DIABETIC CARDIOMYOPATHY

S. Taghavi

Professor of Cardiology

Heart Failure and Heart Transplantation Fellowship

RHC

DEFINITION

- Abnormal cardiac structure and function in the absence of other cardiac risk factors
- Prevalence
  - T1DM: 14.5%
  - T2DM: 35.0%
- The risks of diabetic cardiomyopathy and HF are correlated with the level of glycaemic control
  - each 1% increase in glycated hemoglobin
    - 30% increased risk in T1DM
    - 8% increased risk in T2DM

CARDIOMYOPATHY IN T1DM AND T2DM

- Reduced insulin-mediated mitochondrial glucose oxidation
- insulin resistance
  - increased free fatty acid uptake by cardiomyocytes via the fatty acid translocase CD36
  - impairs mitochondrial fatty acid β-oxidation
  - greater mitochondrial dysfunction and accumulation of toxic lipid metabolites in the heart

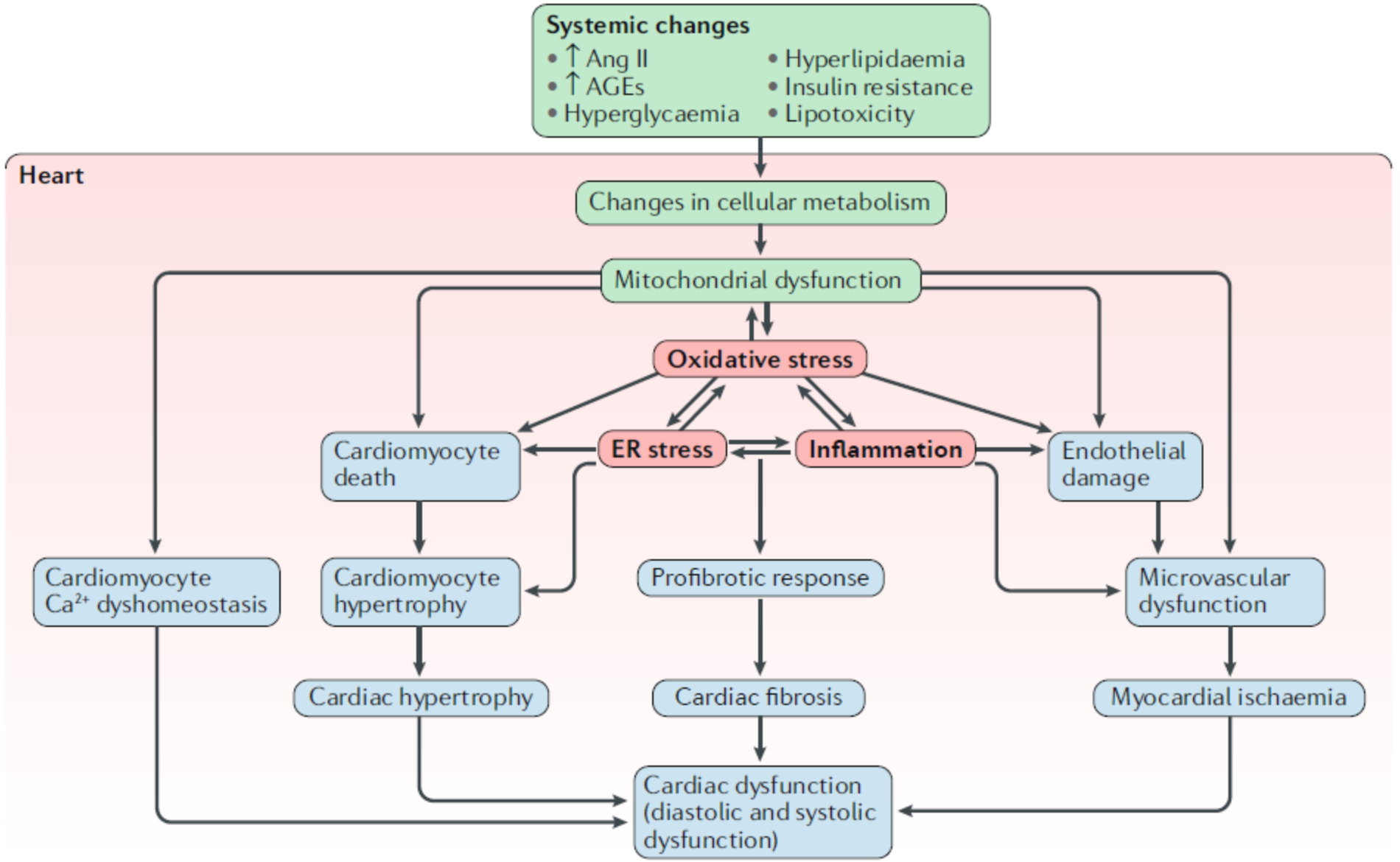
CARDIOMYOPATHY IN T1DM AND T2DM

- T2DM
  - HFpEF
  - increased myocardial collagen deposition
  - concentric left ventricular (LV) remodelling and hypertrophy
    - coronary microvascular inflammation
    - paracrine effects on cardiomyocytes
  - symptoms of HFrEF occur later

- T1DM
  - HFrEF
  - cardiomyocyte loss
  - LV remodelling
  - increased myocardial collagen deposition
  - Arrhythmias
    - mitochondrial dysfunction
    - abnormal Ca2+ transport
    - autonomic neuropathy

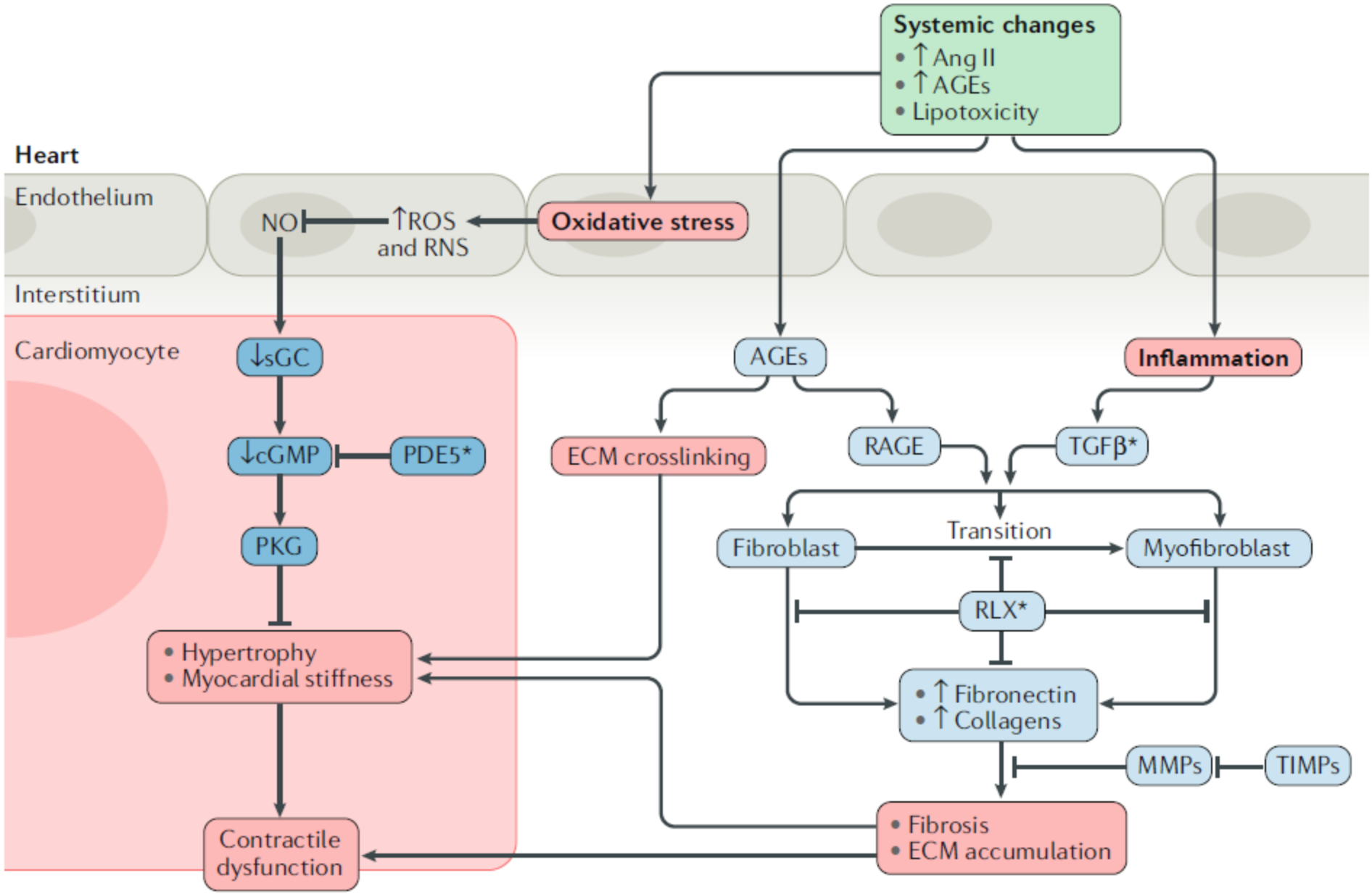
PATHOPHYSIOLOGY OF DIABETIC CARDIOMYOPATHY
LACK OF INSULIN OR INSULIN RESISTANCE

- metabolic shift in cardiomyocytes
- fatty acid intake and β-oxidation
- intracellular lipid accumulation and lipotoxicity
- intracellular fatty acid concentration
- mitochondrial dysfunction
  - increased generation of reactive oxygen species (ROS) and reactive nitrogen species
  - cardiomyocyte death
  - cardiac hypertrophy and inflammation
  - progressive profibrotic response that induces extracellular matrix (ECM) remodeling and fibrosis
- phosphorylation of titin
  - cardiomyocyte hypertrophy and myocardial
    - cardiomyocyte passive tension
- disrupted Ca2+ cycling and increased fibrotic scarring
  - contractile dysfunction and arrhythmia


Systemic changes
• ↑ Ang II
• ↑ AGEs
• Hyperglycaemia
• Hyperlipidaemia
• Insulin resistance
• Lipotoxicity
Heart
Changes in cellular metabolism
Mitochondrial dysfunction
Oxidative stress
Cardiomyocyte death
ER stress
Inflammation
Endothelial damage
Cardiomyocyte Ca2+ dyshomeostasis
Cardiomyocyte hypertrophy
Profibrotic response
Microvascular dysfunction
Cardiac hypertrophy
Cardiac fibrosis
Myocardial ischaemia
Cardiac dysfunction (diastolic and systolic dysfunction)

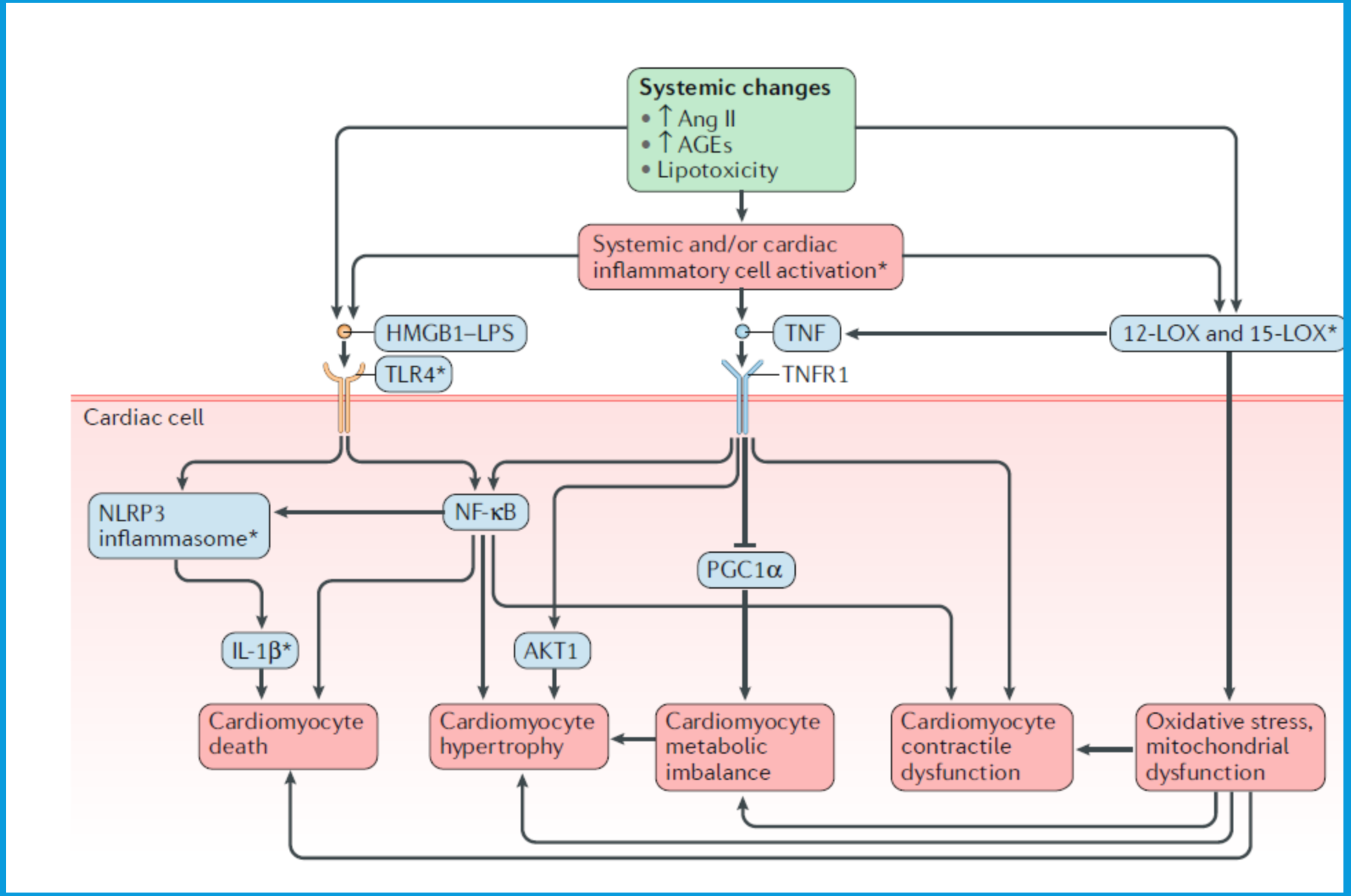
CARDIAC REMODELLING AND DYSFUNCTION

- AGEs generated by the exposure of proteins and lipids to high glucose levels
  - impair ECM degradation by MMPs
  - increase cardiac stiffness
  - early diastolic dysfunction
  - promote the differentiation of fibroblasts into myofibroblasts
    - proliferate and induce ECM
    - secreting profibrotic cytokines and matrix proteins
- TGFβ, TNF, angiotensin II and various interleukins
  - impaired cardiac contractility and late systolic dysfunction
  - deposition of structural ECM proteins and matricellular macromolecules
- Reduced NO signalling
  - soluble guanylate cyclase (sGC) activity and cyclic GMP (cGMP
  - abolishes the protective effects of protein kinase G (PKG)
  - cardiomyocyte hypertrophy and stiffness
- Significantly higher level of type III collagen


Systemic changes
• ↑ Ang II
• ↑ AGEs
• Lipotoxicity
Heart
Endothelium
NO
↑ROS and RNS
Oxidative stress
Interstitium
Cardiomyocyte
↓sGC
↓cGMP
PDE5*
PKG
• Hypertrophy
• Myocardial stiffness
Contractile dysfunction
AGEs
ECM crosslinking
RAGE
Inflammation
TGFβ*
Transition
Fibroblast
Myofibroblast
RLX*
• ↑ Fibronectin
• ↑ Collagens
MMPs
TIMPs
• Fibrosis
• ECM accumulation

CARDIAC INFLAMMATION

- inflammatory cells
  - cytokines, chemokines and exosomes
    - cardiomyocyte hypertrophy and ECM remodeling
  - accumulation and infiltration of pro-inflammatory macrophages and lymphocytes
    - TNF, IL-6, IL-1β, interferon-γ and TGFβ
    - induce or exacerbate cardiac injury
    - adverse remodeling


Systemic changes
• ↑ Ang II
• ↑ AGEs
• Lipotoxicity
Systemic and/or cardiac inflammatory cell activation*
HMGB1–LPS
TLR4*
TNF
TNFR1
12-LOX and 15-LOX*
Cardiac cell
NLRP3 inflammasome*
NF-κB
PGC1α
IL-1β*
AKT1
Cardiomyocyte death
Cardiomyocyte hypertrophy
Cardiomyocyte metabolic imbalance
Cardiomyocyte contractile dysfunction
Oxidative stress, mitochondrial dysfunction

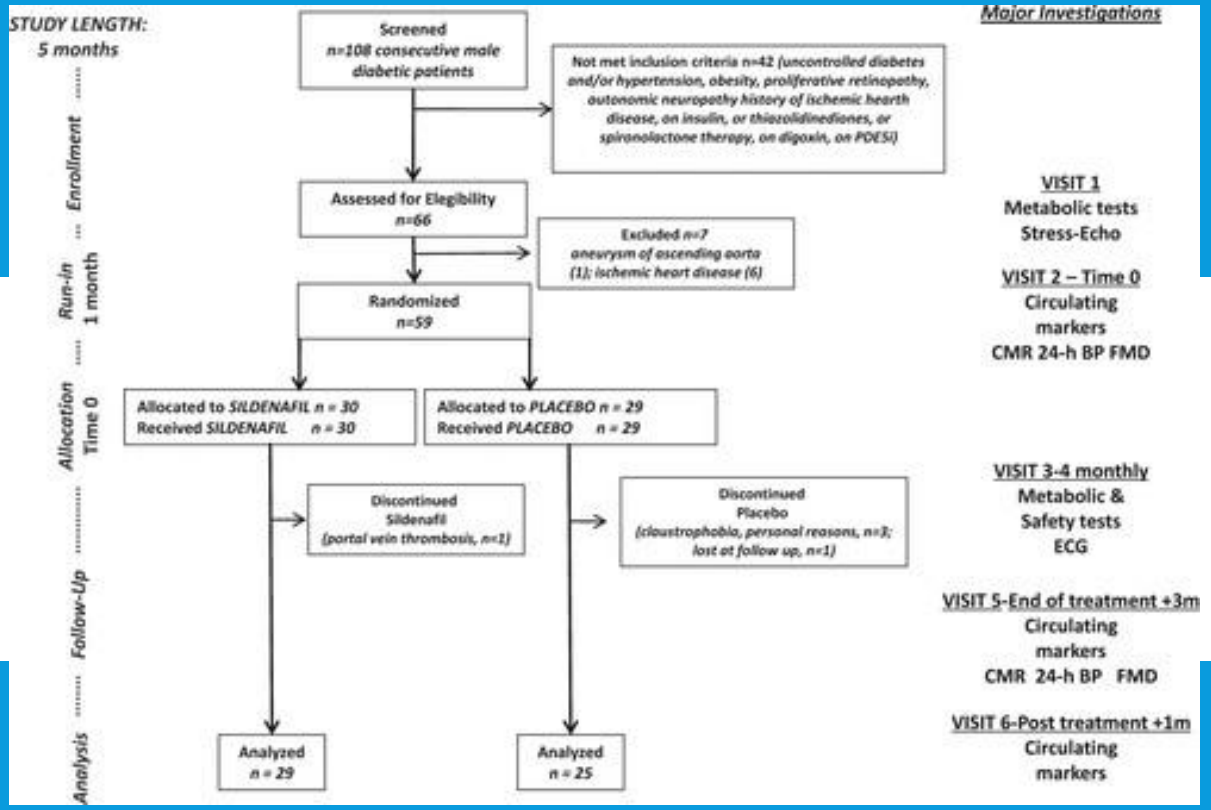
POTENTIAL THERAPEUTIC STRATEGIES

CARDIAC REMODELING AND DYSFUNCTION PRECLINICAL STUDIES

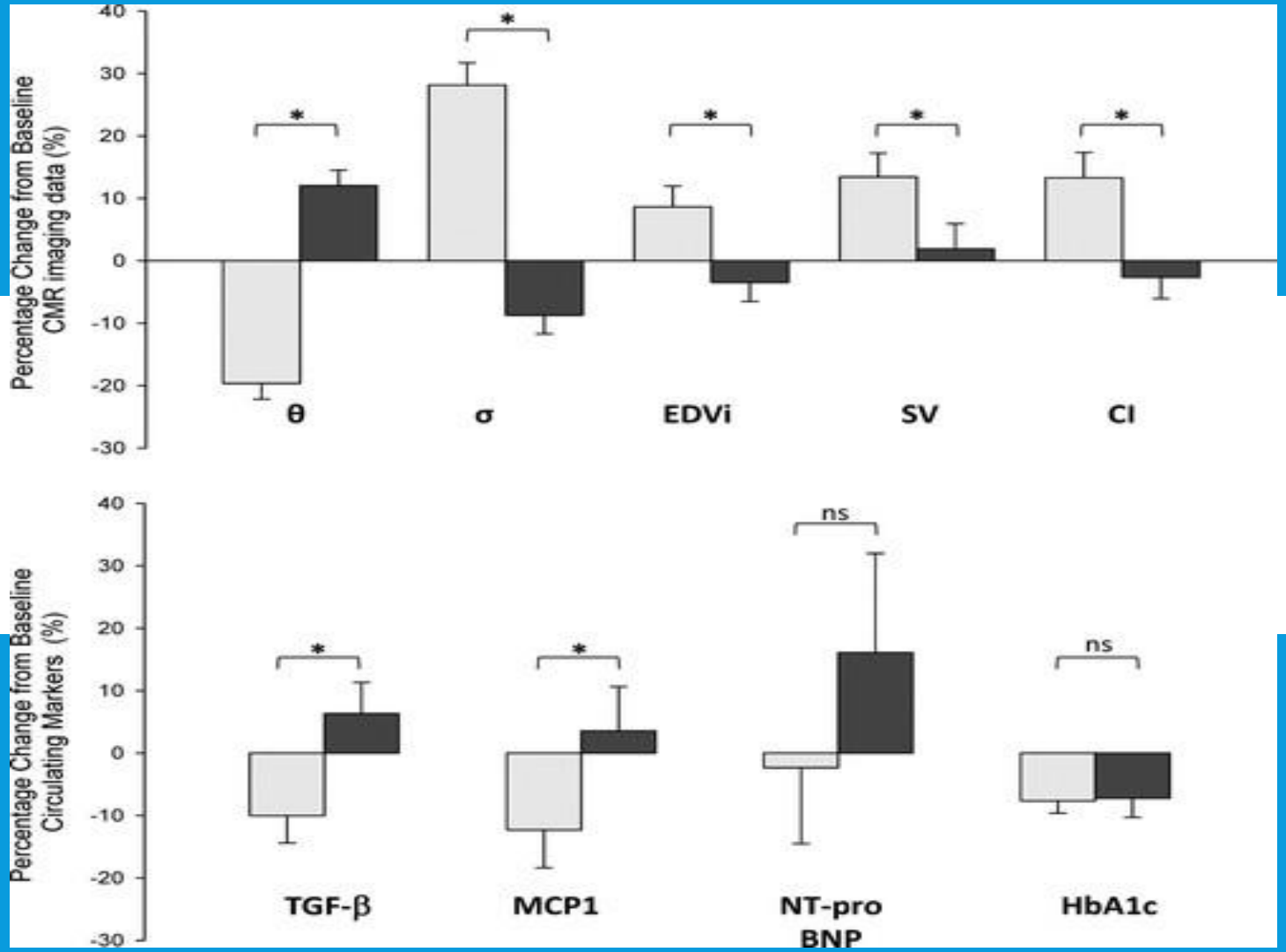
- Anti-fibrotic pathways to prevent adverse cardiac remodeling in animal models of diabetes
  - collagen production stimulated by TGFβ signaling: cinnamoyl anthranilate
  - Strategies to restore cGMP
    - PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil
- SGLT2 inhibitor empagliflozin
  - reduced cardiac hypertrophy, fibrosis, oxidative stress and apoptosis
  - rescuing the diabetes-induced suppression of the sGC–cGMP–PKG pathway
- Relaxin
  - antifibrotic hormone
  - preventing collagen production
  - downregulating fibroblast-to-myofibroblast transition and by stimulating MMP production

CARDIAC REMODELING AND DYSFUNCTION

Clinical studies



Elisa Giannetta. Circulation. Chronic Inhibition of cGMP Phosphodiesterase 5A Improves Diabetic Cardiomyopathy, Volume: 125, Issue: 19, Pages: 2323-2333, DOI: (10.1161/CIRCULATIONAHA.111.063412)



Elisa Giannetta. Circulation. Chronic Inhibition of cGMP Phosphodiesterase 5A Improves Diabetic Cardiomyopathy, Volume: 125, Issue: 19, Pages: 2323-2333, DOI: (10.1161/CIRCULATIONAHA.111.063412)

CARDIAC INFLAMMATION

Clinical studies

CARDIAC OXIDATIVE STRESS PRECLINICAL STUDIES

- Sulforaphane
  - Cruciferous vegetables
  - expression of numerous genes encoding antioxidant proteins
  - attenuating cardiac dysfunction, oxidative damage, inflammation, fibrosis and hypertrophy
- N-acetylcysteine
  - normalized the levels of oxidative stress
  - prevented the development of diabetic cardiomyopathy
- Zinc
  - attenuated cardiac fibrosis and dysfunction2
  - prevented the development of diabetic cardiomyopathy
  - prevented diabetes-induced peripheral nerve damage

CARDIAC OXIDATIVE STRESS CLINICAL STUDIES

- Zinc supplementation
- Sulforaphane

DIABETES-INDUCED METABOLISM DISTURBANCES

- Critical mechanisms involved in the development of diabetic cardiomyopathy
  - insulin resistance
  - abnormal glucose metabolism
  - excessive fatty acid oxidation and lipid accumulation in the heart

- Fenofibrate
  - reduced fibrosis and fat (triacylglycerol) accumulation in the heart
  - metformin was more effective than fenofibrate in reducing fat content, however, with no effect on the reduction of fibrosis
- Trientine, a copper-selective chelator
  - improved cardiac function in rats with diabetes with significant left ventricular impairment
- zinc supplementation
- angiotensin-converting enzyme inhibitors (captopril), b-blockers (timolol), and spironolactone.
  - beneficial effects in protecting against myocardial damage in experimental models
- SGLT2 inhibitors
  - reduced hospitalization for HF in patients with diabetes at high cardiovascular risk
  - this effect was independent of the presence of HF at baseline
  - In animal studies
    - slowed down atherosclerosis progression, and improved left ventricular negative remodeling and myocardial contractility
  - beneficial cardiovascular effects that cannot be attributable to glucose-lowering alone

KEY POINTS

- Diabetic cardiomyopathy occurs in absence of other cardiovascular diseases.
- The main metabolic abnormalities resistance to the metabolic actions of insulin in heart tissue, compensatory hyperinsulinemia, and the progression of hyperglycemia
- Two stages of diabetic cardiomyopathy are described:
  - left ventricular hypertrophy and impaired diastolic function
  - cardiac fibrosis and systolic dysfunction
- No target treatments have been tested in diabetic cardiomyopathy