Patho-physiology and Management of Diabetic Cardiomyopathy

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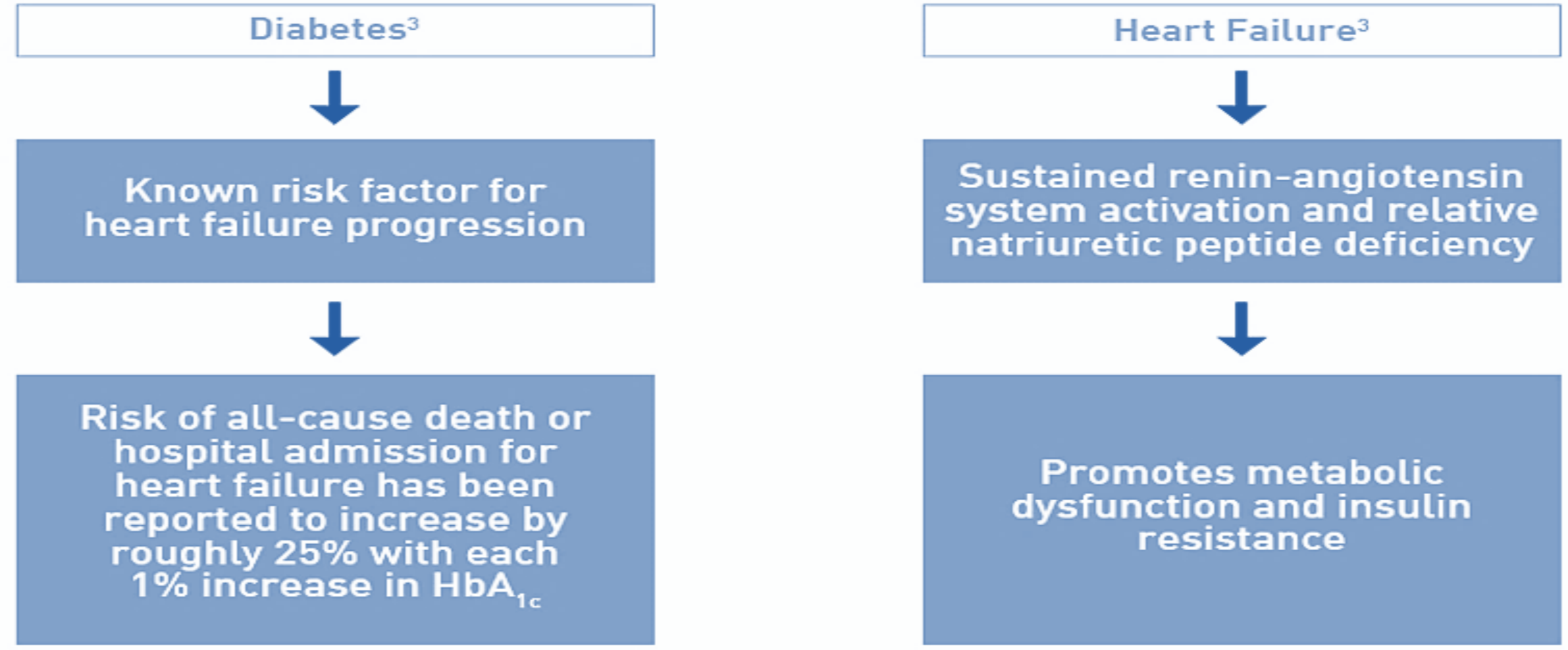
Heart Failure & Diabetes – Mutual Association

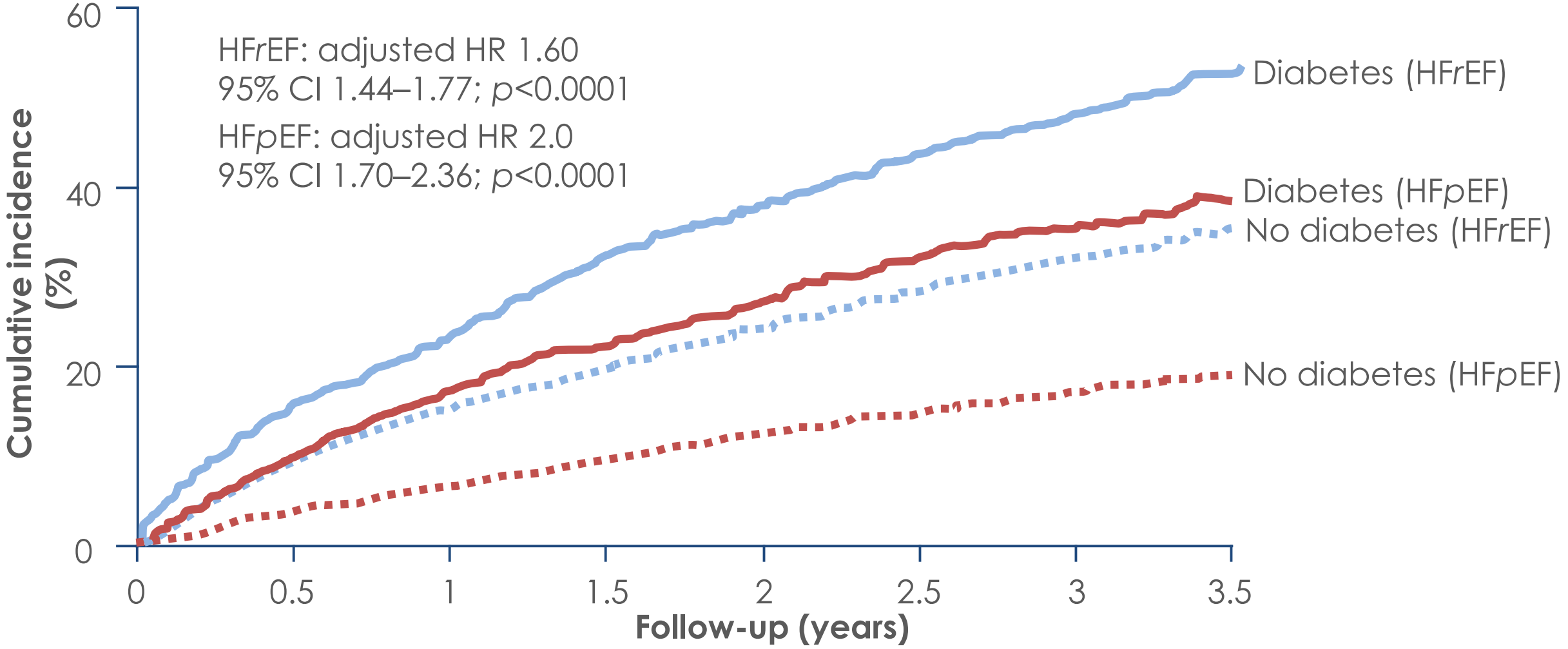


Heart Failure and Diabetes are common companions

- At least a third of all patients with heart failure have diabetes.
- Increasing numbers of older patients with T2 DM.
- Improved survival from cardiovascular events
- Current management is focused on targeting modifiable risk factors for heart failure
  - hyperglycemia, dyslipidemia, hypertension, obesity and anemia.
- But none of these interventions substantially prevents heart failure or improves its outcomes.

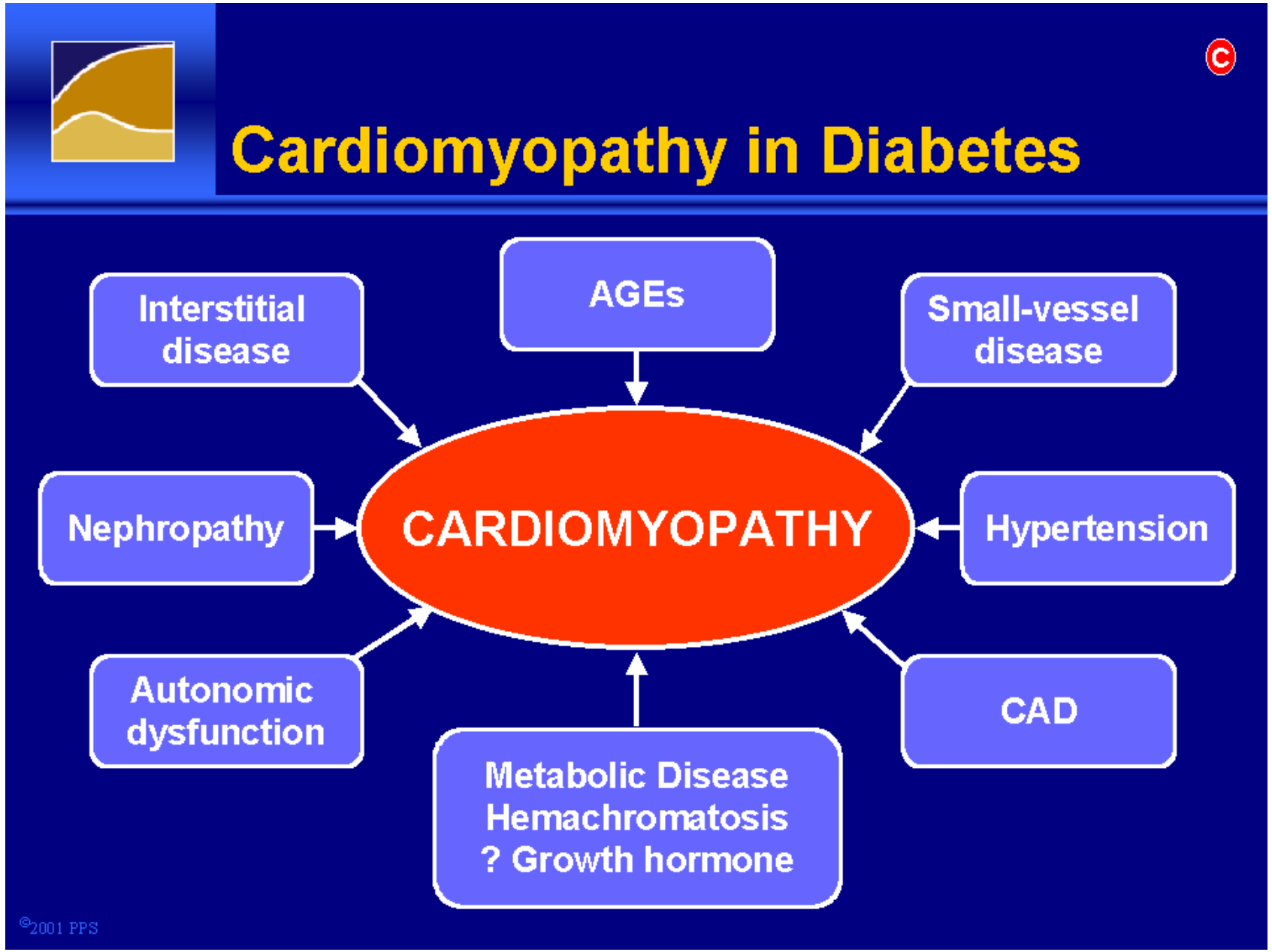
Curr Cardiol Rev. 2016 Aug; 12(3): 249–255

Diabetes Increases Risk of Hospitalization or Death due to Heart failure

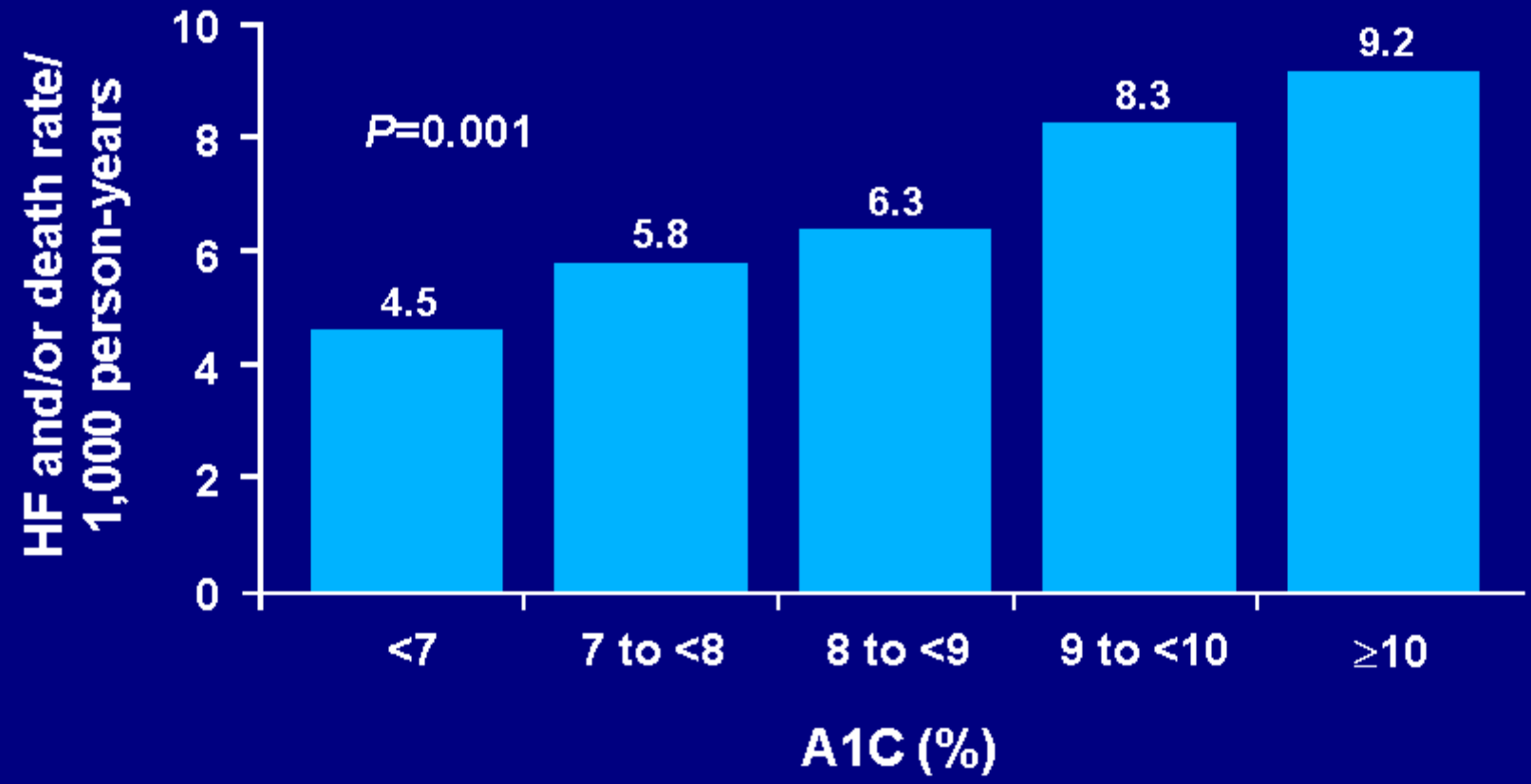


HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

MacDonald et al. Eur Heart J 2008;29:1377-85.


Cardiomyopathy in Diabetes
AGEs
Interstitial disease
Small-vessel disease
Nephropathy
CARDIOMYOPATHY
Hypertension
Autonomic dysfunction
CAD
Metabolic Disease
Hemachromatosis
? Growth hormone
©2001 PPS

Glycemic Control and Risk of Development of HF in Diabetes



HF=heart failure.

Data from Iribarren C et al. *Circulation*. 2001;103:2668-2673.

Diabetic Cardiomyopathy(Panja M et al JAPI 1993)

N=42 Age=34-51years

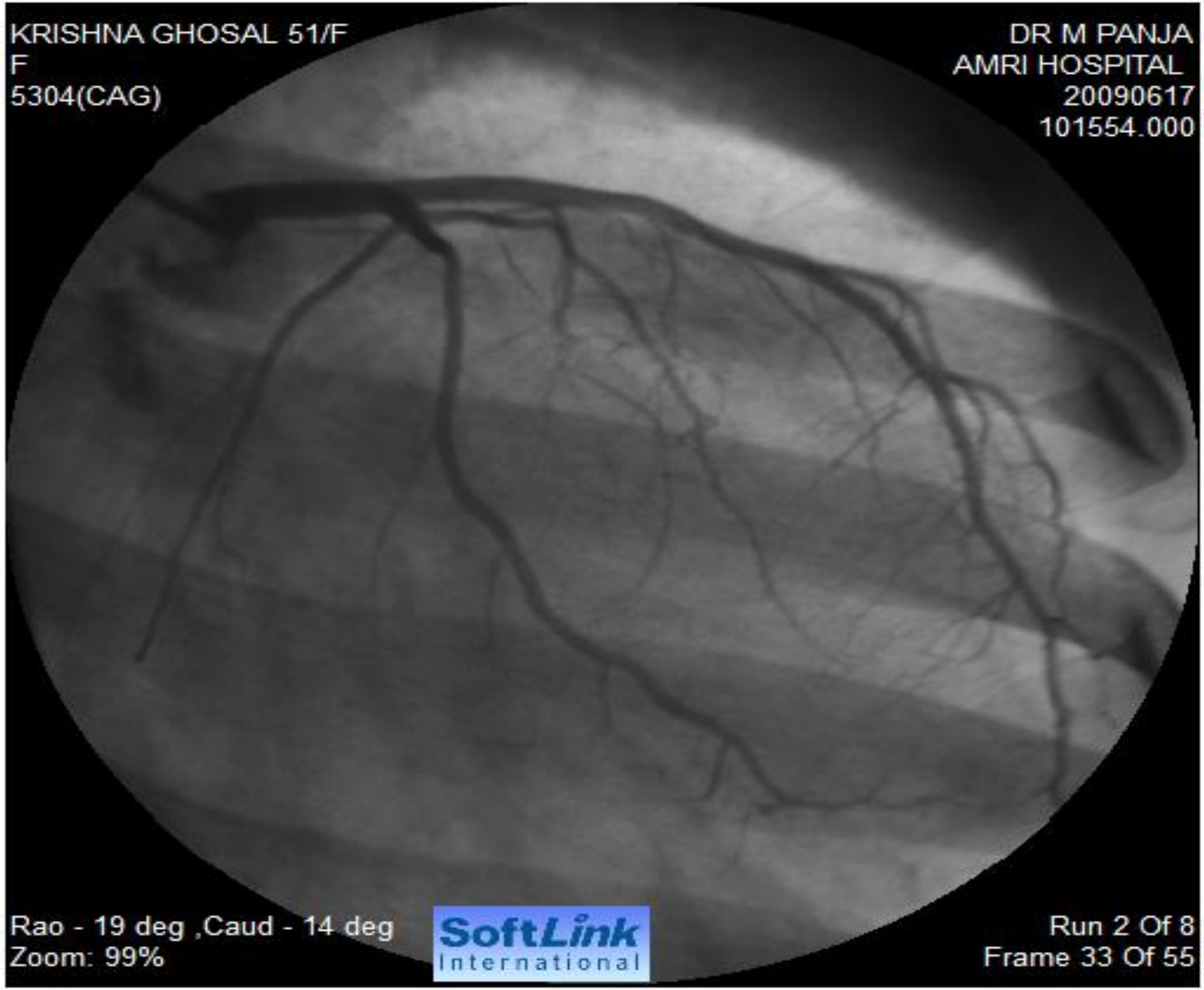
Cardiac findings:

- EF=20-50%(mean 40.06%)
- Generalized Chamber Dilatation=21.4%
- ECG= 1.Nonspecific ST-T changes 100%
  2.RBBB-19%; LBB- 3%
- Coronary angiography No Epicardial Stenosis(>50%)
- No other Risk Factors like Hypertension,IHD consistently present

EFFECTS OF DERANGED MYOCARDIAL METABOLISM CANNOT BE RULED OUT

ASSOCIATED ABNORMALITY

1. Neuropathy 13
2. Retinopathy 11
3. Nephropathy 5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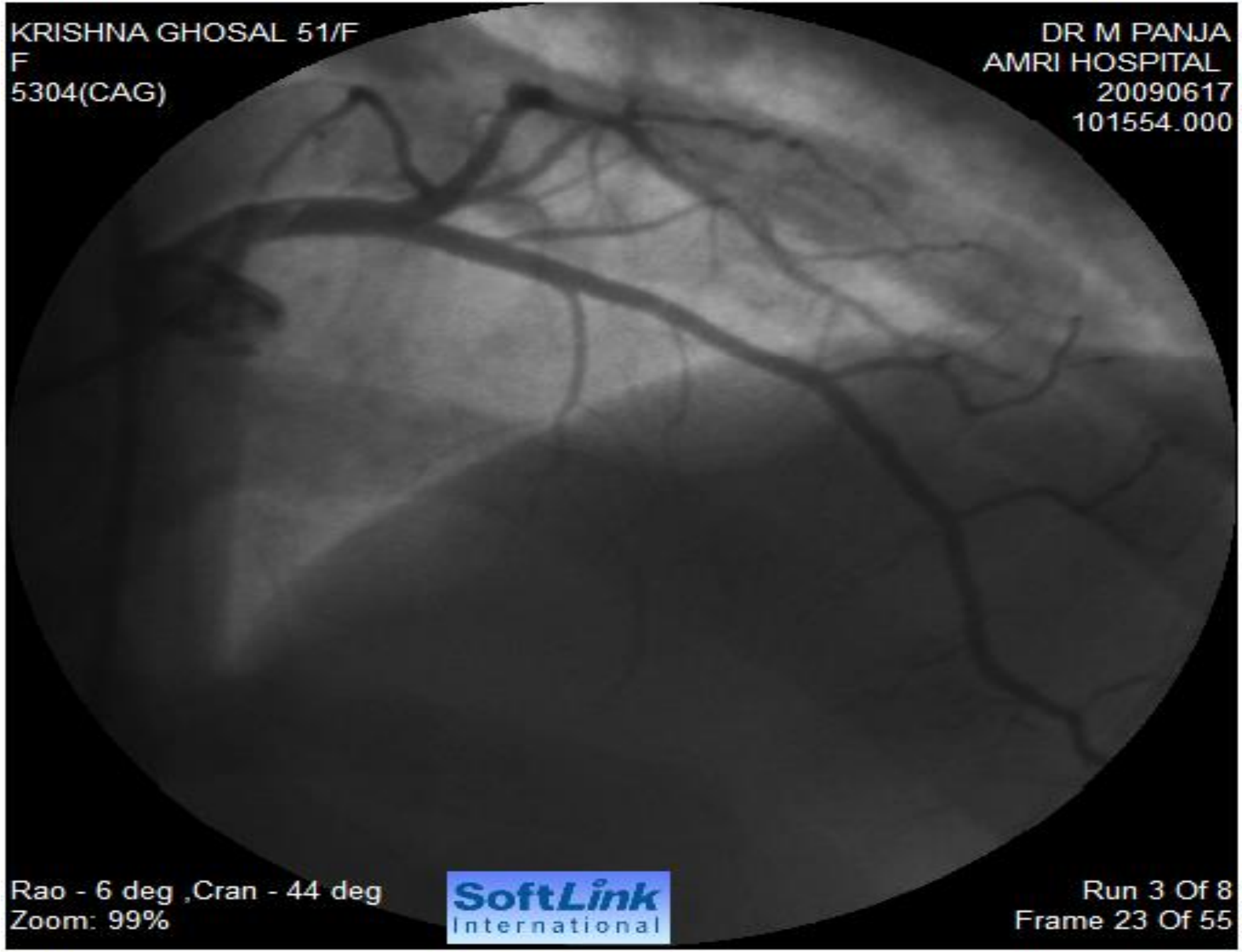
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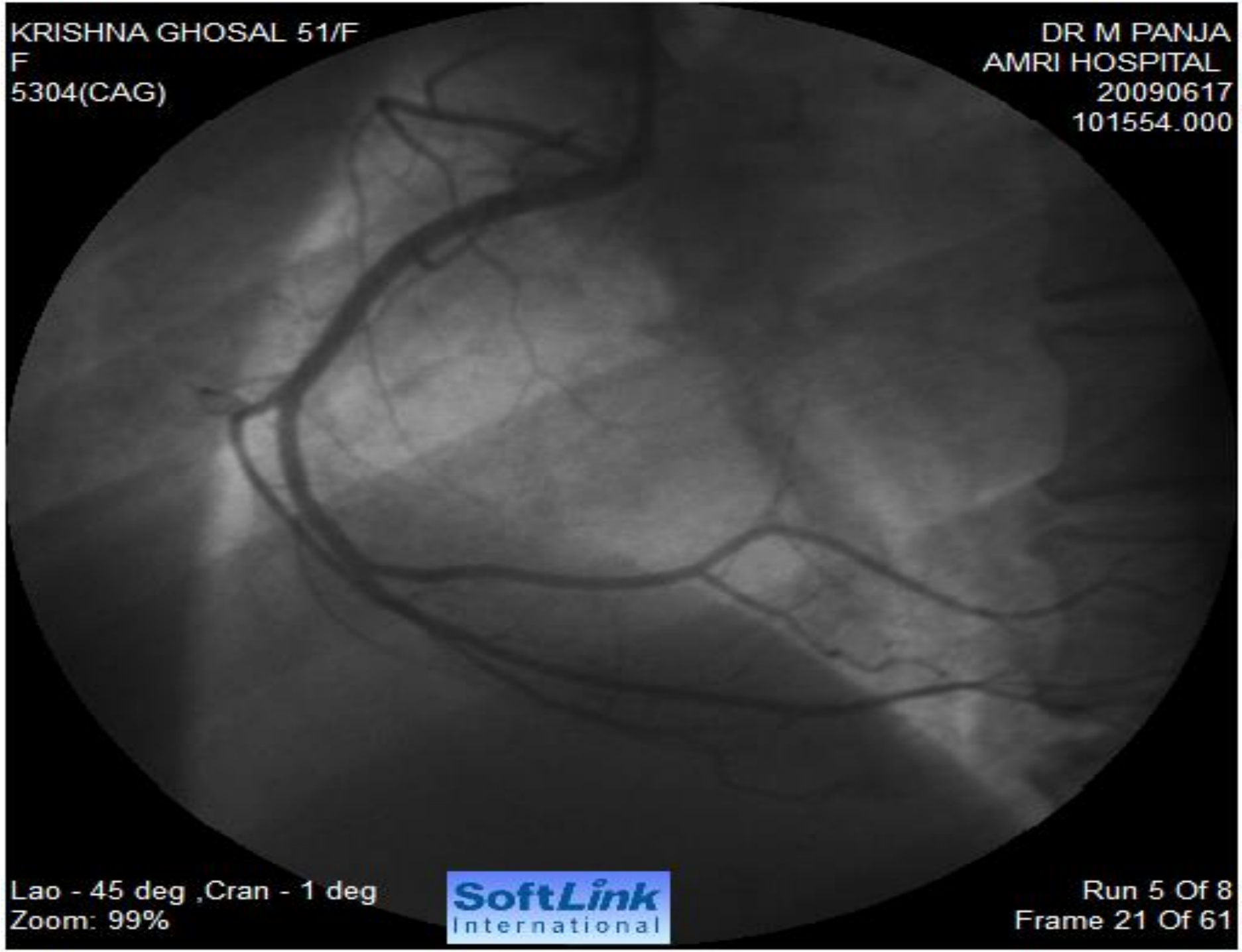
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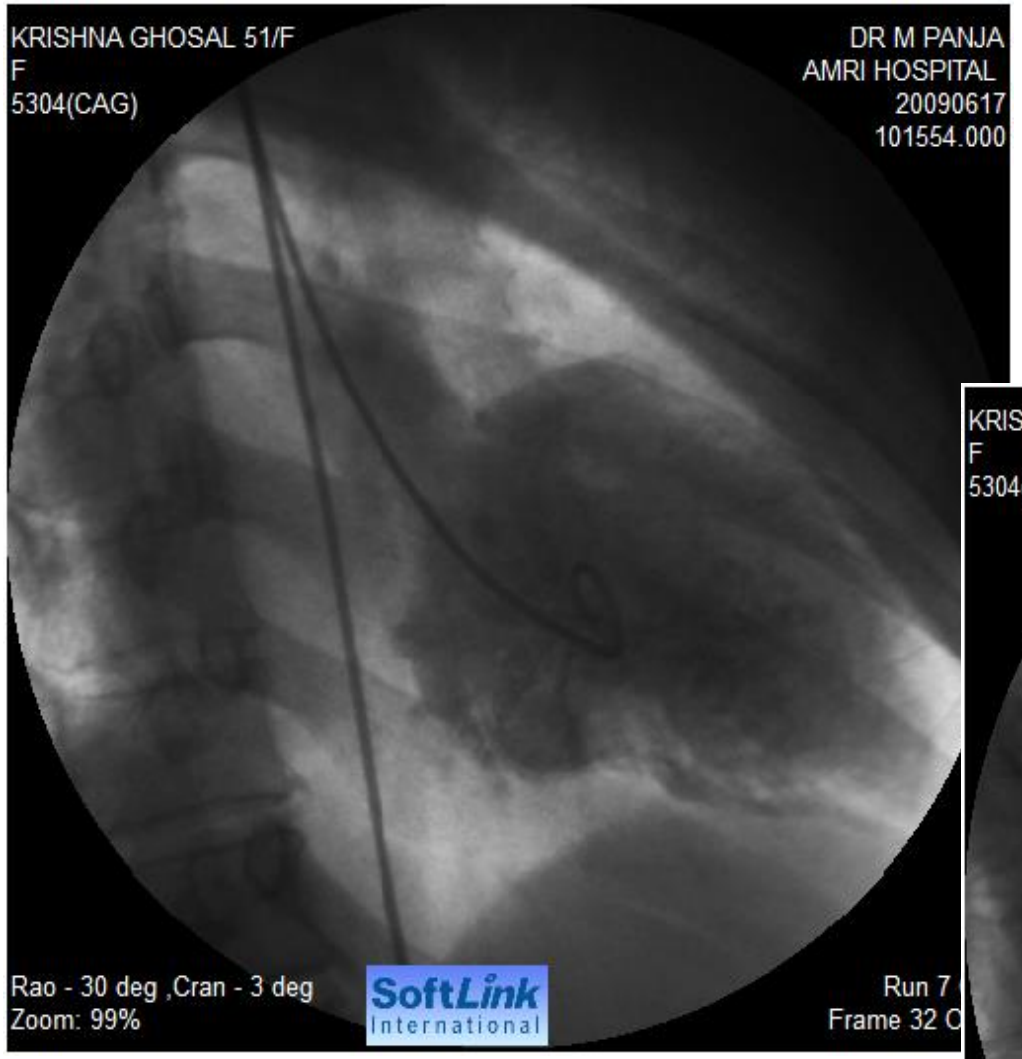
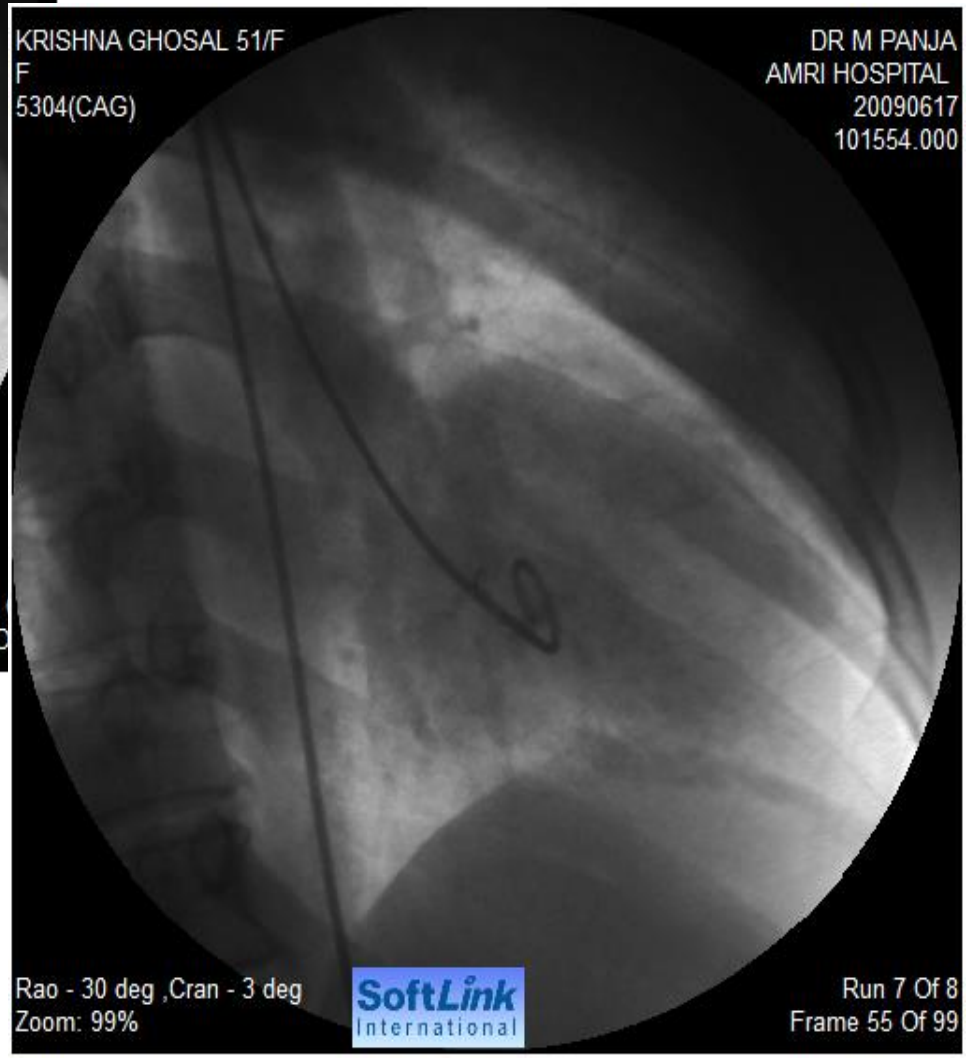




-EF- 20%

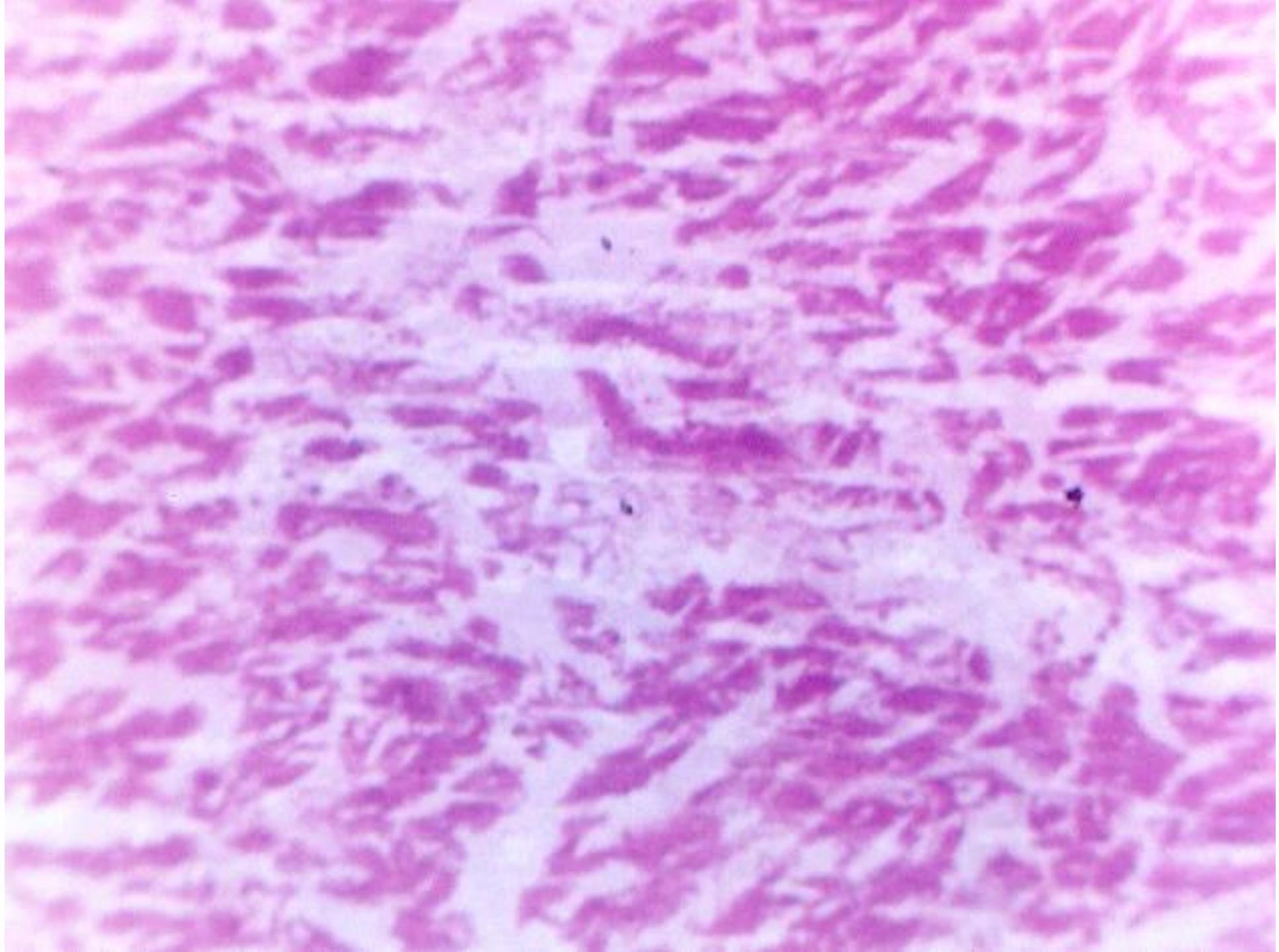
-ECG Bifasicular block

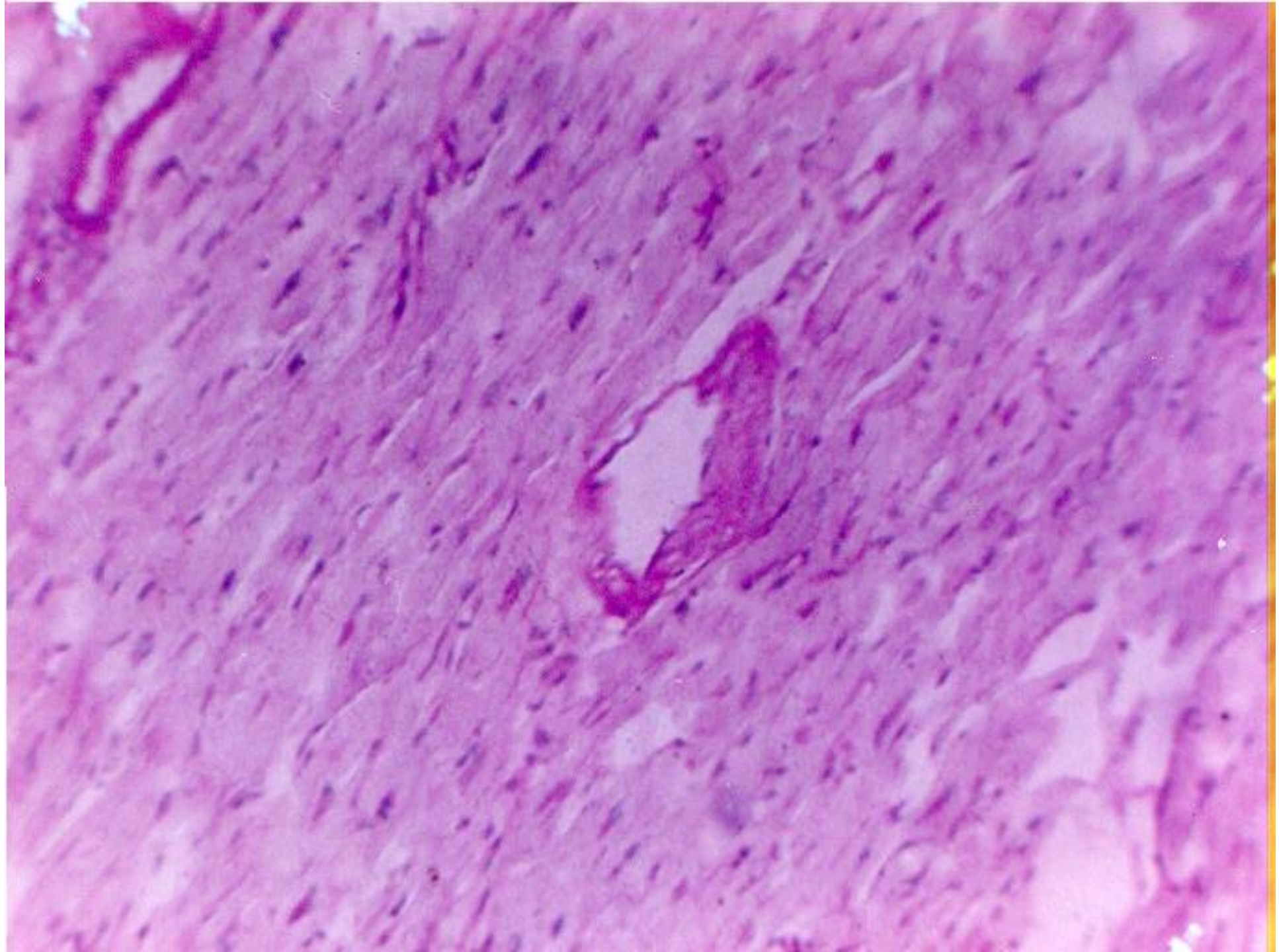
FOUND IN MEDIUM AND LARGE SIZED CORONARY ARTERIES AS *WELL AS SMALL VESSELS.*

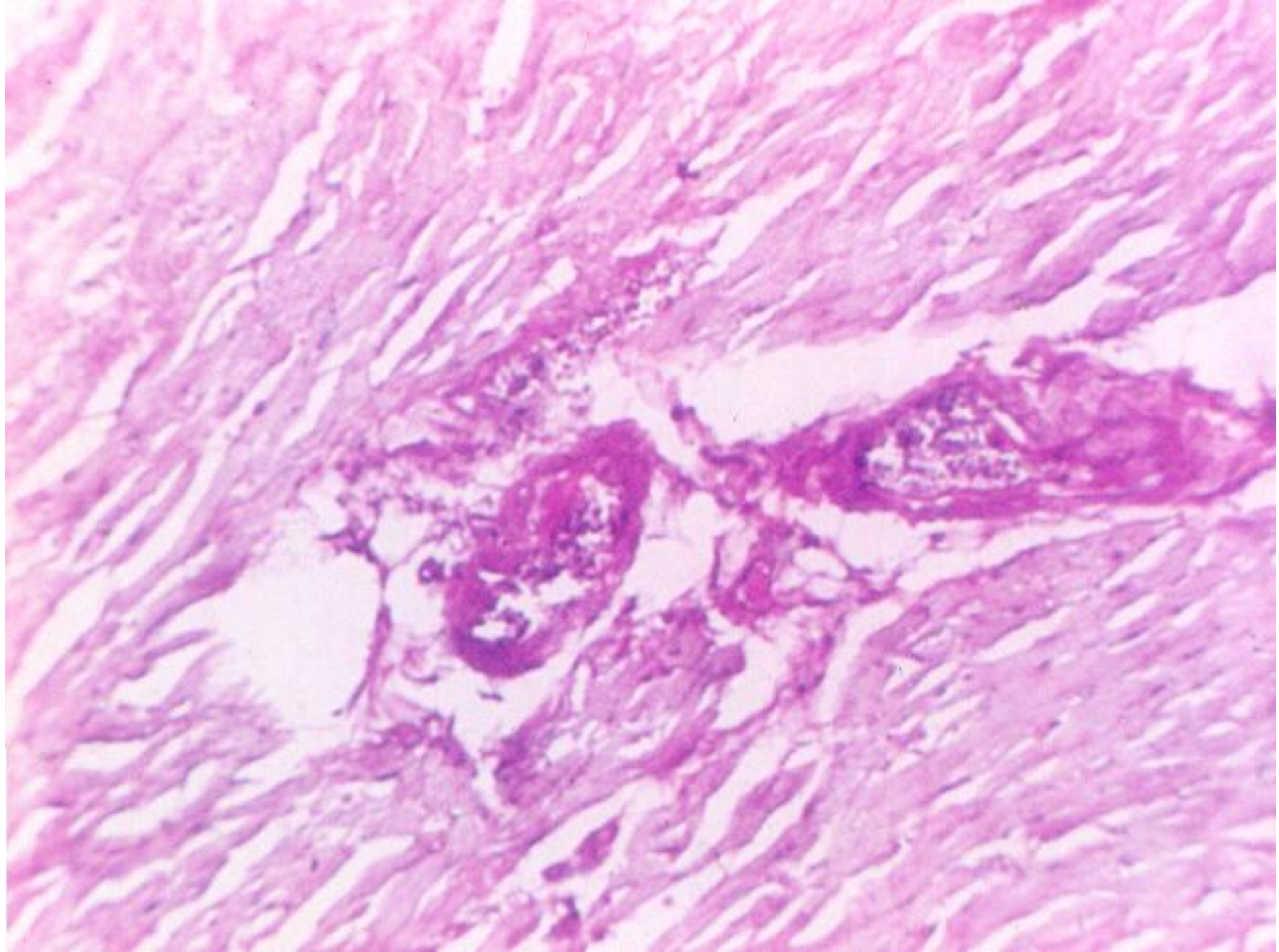
MAJORITY HAD MICROANGIOPATHY AT OTHER SITES

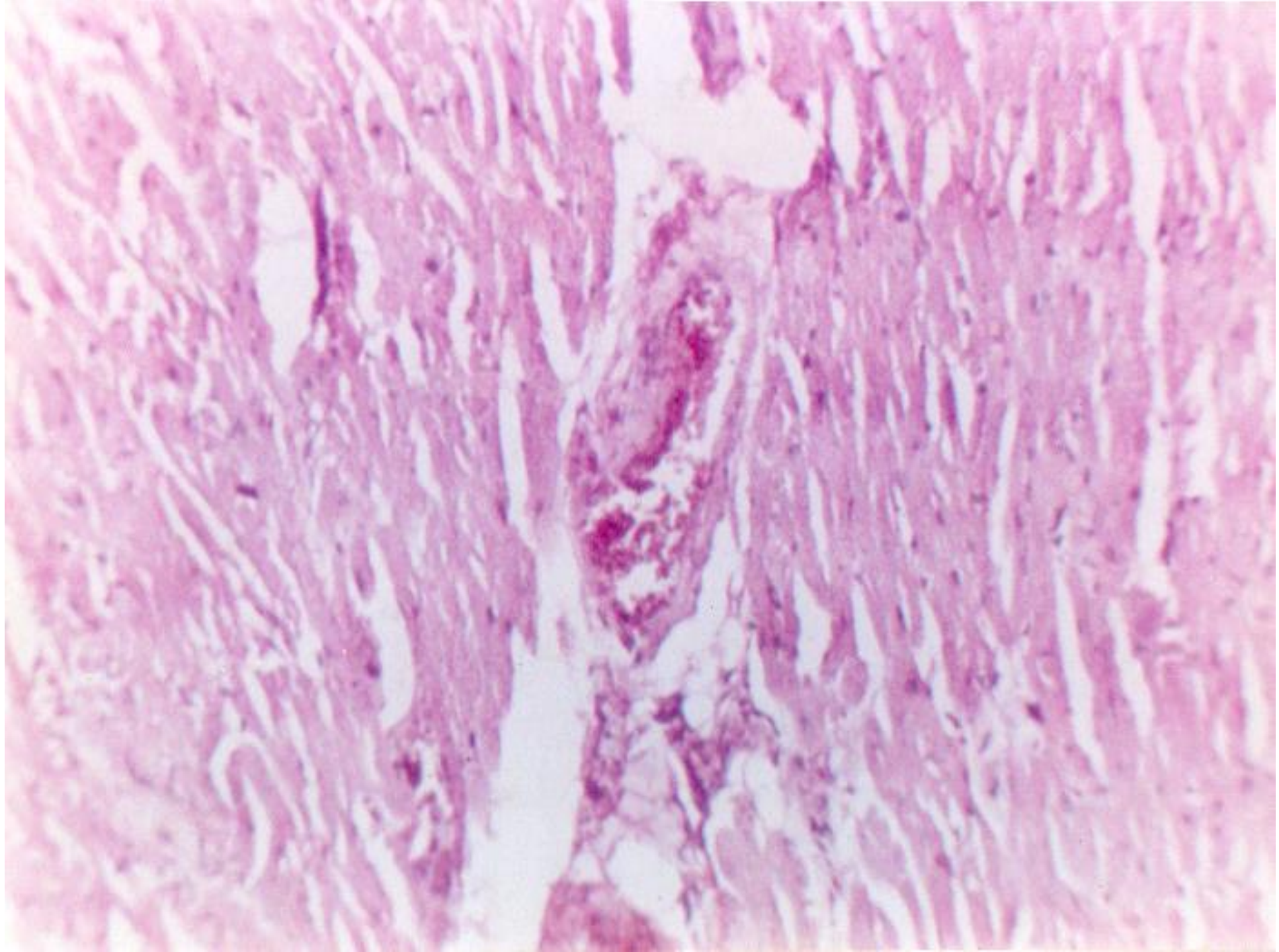
*(*Monotosh Panja et al.Report on small vessel changes in the diabetic Heart.J.Assoc Phy India 24:637,1976.)

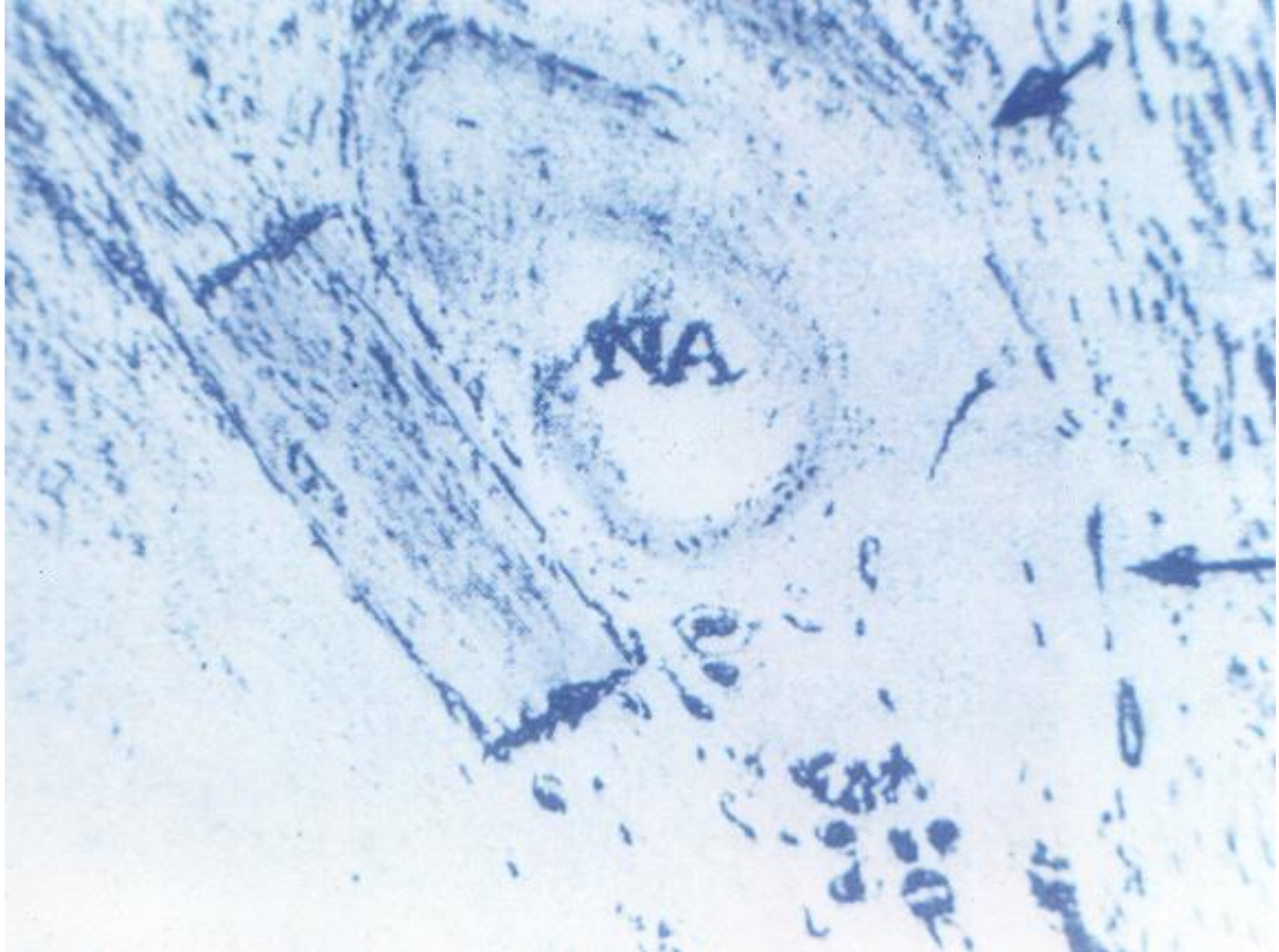
- Intramural periodic acid-schiff(PAS) positive material and hyaline thickening ± endothelial cell proliferation in intramural & extramural coronary arteries
- Increased thickening of capillary basement membrane
- Interstitial infiltration with PAS positive material
- Perivascular and interstitial fibrosis
- Degeneration and fragmentation of myocytes










NA

CONDUCTION DEFECT IN DIABETIC HEARTS (Jr. Diab. Assoc. 1976)

- 22% of patients with history of DM for 10 yrs. showed evidence of fascicular blocks
- Necropsy specimen showed proliferative changes characteristic of diabetic microangiopathy in intramural coronary vessels (irresp. of pr. of HTN)
- This microangiopathy may be responsible or otherwise unexplained complications like cardiomegaly, cardiac failure & conduction defects (esp. bifasc. block) observed in diabetics

(Dutta A.L, Panja M, JAPI 1976)

- CAD 61.3%(AMI 40%,Ischemia(21.3%)
- Intraventricular Conduction Defects(RBBB-19.5% LBBB-2.5%)
- Cardiomyopathy 17.3%
- Arrhythmia 10.7%

Dr. A L Dutta & Dr. M. Panja et al 1976 **(Cardiac Involvement In Diabetes.J.Diabetic Assoc 16:43,1976)**

Diabetic Cardiomyopathy

Pathologically characterized by ventricular hypertrophy, myocardial fibrosis and fat droplet deposition

Other physical characteristics:

Early changes in diastolic function – *affects up to 75% asymptomatic diabetic patients*

Collagen deposition

Presence of advanced glycosylation end products [AGEs]

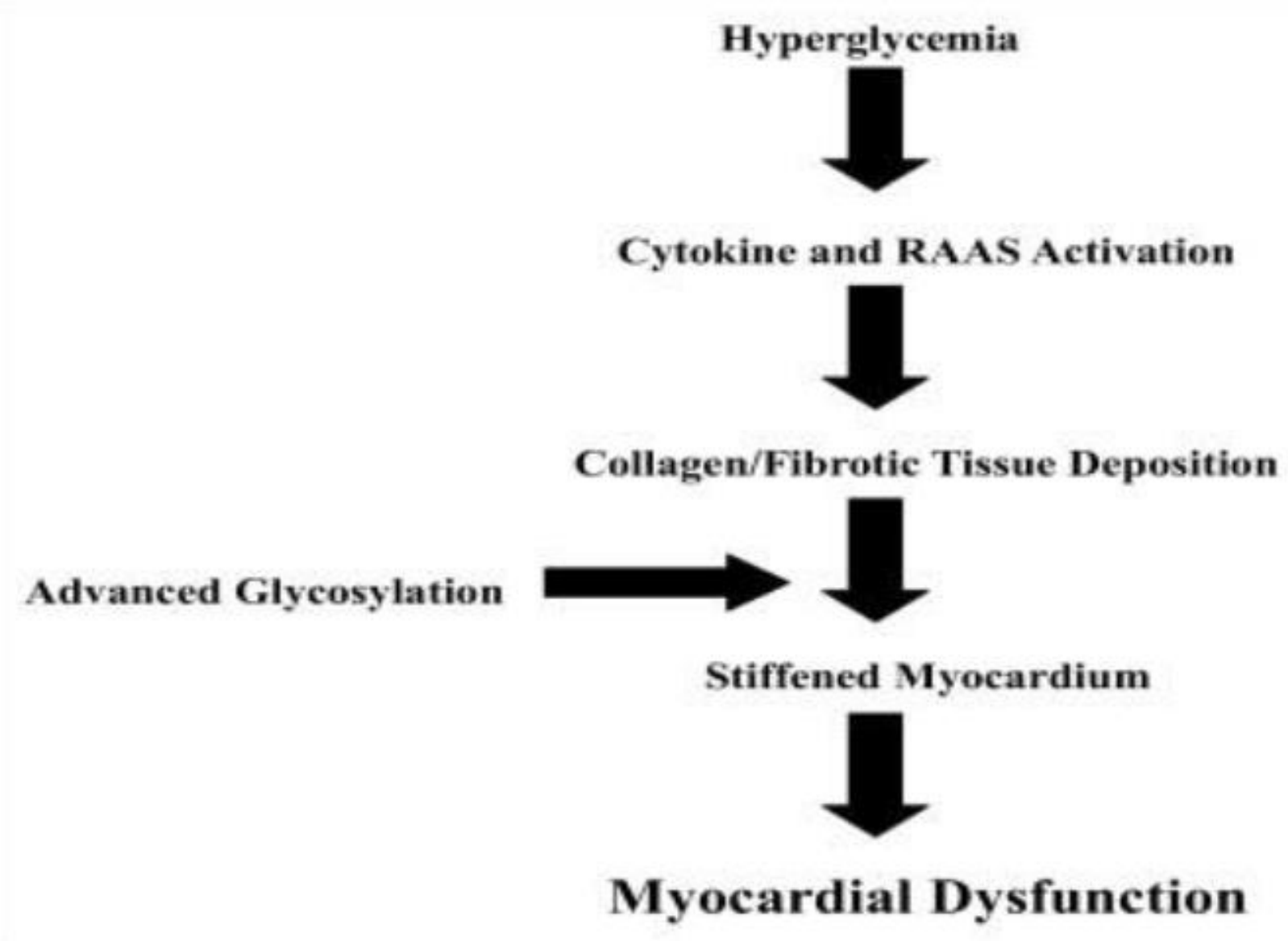
Late compromise of LV systolic function

- Earliest evidence is seen in long-axis systolic dysfunction with NL EF

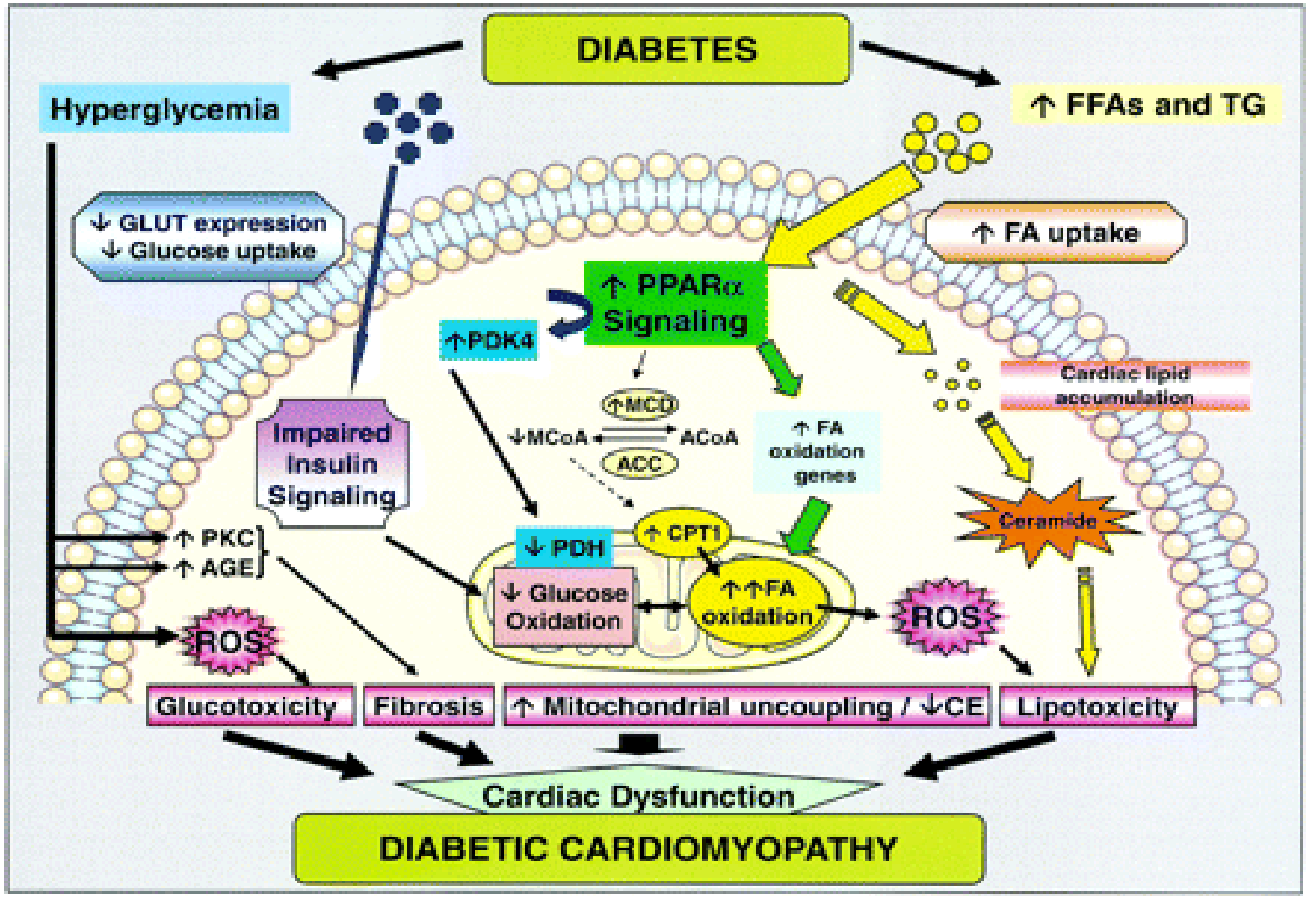
Diabetic Cardiomyopathy

- Mechanisms/Pathophysiology
  - Hyperglycemia
    - Increased ROS
  - Hyperinsulinemia
    - Activation of SNS & RAAS
  - Advanced Glycation End Products
    - Increased due to oxidative stress
    - RAGE [receptor for AGE] is also increased
    - Collagen Deposition
    - Change in cardiac myosin expression
  - Enhanced Free Fatty Acid Utilization
    - Leads to FFA accumulation & lipotoxicity

Diabetic Cardiomyopathy



Circulation.
2007;115:3213



Potential contributors to the development of diabetic cardiomyopathy. Increased free FA (FFA) activates PPAR-α signaling, leading to the increased transcription of many genes involved in FA oxidation. Increased FA oxidation leads to the generation of ROS at the level of the electron transport chain. ROS, which also can be generated by extramitochondrial mechanisms such as NADPH oxidase, plays a critical role in several pathways involved in the pathogenesis of diabetic cardiomyopathy, including lipotoxicity, cell death, and tissue damage, as well as mitochondrial uncoupling and reduced cardiac efficiency. TG indicates triglycerides; GLUTs, glucose transporters; PDK4, pyruvate dehydrogenase kinase 4; MCD, malonyl-coenzyme A decarboxylase; MCoA, malonyl-coenzyme A; ACoA, acetyl-coenzyme A; ACC, acetyl coenzyme A carboxylase; CPT1, carnitine palmitoyl-transferase 1; PDH, pyruvate dehydrogenase; CE, cardiac efficiency; PKC, protein kinase C; and AGE, glycation end products.

Diabetic cardiomyopathy: pathophysiology and clinical features

Heart Fail Rev (2013) 18:149–166

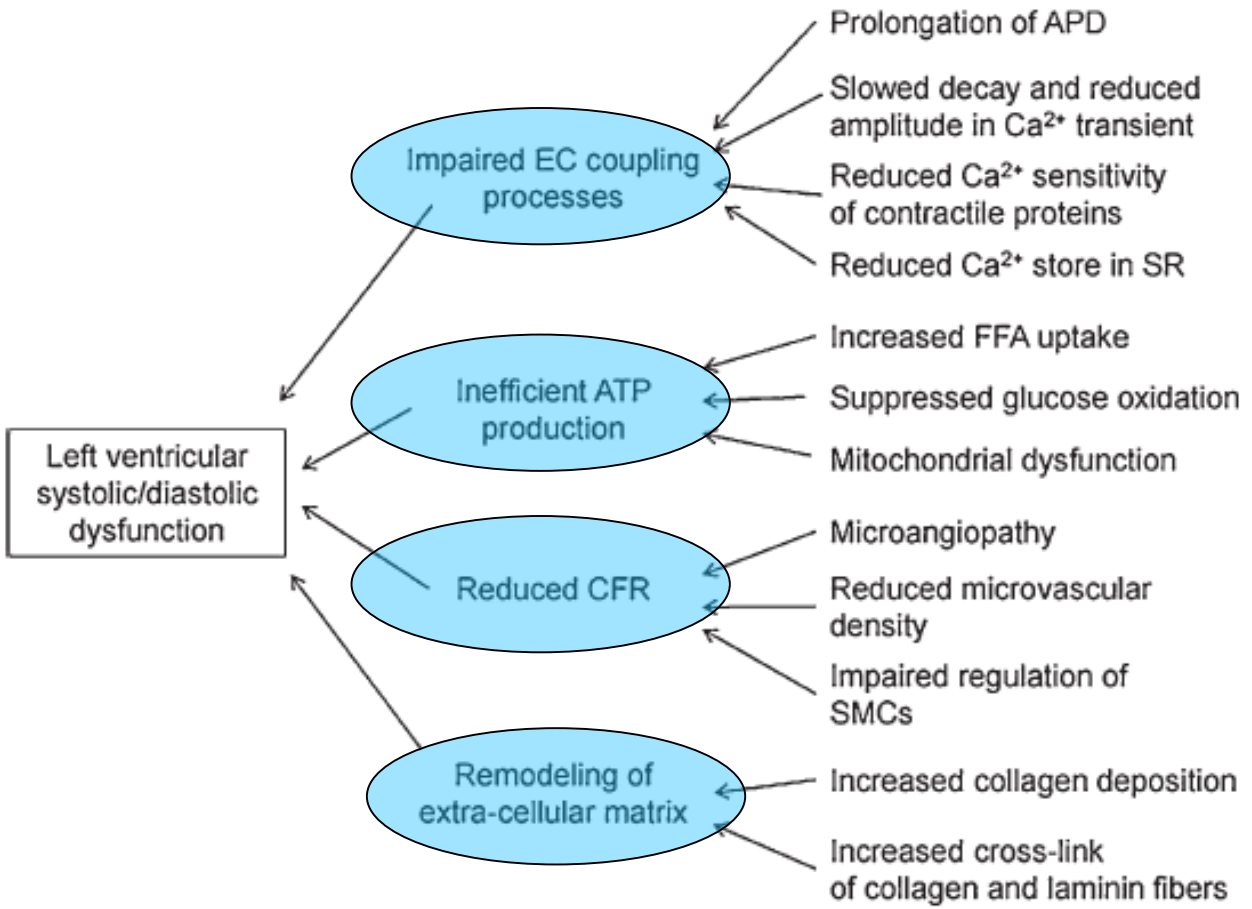
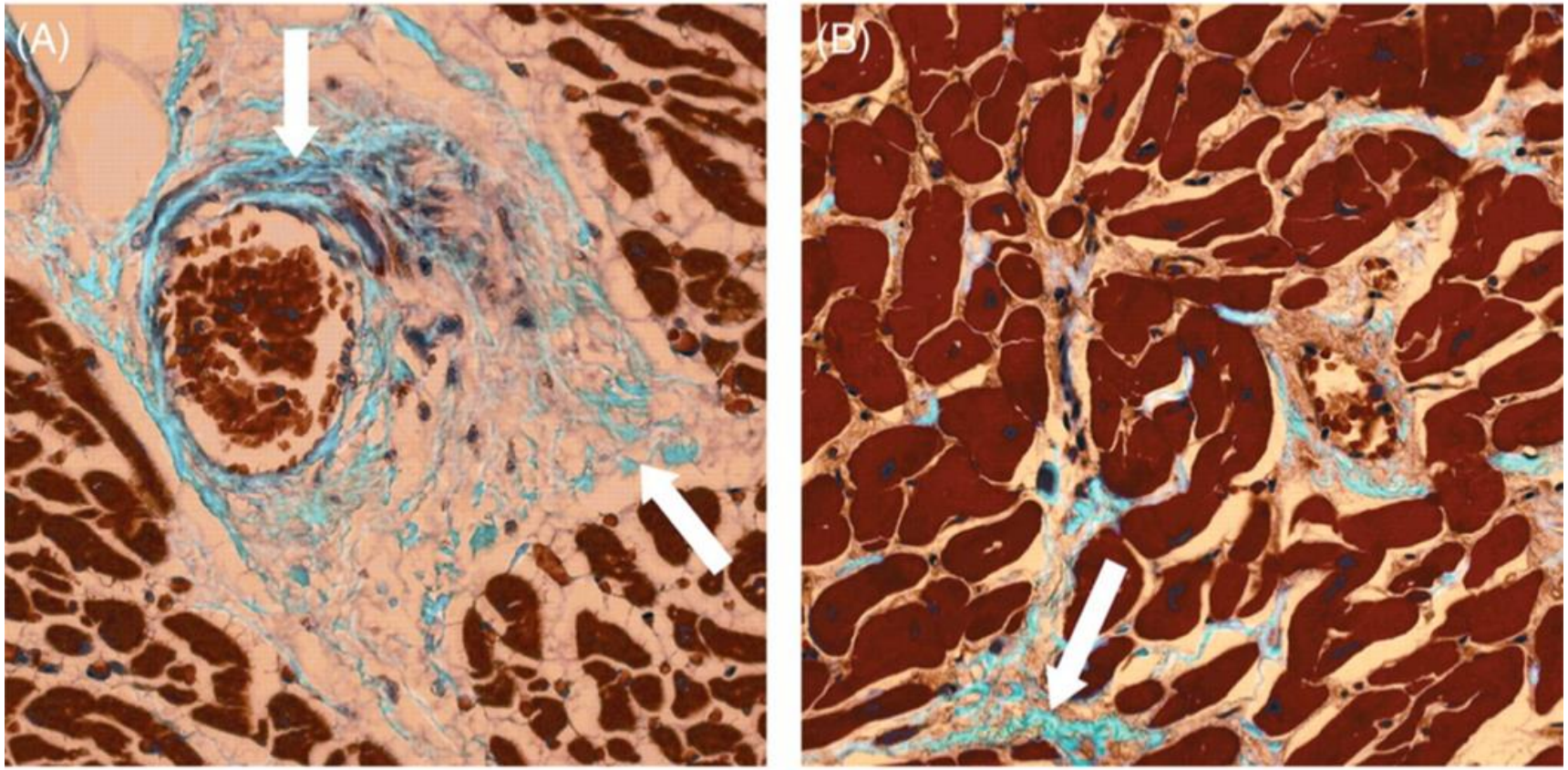


Fig. 1 Proposed mechanisms of contractile dysfunction by diabetes. *EC coupling* excitation–contraction coupling, *APD* action potential duration, *SR* sarcoplasmic reticulum, *FFA* free fatty acid, *CFR* coronary flow reserve, *SMC* smooth muscle cell

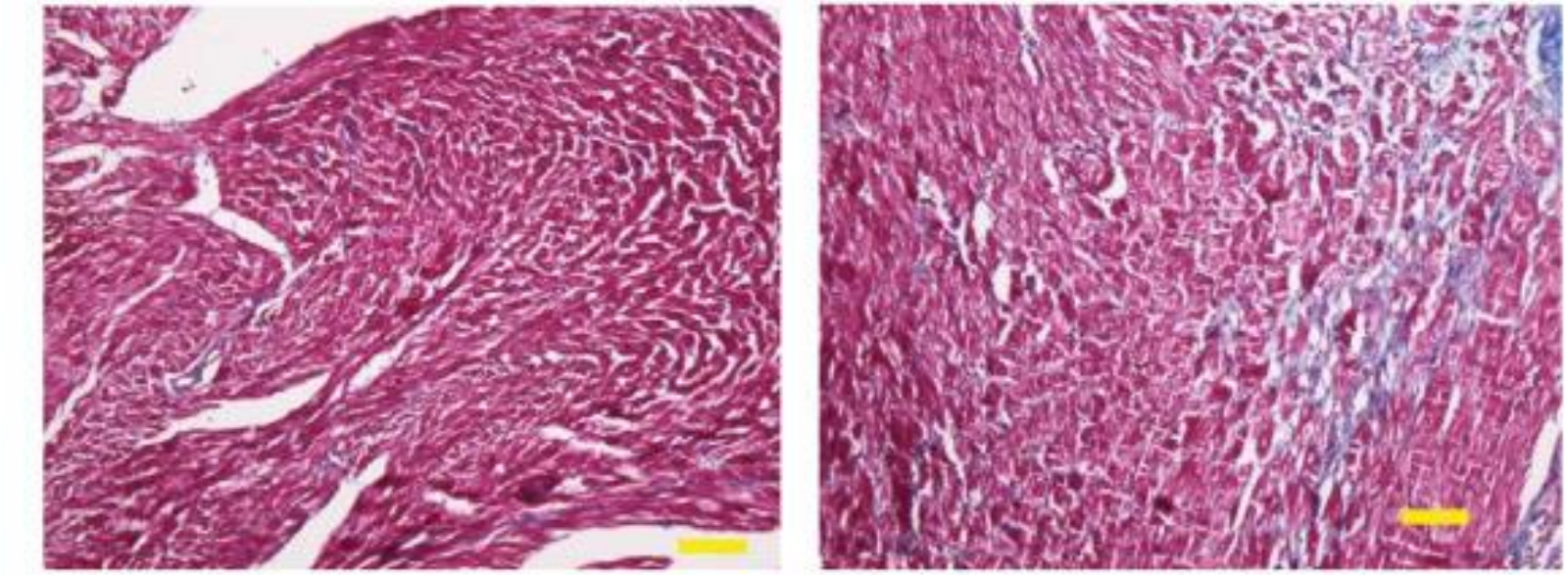
Diabetic Cardiomyopathy



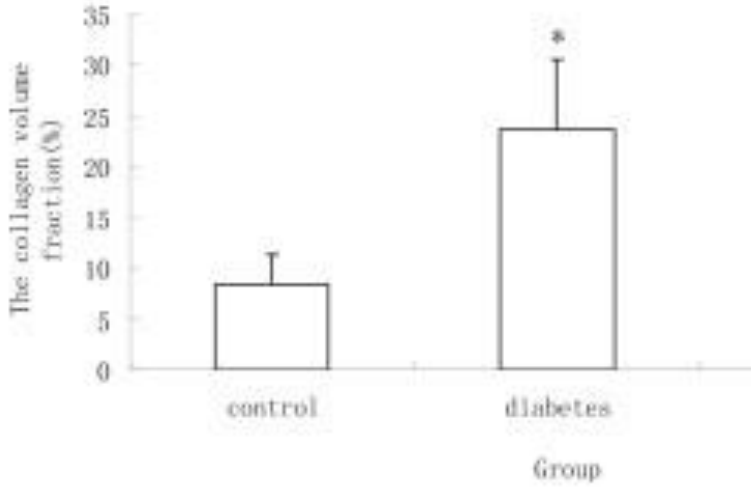
Diabetic cardiomyopathy: mild myocardial interstitial fibrosis stained in blue with Masson trichrome (white arrow) in a patient with long-duration type 1 diabetes mellitus at autopsy, with perivascular fibrosis (A) and mild fibrosis between myocytes (B).

Diabetic Cardiomyopathy

A



B



A) Fibrotic infiltration in the myocardium with Masson's trichrome staining. Area stained blue represent fibrotic infiltration. Magnification at 200×, scale bar is 100 μm.

B) Quantitative analysis of fibrosis. The collagen volume fraction was higher in the diabetic group than in the control group

Therapeutic strategies for diabetic cardiomyopathy

Diabetic cardiomyopathy treatment	Therapeutic strategy	DCM type
Glycemic control	Insulin therapy	T1D
	Thiazolidinediones	T2D
	Metformin	T2D
	Glucagon-like peptide-1; Dipeptidyl peptidase inhibitors	T2D
	Alpha-glucosidase inhibitors	T2D
Adrenergic blockade	β-blockers	T1D & T2D
Cholesterol reduction	Statins	Efficacy questionable for DCM
Exercise training	–	T1D & T2D
Antioxidants	–	T1D & T2D
RAAS	ACEIs	T1D & T2D
	ARBs	T1D & T2D
	Aldosterone antagonist	T1D & T2D
Calcium upregulation	Calcium channel blockers	Efficacy questionable for T1D

Heart fail rev 2013

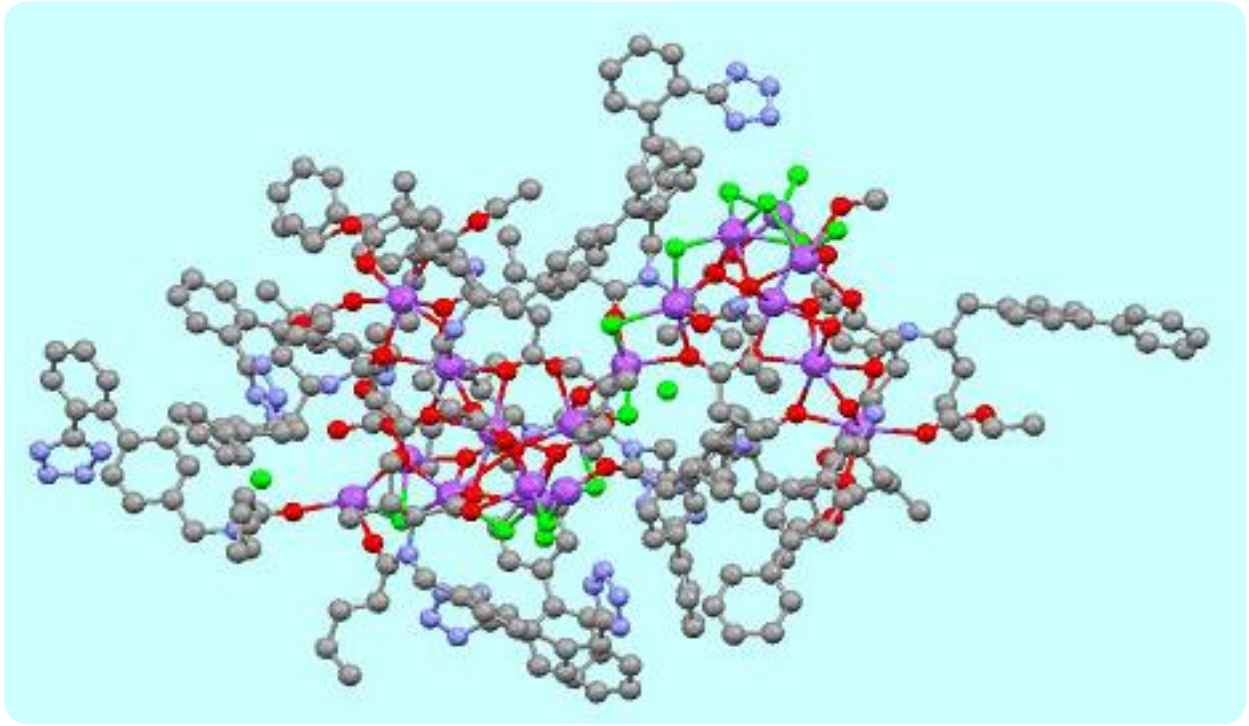
Drugs for management of Heart Failure in patients with Diabetes

- Diuretics
- Beta-blockers

- ACE-I
- ARB
- Vymada (ARNi)

ARNi is a first-in-class angiotensin receptor neprilysin inhibitor (Vymada)

- It is a novel drug which delivers simultaneous **neprilysin inhibition** and **AT_1 receptor blockade** [1–3]
- It is a salt complex that comprises the two active components in a 1:1 molar ratio: [2,3]
  - **sacubitril** (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
  - **valsartan** – an AT_1 receptor blocker



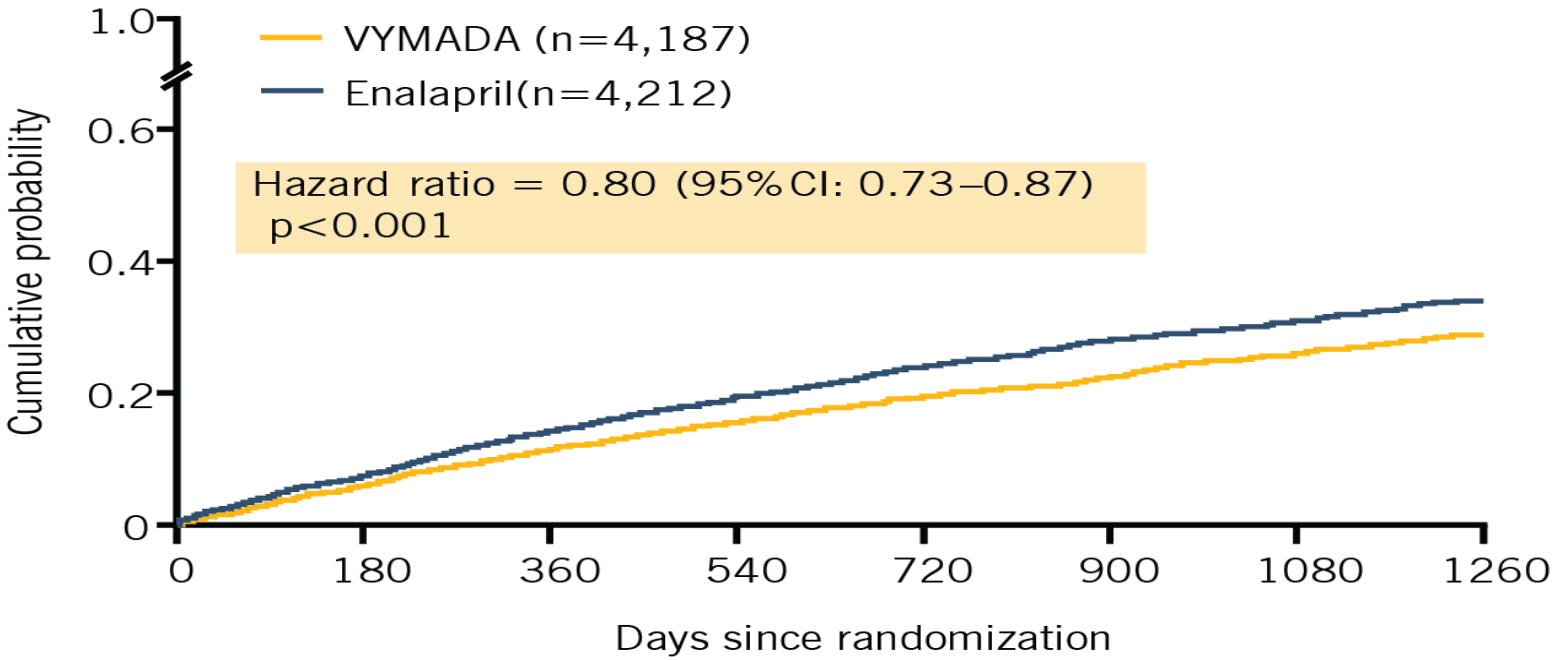
3D Vymada structure [2]

Vymada = angiotensin receptor neprilysin inhibitor; **AT_1** = angiotensin II type 1

1. Bloch, Basile. J Clin Hypertens 2010;12:809–12; **2.** Gu et al. J Clin Pharmacol 2010;50:401–14; **3.** Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

PARADIGM-HF: primary endpoint

Composite of death from CV causes or first hospitalization for HF



No at risk								
Vymada	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

McMurray et al. N Engl Med 2014;371:993-1004.

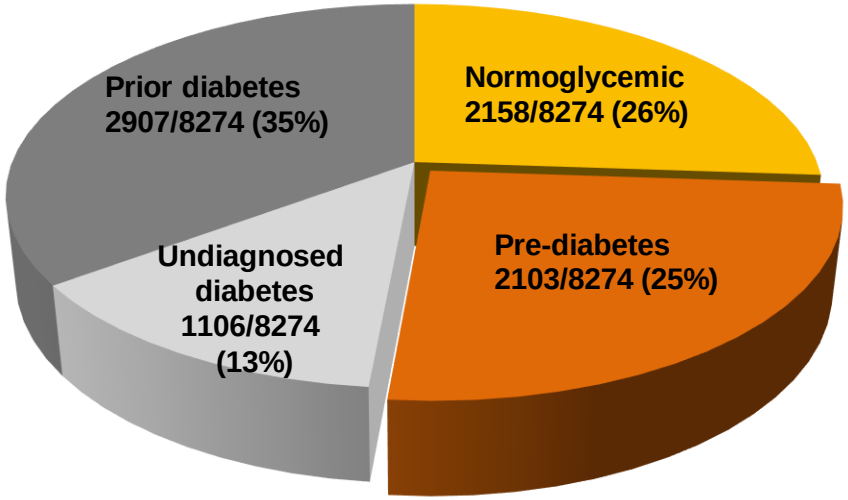
Distribution of patients according to glycemic status in the PARADIGM-HF

Of the 8399 patients randomized in the PARADIGM-HF study, 8274 had a measurement of HbA1c at baseline

A total of 2907 patients (35%) had a known history of diabetes

In the remaining 5367 patients, analysis of HbA1c measurements indicated that

- 26% were normoglycemic
- 25% were pre-diabetic
- 13% were considered to have undiagnosed diabetes

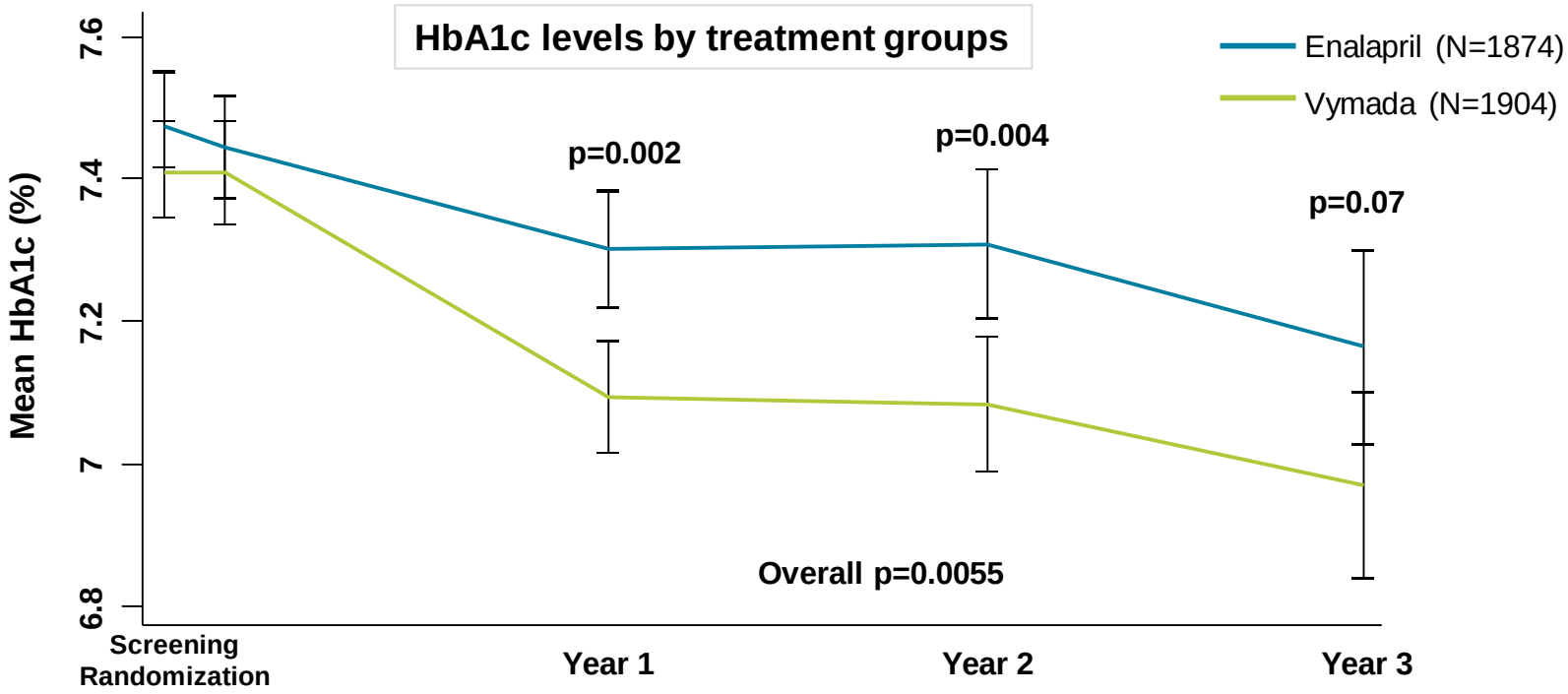


HbA1c, glycosylated haemoglobin;

168.Kristensen et al., Circ Heart Fail. 2016 Jan; 9(1): e002560

NOVARTIS

ARNI (sacubitril/valsartan)- Reduction in HbA1c



Decrease in HbA_{1c} was persistently and significantly greater in patients receiving sacubitril/valsartan vs enalapril over 3 years

175. Seferovic J P. J P. et al. Lancet Diabetes Endocrinol. 2017 ; 5(5) : 333-340. doi:10.1016/S2213-8587(17)30087-6

Heart Failure Drugs to Use with Caution in Diabetes

Diuretics	• Diuretics increase the incidence of DM • Loop diuretics may be better tolerated, as thiazides promote hyperglycemia
β - blockers	• Precipitate DM • Carvedilol and Nebivolol with vasodilating actions are less metabolic effective. • MERIT HF trial has shown that metoprolol improves survival similarly to DM and Non- DM patients
Mineralocortcoid receptor antagonists	• EPHESUS study has shown that in post myocardial infraction patients with DM eplerenone decreases mortality. • Special attention to be given to renal function and hyperkalemia

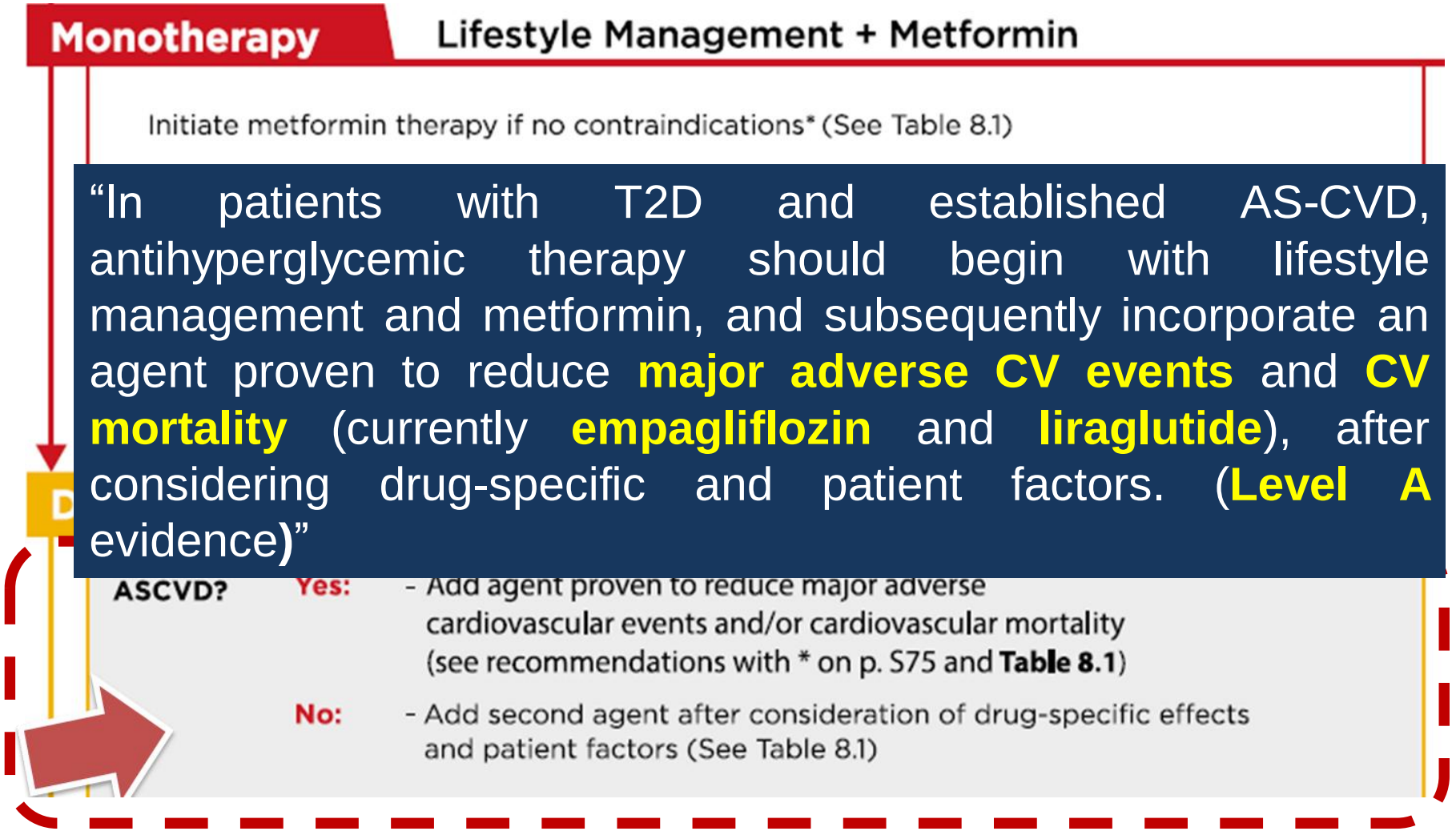
Card Fail Rev 2017 Apr; 3(1): 52–55.

Major Trials and CV Outcomes in T2DM

	CV Events	CV Mortality	Heart Failure
Intensive vs. less intensive glycemic control			Admission to hospital/ fatal heart failure
ACCORD	↔	↑	↔
ADVANCE	↔	↔	↔
UKPDS	↔	↔	↔
VADT	↔	↔	↔
Individual glucose-lowering drug vs. placebo (since 2008 FDA guidance)			Hospitalization for heart failure
ELIXA	↔	↔	↔
EXAMINE	↔	↔	↔
SAVOR-TIMI 53	↔	↔	↑ (HR 1.27)
TECOS	↔	↔	↔
EMPA-REG OUTCOME	↓ (HR 0.86)	↓ (HR 0.62)	↓ (HR 0.65)
LEADER	↓ (HR 0.87)	↓ (HR 0.78)	↔
SUSTAIN-6	↓ (HR 0.74)	↔	↔
CANVAS	↓ (HR 0.86)	↔	↓ (HR 0.67)

Zinman B et al. Diabetes Care 2017;40:1302-13.

American Diabetes Association (ADA)
Standards of Medical Care in Diabetes - 2018



"In patients with T2D and established AS-CVD, antihyperglycemic therapy should begin with lifestyle management and metformin, and subsequently incorporate an agent proven to reduce **major adverse CV events** and **CV mortality** (currently **empagliflozin** and **liraglutide**), after considering drug-specific and patient factors. (**Level A** evidence)"

ESC Recommendations:
Empagliflozin for Prevention of Heart Failure or Death

Recommendations	Class [a]	Level [b]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B

2016 ESC Guidelines for the Diagnosis and treatment of Acute & Chronic Heart Failure

ESC’2016 Guidelines - In patients with diabetes and HF

- Metformin should be the treatment of choice in patients with HF. (Contraindicated in patients with severe renal or hepatic impairment, because of the risk of lactic acidosis.)
- Insulin is required for patients with type 1 diabetes and to treat symptomatic hyperglycemia in patients with type 2 diabetes and pancreatic islet β cell exhaustion. (Insulin is a powerful sodium-retaining hormone, and when combined with a reduction in glycosuria, may exacerbate fluid retention)
- Sulphonylurea derivatives have been associated with an increased risk of worsening HF and should be used with caution.
- TZDs cause sodium and water retention and increased risk of worsening HF and hospitalization and are not recommended in patients with HF.
- Gliptins which increase incretin secretion improve glycaemic indices but do not reduce and may increase the risk of cardiovascular events and worsening HF.
- Recently, Empagliflozin, reduced hospitalization for HF and mortality, but not myocardial infarction or stroke, in patients with diabetes at high cardiovascular risk, some of whom had HF.

Devices and Transplant – In Heart Failour and Diabetic Cardiomyopathy

- Cardiac Resynchronization Therapy (CRT) – Reduces the morality, morbidity and rehospitalization for heart failure.
- Implantable Cardioverter Defibrillator (ICD) – Reduces the Sudden Cardiac death.
- Mitral MITRA clip – COAPT trial showed the efficacy of functional MR.
- Dynamic Cardiomyoplasty – Latissimus Dorsi Muscle rapped the heart and electrical stimulation by pacemaker electrodes synchronise the contraction of the heart like biventricular pace maker. It acts as a bridge between the medical therapy and heart failure.
- Finally transplant of the heart prolongs the life.

Take Home Points

- Pathophysiology of diabetics cardio-myopathy is complex situation and micro angiopathy of diabetic heart plying a main role and effect of delayed myocardial metabolism can not be ruled out
- ~ 70% of Heart Failure patients are diabetic
- Polypharmacy is for poor compliance in HF, so reducing the number of drugs.
- TZDs should be avoided for the treatment of diabetes in patients with Heart Failure
- Sulphonylurea derivatives should be used with caution
- ARNI treatment was beneficial compared to enalapril, irrespective of HbA1c concentration and diabetes status
- Mitral MITRA clip – COAPT trial showed the efficacy of functional MR.
- In spite of CRT/ICD addition to medical failed medical therapy, Heart transplantation the final call.

THANK YOU