HFpEF Masterclasses
In centers of expertise

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FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

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Pôle cardio-vasculaire et pulmonaire
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Risk factors, comorbidities and etiologies of HFpEF

Déclaration de Relations Professionnelles
Disclosure Statement of Financial Interest

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Risk factors, etiologies and co-morbidities

Risk factors	CV diseases	Precipitating factors
Age	Ischaemic	Sodium overload
Gender	Hypertension	Hypertension
Smoking	Valvular	Ischemia
Hypertension	Infiltrative	SV tachycardia
Diabetes mellitus	Toxic	Acute renal failure
Hypercholesterolemia	Inflammatory	Thyrotoxicosis
	Metabolic	Anaemia
Obesity		Infection
Inactivity		Drugs
Chronic kidney disease		
Sleep apnea syndrome		

ESC Guidelines: Etiologies of HFpEF

Cause	Examples of presentations
CAD	Myocardial infarction Angina or "angina-equivalent" Arrhythmias
Hypertension	Heart failure with preserved systolic function Malignant hypertension/acute pulmonary oedema
Valve disease	Primary valve disease e.g., aortic stenosis Secondary valve disease, e.g. functional regurgitation Congenital valve disease
Arrhythmias	Atrial tachyarrhythmias Ventricular arrhythmias
CMPs	All Dilated Hypertrophic Restrictive ARVC Peripartum Takotsubo syndrome Toxins: alcohol, cocaine, iron, copper
Congenital heart disease	Congenitally corrected/repaired transposition of great arteries Shunt lesions Repaired tetralogy of Fallot Ebstein's anomaly
Infective	Viral myocarditis Chagas disease HIV Lyme disease
Drug-induced	Anthracyclines Trastuzumab VEGF inhibitors Immune checkpoint inhibitors Proteasome inhibitors RAF+MEK inhibitors
Infiltrative	Amyloid Sarcoidosis Neoplastic
Storage disorders	Haemochromatosis Fabry disease Glycogen storage diseases
Endomyocardial disease	Radiotherapy Endomyocardial fibrosis/eosinophilia Carcinoid
Pericardial disease	Calcification Infiltrative
Metabolic	Endocrine disease Nutritional disease (thiamine, vitamin B1 and selenium deficiencies) Autoimmune disease
Neuromuscular disease	Friedreich's ataxia Muscular dystrophy

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McDonagh: *Eur Heart J 2021;40:3297*

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Pericardial disease	Calcification Infiltrative

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HFA-ESC consensus paper: HFpEF

Table 2 Potential specific aetiologies underlying heart failure with preserved ejection fraction-like syndromes in Step 4 (F_2)

Abnormalities of the myocardium		
Ischaemic		Myocardial post-infarction/scar[49] Myocardial stunning[50] Epicardial coronary artery disease[51] Microvascular and endothelial dysfunction[52,53–55]
Toxic	Recreational substance abuse	Such as alcohol,[56] cocaine,[57] and anabolic steroids[58]
	Heavy metals	Such as iron,[59] lead,[60] cadmium,[60] cobalt,[61] copper (M. Wilson)[62]
	Medications	Such as chloroquine,[63] ergotamine,[64] cytostatic drugs (e.g. anthracyclines),[64] immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab)[64]
	Radiation	Mean cardiac radiation doses > 3 Gy[65,66]
Immune and inflammatory	Related to infection	Such as cardiotropic viruses,[67,68] HIV,[69–71] hepatitis,[72] helminths,[73] parasites (e.g. Chagas' disease[74])
	Not related to infection	Lymphocytic myocarditis,[75–79] autoimmune diseases (e.g. rheumatoid arthritis,[80] connective tissue disorders like scleroderma,[81] M. Raynaud,[55] systemic lupus erythematosus,[82] dermato/polymyositis,[83] and hypersensitivity and eosinophilic myocarditis[73,84–87]
Infiltrative	Related to malignancy	Direct infiltrations and metastases[88–90]
	Not related to malignancy	Amyloidosis,[19,91] sarcoidosis,[92,93] primarily and secondary haemochromatosis,[94–96] storage diseases[97] (e.g. Fabry disease,[98,99] Danon disease,[100–102] Pompe disease,[99,102] PRKAG2 deficiency,[99] Gaucher's disease[99])[103,104,105,106]
Metabolic	Hormonal	Such as thyroid diseases,[107,108] parathyroid diseases,[109] acromegaly,[110] GH deficiency,[111] Cushing disease,[112] Conn's disease,[113] Addison disease,[114] phaeochromocytoma,[115] pathologies related to pregnancy and peripartum[116,117]
	Nutritional	Such as deficiencies in thiamine,[118] L-carnitine,[119] selenium,[120] (functional) iron,[121,122] complex malnutrition (e.g. AIDS, infections,[73] anorexia nervosa[73,123,124])
Genetic	Diverse forms	Such as HCM,[97,125,126] restrictive cardiomyopathies,[103,104,106] hypertrophic form of non-compaction cardiomyopathy,[127,128] early forms of muscular dystrophies (Duchenne/Becker disease[129]).
Endomyocardial		HES,[84] EMF,[71,127] endocardial fibroelastosis,[128] carcinoid,[130,131] endocardial calcification (Paget's disease[132])
Abnormalities of loading conditions		
Hypertension		Primary and secondary forms of hypertension[112,113,115,130,131]
Valvular and structural defects	Acquired	Heart valve diseases[133,134]
Valvular and structural defects	Congenital	Septal defects[132,135,136]
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis and pericardial effusion[137,138]
	Endomyocardial	HES,[86] EMF,[73,139] endocardial fibroelastosis,[140] carcinoid,[141,142] endocardial calcification (Paget's disease[143])
High output states		Severe anaemia,[144] sepsis,[145] thyrotoxicosis,[105] arteriovenous fistula,[146] and pregnancy[147]
Volume overload		Renal failure and fluid overload[148,149,150]
Abnormalities of the cardiac rhythm		
Rhythm disorders		Atrial/ventricular arrhythmias, pacing, conduction disorders[38,151–153]

- Abnormalities of the myocardium
  - Ischemic
  - Toxic
  - Immune and inflammatory
  - Infiltrative
  - Metabolic
  - Genetic
  - Endomyocardial
- Abnormalities of loading conditions
  - Hyperpression
    - Hypertension
    - Valvular diseases
    - Pericardial
    - Endomyocardial
    - High output
    - Volume overload
  - Abnormalities of cardiac rhythm

Pieske: Eur Heart J 2019;40:3297

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HFA-ESC consensus paper: Real etiologies of HFpEF

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    - Volume overload
  - Abnormalities of cardiac rhythm

Pieske: Eur Heart J 2019;40:3297

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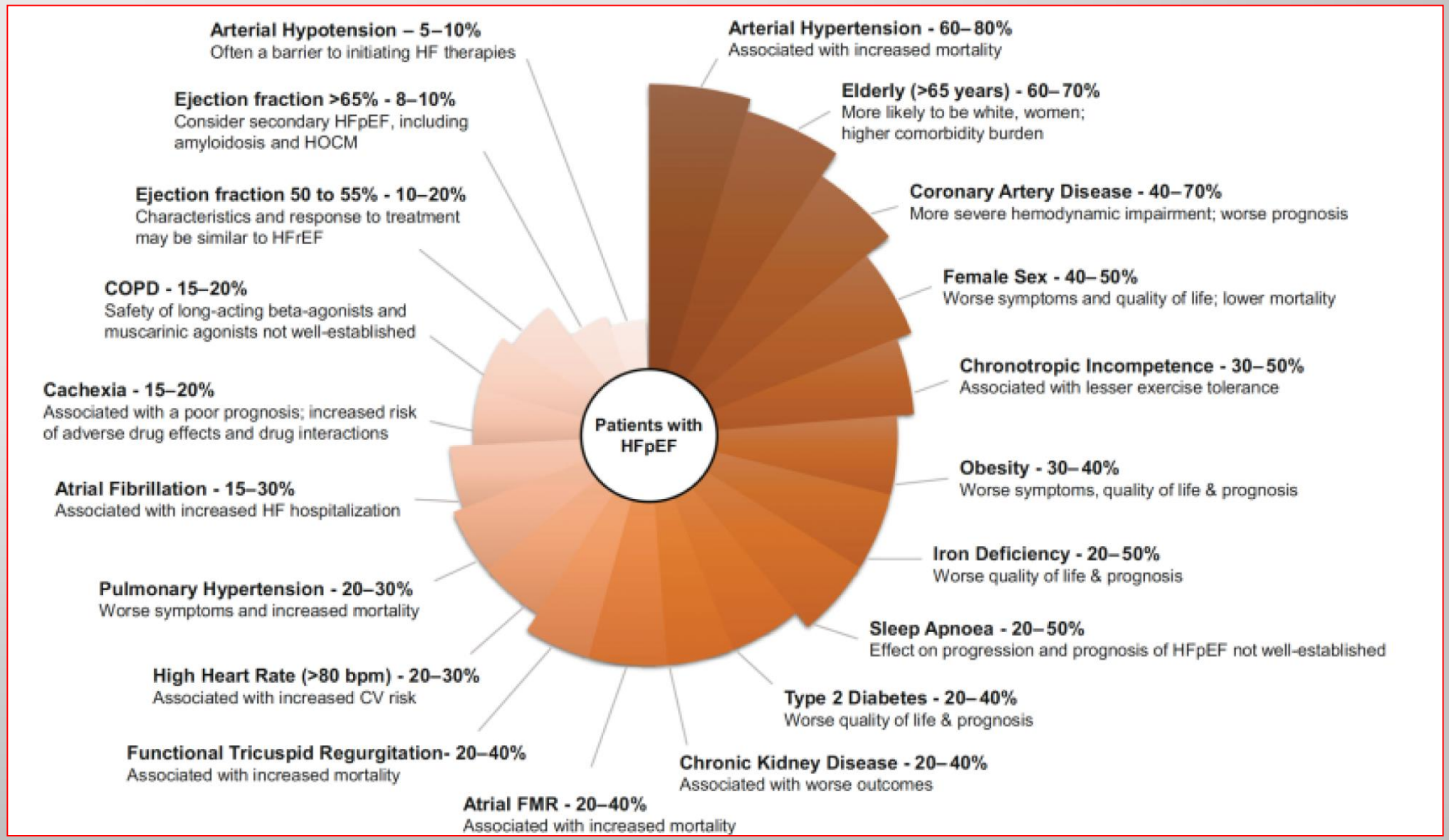
Phenotypes of HFpEF



Anker: Eur J Heart Fail 2023; 25: 936

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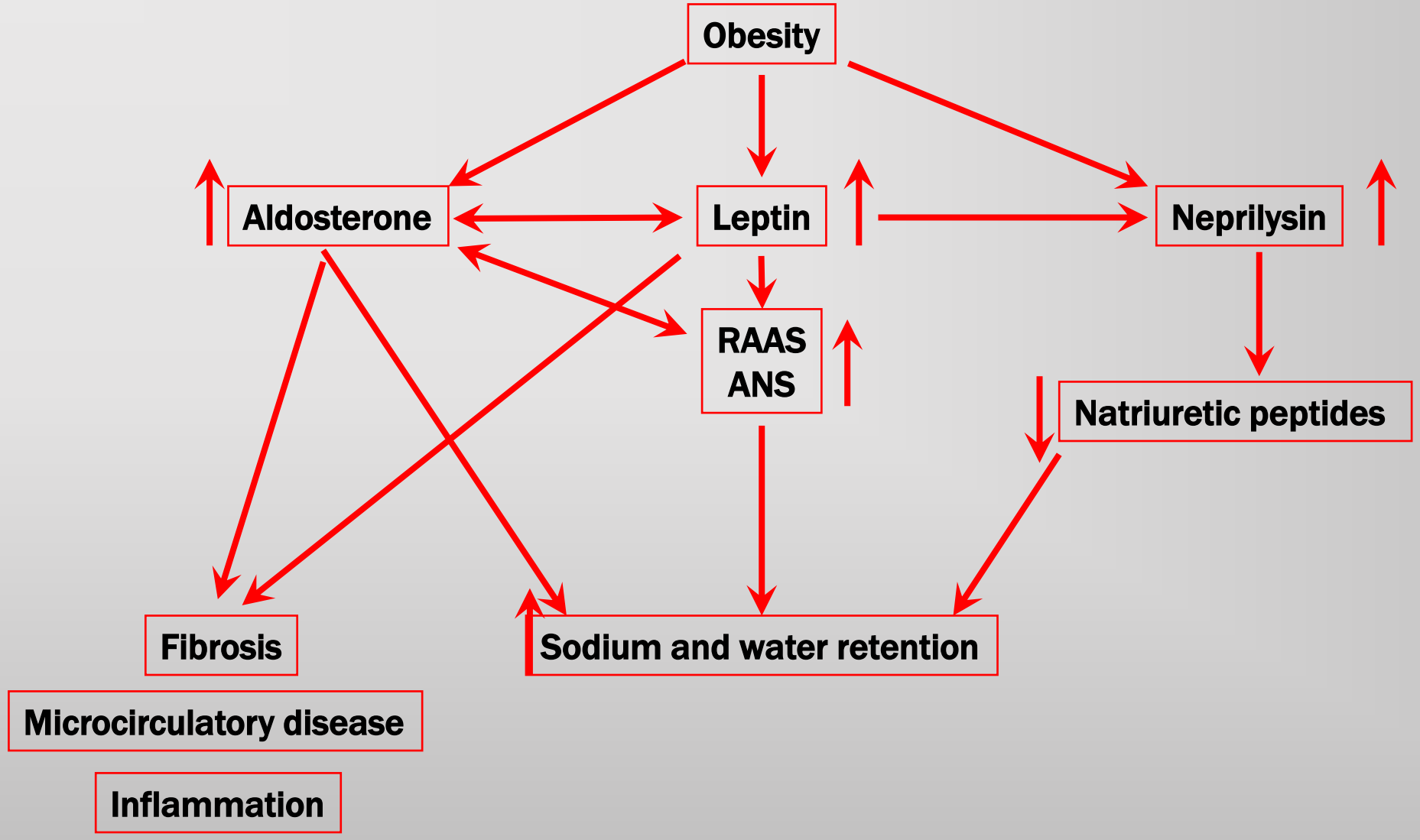
Obesity and HFpEF



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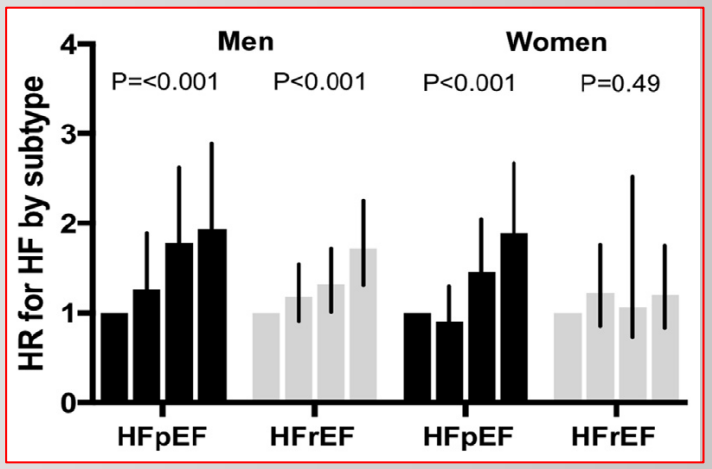
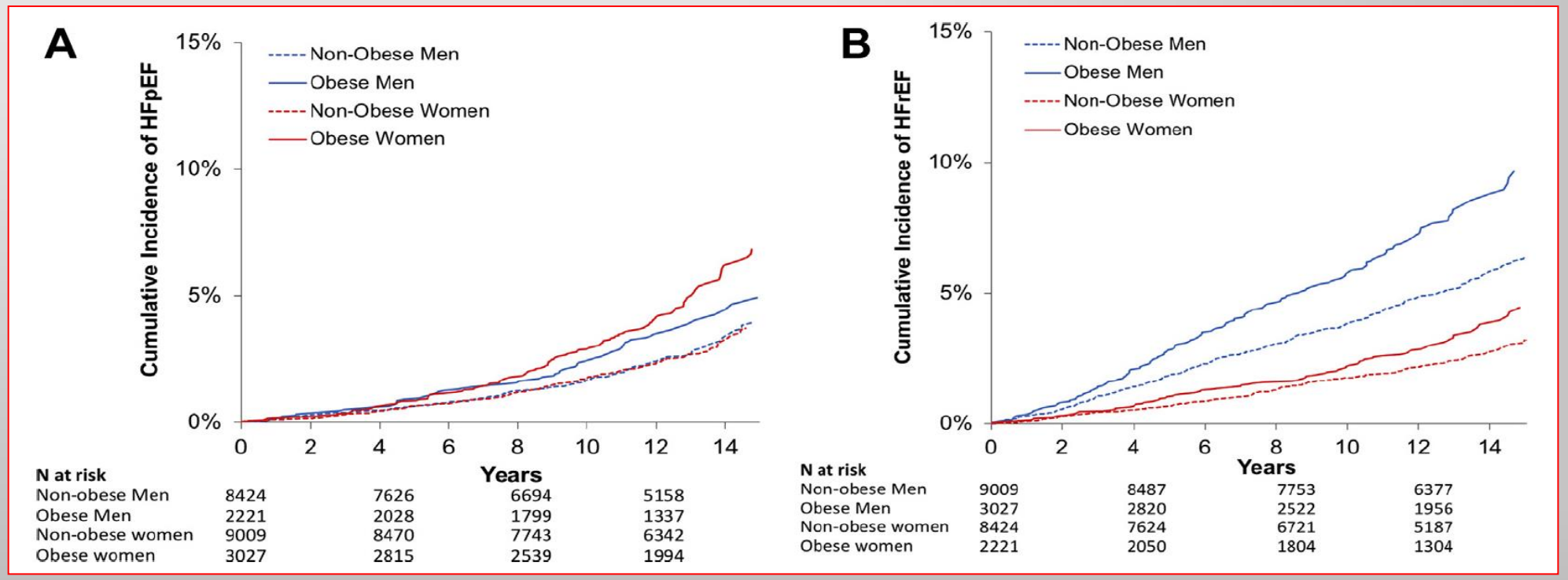
Incidence of HF, BMI and gender

- 22681 subjects from 4 different epidemiological cohorts (53% of women)
- Median follow-up of 12 yrs with 628 HFpEF patients (LVEF ≥50%) and 835 HFrEF patients (LVEF < 50%)





Savji: JACC Heart Fail 2018;6: 701

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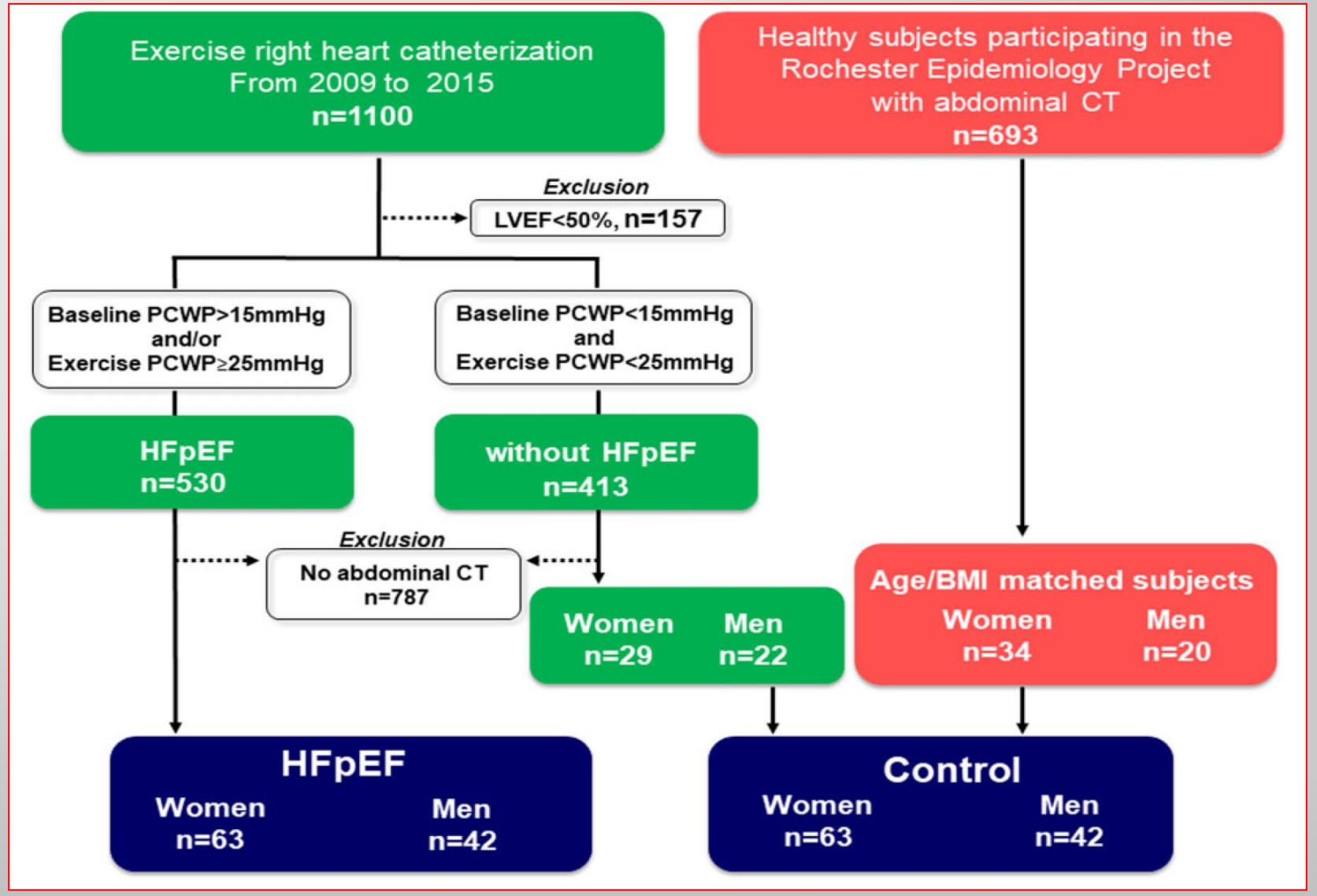
HFpEF: Obesity, gender and type of fat



Sorimachi: Eur Heart J 2021; 42: 1595

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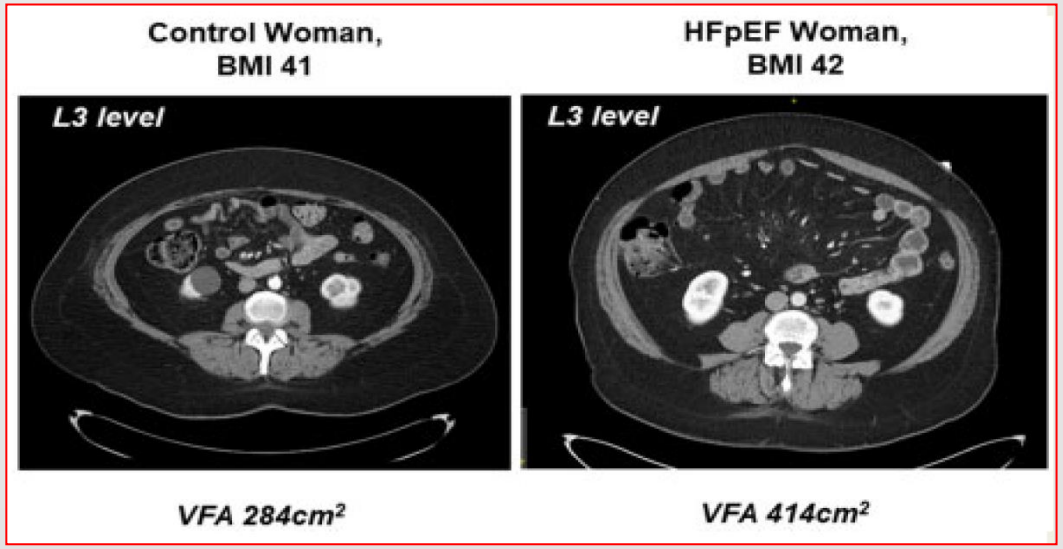

Women	Multivariable model (R^2 = 0.54)			
	β	95%CI	*P*-value	VIF
Age (years)	0.90	(-0.04, 1.85)	0.06	1.2
BMI (kg/m²)	8.56	(7.01, 10.1)	<0.0001	1.0
Hypertension	-14.1	(-40.4, 12.1)	0.3	1.2
Diabetes mellitus	13.7	(-17.6, 44.9)	0.4	1.1
HFpEF	36.0	(12.2, 59.8)	0.003	1.0
Men	**Multivariable model (R^2 = 0.52)**			
	β	95%CI	*P*-value	VIF
Age (years)	3.03	(1.60, 4.45)	<0.0001	1.1
BMI (kg/m²)	12.7	(9.66, 15.8)	<0.0001	1.1
Hypertension	35.5	(-8.07, 79.0)	0.1	1.1
Diabetes mellitus	5.7	(-51.8, 63.1)	0.8	1.1
HFpEF	37.0	(-2.57, 76.6)	0.07	1.1

Table 2 **Abdominal fat distribution**

	Control women (*n* = 63)	HFpEF women (*n* = 63)	*P*-value	Control men (*n* = 42)	HFpEF men (*n* = 42)	*P*-value
VAT area (cm²) **Visceral**	139 ± 72	186 ± 112	0.006	252 ± 92	294 ± 158	0.1
Height-indexed VAT (cm²/m²)	50 ± 27	70 ± 42	0.01	82 ± 29	93 ± 49	0.2
Weight-indexed VAT (cm²/kg)	1.6 ± 0.7	2.0 ± 1.1	0.01	2.6 ± 0.8	2.8 ± 1.2	0.4
BMI-indexed VAT (cm²*m²/kg)	4.3 ± 2.0	5.4 ± 2.8	0.007	8.0 ± 2.5	9.0 ± 4.0	0.2
SAT area (cm²) **Sub-Cut**	258 ± 114	314 ± 163	0.03	215 ± 121	253 ± 149	0.2
Height-indexed SAT (cm²/m²)	99 ± 44	117 ± 59	0.05	69 ± 36	79 ± 47	0.1
Weight-indexed SAT (m²/kg)	3.1 ± 1.0	3.5 ± 1.2	0.05	2.1 ± 0.7	2.4 ± 0.9	0.2
BMI-indexed SAT (m²*m²/kg)	8.0 ± 2.6	9.2 ± 3.2	0.03	6.6 ± 2.5	7.5 ± 3.1	0.1

Sorimachi: Eur Heart J 2021; 42: 1595

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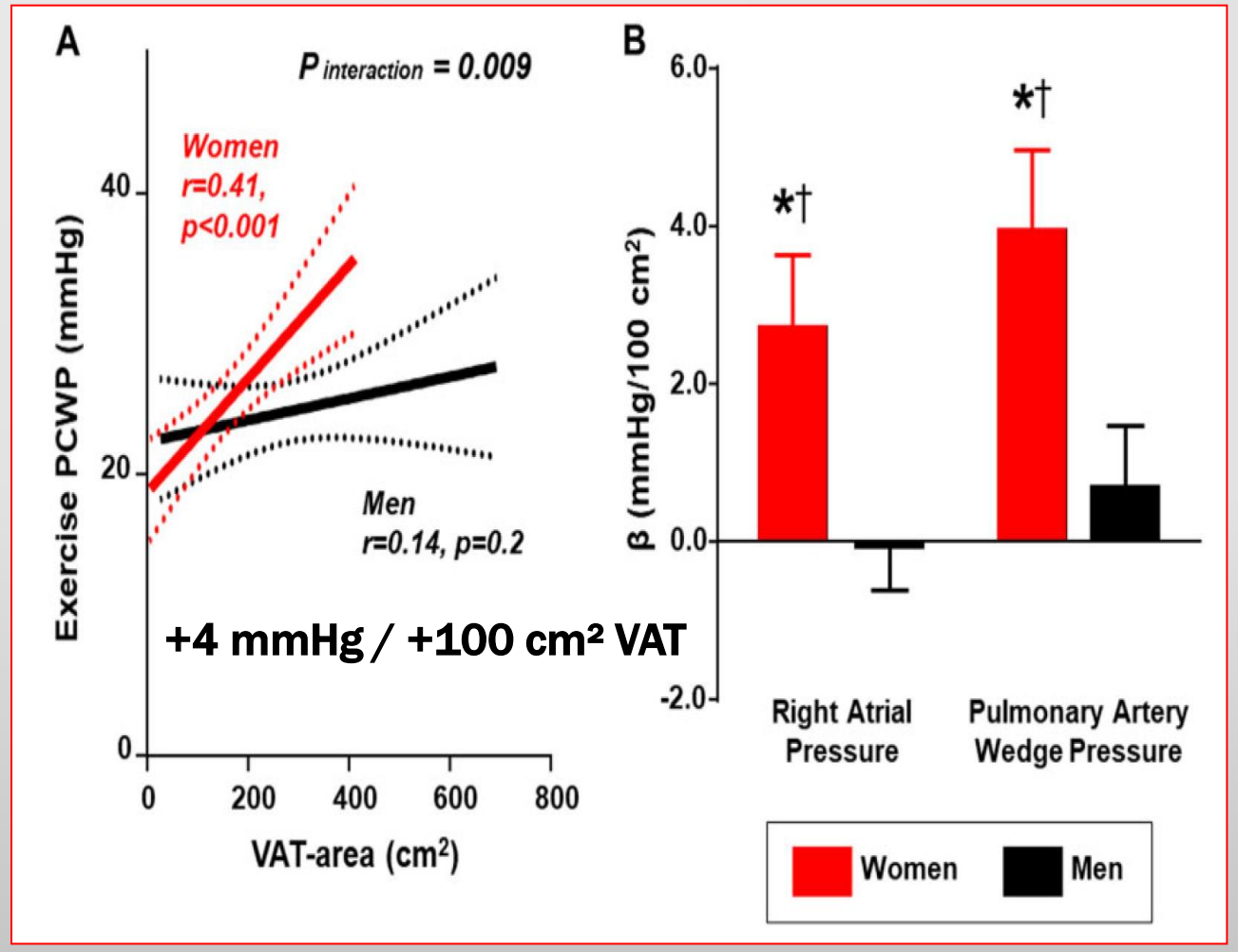
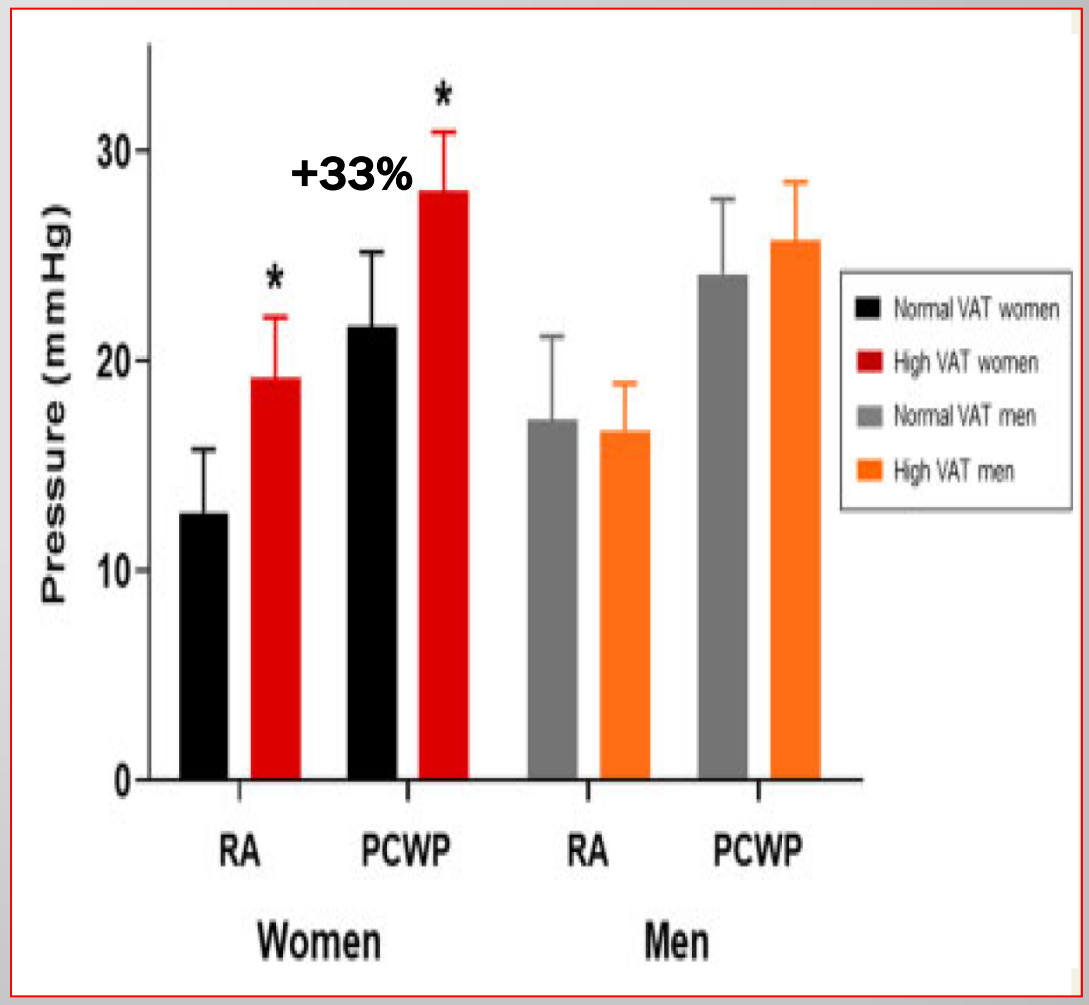
HFpEF: Obesity, gender and type of fat





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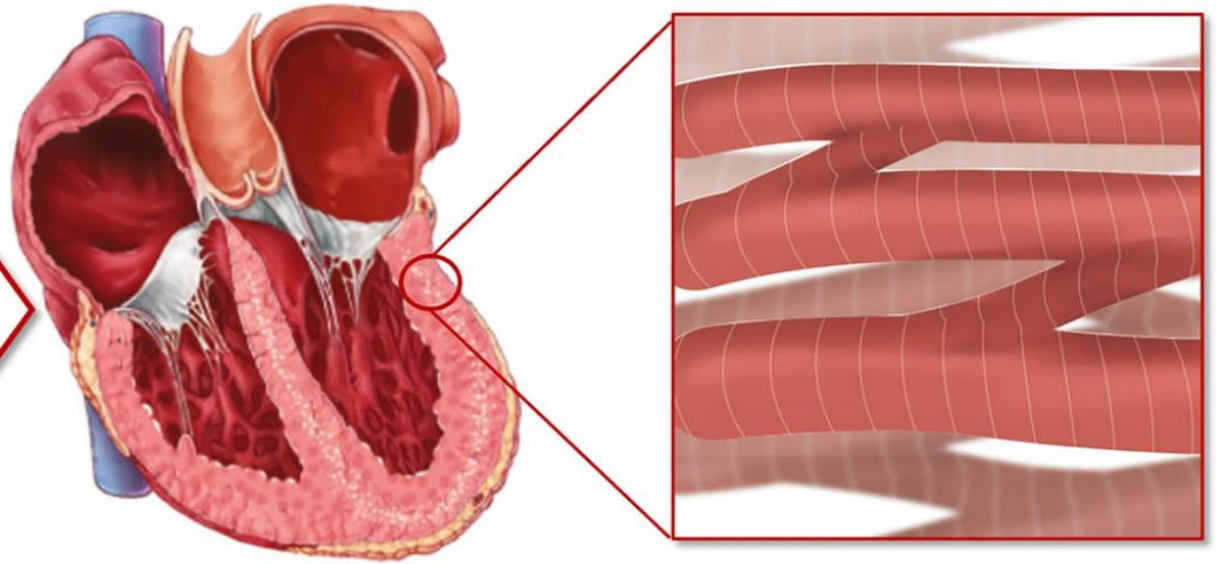
Diabetic myocardial disorder

Systemic alterations

- Insulin resistance
- Hyperglycaemia
- Hyperlipidaemia
- RAAS activation
- AGEs
- Autonomic dysfunction

Cellular and molecular processes



Cardiac consequences

- Myocardial hypertrophy and fibrosis
- Apoptosis
- Systolic and diastolic dysfunction
- Microvascular dysfunction

- Metabolic perturbations, mitochondrial & endoplasmic reticulum dysfunction.
- Impaired myocardial efficiency.
- Glucotoxicity, lipotoxicity, increased oxidative stress.
- Epigenetic changes and alterations in cellular pathways.
- Posttranslational titin modifications, impaired passive tension.

Seferovic: Eur J Heart Fail 2024; 26: 1893

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Diabetes and heart failure

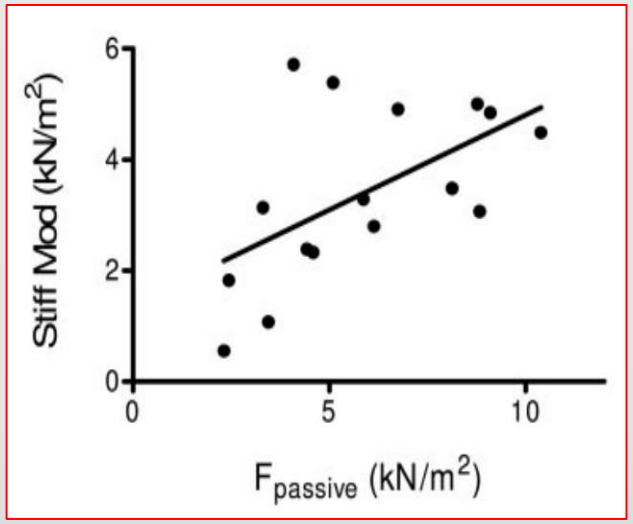
- Study 1: LV endomyocardial biopsies in 44 patients without CAD, admitted for HF decompensation
  - 22 patients with HFpEF
  - 22 patients with HFrEF

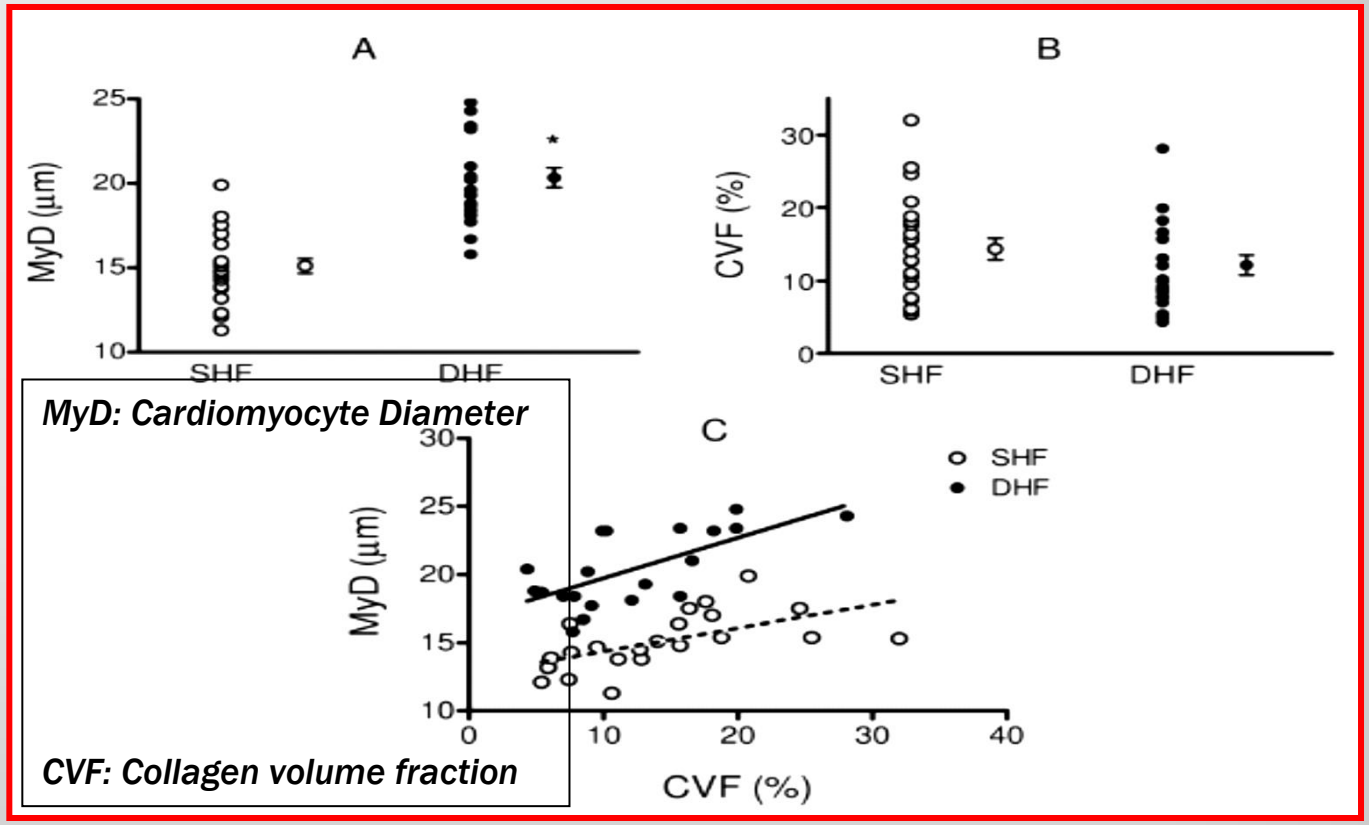
van Heerebeek: Circulation 2006;113:1966

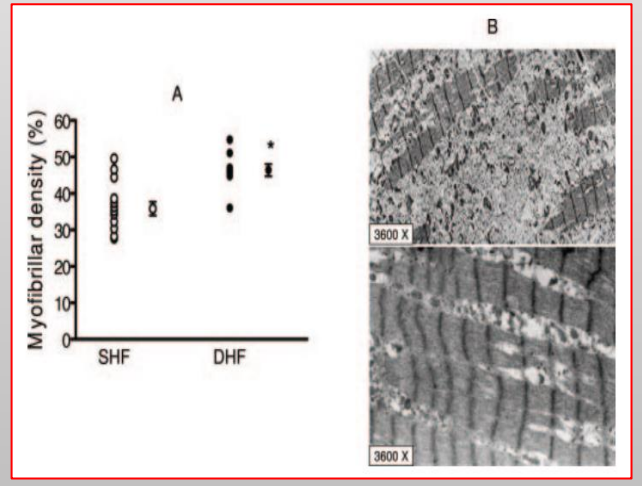
- Study 2: LV endomyocardial biopsies in 64 patients without CAD, admitted for HF decompensation
  - 26 diabetic patients
    - 16 patients with HFpEF
    - 10 patients with HFrEF
  - 38 non-diabetic patients
    - 12 patients with HFpEF
    - 26 patients with HFrEF

van Heerebeek: Circulation 2008;117:43

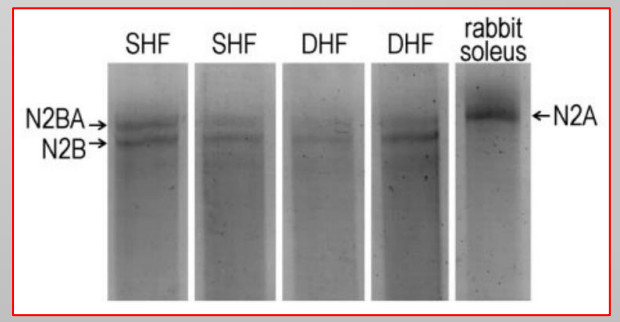
Systolic vs “Diastolic” myocardial stiffness







- Myocyte hypertrophy in « DHF »
- Decrease myofibrillar density in SHF
- Increase myocardial stiffness in « DHF »
- Increase level of stiff Titin isoform (N2B)



van Heerebeek: Circulation 2006;113:1966

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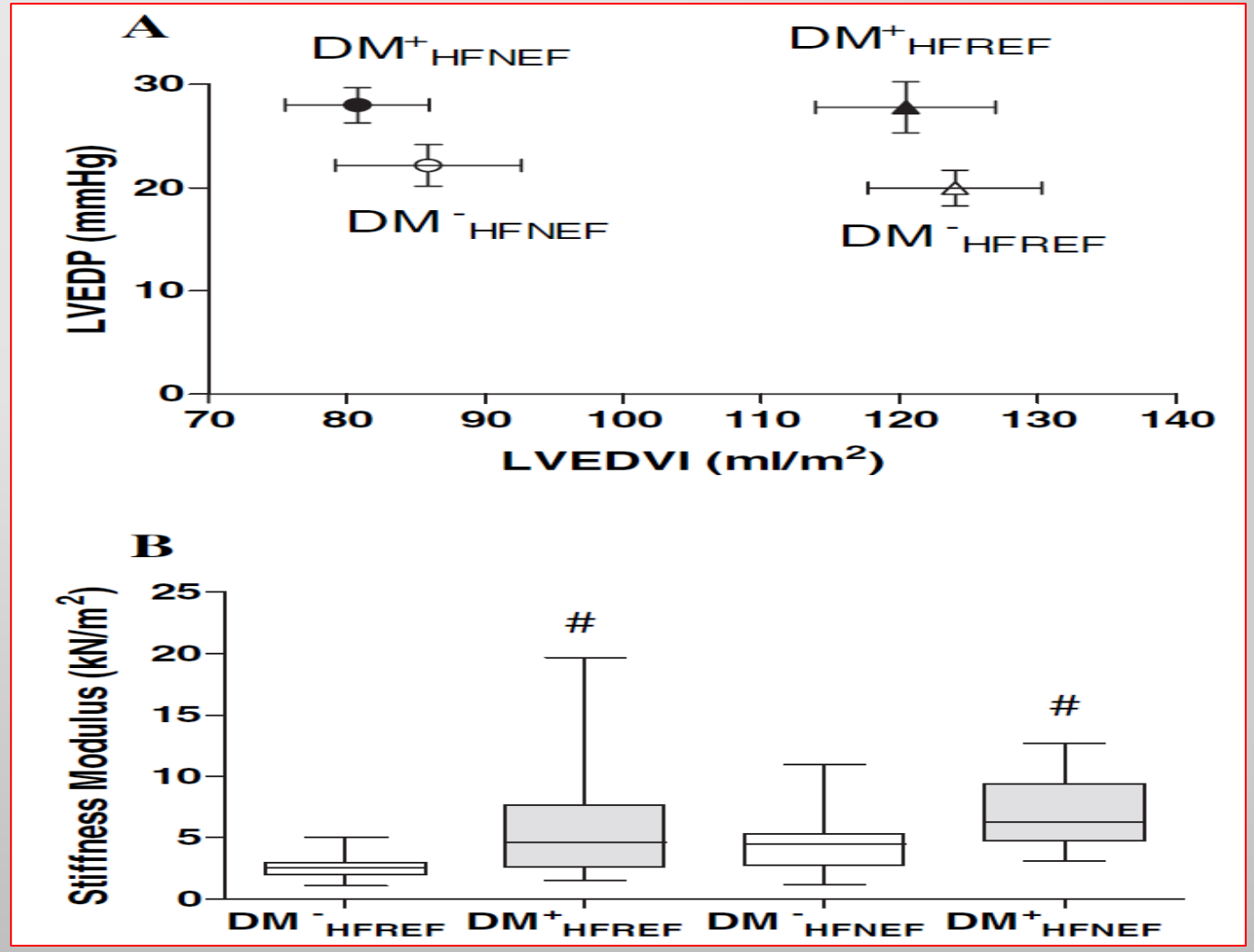
Diabetic Heart

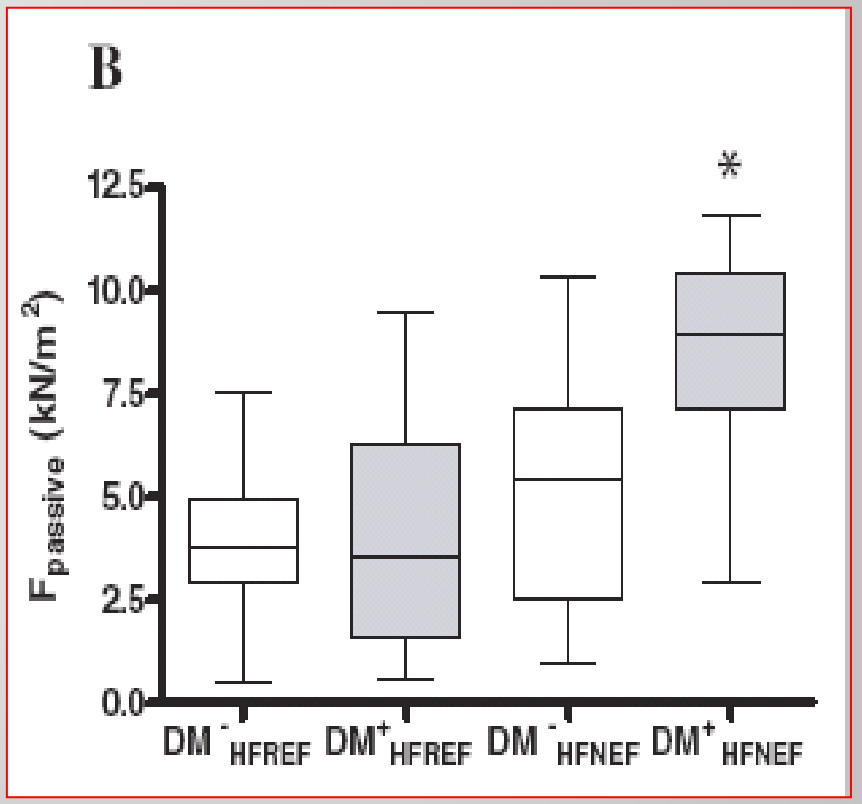
- Increase diastolic LV stiffness in diabetic cardiopathy



van Heerebeek. Circulation 2008;117:43

Diabetes: HFpEF

- Increase cardiomyocyte resting tension (Fpassive) in diabetic patients with HFpEF
- Correlation with Z lines thickness
- Correlation with myocardial stiffness (r= 0.55) and with the duration of diabetes (r = 0.35)



van Heerebeek. Circulation 2008;117:43

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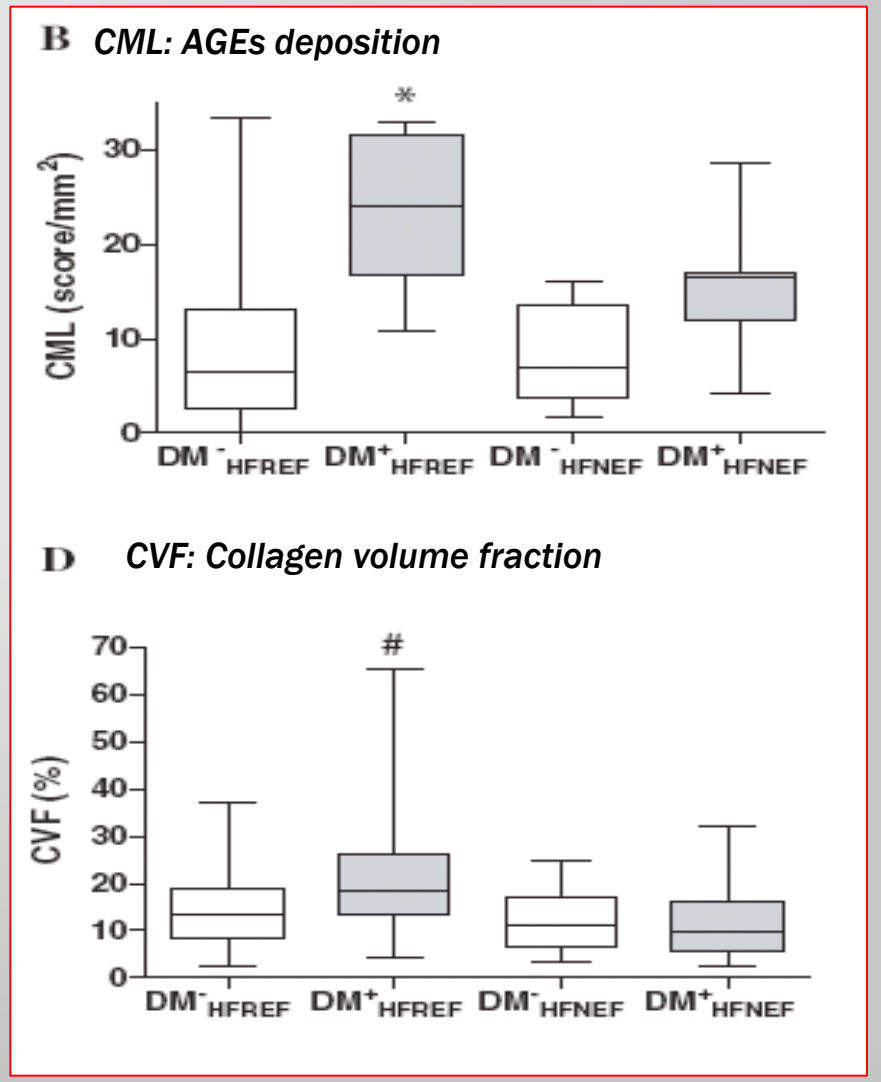
Diabetes: HFrEF

- Increase AGEs deposition in diabetics with HFrEF
- Increase collagen content
- Significant correlation between CVF (collagen) and glycosylated hemoglobin (r = 0.61) and between CVF and myocardial stifness



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Conclusion: Etiologies - Phenotypes

- Secondary HFpEF
  - Specific cardiomyopathies
    - Restrictive – Hypertrophic ….
  - Pericardial diseases

- Non secondary HFpEF: Primary HFpEF (risk factors, phenotypes +++)
  - Abnormalities of the myocardium: ischemic
  - Abnormalities of the loading conditions:
    - Hyperpression: Hypertension, valvular
    - Volume overload
  - Abnormalities of the cardiac rhythm