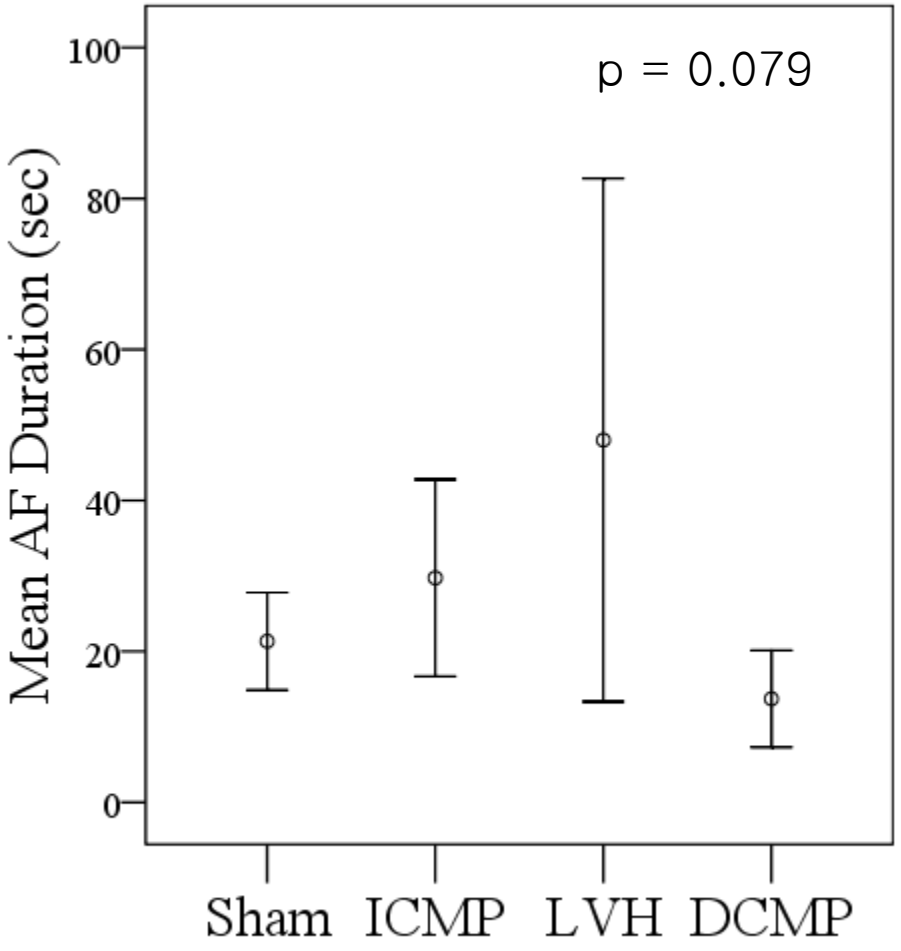
DCMP group

Results

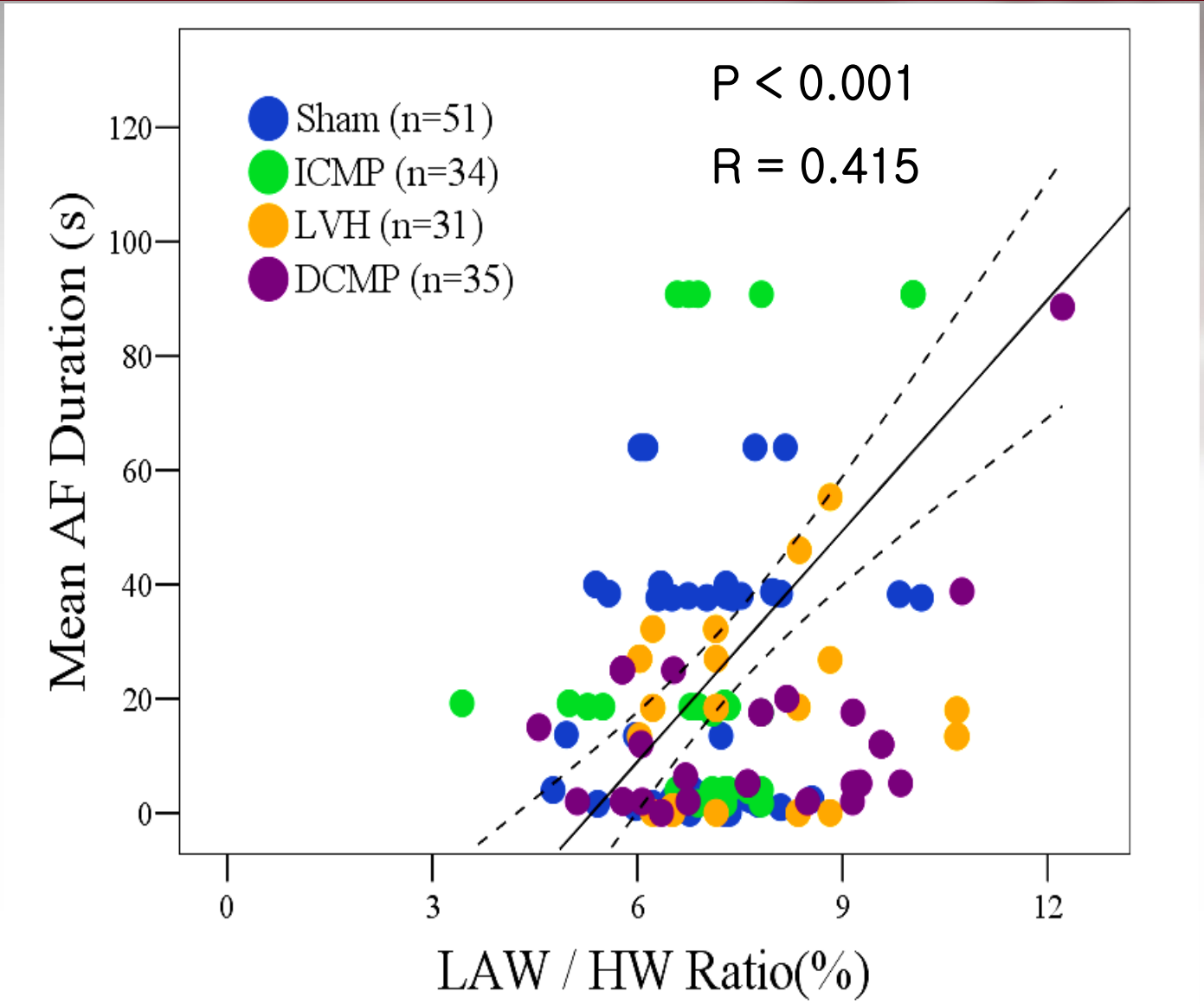
Variables	ICMP group		LVH group		DCMP group	
	Sham-ICMP (n = 17)	ICMP (n = 34)	Sham-LVH (n = 16)	LVH (n = 31)	Sham-DCMP (n = 18)	DCMP (n = 35)
Heart rate (bpm)	225.3 ± 18.4†	211.0 ± 10.7†	227.1 ± 21.8†	220.8 ± 11.2†	230.2 ± 20.1†	207.1 ± 8.8†
SBP (mmHg)	139.9 ± 5.2	140.4 ± 5.3	141.6 ± 5.7	140.5 ± 5.4	141.2 ± 5.5	138.7 ± 4.9
DBP (mmHg)	105.3 ± 4.0	105.6 ± 4.1	106.3 ± 4.8	105.7 ± 4.3	106.1 ± 4.6	104.6 ± 4.1
Body weight (g)	436.9 ± 40.5	448.1 ± 43.9	441.7 ± 38.3	434.7 ± 31.8	442.1 ± 38.1	448.7 ± 81.4
Heart weight (g)	1.84 ± 0.16	1.82 ± 0.11	1.81 ± 0.18‡	1.92 ± 0.22‡	1.81 ± 0.15‡	1.52 ± 0.17‡
HW / BW ratio	0.42 ± 0.02	0.41 ± 0.03	0.41 ± 0.03†	0.44 ± 0.04†	0.41 ± 0.02‡	0.37 ± 0.06‡
IVS (mm)	2.01 ± 0.14	1.91 ± 0.21	2.02 ± 0.17‡	2.45 ± 0.20‡	2.00 ± 0.17‡	1.54 ± 0.20‡
PW (mm)	2.04 ± 0.14	1.94 ± 0.20	2.02 ± 0.23‡	2.65 ± 0.40‡	2.07 ± 0.21‡	1.60 ± 0.16‡
LVID (mm)	3.85 ± 0.25	3.95 ± 0.46	3.89 ± 0.23‡	3.45 ± 0.21‡	3.84 ± 0.25	4.12 ± 0.44
LV mass (mg)	966.0 ± 38.7†	927.3 ± 72.9†	967.3 ± 33.5‡	1096.0 ± 114.2‡	967.3 ± 37.8‡	866.3 ± 66.3‡
RA mass (mg)	131.7 ± 25.7	120.0 ± 29.2	128.9 ± 32.4	114.7 ± 18.1	131.9 ± 27.0‡	119.1 ± 18.9‡
LA mass (mg)	129.6 ± 28.8	130.0 ± 27.1	125.4 ± 13.1‡	151.3 ± 37.5‡	127.5 ± 22.4†	115.3 ± 29.1†
LAW/HW ratio (%)	7.00 ± 1.20	7.15 ± 1.35	7.00 ± 0.97‡	7.89 ± 1.77‡	7.04 ± 1.16	7.62 ± 1.89
Electrophysiologic study						
AF Inducibility (%)	45.3 ± 38.1	50.7 ± 41.6	44.0 ± 35.6‡	77.3 ± 29.1‡	45.3 ± 37.4	58.7 ± 38.9
AF Duration (sec)	20.8 ± 23.6	29.7 ± 34.9	21.5 ± 21.2	48.0 ± 92.8	21.7 ± 21.1	13.7 ± 17.2
Hemodynamic study						
dP/dt_{max} (mmHg/s)	2657.0 ± 203.1‡	2343.0 ± 267.2‡	2686.0 ± 225.4	2527.7 ± 164.1	2675.0± 200.3‡	1522.6 ± 157.3‡
dP/dt_{min} (mmHg/s)	-1443.0 ± 301.0	-1328.7 ± 256.1	-1503.3 ± 351.0‡	-1011.3 ± 162.5‡	-1500.0 ± 337.5‡	-1032.5 ± 92.2‡
Peak LVP (mmHg)	144.7 ± 6.7‡	136.3 ± 6.6‡	144.3 ± 5.6‡	148.2 ± 7.2‡	145.3 ± 6.1‡	131.0 ± 7.9‡

Results - Electrophysiologic Study





LAW/HW Ratio vs. Mean AF Duration



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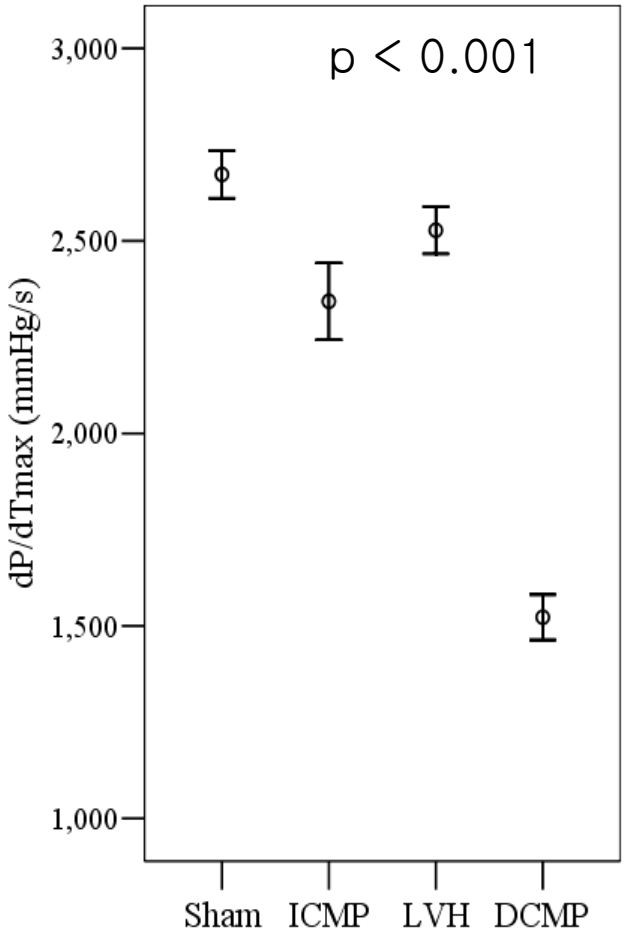
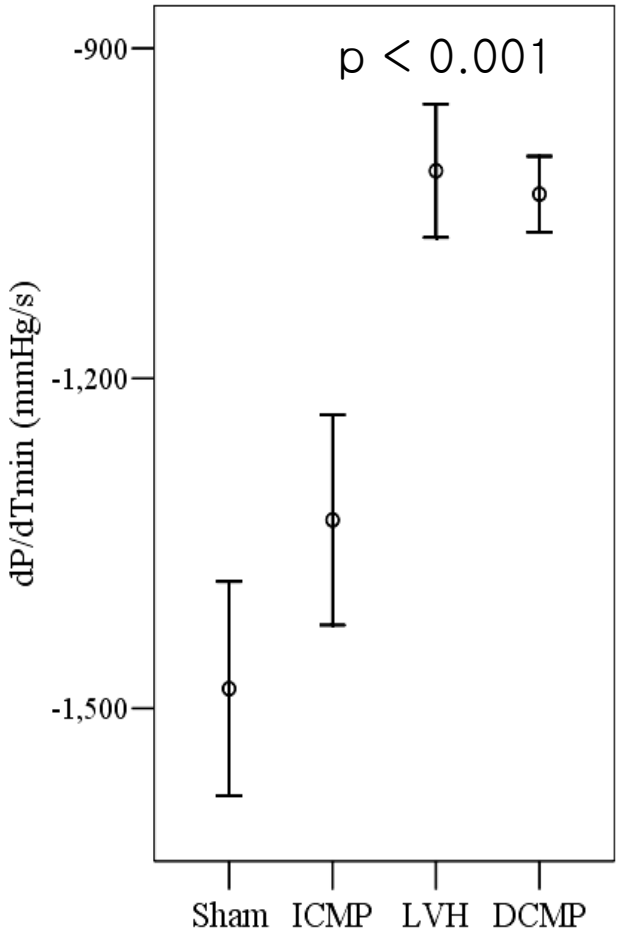
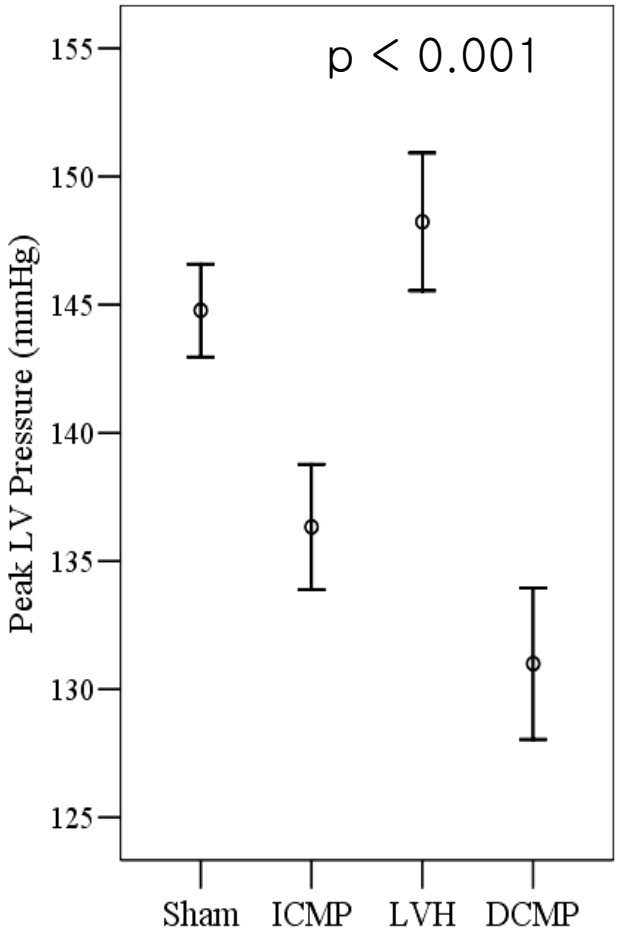
Results - Hemodynamic Study







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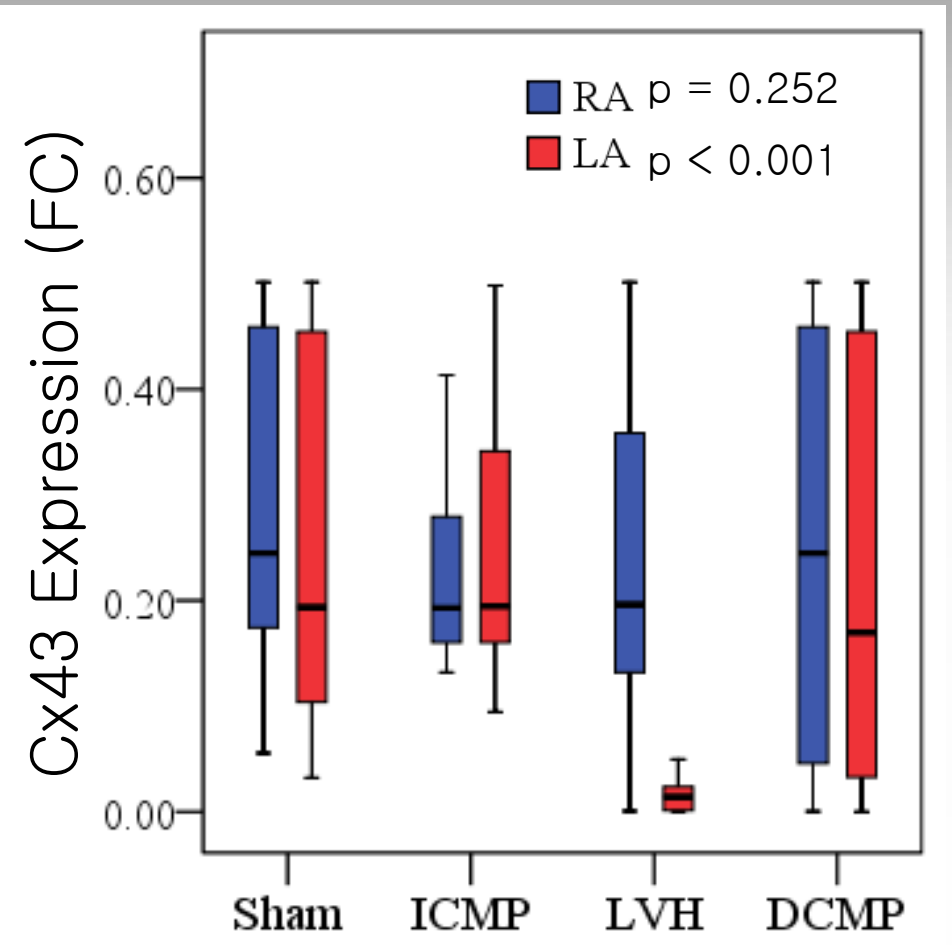
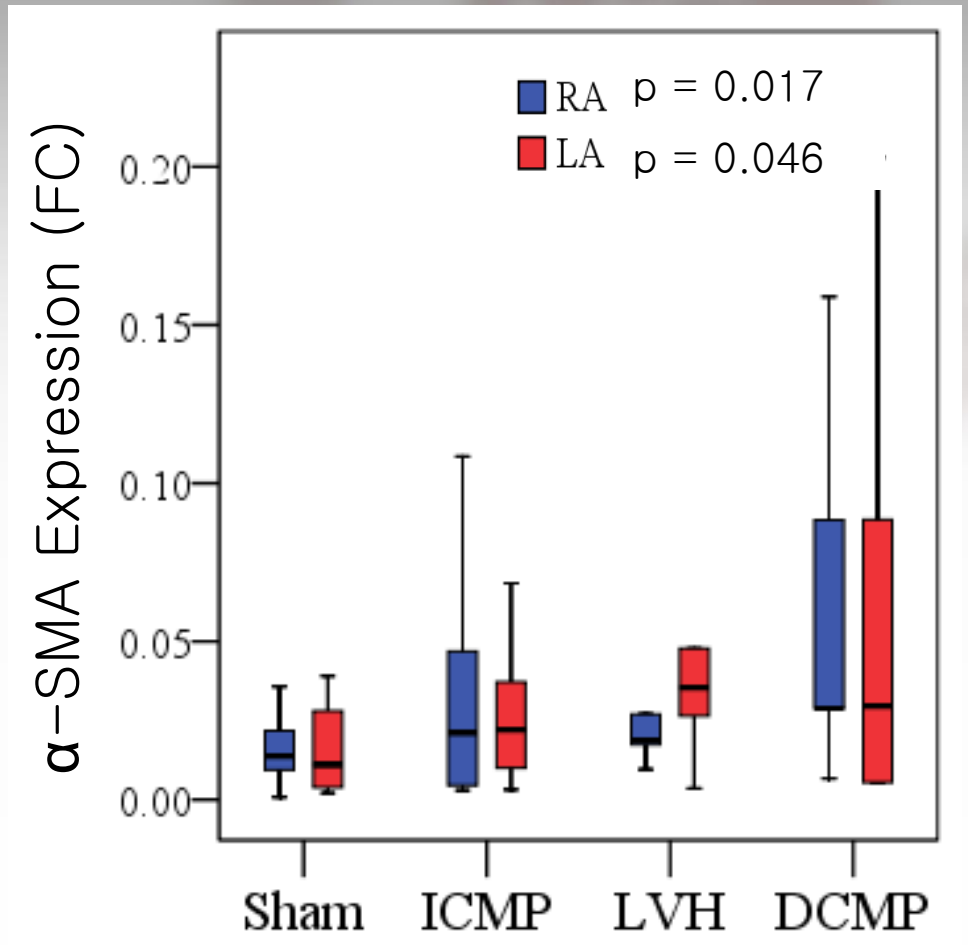
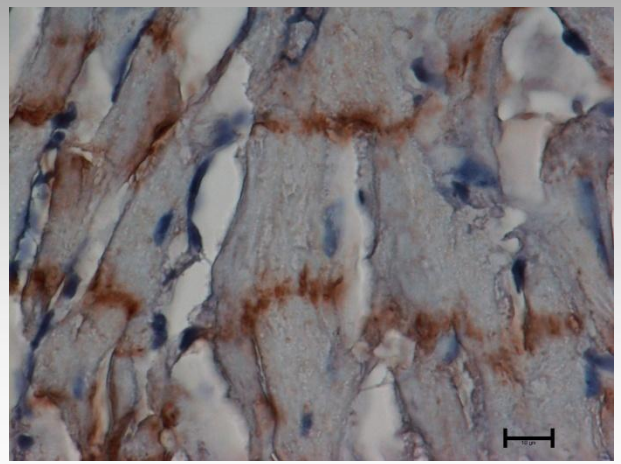
Quantitative RT-PCR

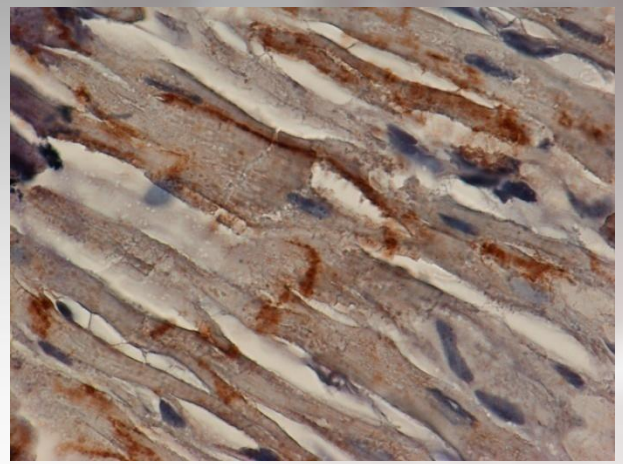




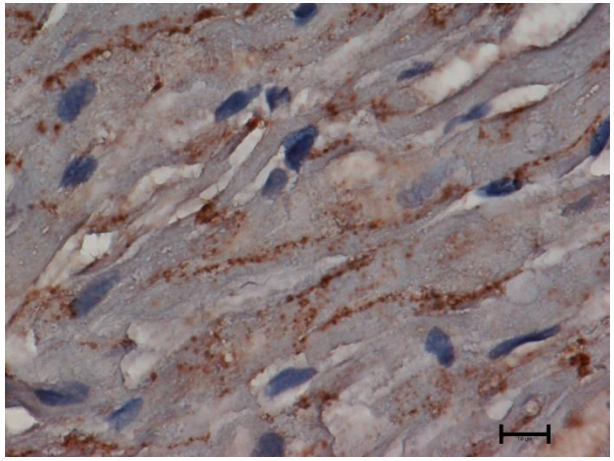
Immunohistochemical Stain – Cx43



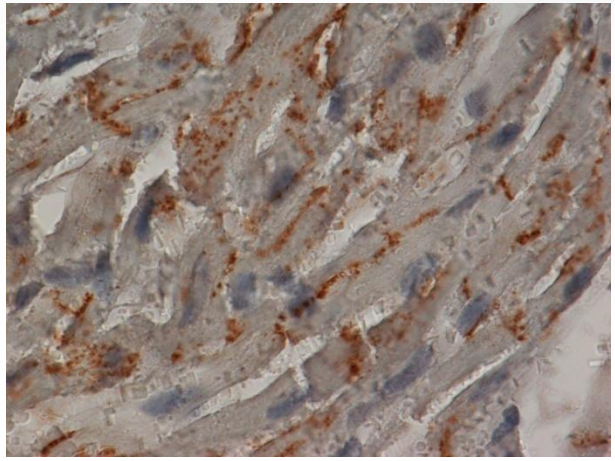
Sham group (x1000)



ICMP group (x1000)



LVH group (x1000)



DCMP group (x1000)

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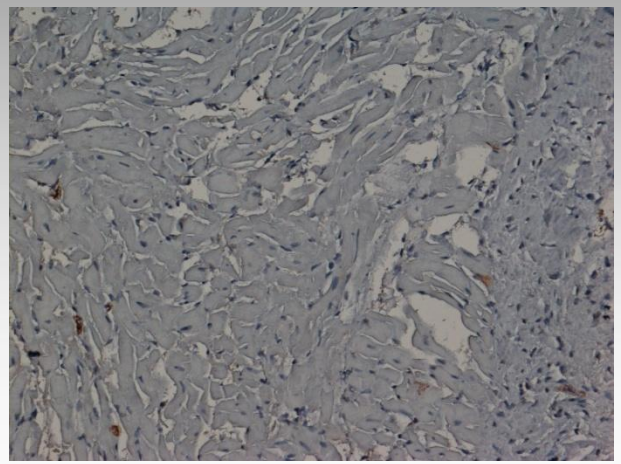
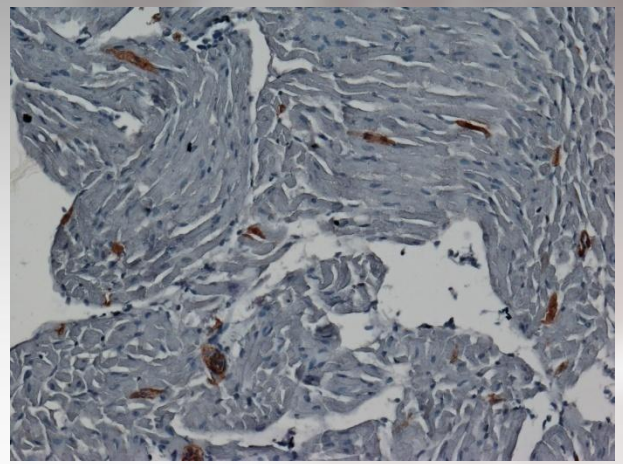
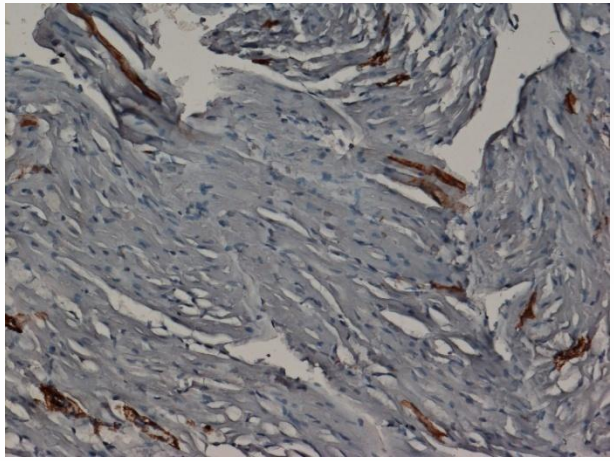
Immunohistochemical Stain – α-SMA



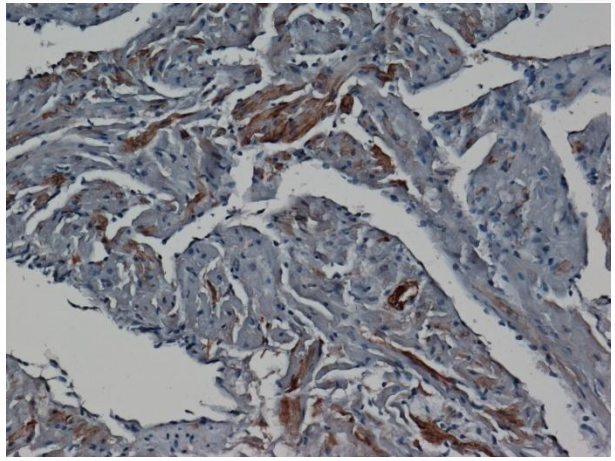
Sham group (x200)



ICMP group (x200)



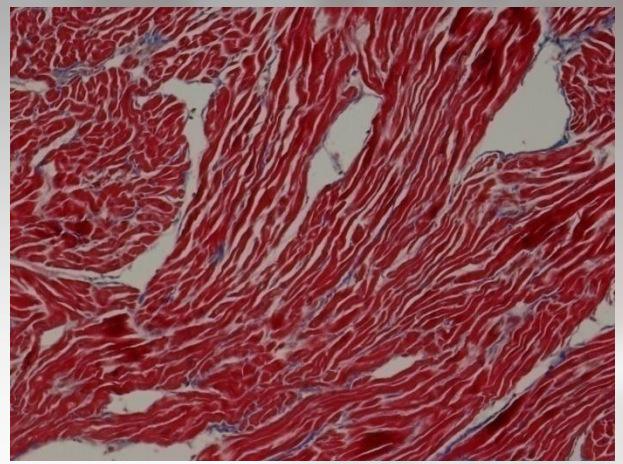
LVH group (x200)



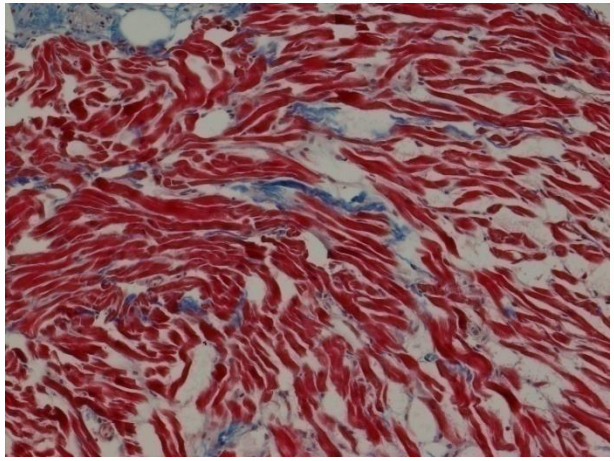
DCMP group (x200)

Masson's Trichrome Stain

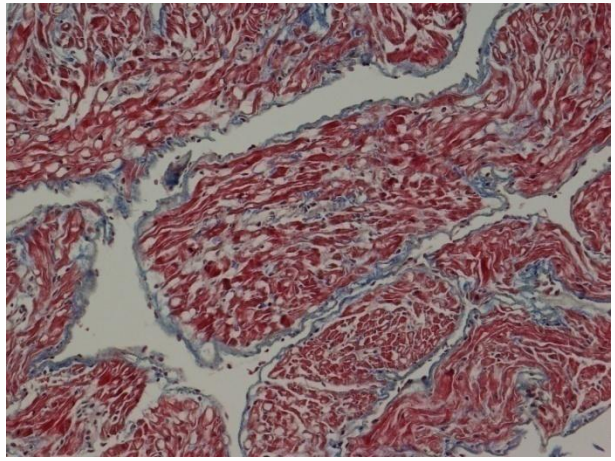
Sham group (x200)



ICMP group (x200)



LVH group (x200)



DCMP group (x200)

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Conclusions

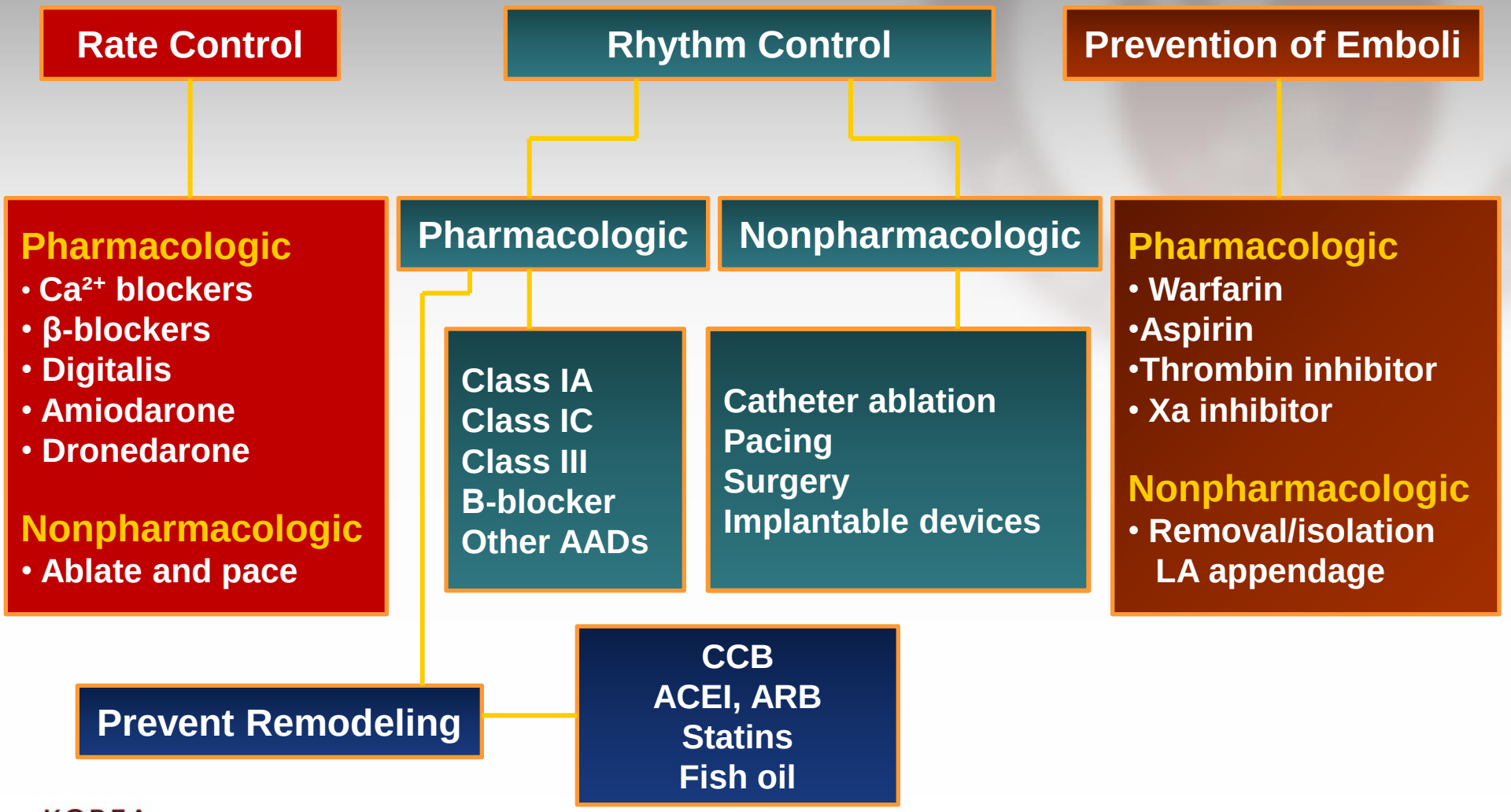
- DCMP and ICMP without end-stage heart failure had no AF-susceptible remodeling because decreased peak LV pressure caused by increased LVID, even though they had substantial LV systolic dysfunction.

- In LVH with preserved LV systolic function, pressure overload caused by LV diastolic dysfunction might play an important role in AF susceptible remodeling via depressed Cx43 expression as well as CX43 lateralization.

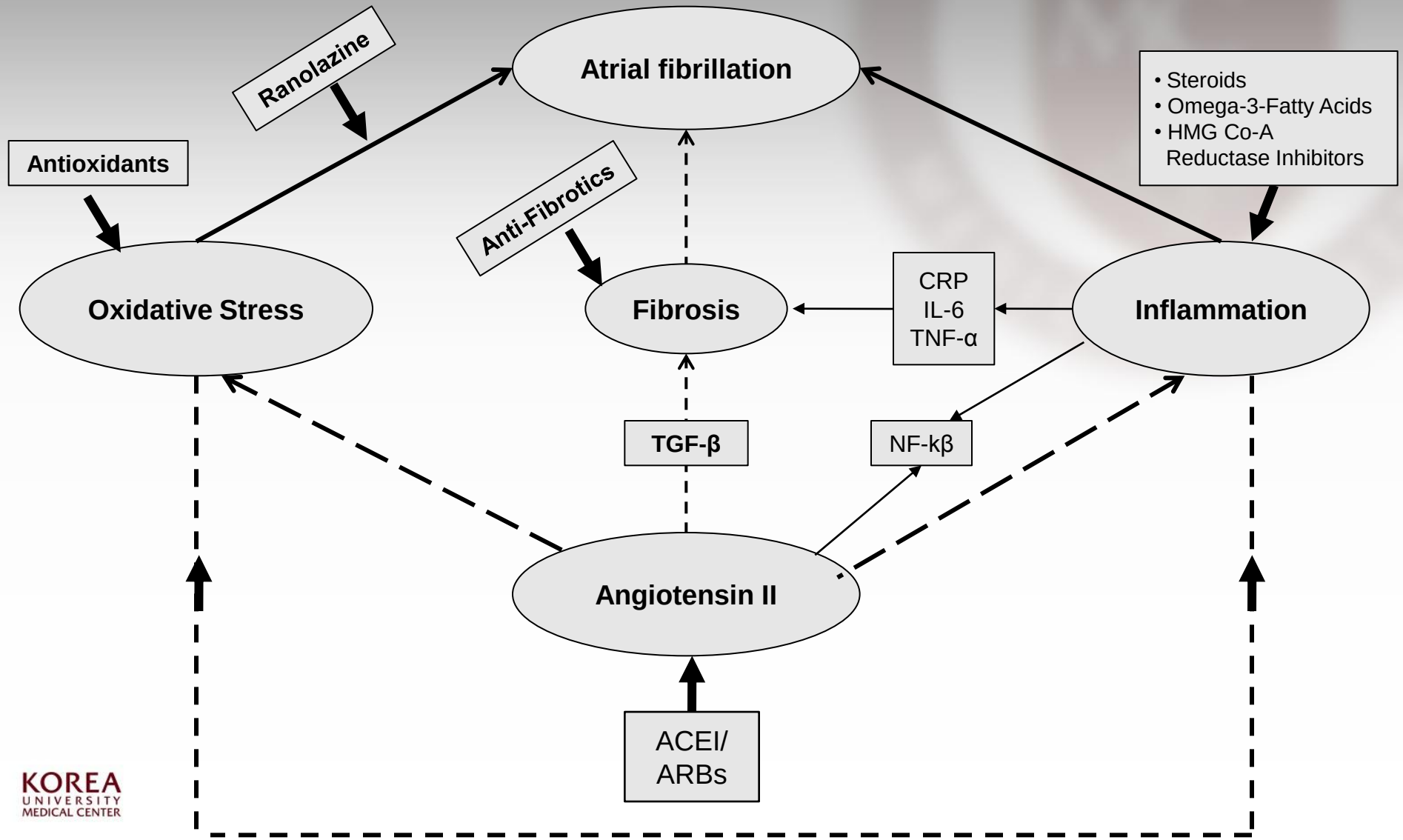
Contents

- **Epidemiology**
- **Pathophysiology**
  - **Diastolic dysfunction (pressure-induced stretch)**
- **Upstream treatment**
- **New guideline of anticoagulation**

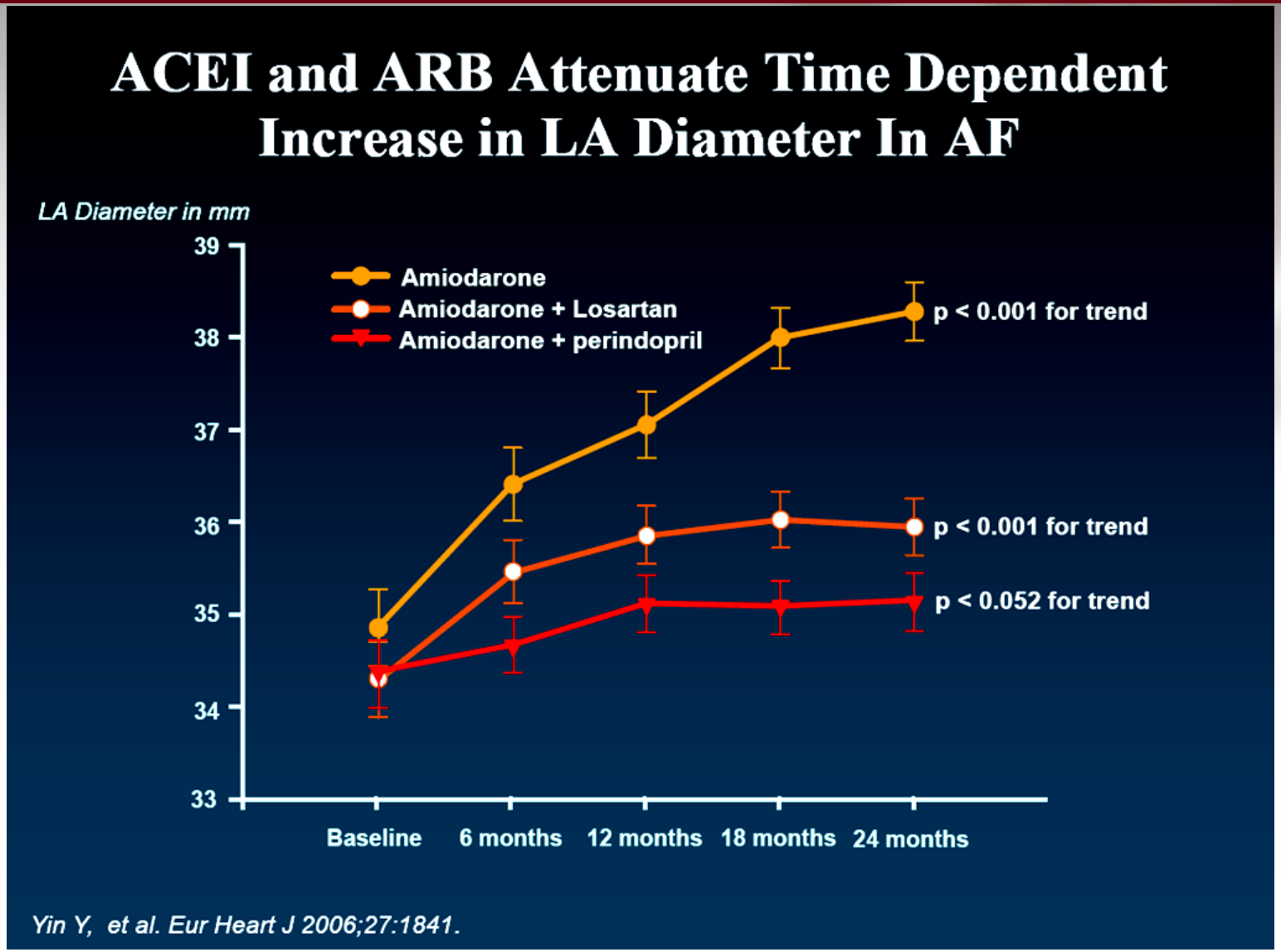
Treatments



Treatments

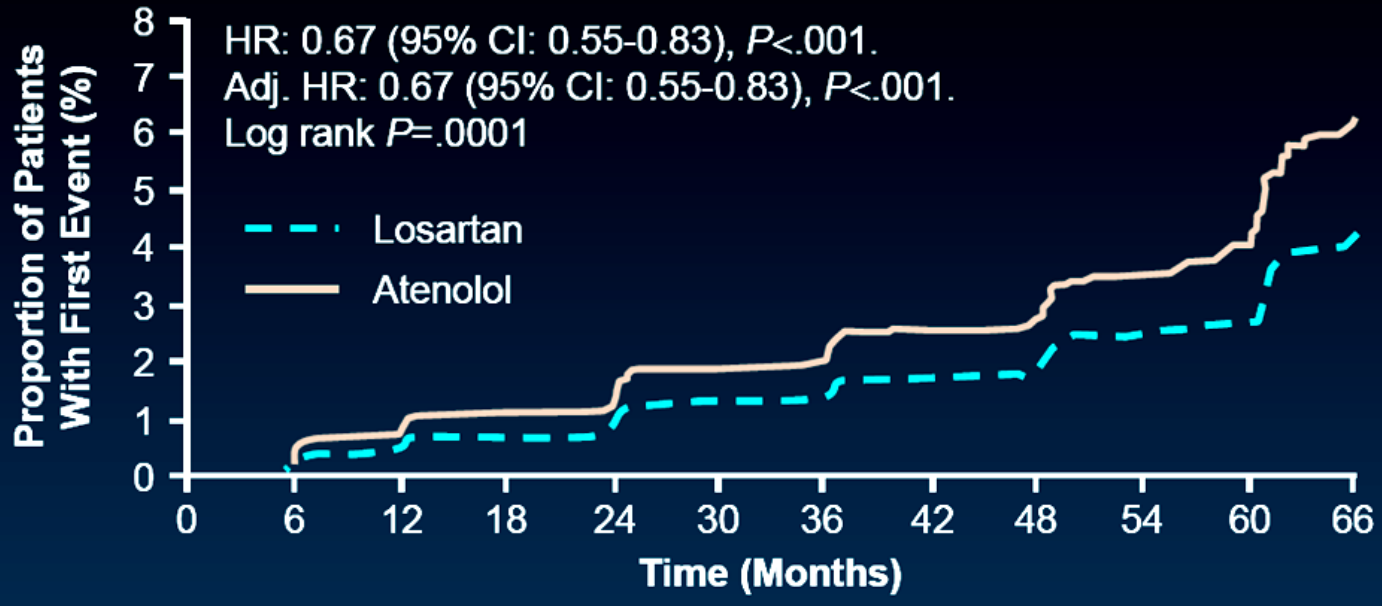

Ranolazine
Atrial fibrillation
• Steroids
• Omega-3-Fatty Acids
• HMG Co-A Reductase Inhibitors
Antioxidants
Anti-Fibrotics
Oxidative Stress
Fibrosis
CRP
IL-6
TNF-α
Inflammation
TGF-β
NF-kβ
Angiotensin II
ACEI/
ARBs

ACEI/ARB


ACEI and ARB Attenuate Time Dependent Increase in LA Diameter In AF
LA Diameter in mm
39
38
37
36
35
34
33
Amiodarone
Amiodarone + Losartan
Amiodarone + perindopril
p < 0.001 for trend
p < 0.001 for trend
p < 0.052 for trend
Baseline
6 months
12 months
18 months
24 months
Yin Y, et al. Eur Heart J 2006;27:1841.

ACEI/ARB

Losartan Is Superior to Atenolol in Suppressing AF in the LIFE Study



- Losartan reduced AF compared to atenolol (HR 0.67; *P*<.001) in 342 hypertensive patients with LVH and AF
- Losartan also reduced stroke (HR 0.49; CI 0.29-0.86; *P*=.01)

Wachtell et al. J Am Coll Cardiol. 2005;45:712-719

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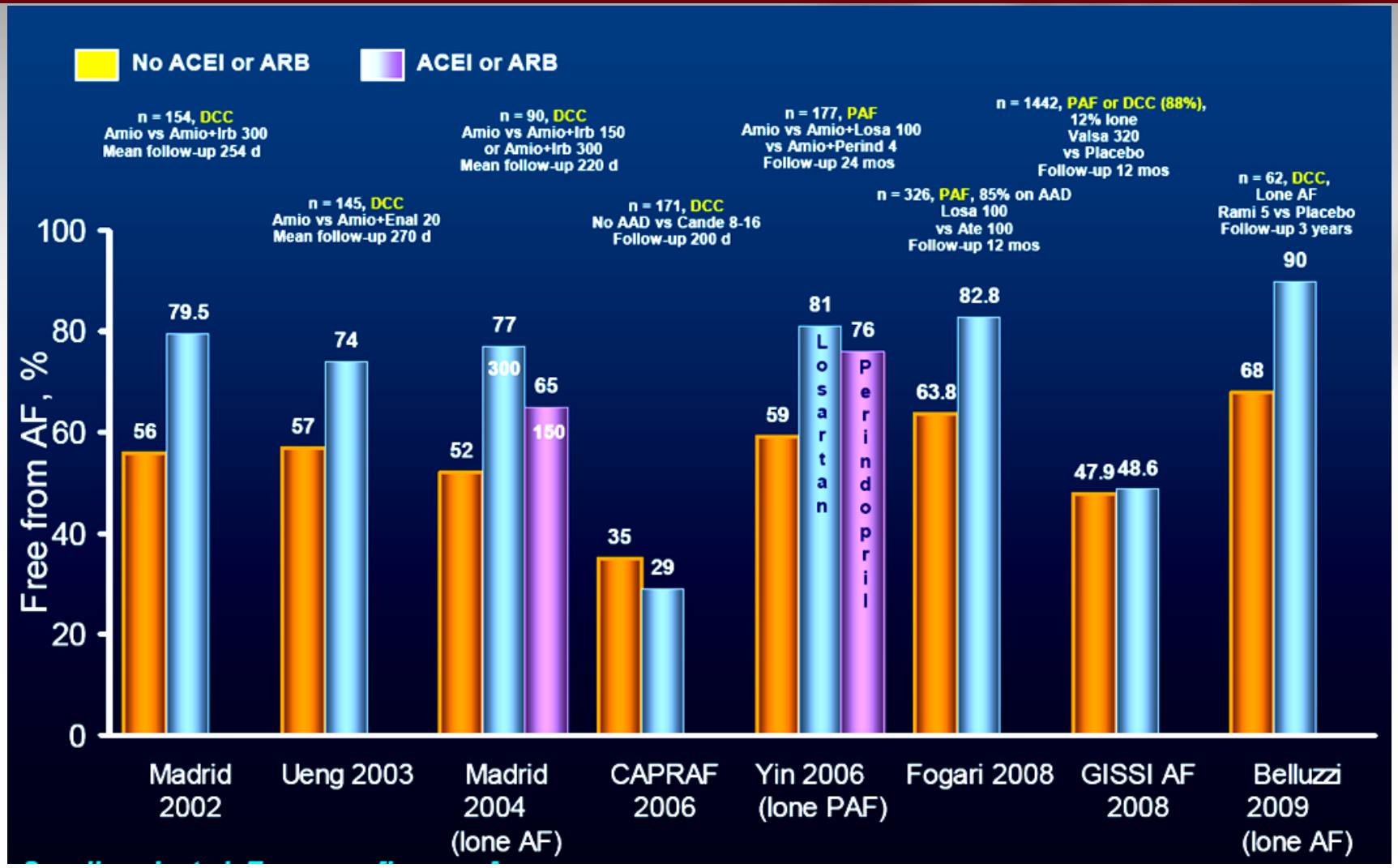
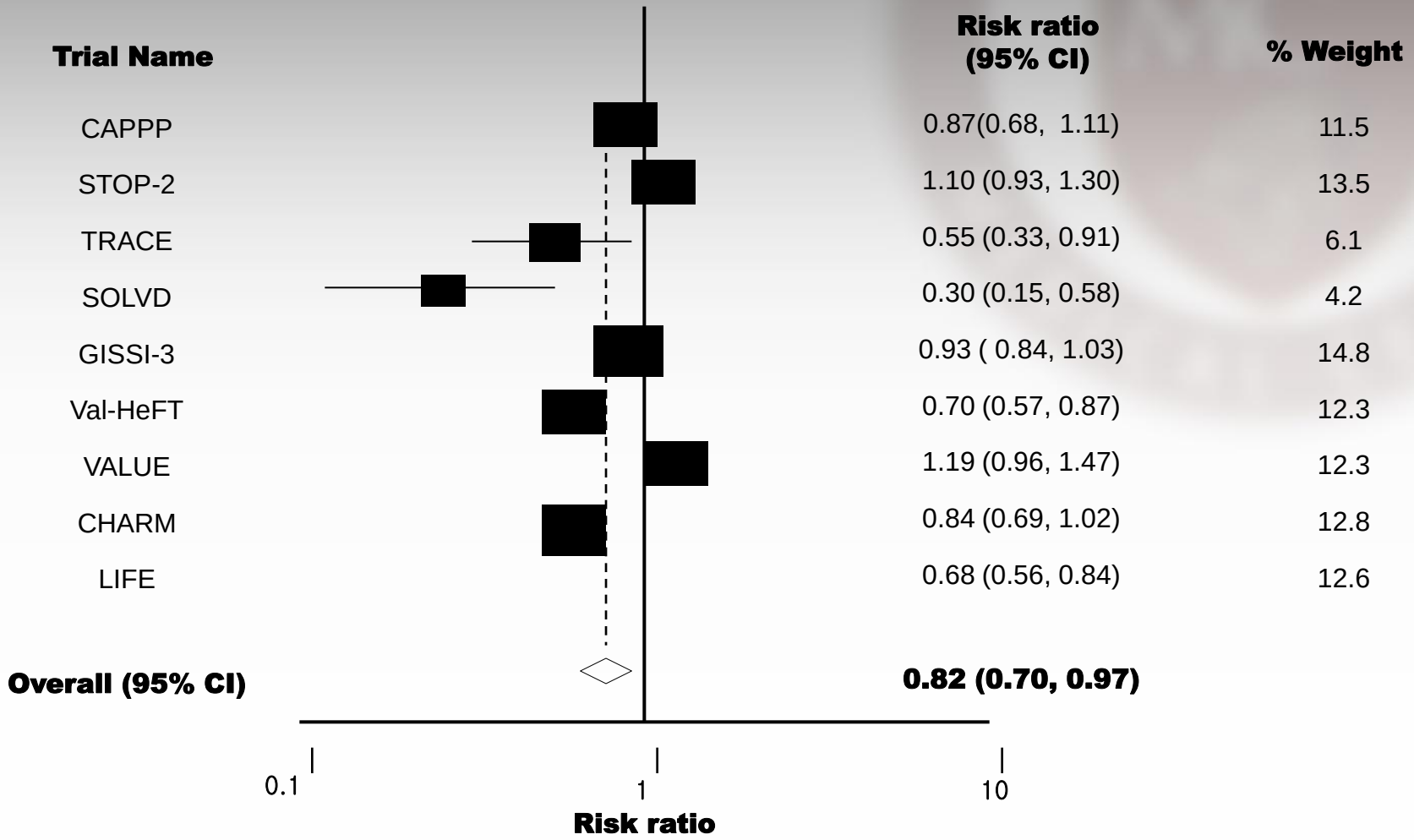
ACEI/ARB


No ACEI or ARB
ACEI or ARB
n = 154, DCC
Amio vs Amio+Irb 300
Mean follow-up 254 d
n = 145, DCC
Amio vs Amio+Enal 20
Mean follow-up 270 d
n = 90, DCC
Amio vs Amio+Irb 150
or Amio+Irb 300
Mean follow-up 220 d
n = 171, DCC
No AAD vs Cande 8-16
Follow-up 200 d
n = 177, PAF
Amio vs Amio+Losa 100
vs Amio+Perind 4
Follow-up 24 mos
n = 326, PAF, 85% on AAD
Losa 100
vs Ate 100
Follow-up 12 mos
n = 1442, PAF or DCC (88%),
12% lone
Valsa 320
vs Placebo
Follow-up 12 mos
n = 62, DCC,
Lone AF
Rami 5 vs Placebo
Follow-up 3 years
Free from AF, %
100
80
60
40
20
0
56
79.5
57
74
52
77
300
65
150
35
29
59
81
Losartan
76
Perindopril
63.8
82.8
47.9
48.6
68
90
Madrid 2002
Ueng 2003
Madrid 2004 (lone AF)
CAPRAF 2006
Yin 2006 (lone PAF)
Fogari 2008
GISSI AF 2008
Belluzzi 2009 (lone AF)

ACEI/ARB



Forest plot and RR of individual trial and summary pooled estimate

Treatments

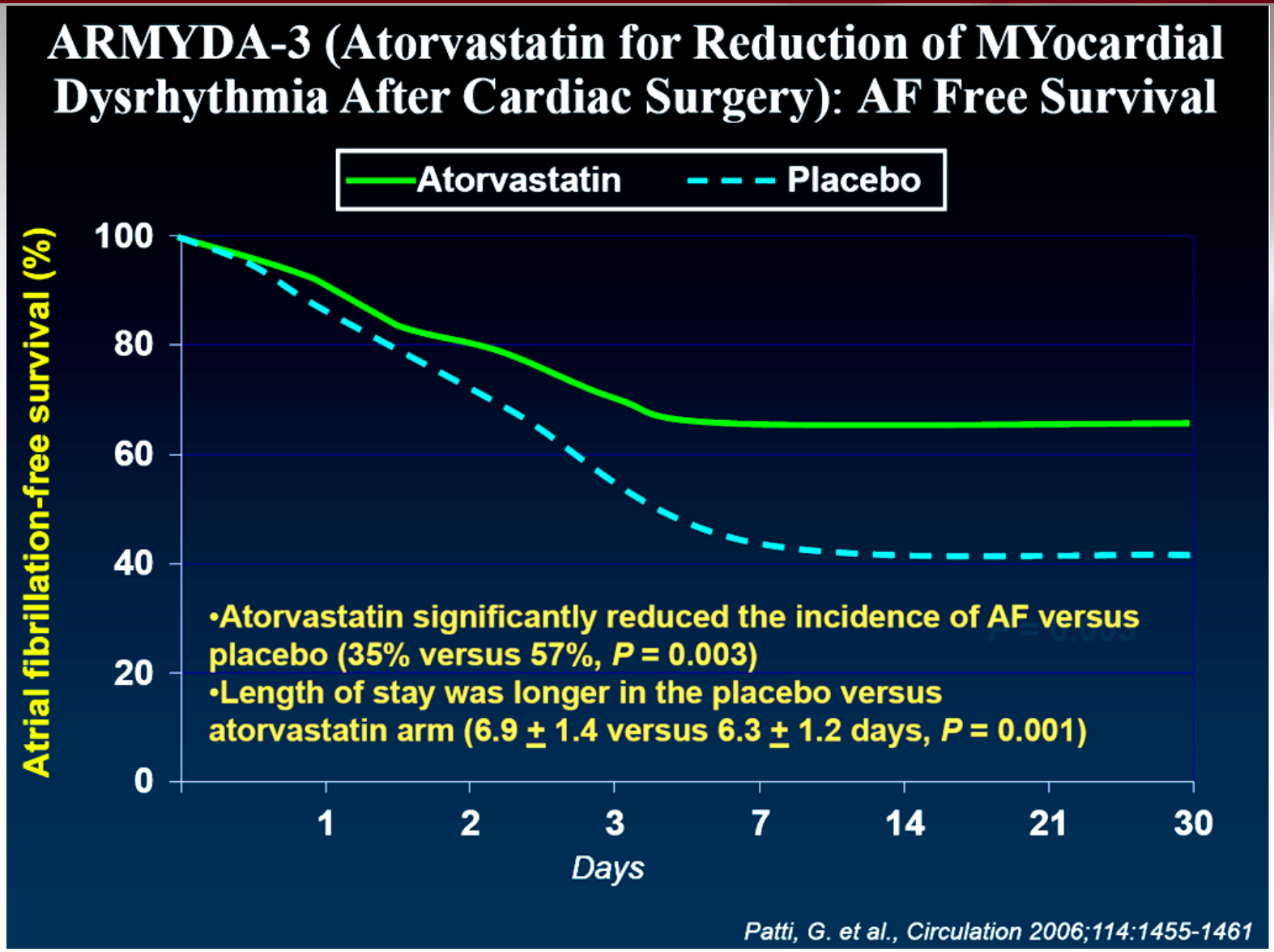
Thiazide diuretics	β-blockers	Calcium antagonists (dihydropyridines)	Calcium antagonists (verapamil / diltiazem)
• Isolated systolic hypertension (elderly) • Heart failure • Hypertension in blacks	• Angina pectoris • Post-myocardial infarction • Heart failure • Tachyarrhythmias • Glaucoma • Pregnancy	• Isolated systolic hypertension (elderly) • Angina pectoris • LV hypertrophy • Carotid/coronary atherosclerosis • Pregnancy • Hypertension in blacks	• Angina pectoris • Carotid atherosclerosis • Supraventricular tachycardia

ACE inhibitors	Angiotensin receptor antagonists	Diuretics (antialdosterone)	Loop diuretics
• Heart failure • LV dysfunction • Post-myocardial infarction • Diabetic nephropathy • Non-diabetic nephropathy • LV hypertrophy • Carotid atherosclerosis • Proteinuria/microalbuminuria • Atrial fibrillation • Metabolic syndrome	• Heart failure • Post-myocardial infarction • Diabetic nephropathy • Proteinuriam/microalbuminuria • LV hypertrophy • Atrial fibrillation • Metabolic syndrome • ACEI-induced cough	• Heart failure • Post-myocardial infarction	• End-stage renal disease • Heart failure

Mancia G et al. *Eur Heart J*;28:1462–1536

ESH/ESC 2007 Hypertension Guidelines
Conditions Favouring Some Antihypertensives vs Others

Statin



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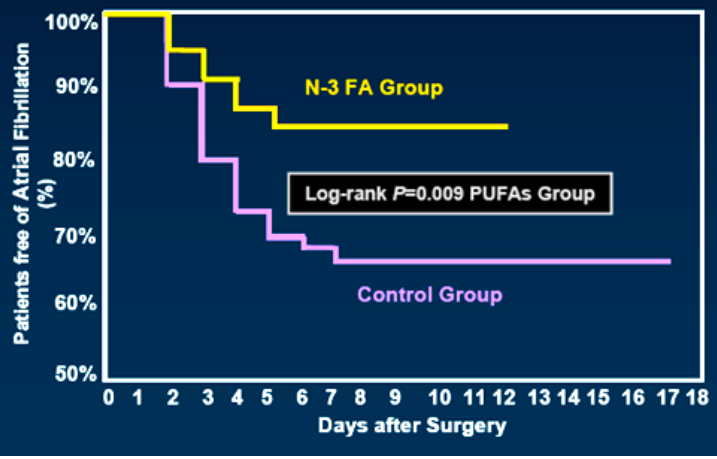
Omega-3

Omega-3 for Prevention of Atrial Fibrillation Post-CABG

- 160 patients awaiting CABG
- Randomized to usual care or EPA+DHA (1.7 g/d)
- From 5 days pre-surgery through hospitalization
- Endpoint was AF detected by ECG during hospitalization. AF >5 min or requiring intervention

	Control (n=81)	N-3 FA (n=79)	*P*
Post CABG AF	33%	15%	0.013
Hours of AF	24	16	0.12
Length of Stay	8.2 days	7.3 days	0.017



Calo L et al. J Am Coll Cardiol. 2005;45:1723-1728

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CHA_2DS_2VASc

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

CHA_2DS_2VASc

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Conclusions

- AF is the most common sustained cardiac arrhythmia and prevalence rates are rising and are expected to reach 12.1 million by 2050.
- Once AF begins, there are multiple adverse outcomes and therefore prevention is imperative.
- Modifiable risk factors may differ depending on the population studies and the subtype of AF examined.
- Further research in ethnically and medically diverse population is needed on prevention and prediction, and eventually involving randomized trials of promising interventions.

Thank you for your attentions !

Korea University Cardiovascular Center