Prevalence and Prognostic Implications of Diabetic Cardiomyopathy

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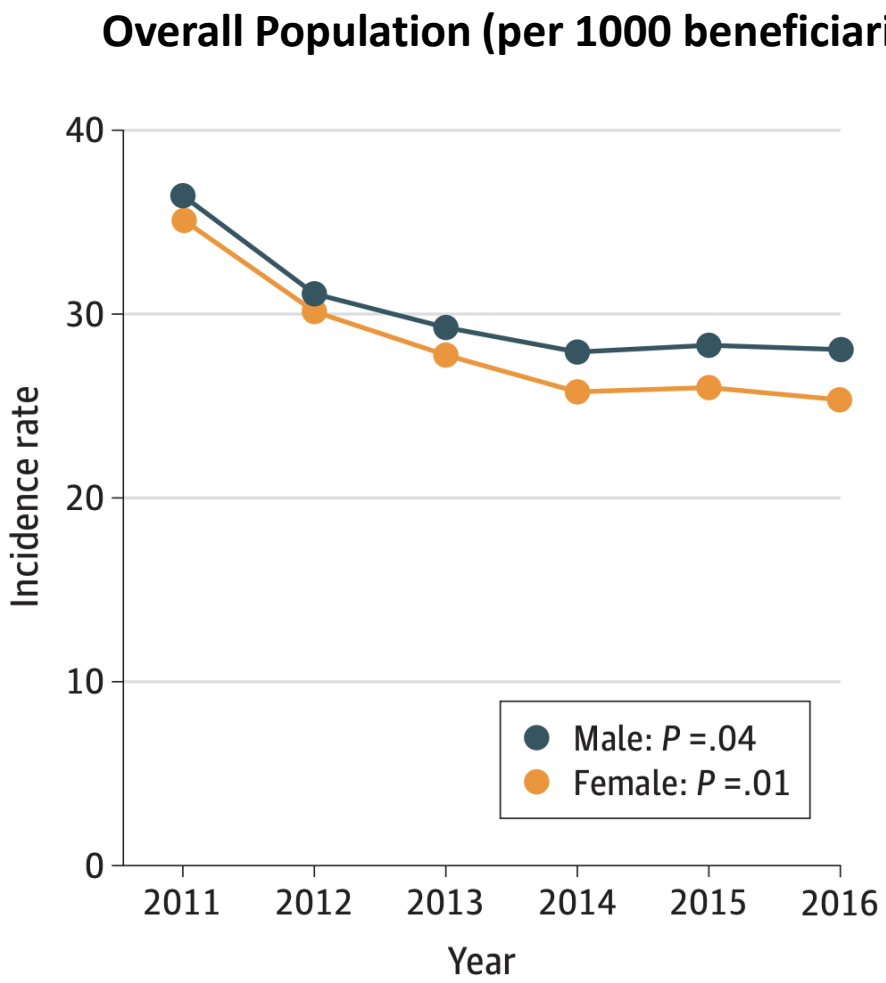
06/25/2022

Disclosures

- Consultant: Tricog Health, Lilly USA, Rivus, Roche
- Research Support: Gilead, Applied therapeutics
- Other: Merck, Pfizer

Trends in Heart Failure Incidence (2011 – 2016)

National Level 5% Medicare Claims data (age 73 y, 56% women, 250,000 incident HF cases)



Khera, Pandey et al. JAMA Network Open 2021

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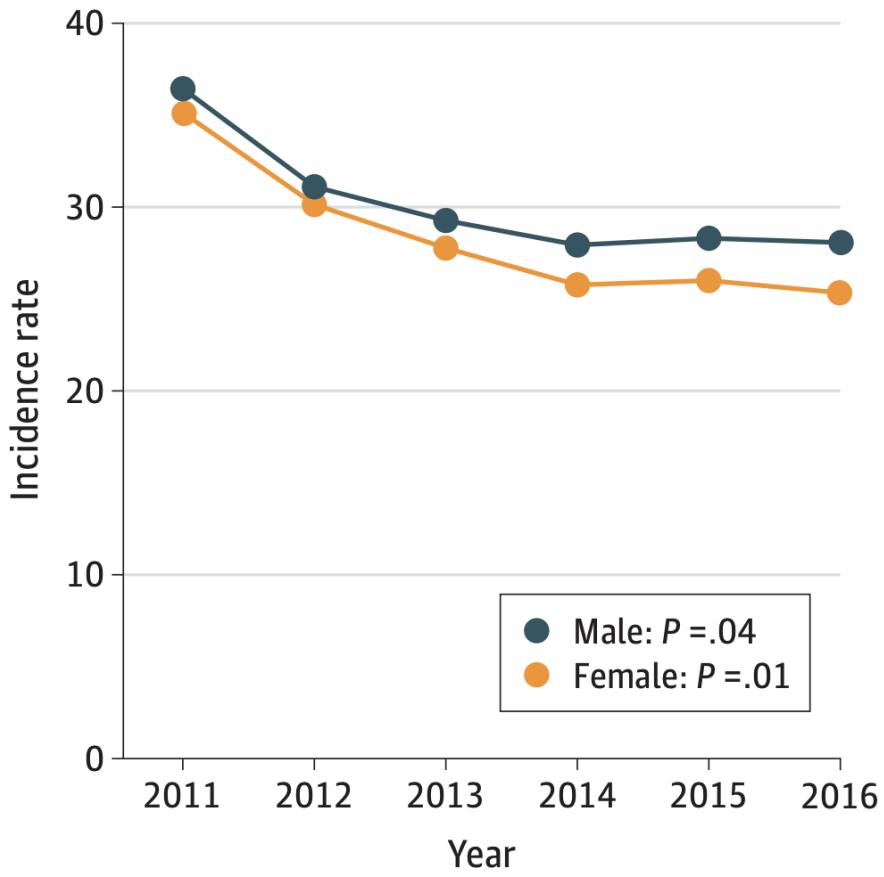
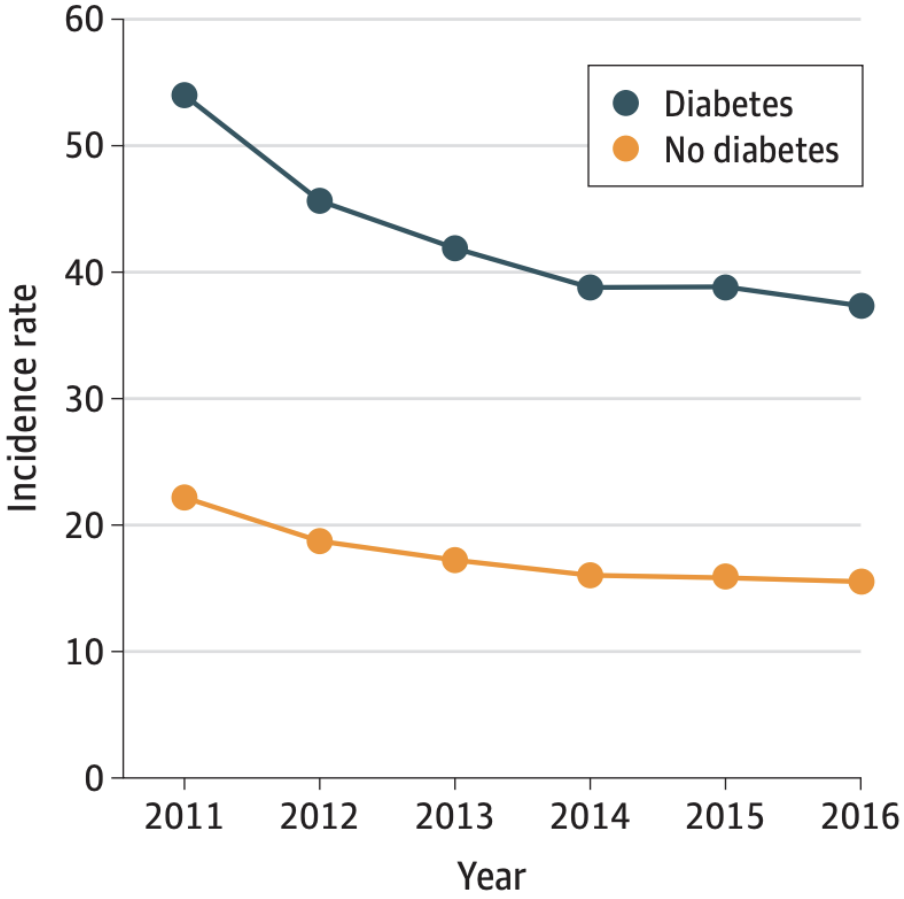
Overall Population (per 1000 beneficiaries)

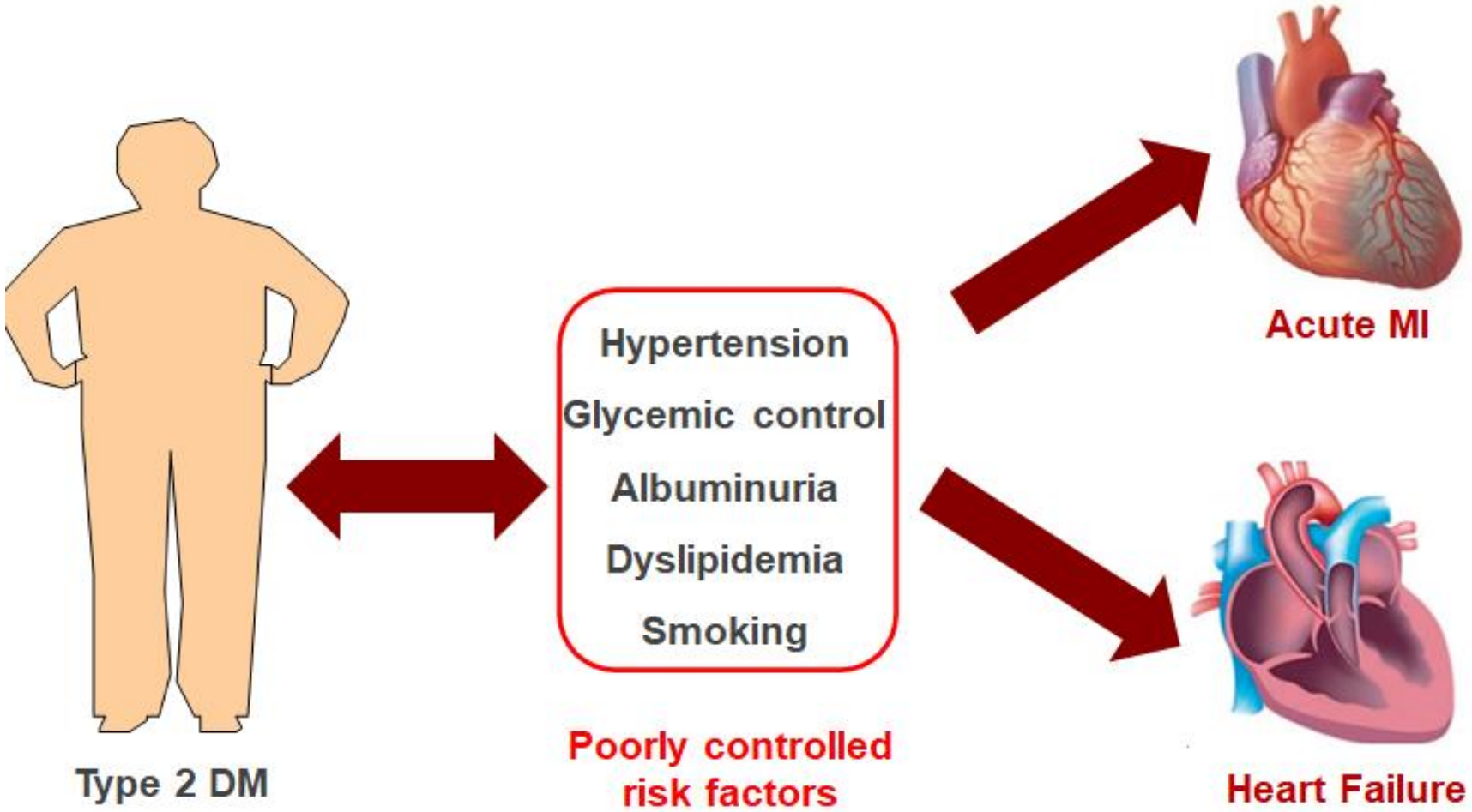


Stratified by Diabetes Status



Khera, Pandey et al. JAMA Network Open 2021

Diabetes, CV Risk Factors & Risk of HF & MI



Adapted from Rashwani et al. NEJM 2018

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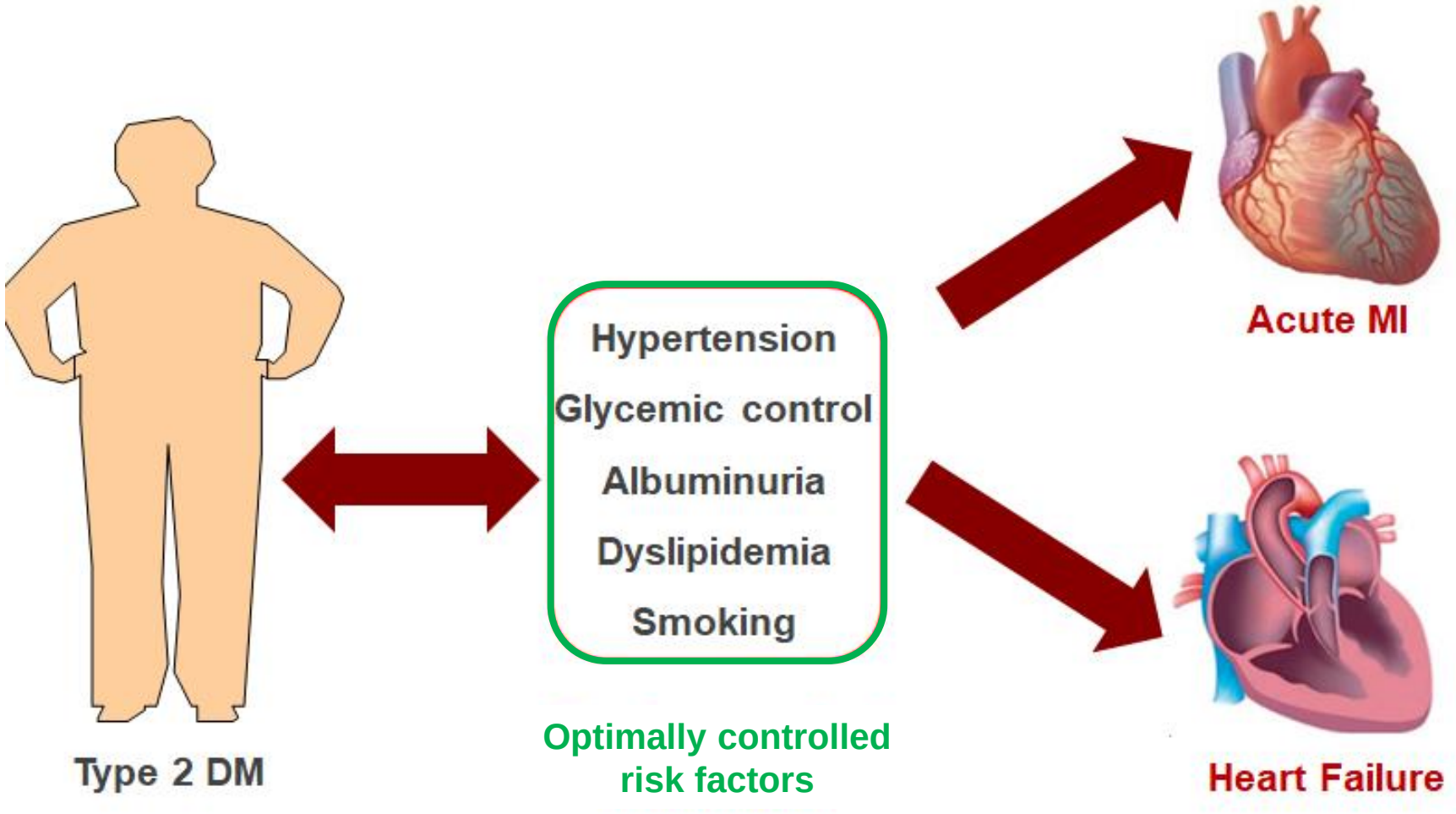

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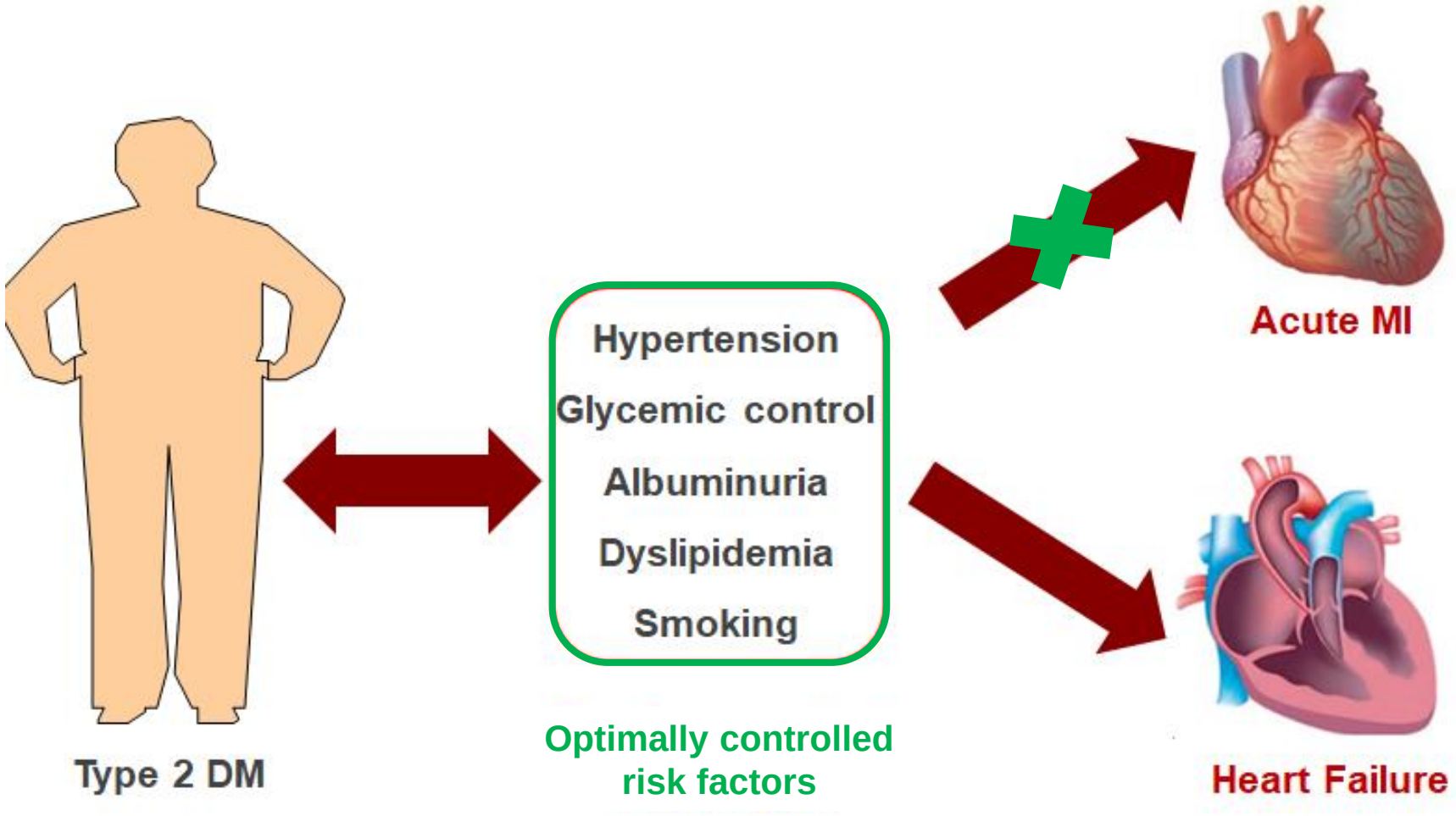

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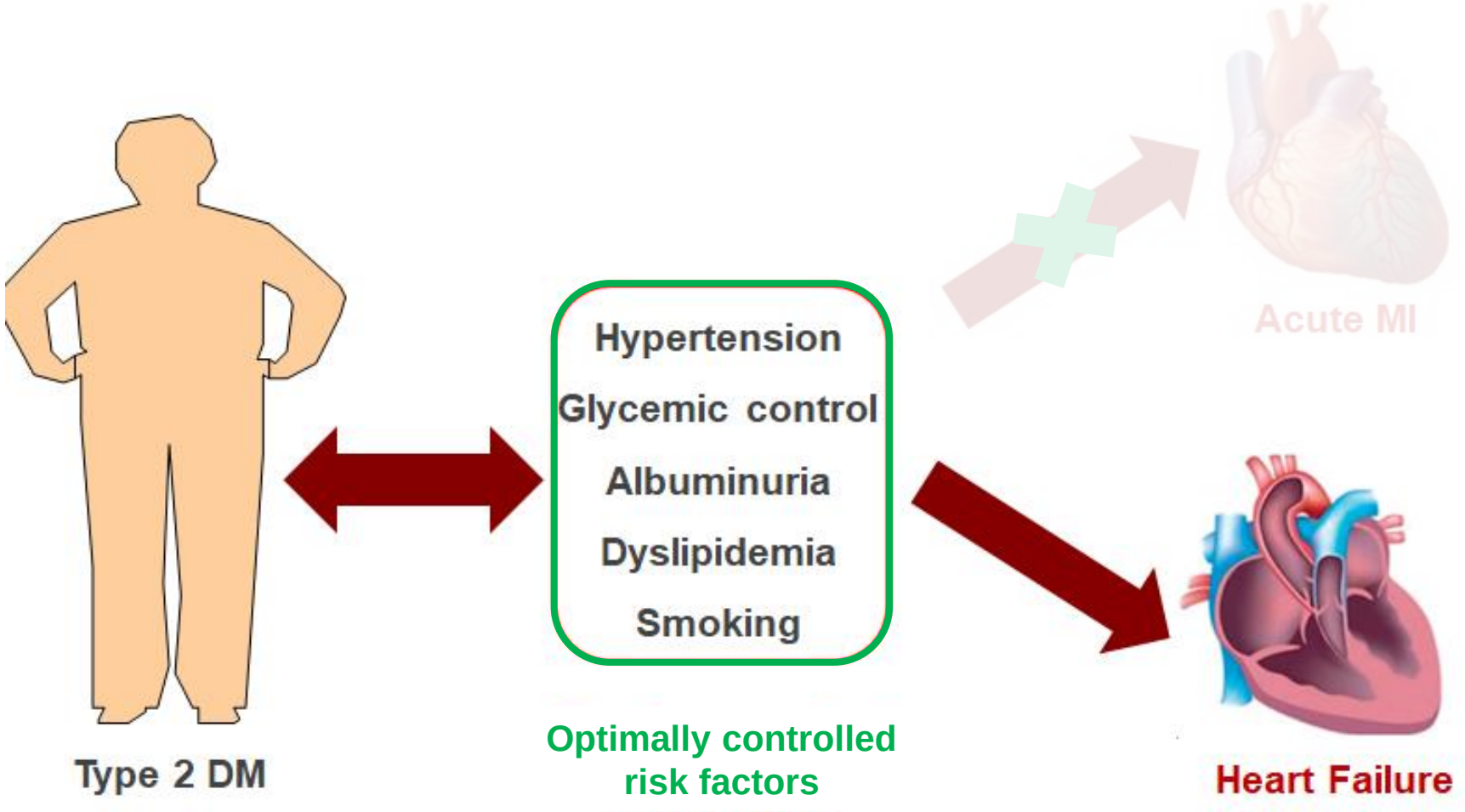

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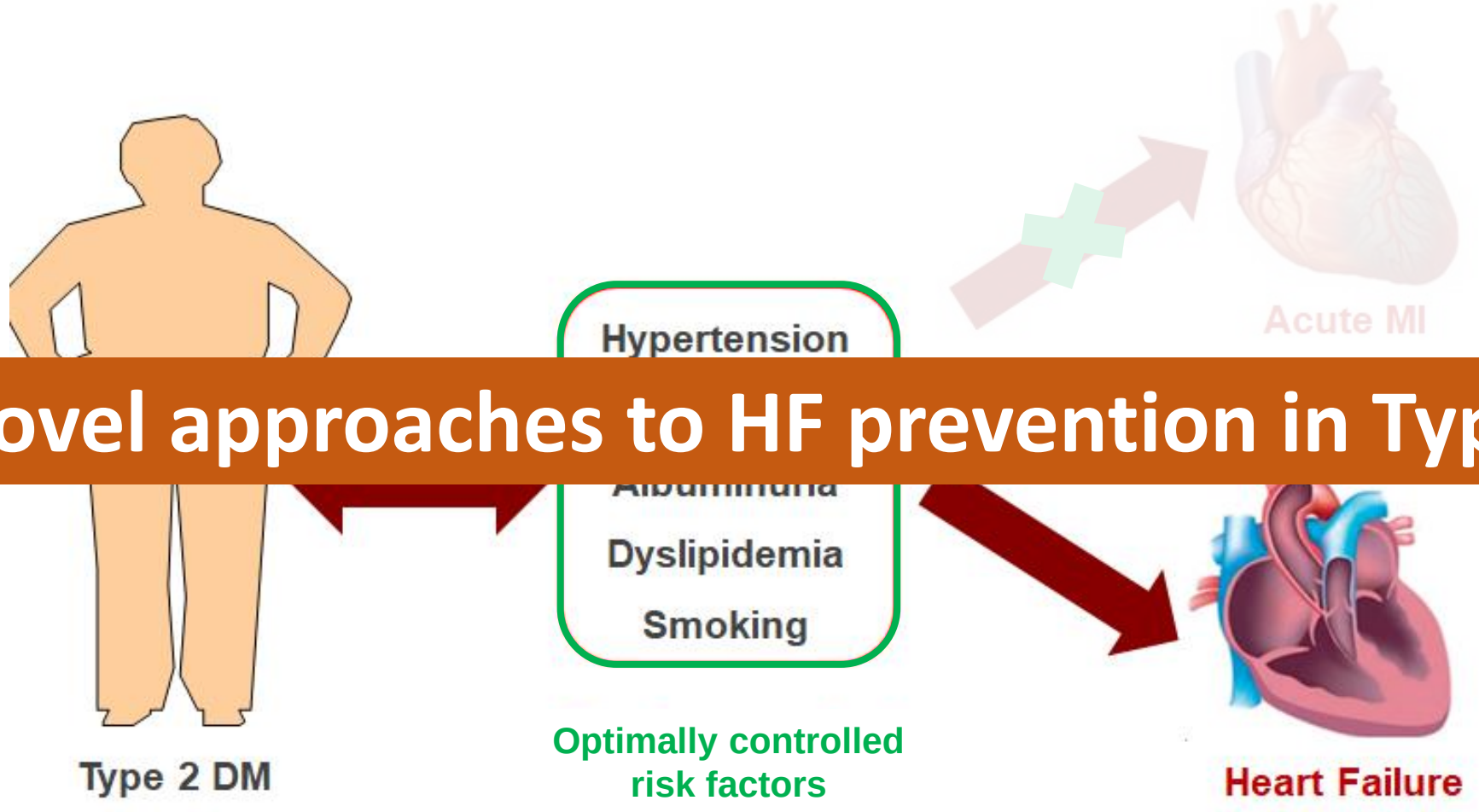
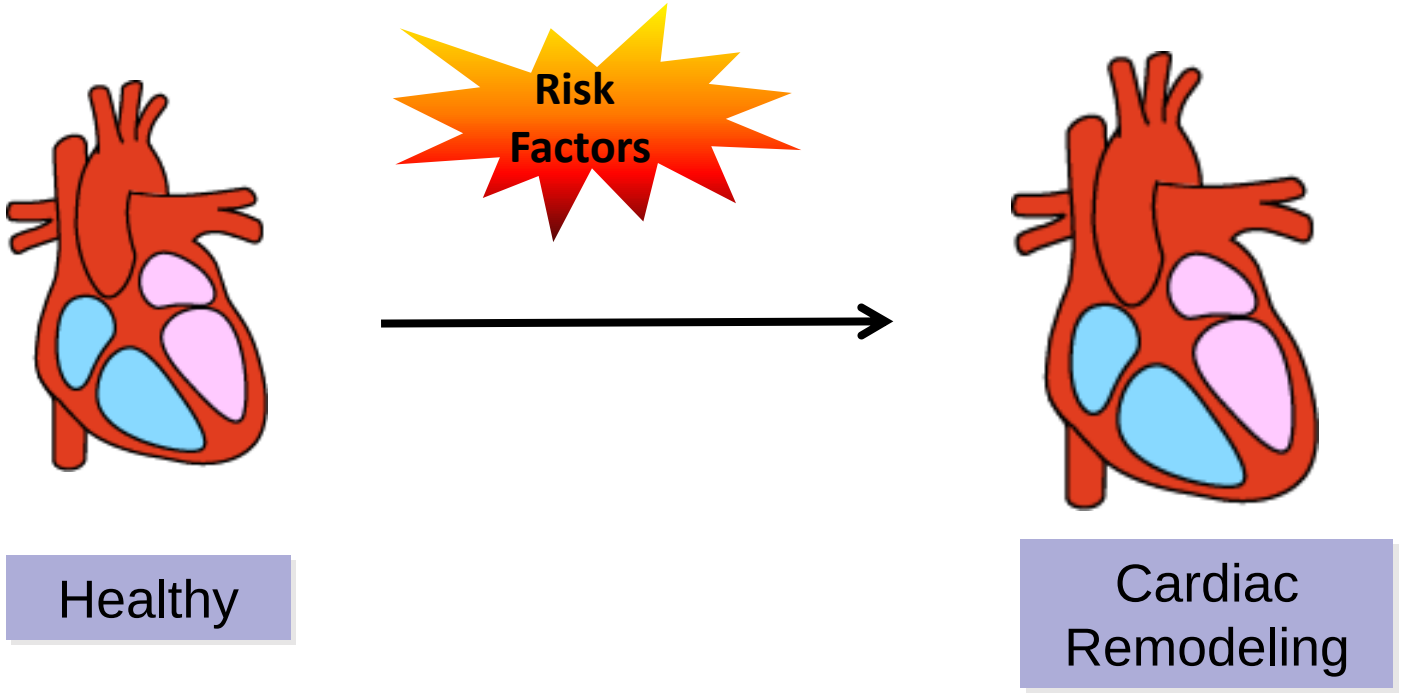


Need novel approaches to HF prevention in Type 2 DM

Adapted from Rashwani et al. NEJM 2018

Pathophysiology of HF Development



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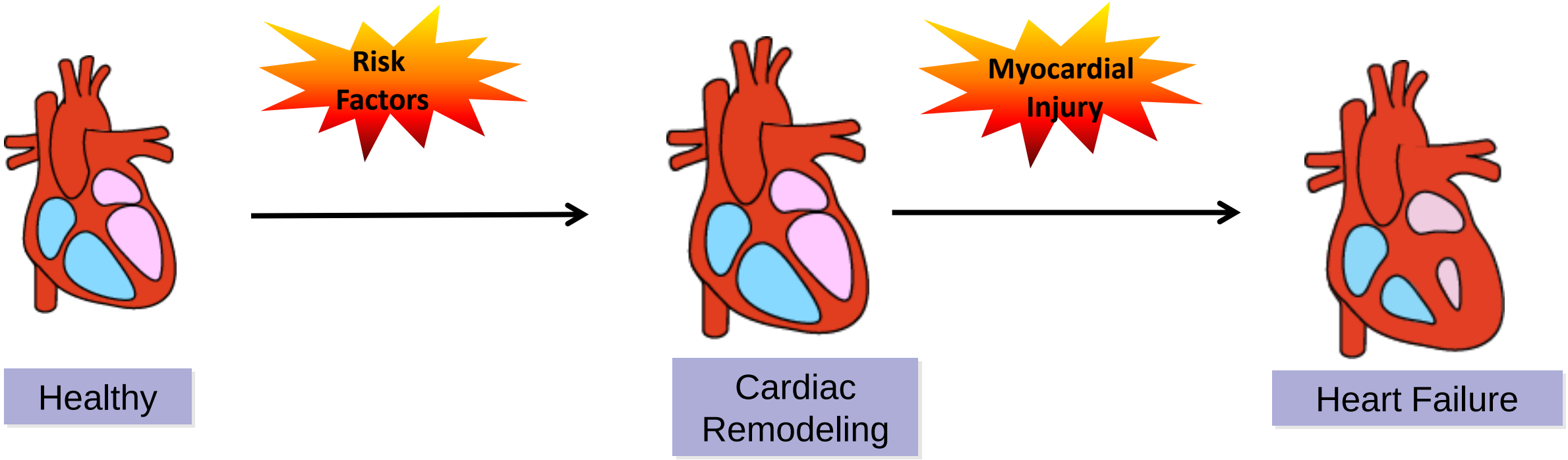

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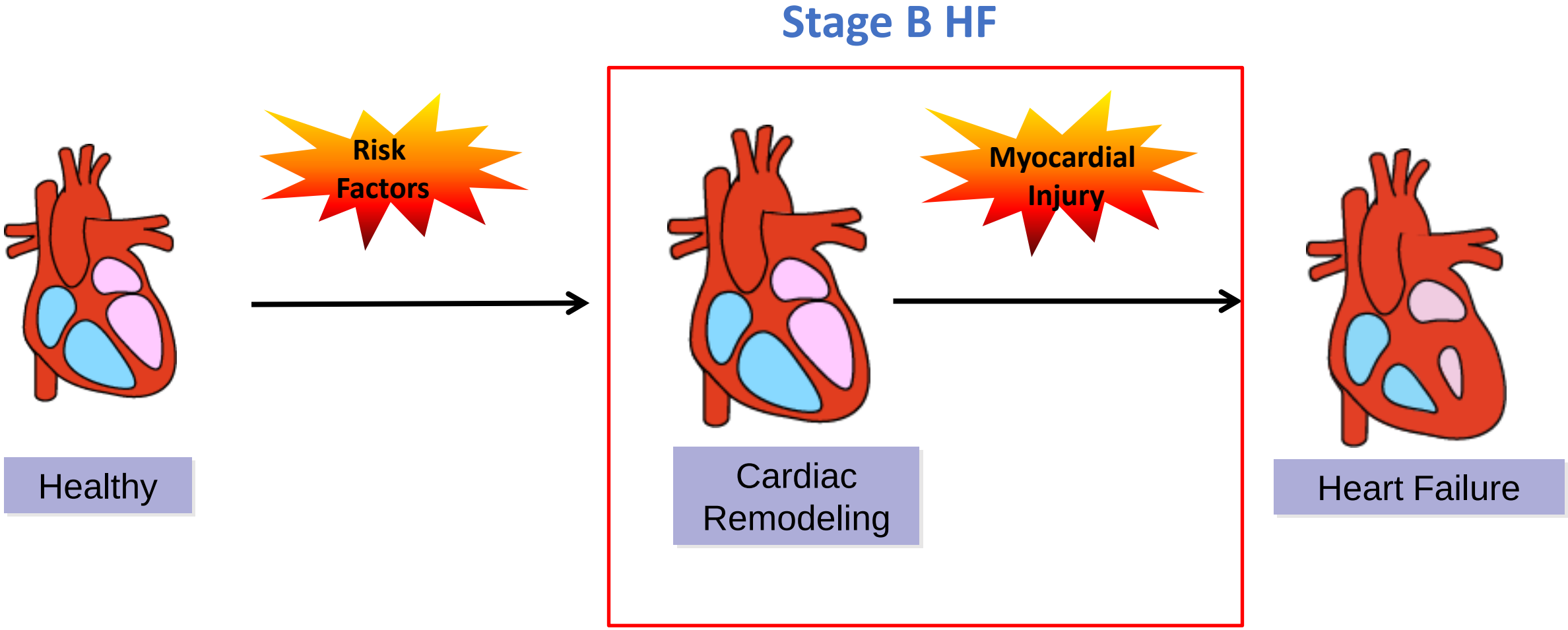


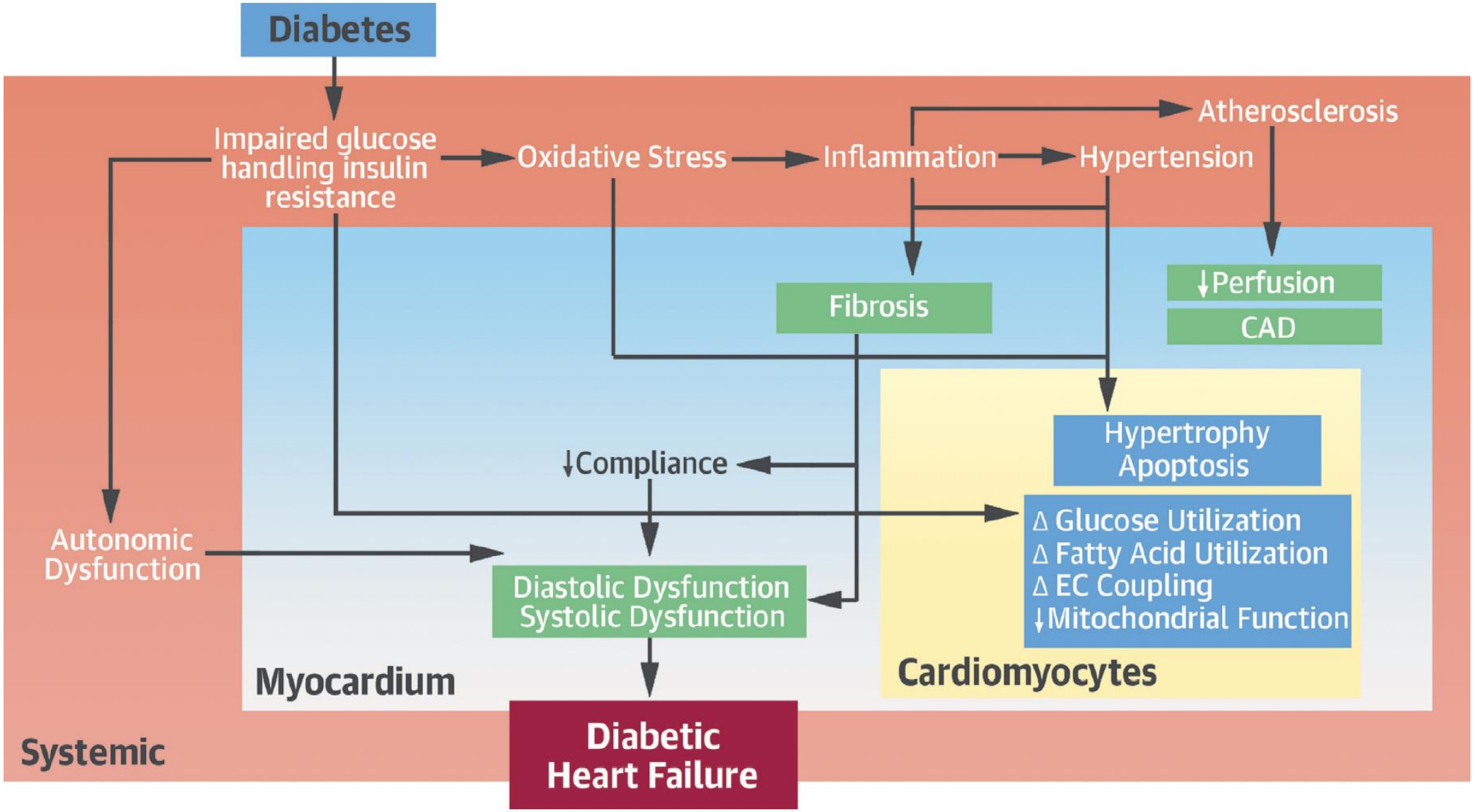
Diabetic Cardiomyopathy: Stage B HF Phenotype

Stage	Description	Functional Capacity (Peak VO_2)
Diabetes Stage A Heart Failure	• Metabolic derangement of the myocardium due to diabetes	**~28** ml/kg/min
Diabetic Cardiomyopathy: Stage B Heart Failure	• **Cardiac structural abnormalities** • **Early symptoms of DbCM** • **Impaired functional capacity (~75% normal)**	**~25% decrease** **≤21** ml/kg/min
Stage C Heart Failure	• Overt Heart Failure • HFpEF or HFrEF • Significant impact on daily activities	**>30% decrease** **10-15** ml/kg/min
Stage D Heart Failure	• Refractory Heart Failure requiring specialized interventions (e.g., Left Ventricular Assist Device) • Inability to complete daily activities	

HFpEF = Heart Failure with Preserved Ejection Fraction HFrEF = Heart Failure with Reduced Ejection Fraction

Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: ; Cardiovasc Imaging 2018; From et al. JACC 2010

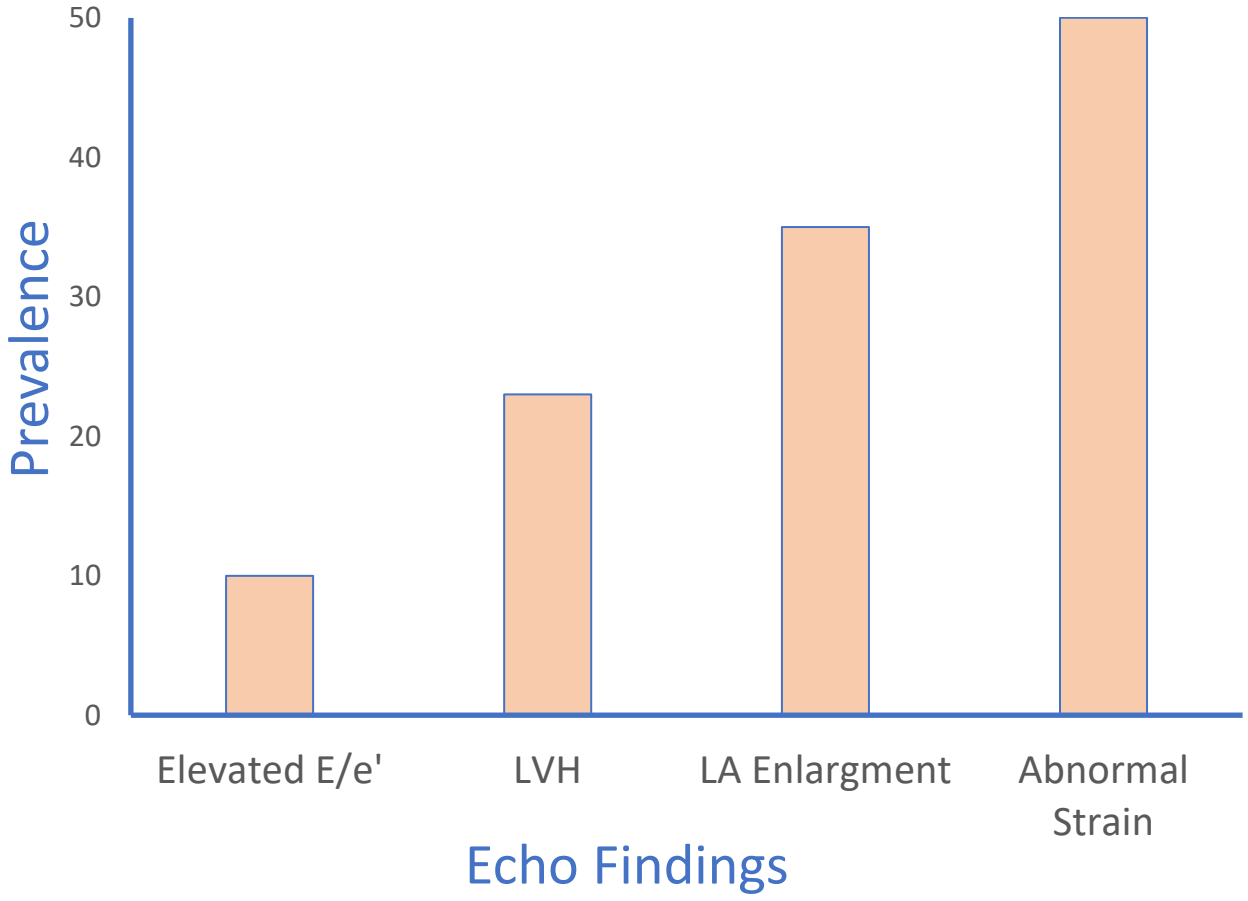
Potential Mechanisms

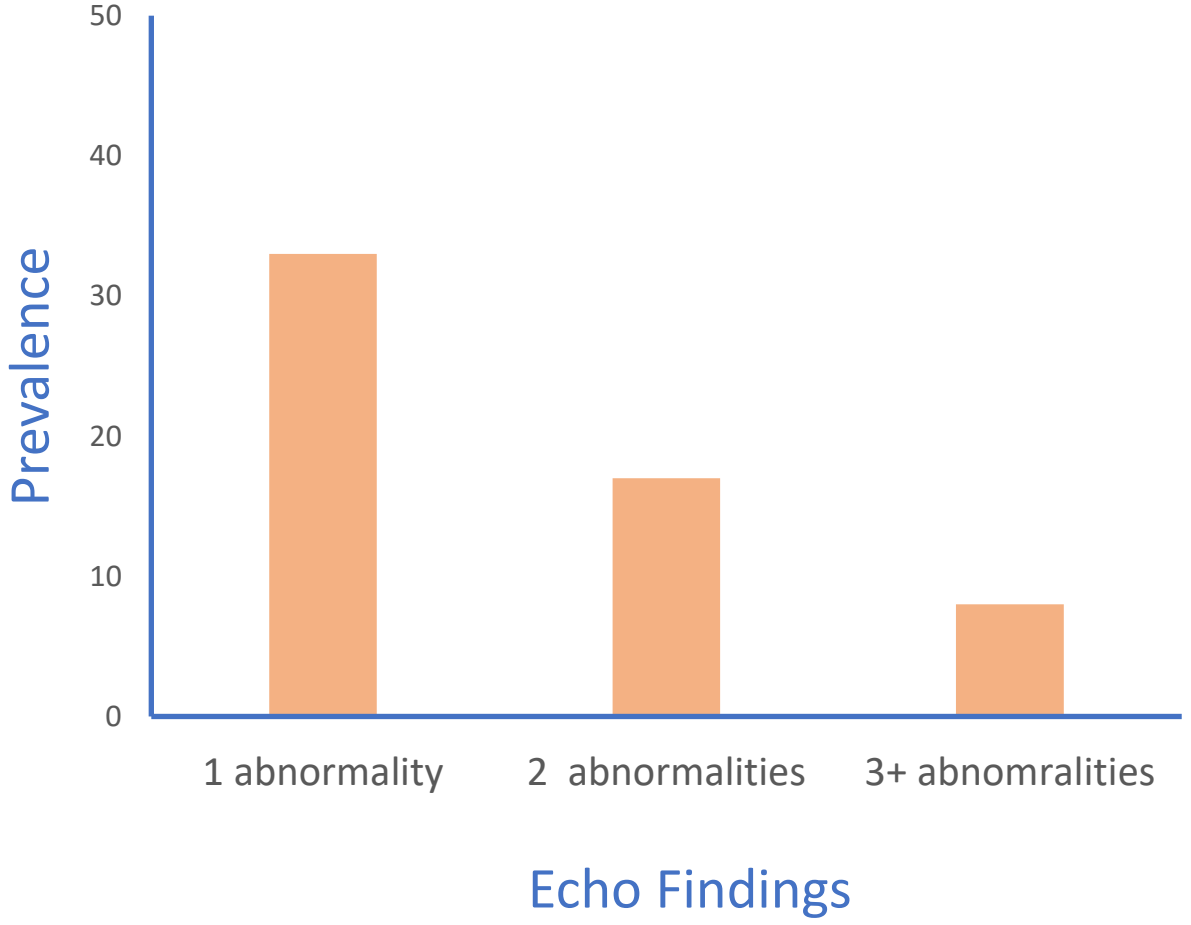


Marwick et al. JACC 2018

Diabetic Cardiomyopathy: Cardiac Impairments

N = 290 asymptomatic, community dwelling type 2 DM individuals, no ischemic heart disease
Mean age = 71 years, 55% Men
18 month follow up , 49 HF or death events





Wang et al. JACC Imaging 2018

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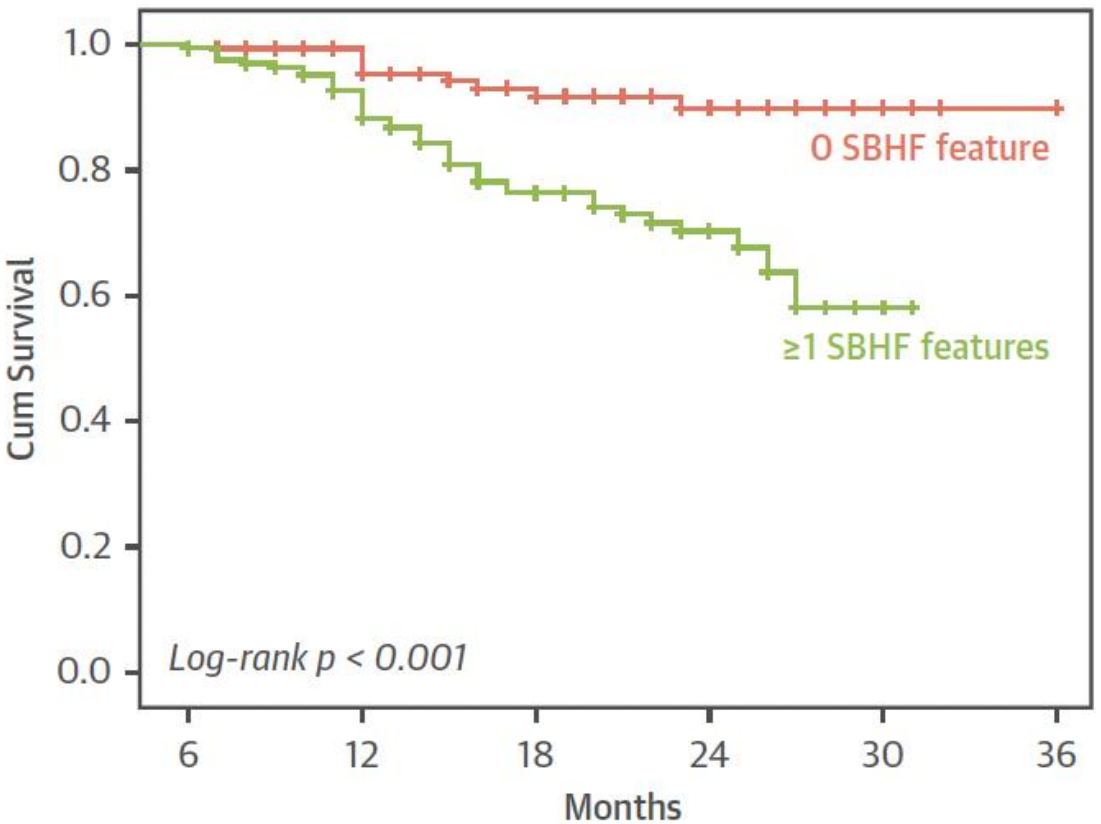
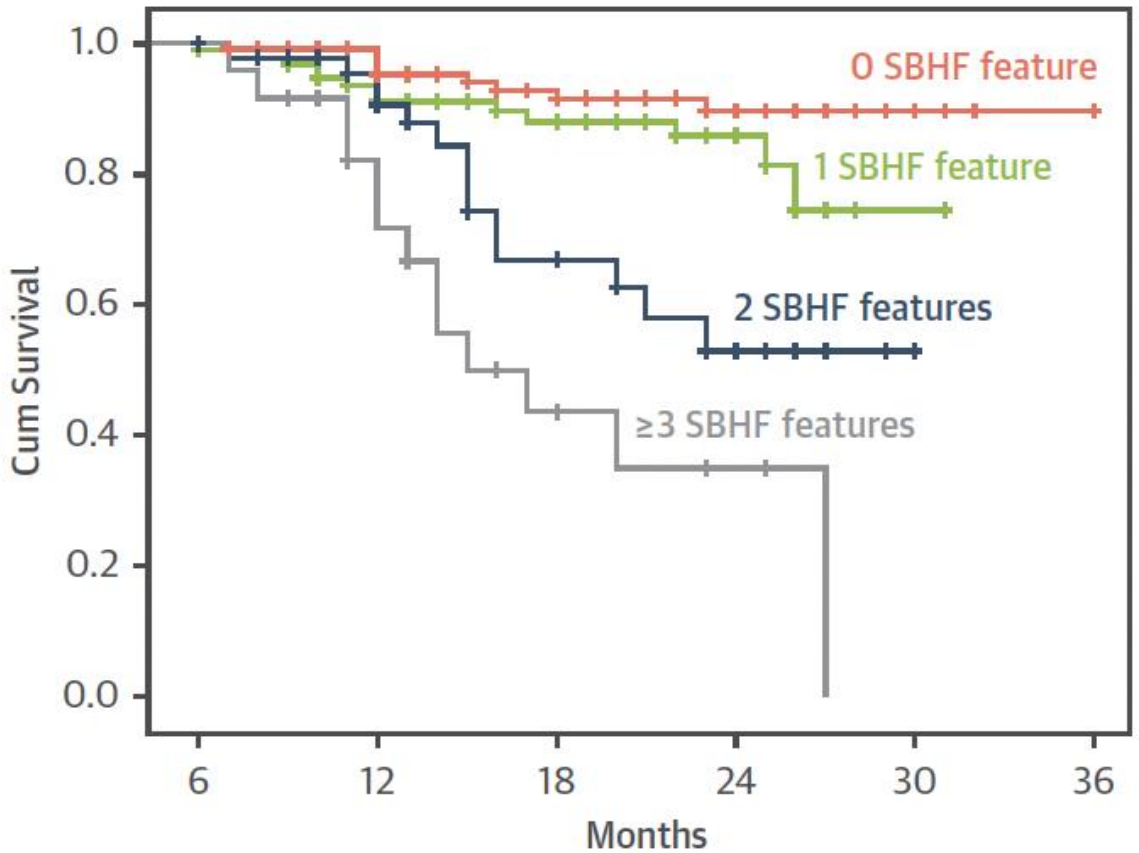




Wang et al. JACC Imaging 2018

Subclinical Cardiac Abnormalities and HF Risk

↑ Biomarkers + LVH → ↑↑ HF risk

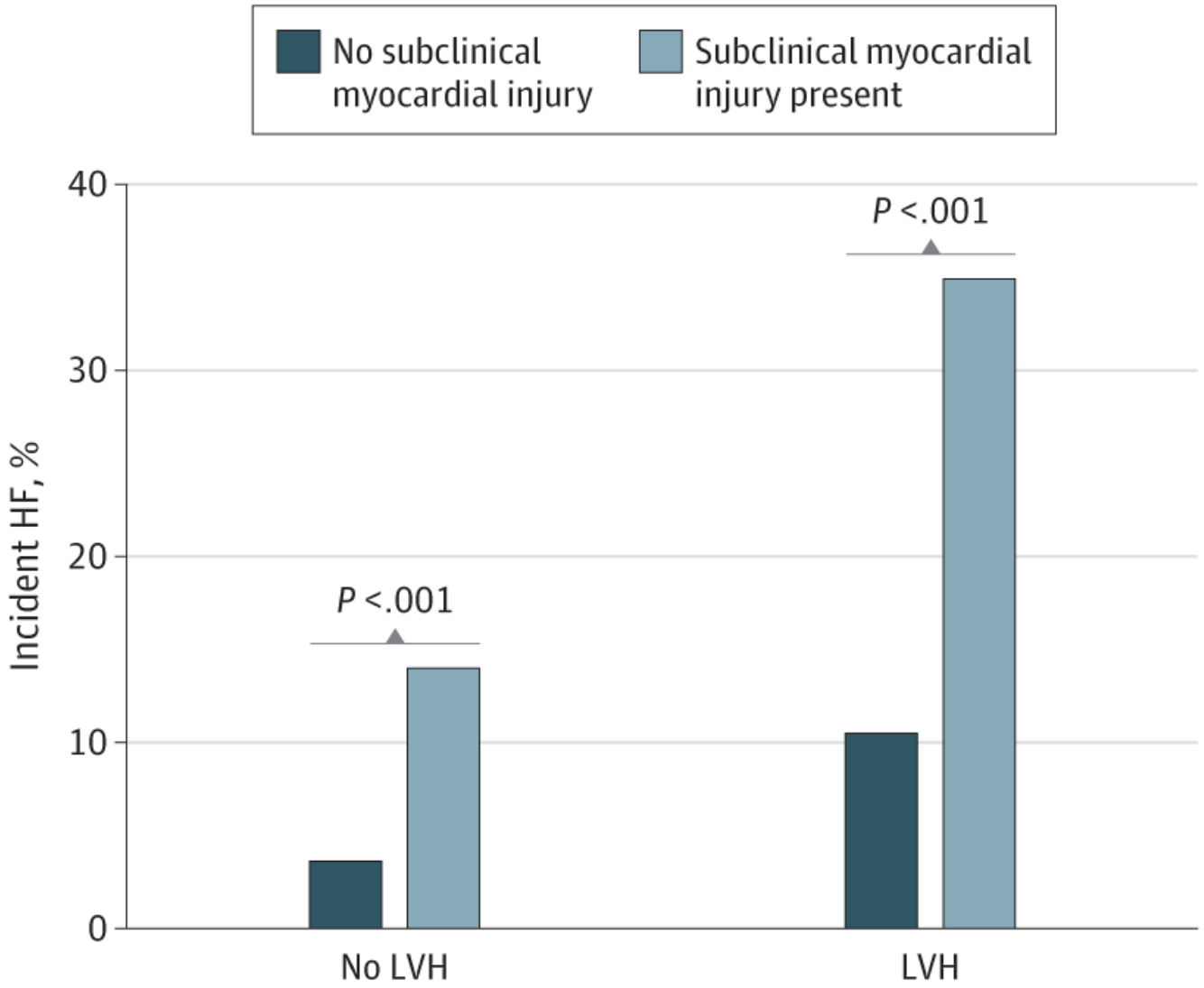
Jackson Heart Study

N = 3,987 community dwelling adults

64% Women, 6% with LVH by echo

25% with myocardial injury (hs-TnI > 6 ng/l)

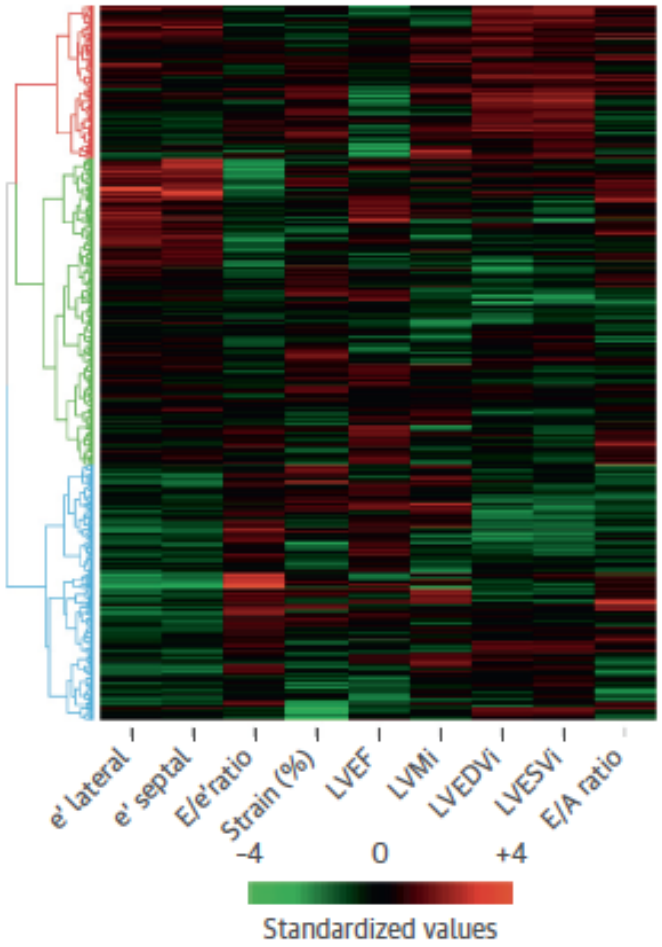
285 HF events over 10 year follow up

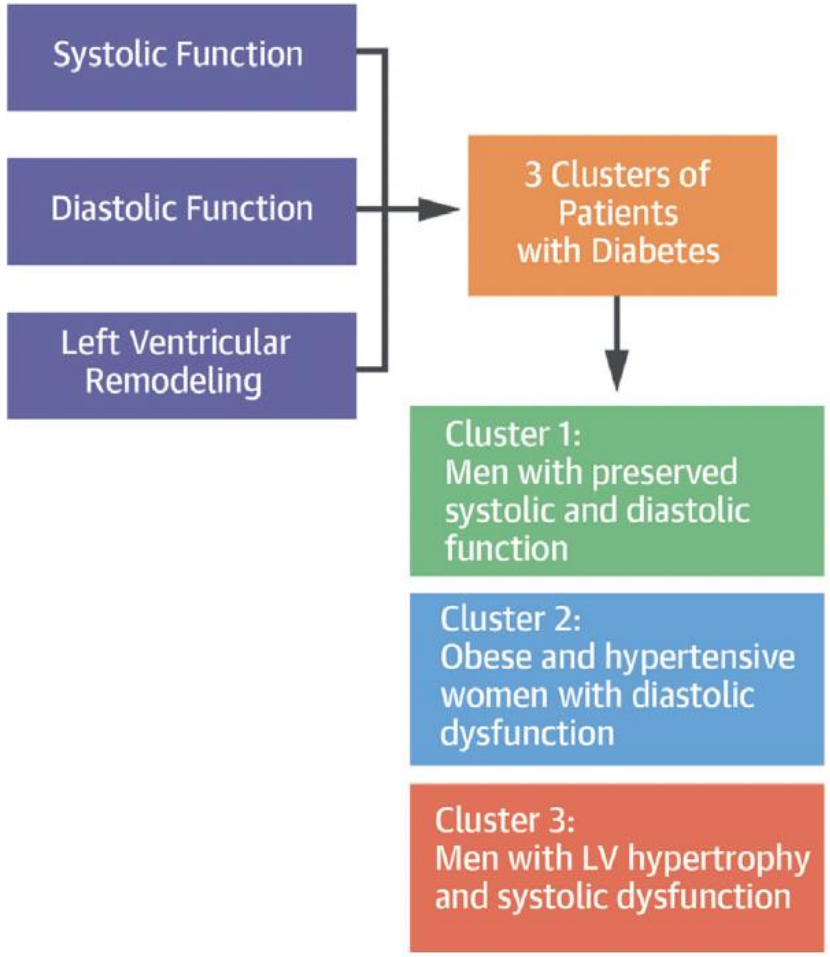


Pandey, et al JAMA Cardiology 2019

Phenotypic Variation in Diabetic Cardiomyopathy

Clustering analysis in 842 patients with type 2 DM
3 identified clusters with distinct echo characteristics





Ernade et al. JACC 2017

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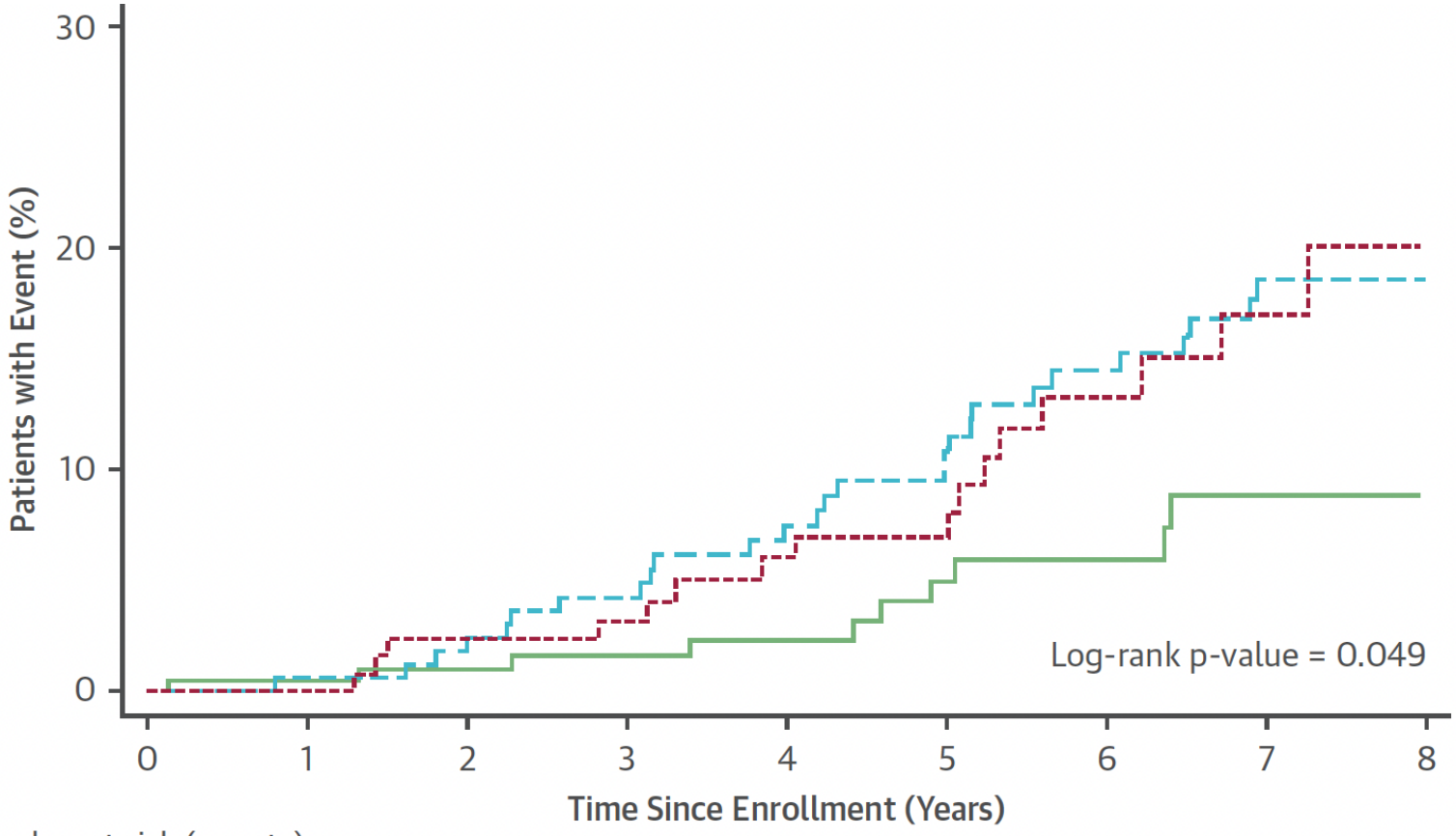


Number at risk (events)

Cluster 1	214	(1)	200	(1)	180	(1)	156	(1)	125	(3)	102	(1)	79	(2)	45	(0)	16
Cluster 2	168	(1)	165	(2)	162	(4)	155	(5)	140	(5)	131	(5)	112	(5)	84	(0)	42
Cluster 3	139	(0)	133	(3)	125	(1)	114	(3)	95	(1)	84	(5)	54	(2)	35	(1)	6

Ernade et al. JACC 2017

Identifying Diabetic Cardiomyopathy

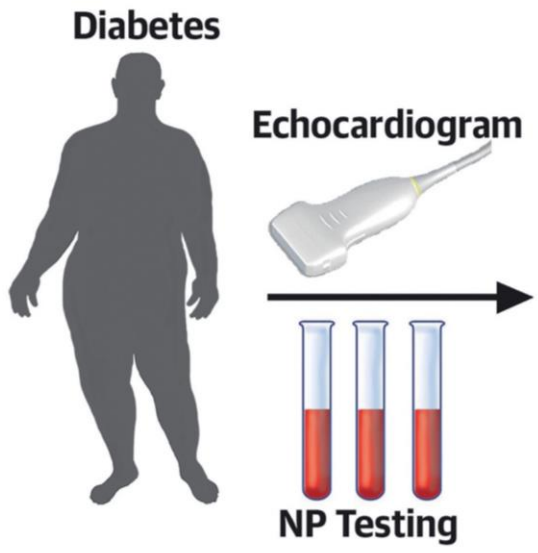
Diabetic cardiomyopathy can be identified via echocardiogram abnormalities and cardiac biomarkers in the absence of other etiologies of abnormalities in cardiac structure and function such as ischemic heart disease

- ☑ **Confirm echocardiographic abnormalities common in DbCM patients:**
  - ❑ Left Ventricular Hypertrophy (LVH)
  - ❑ Impaired Global Longitudinal Strain (GLS)
  - ❑ Left Atrial Enlargement (LAE)
  - ❑ Diastolic Dysfunction (abnormal E/e')
- ☑ **Confirm elevation of NT-ProBNP biomarker**
- ☑ **Confirm elevation of high sensitivity troponin biomarker**
- ☒ **Exclude:**
  - ❑ Coronary Artery Disease
  - ❑ Valvular disease
  - ❑ Congenital Heart Failure
  - ❑ Uncontrolled Hypertension

Diabetic Cardiomyopathy: Prevalence

Diabetic Cardiomyopathy

2900 individuals with DM
3 pooled community-based cohorts



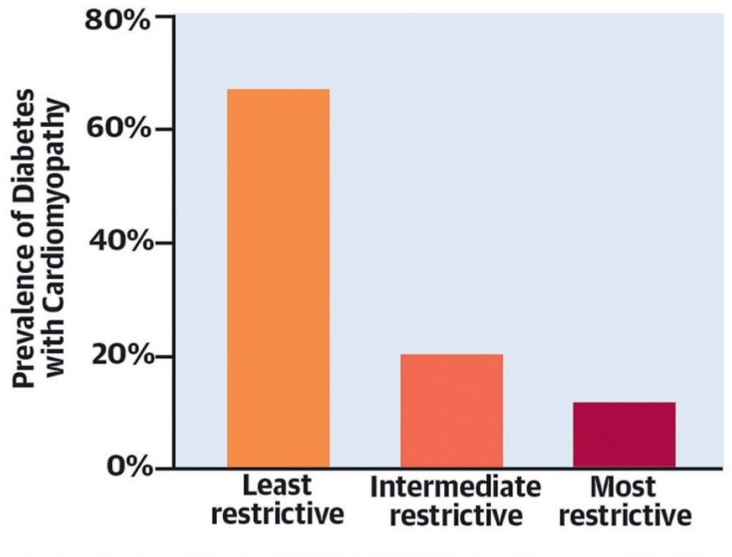
Definitions of Cardiomyopathy

Least Restrictive:
At least 1 of 3 abnormal echo criteria

Intermediate Restrictive:
At least 2 of 3 abnormal echo criteria

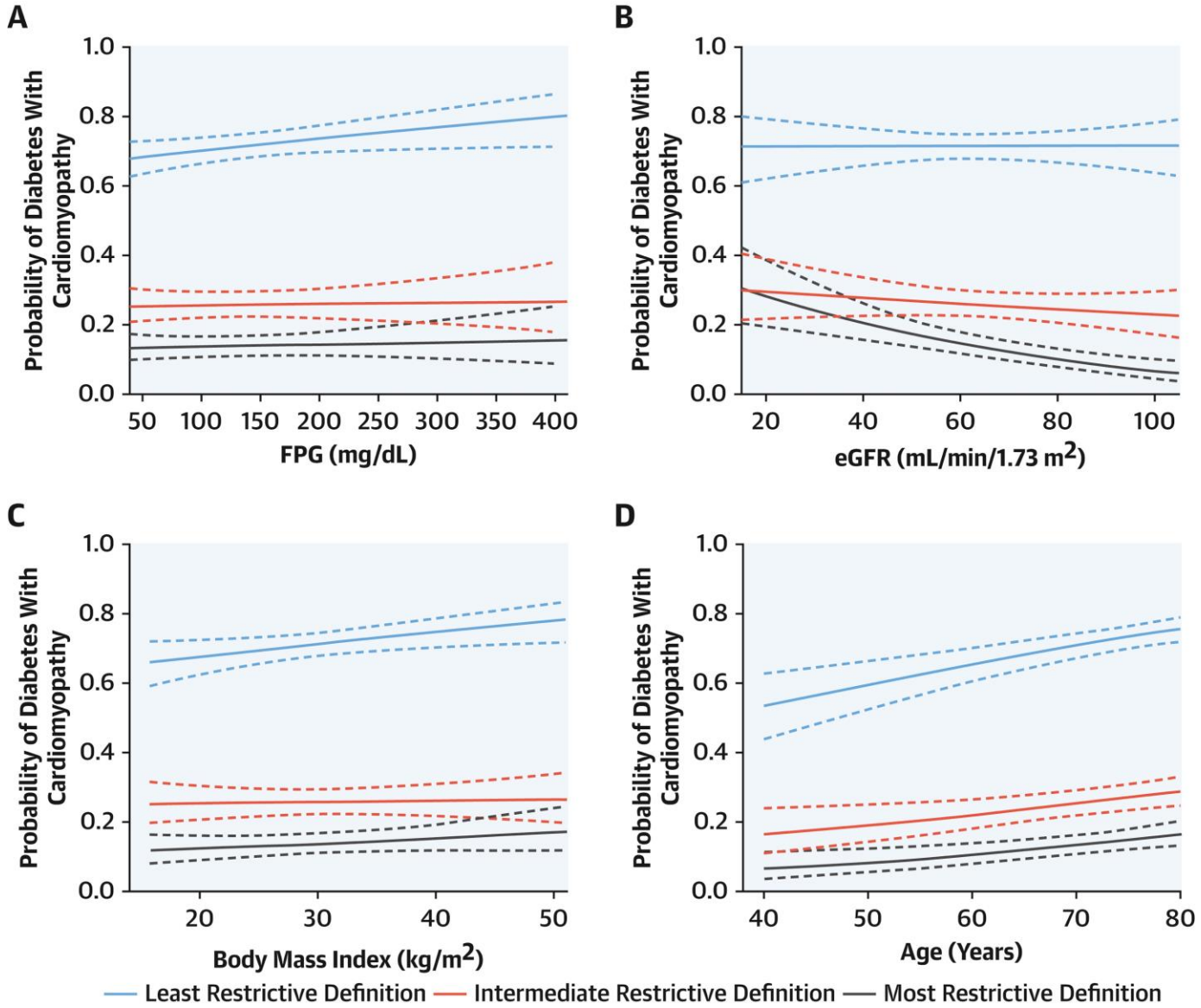
Most Restrictive:
Elevated NP levels and at least 2 of 3 abnormal echo criteria

Prevalance Among Individuals with Diabetes



Segar, Pandey et al JACC 2021

Risk Factors for Diabetic Cardiomyopathy



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Diabetic Cardiomyopathy: Prognostic Implications

	Model 1		Model 2	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Least restrictive criteria (ref: euglycemia)				
Prediabetes	1.19 (0.92-1.55)	0.18	1.12 (0.86-1.46)	0.42
Diabetes without CM	1.40 (0.97-2.03)	0.07	1.28 (0.88-1.86)	0.20
Diabetes with CM	2.56 (1.97-3.33)	<0.001	1.99 (1.50-2.65)	<0.001
Intermediate restrictive criteria (ref: euglycemia)				
Prediabetes	1.19 (0.92-1.55)	0.18	1.12 (0.86-1.46)	0.41
Diabetes without CM	1.83 (1.40-2.40)	<0.001	1.57 (1.18-2.09)	0.002
Diabetes with CM	3.62 (2.59-5.05)	<0.001	2.46 (1.72-3.53)	<0.001
Most restrictive criteria (ref: euglycemia)				
Prediabetes	1.19 (0.92-1.55)	0.18	1.12 (0.86-1.46)	0.41
Diabetes without CM	1.94 (1.49-2.52)	<0.001	1.64 (1.24-2.17)	<0.001
Diabetes with CM	3.99 (2.71-5.86)	<0.001	2.55 (1.69-3.86)	<0.001

Model 1 = age, sex, and race. Model 2 = Model 1 + systolic blood pressure, use of antihypertension medication, body mass index, smoking, alcohol use, estimated glomerular filtration rate, high-density lipoprotein cholesterol, and total cholesterol.

CI = confidence interval; CM = cardiomyopathy; HR = hazard ratio.

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Diabetic Cardiomyopathy: Prognostic Implications

	Least Restrictive Definition		Intermediate Restrictive Definition		Most Restrictive Definition	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Excluding participants with hypertension (n = 2,902; ref: euglycemia)						
Prediabetes	0.89 (0.70-1.13)	0.34	0.89 (0.70-1.13)	0.34	0.89 (0.70-1.13)	0.34
Diabetes without CM	1.17 (0.77-1.78)	0.46	1.20 (0.86-1.66)	0.28	1.21 (0.88-1.66)	0.24
Diabetes with CM	1.45 (1.03-1.96)	0.03	1.77 (1.19-2.93)	0.01	3.02 (1.24-5.88)	0.009
Excluding participants with hypertension or obesity (n = 2,434; ref: euglycemia)						
Prediabetes	0.87 (0.68-1.12)	0.29	0.87 (0.68-1.12)	0.29	0.87 (0.68-1.12)	0.29
Diabetes without CM	1.03 (0.64-1.67)	0.89	1.15 (0.80-1.66)	0.44	1.12 (0.79-1.60)	0.52
Diabetes with CM	1.41 (0.98-2.07)	0.06	1.99 (1.04-3.86)	0.02	3.25 (1.11-8.07)	0.01

Adjusted for age, sex, race, body mass index, smoking, alcohol use, estimated glomerular filtration rate, high-density lipoprotein cholesterol, and total cholesterol. Events were censored at last available follow-up.

CI = confidence interval; CM = cardiomyopathy; HR = hazard ratio.

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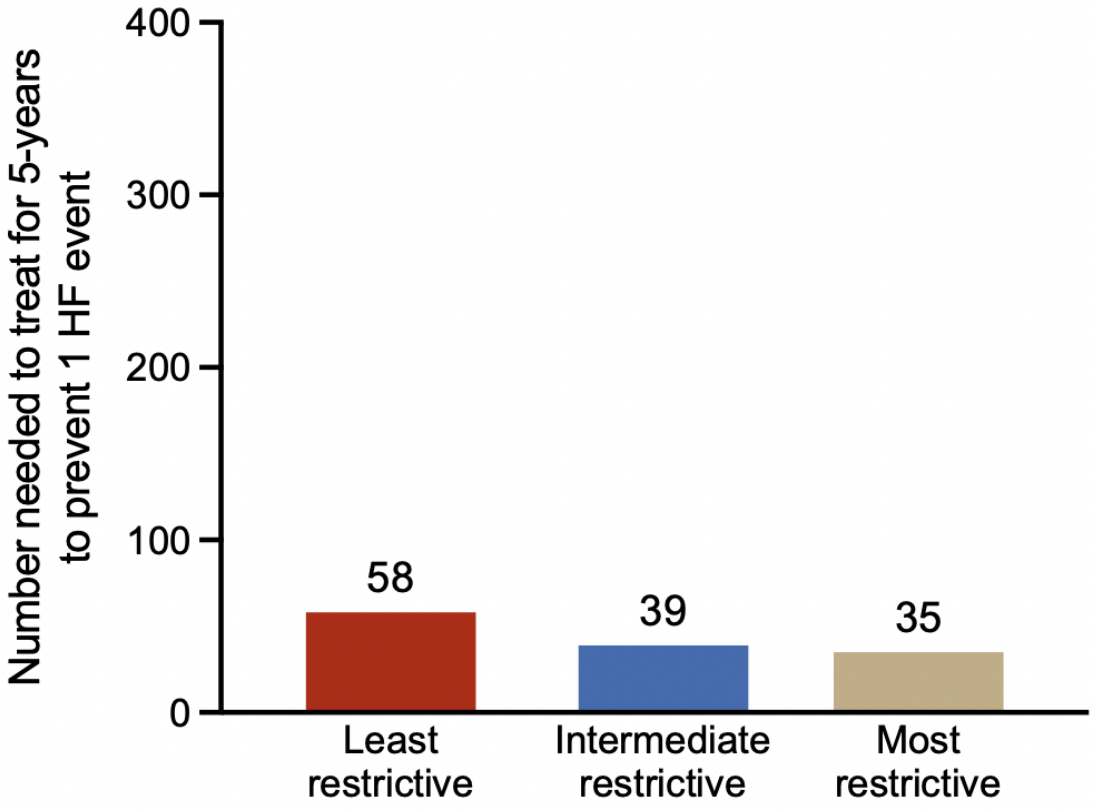
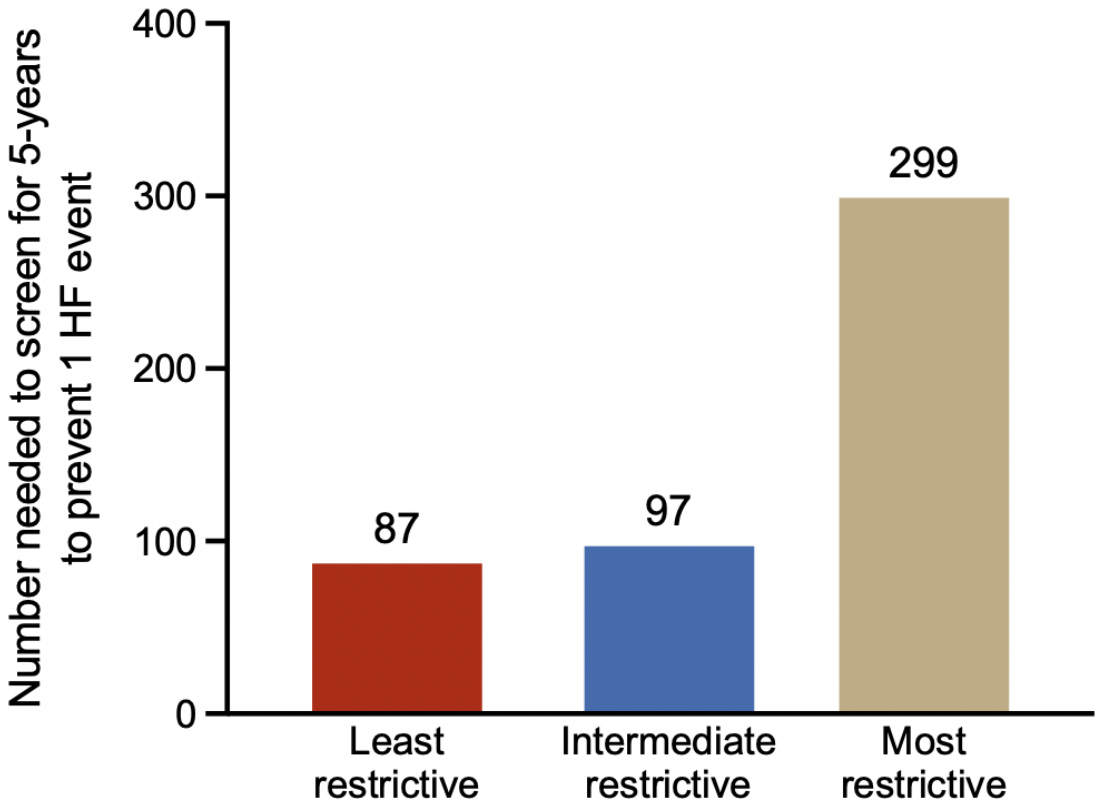
Screening for Diabetic Cardiomyopathy

Assuming a 25% relative risk reduction with an effective therapy





Segar, Pandey et al (unpublished)

Therapies for Diabetic Cardiomyopathy

ClinicalTrials.gov Search Results 11/24/2021

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Evaluation of Alpha-Lipoic Acid in Diabetic Cardiomyopathy	Recruiting	No Results Available	• Diabetic Cardiomyopathies	• Dietary Supplement: Physiomance acide lipoïque gold • Dietary Supplement: Placebo - Physiomance acide lipoïque gold	• Nice Hospital, Nice, France
2	Safety and Efficacy of AT-001 in Patients With Diabetic Cardiomyopathy	Recruiting	No Results Available	• Diabetic Cardiomyopathies	• Drug: AT-001 • Drug: Placebo	• Westside Medical Associates of Los Angeles, Beverly Hills, California, United States • University of California, San Diego (UCSD), La Jolla, California, United States • Clinical Trials Research, Lincoln, California, United States • University of California - Irvine Medical Center, Orange, California, United States • Metabolic Institute of America, Tarzana, California, United States • Lundquist Institute for Biomedical Innovation at Harbor UCLA Medical Center, Torrance, California, United States • ALL Medical Research, LLC, Cooper City, Florida, United States • New Generation of Medical Research, Hialeah, Florida, United States • Broward Research Center, Pembroke Pines, Florida, United States • Progressive Medical Research, Port Orange, Florida, United States • and 70 more
3	The DAPA-MEMRI Trial	Recruiting	No Results Available	• Heart Failure • Diabetic Cardiomyopathies	• Drug: Dapagliflozin 10 milligrams [Farxiga] • Drug: Placebo	• University of Edinburgh, Edinburgh, Scotland, United Kingdom
4	A Study to Evaluate the Effect of IMB-1018972 on Cardiac Energetics in Patients With Type 2 Diabetes (IMPROVE-DiCE)	Recruiting	No Results Available	• Type 2 Diabetes • Diabetic Cardiomyopathies	• Drug: IMB-1018972	• Oxford University Hospital, Oxford, United Kingdom

Conclusion

- Diabetic cardiomyopathy is common among patients with type 2 DM and represents an intermediate biological stage in development of heart failure
- Diabetic cardiomyopathy can be identified using echocardiographic examination and cardiac biomarker assessment
- Presence of diabetic cardiomyopathy identifies individuals at an increased risk of HF
- Results from trials of therapies targeting diabetic cardiomyopathy are awaited

Acknowledgements

Collaborators

Dr. Matthew Segar, THI

Dr. Kershaw Patel, Methodist

Dr. Muthiah Vaduganathan, BWH

Investigators from ARIC, MESA, Look AHEAD and other cohort studies

Study Datasets

BioLINCC
Biologic Specimen and Data Repository Information Coordinating Center
Web Access to NHLBI Biospecimens and Data

Cardiovascular Health Study

Framingham Heart Study

Atherosclerosis Risk in Community Study

Multiethnic study of Atherosclerosis

Dallas Heart Study

Chronic Renal Insufficiency Cohort Study

Look AHEAD Study Cohort

Funding Sources

NIH
National Institute on Aging

GILEAD

APPLIED THERAPEUTICS

Southwestern Health Resources
Texas Health Resources
UTSouthwestern Medical Center