

# UPDATE ON DIABETES AND THE HEART

# Diabetes and the Heart Overview

- Epidemiology and importance of T2DM
- Cardiac implications of diabetes
- Cardiomyopathy and CHF
- Hypertension
- Atherosclerotic complications
- Lifestyle interventions
- Therapies and cardiac implications
- T2DM Which therapy?

# Diabetes and the Heart Overview

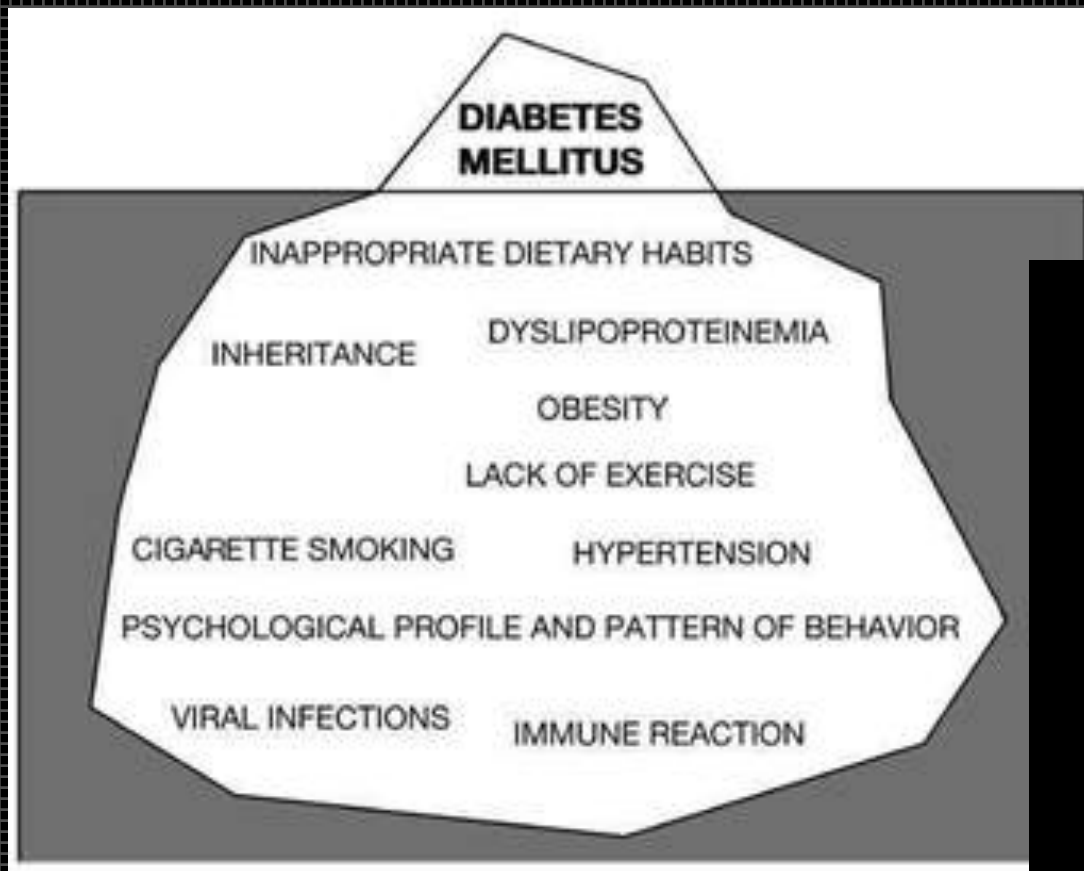
- **Epidemiology and importance of T2DM**
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- Which therapy?

# Diabetes Incidence and Prevalence

- Epidemic worsening worldwide!
- ½ a billion diabetic patients in the world
- UK: 65% increase in CHF in DM vs non DM
  - 48% more likely to have an MI
  - 331% more likely to have a foot amputation
  - 24.9% more likely to have a CVA
  - 139% more likely to have renal failure
- USA and NA 37 million diabetics in 2013
- Young people with T2DM increasing



# Why? Multiple Factors



1960 →



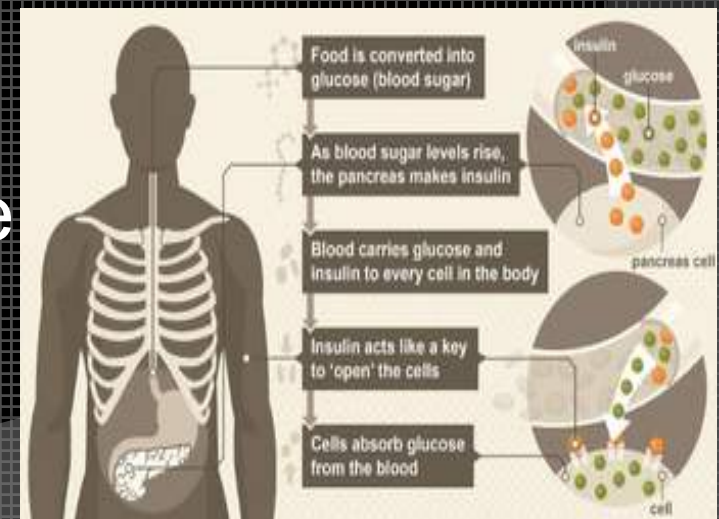
# What are the Adverse Changes?

- Multiple Co-factors in T2DM
- Complex molecular mechanisms
  - - Single nucleotide polymorphisms - genetic
  - - Insulin binding to Tyrosine/Kinase receptors
  - - Glucose transport proteins ( GLUT- 4)
  - - Fat endocrine / ↓ Adiponectin ↓ leptin,
  - - Incretins GLP-1, GIP stimulate Insulin
  - - Increased use of FFA by organs
- What are the Leading Hypotheses for T2DM?

# T2DM TRIUMVIRATE THEORY

De Fronzo 2009

- ① 1. Insulin resistance at level of the liver
  - - hepatic outpouring of glucose: gluconeogenesis and glycogenolysis
  
- ② 2. Insulin resistance in peripheral tissues
  - - inability to uptake glucose
  
- ③ 3. Beta cell fatigue and failure
  - - declining insulin secretion



# THE OMINOUS OCTET

- ① 1 – 2. insulin resistance, level of liver and other cells in periphery
- ② 3. Beta cell failure
- ③ 4. Lipotoxicity fat cells/FFA release
- ④ 5. Incretin system GLP-1 and GIP
- ⑤ 6. Hyperglucagonemia Alpha cell
- ⑥ 7. Kidney SGLT-2 upregulated
- ⑦ 8. Brain and GLP-1

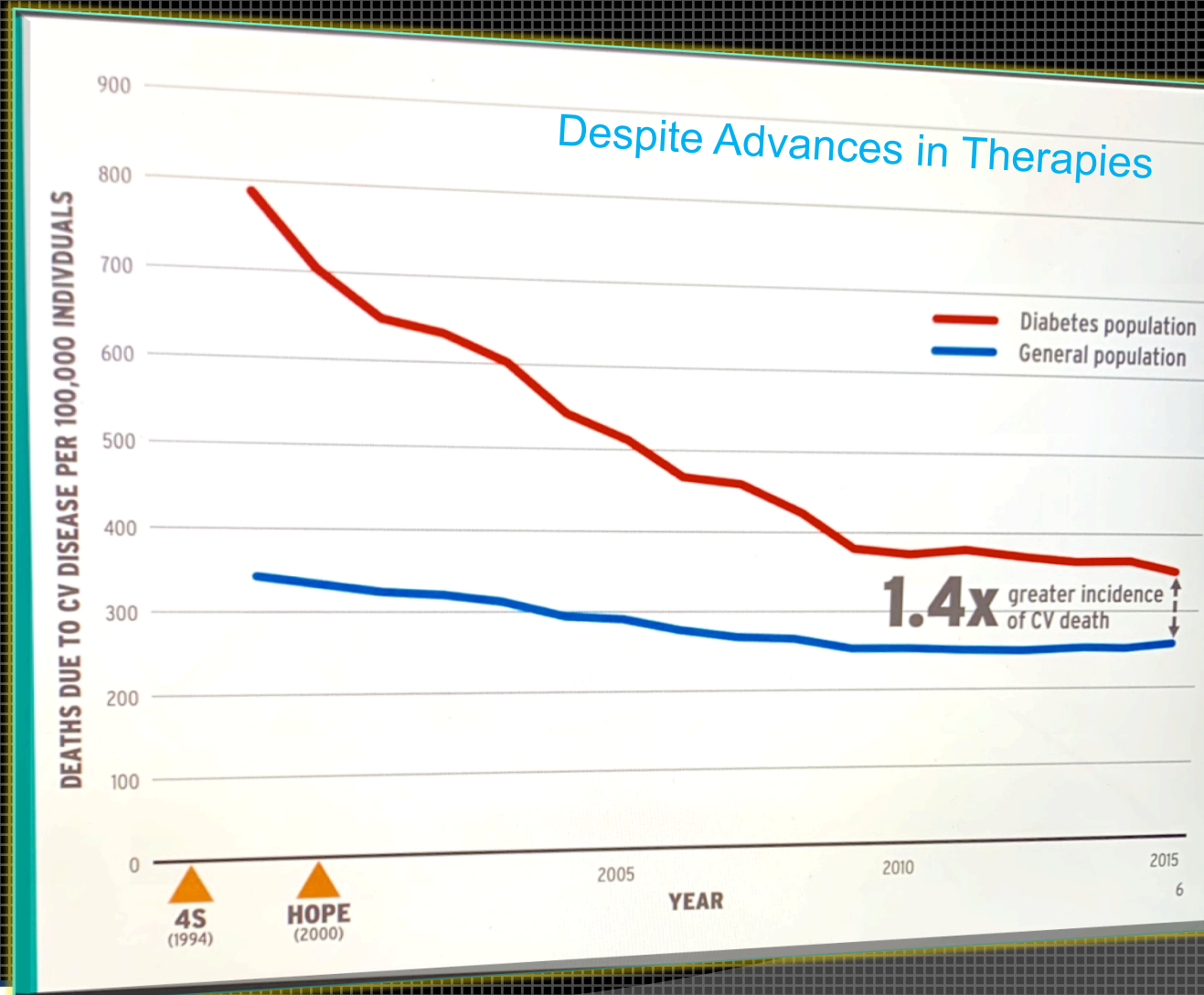
# IGT and progression to T2DM

- 2 Hr plasma glucose on OGTT N <140mg/dl
- But pts in 120-139 range have lost 2/3 of their Beta cells
- Upper tertile IGT (180mg/dl +) have lost 85% of B function
- Dx of T2 DM usually at over 80% lost B cells!
- Pts with IGT are Insulin R & 10% have retinopathy already
- Lipotoxicity occurs when FFA ↓ insulin secretion TZD may ↑
- Primary treatments last few decades:
  - Sulfonylureas to kick start limited B cells
  - Metformin to promote cell use of sugars

# Diabetes and the Heart Overview

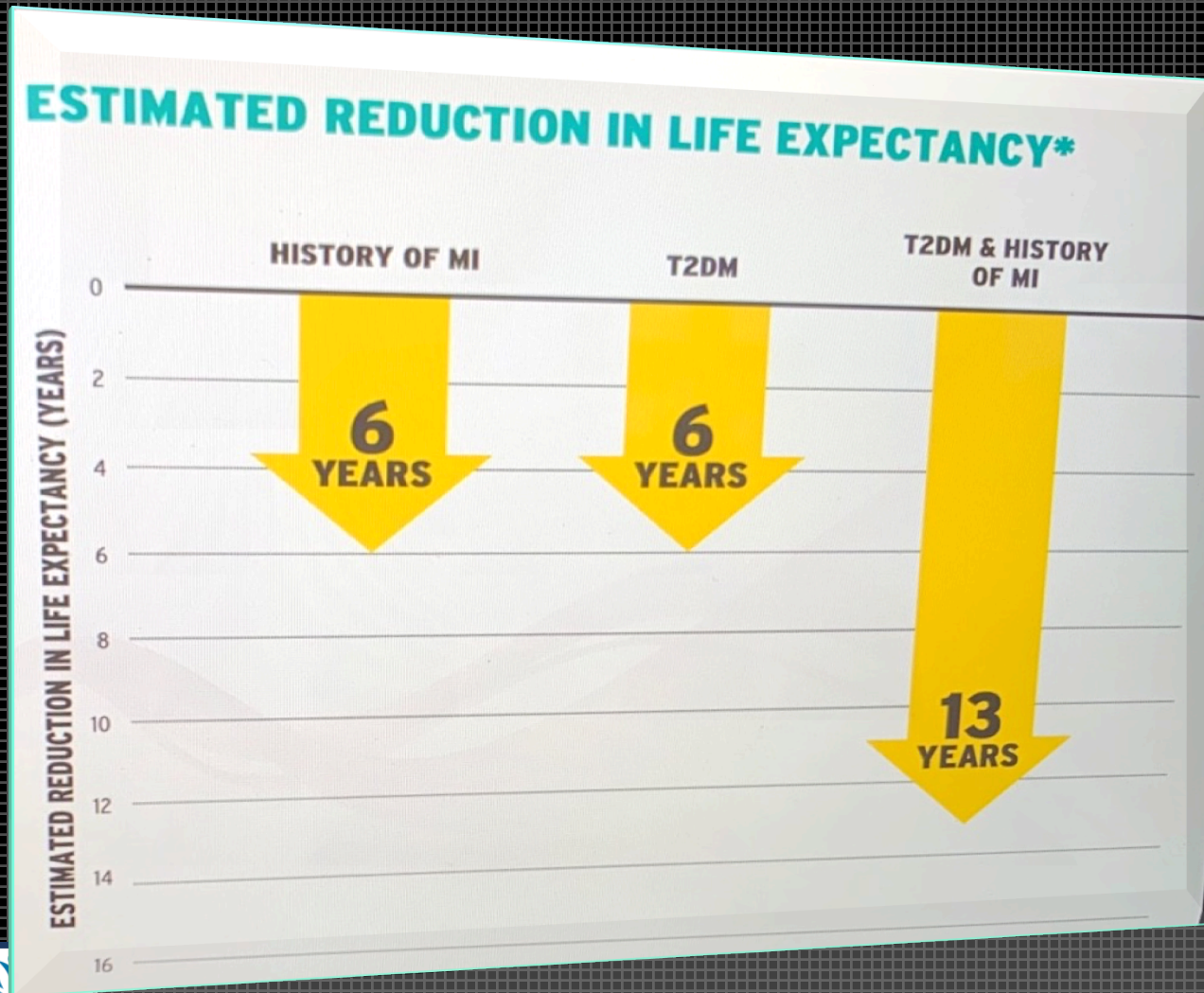
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# CV Death Rates T2DM





# JAMA 2015: 60 year old pts

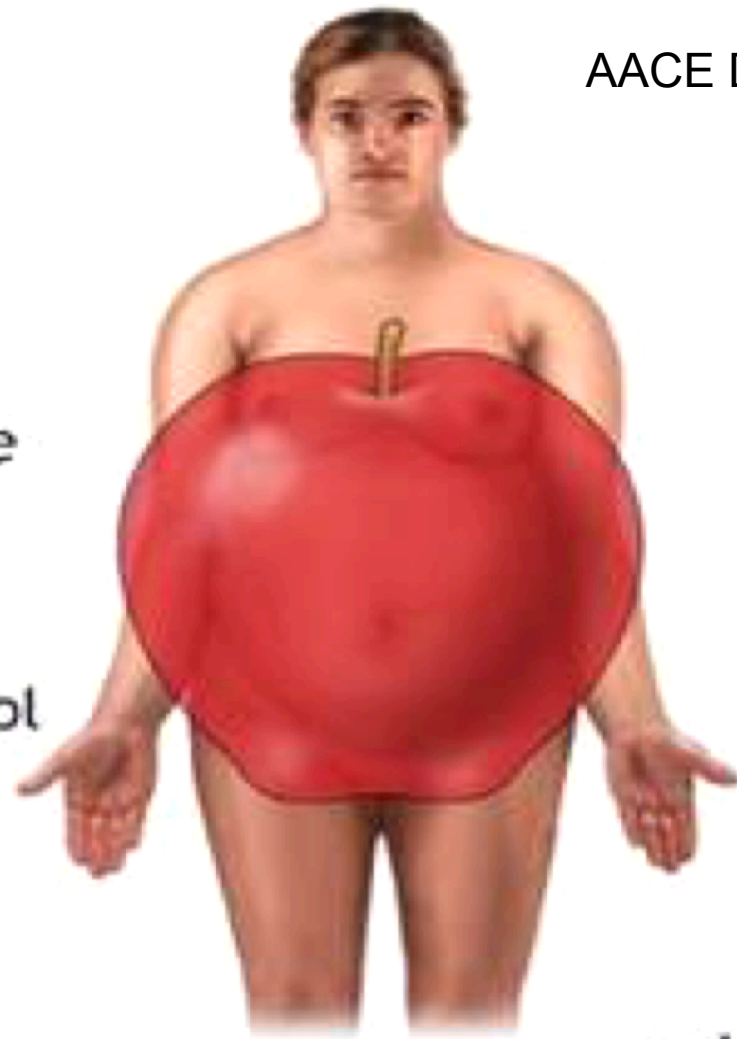




# Contributors to Heart Disease (2-4X)

## Metabolic syndrome (Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance



## AACE Definition

Insulin Resistance

BMI over 30

>130/85

>150

<40 M

<50 F

FBS>110

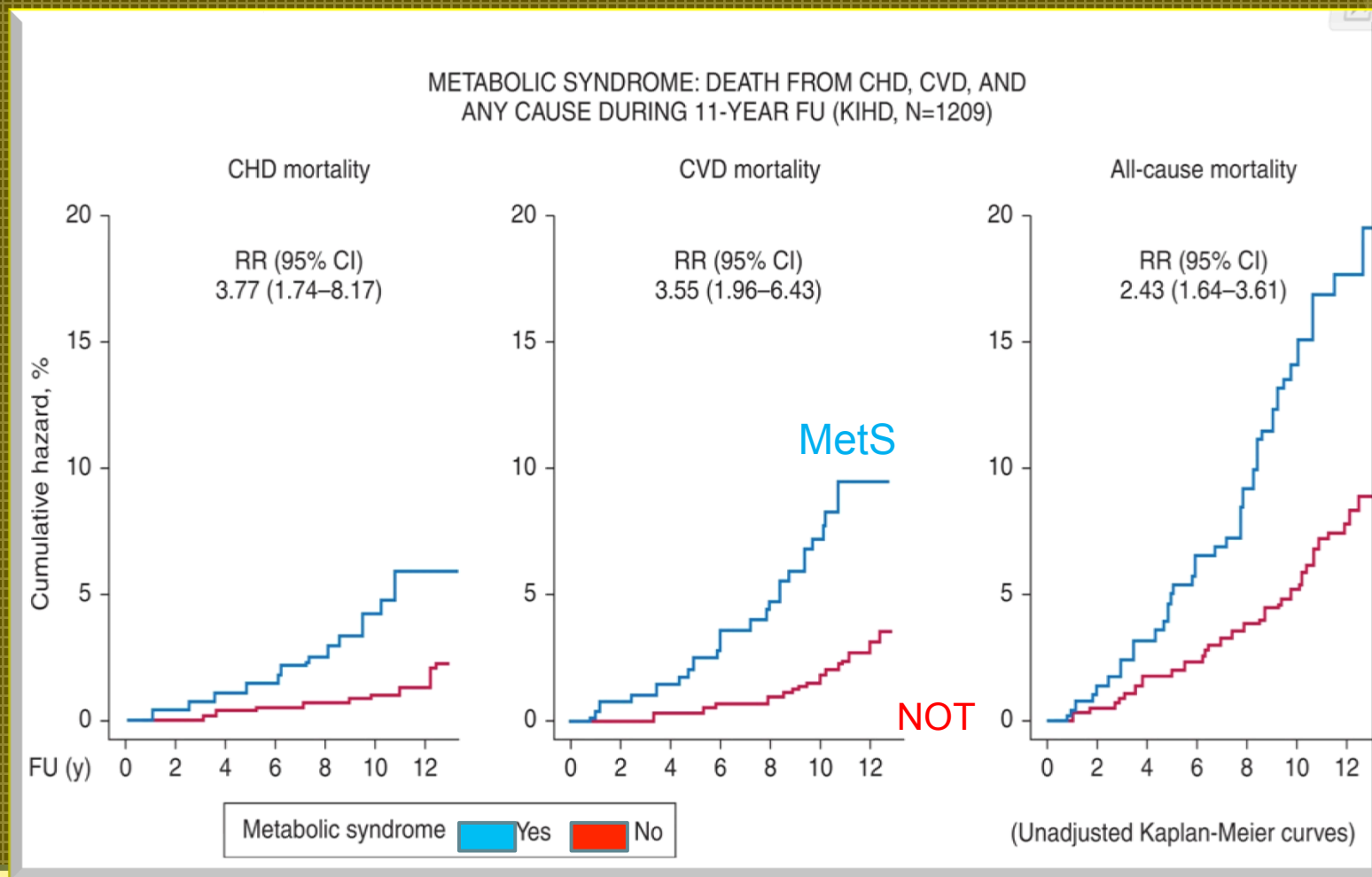
2 hr Glu

140-200

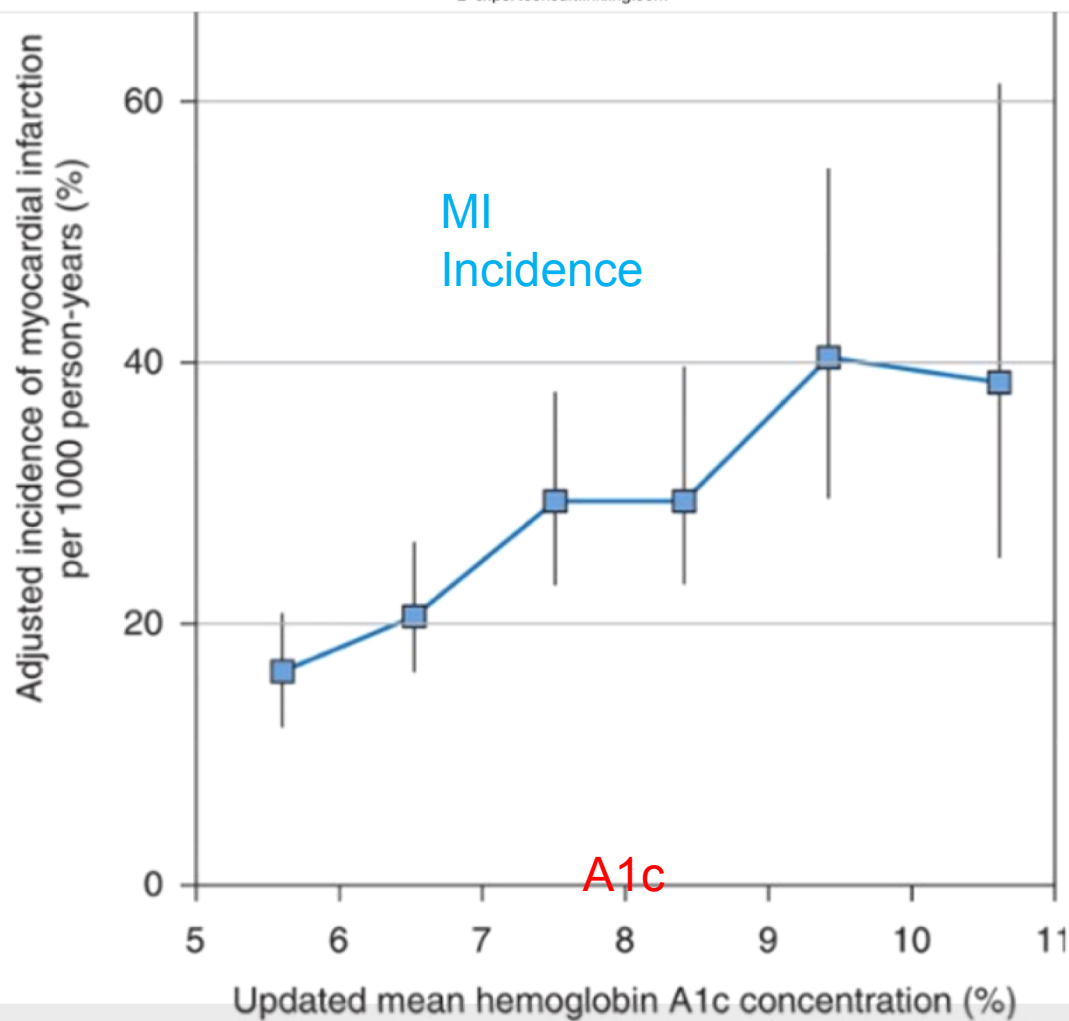
Definition prevalence in NHANES >20yo 34.5%



# Impact of T2DM /MetS on the Heart



# Impact of T2DM on the Heart



Proteinuria

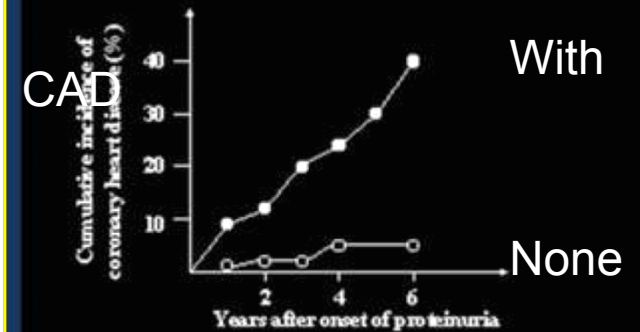


Fig. 1. Cumulative incidence of coronary heart disease in patients with (●—●) and without (○—○) proteinuria. Chi-square: 14.3;  $p < 0.001$

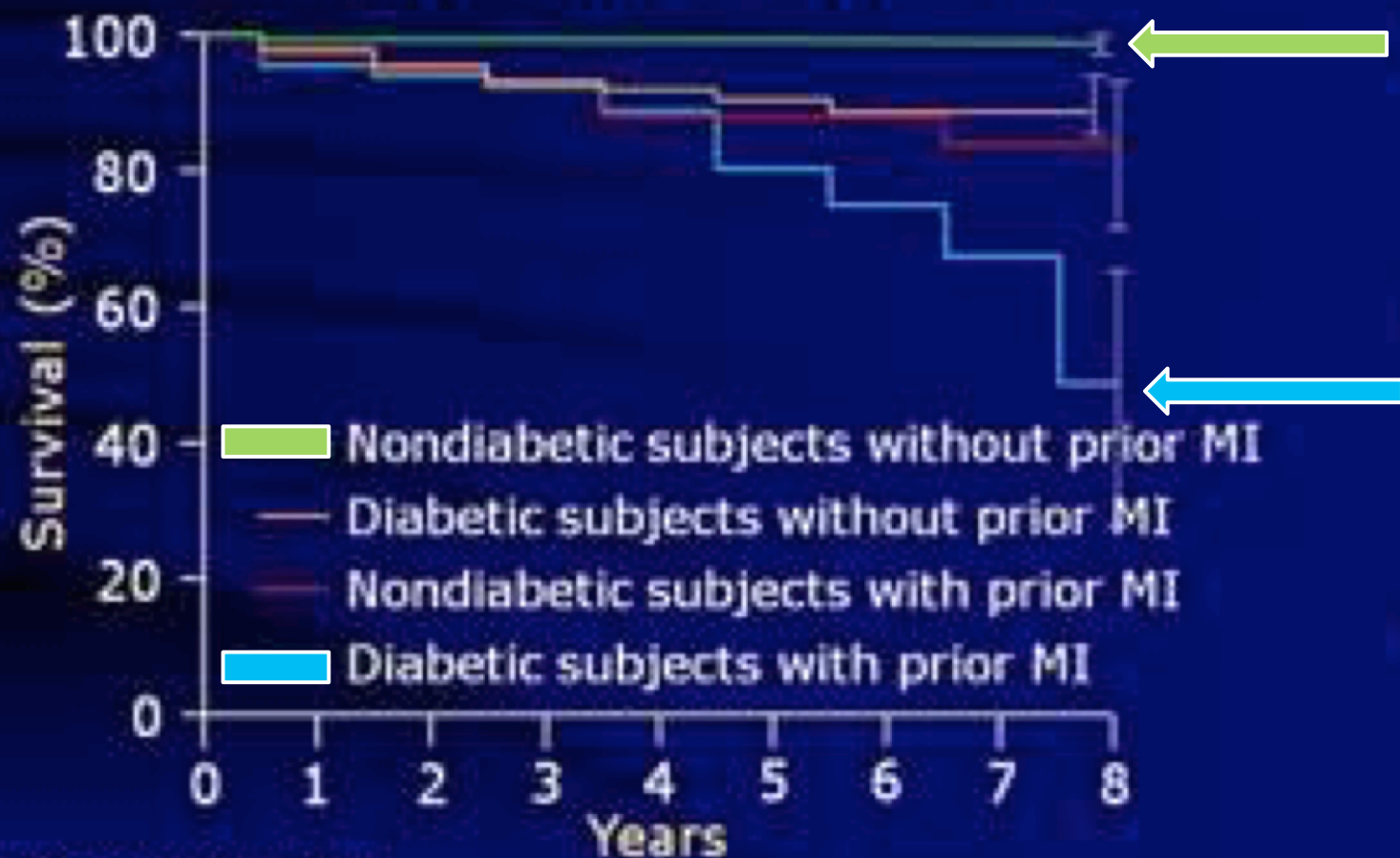
Adapted from: Jensen T, et al. *Diabetologia* 1987; 30: 144-48.

# ...Contributors to Heart Disease

- Other Factors (MetS 5x risk of T2DM)
  - - Waist circumference
  - - Atherogenic dyslipidemia
  - - Elevated apo B, small dense LDL, Small HDL
- Proinflammatory state
  - Increased CRP levels, ↑ TNF-a ↑ IL-6
- Pro Thrombotic state
  - PAI – 1, fibrinogen, hormonal factors



# Probability of Death From CHD in Patients With NIDDM and in Nondiabetic Patients. With and Without Prior MI



Kaplan-Meier estimates

Haffner SM et al. *N Engl J Med* 1998;339:229-234

# Diabetes and the Heart /Agenda

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# Diabetic Cardiomyopathy

- Is this a thing?

# Diabetic Cardiomyopathy

- Is this a thing? **YES**
  
- Oh yes, and all diabetics are considered to have **Stage A CHF** and **CAD equivalence !**



# Stage A Heart Failure

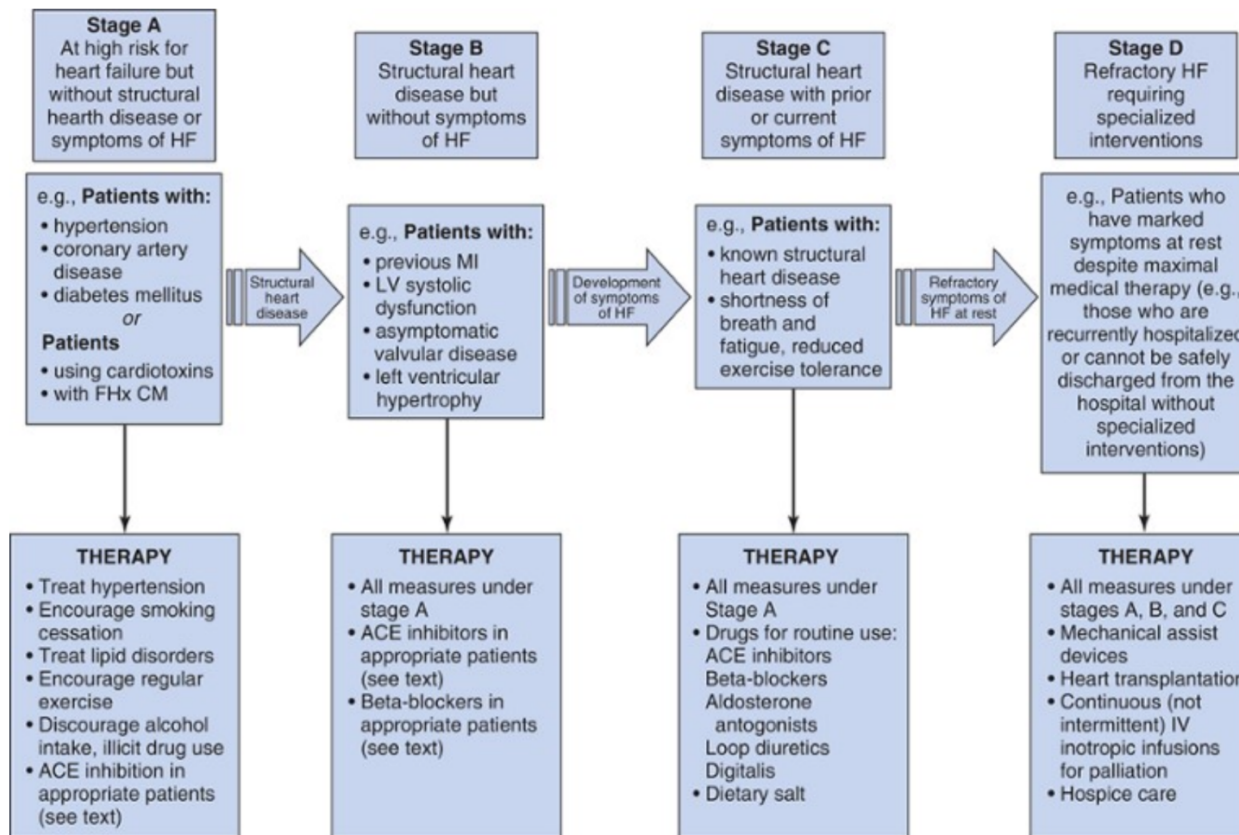
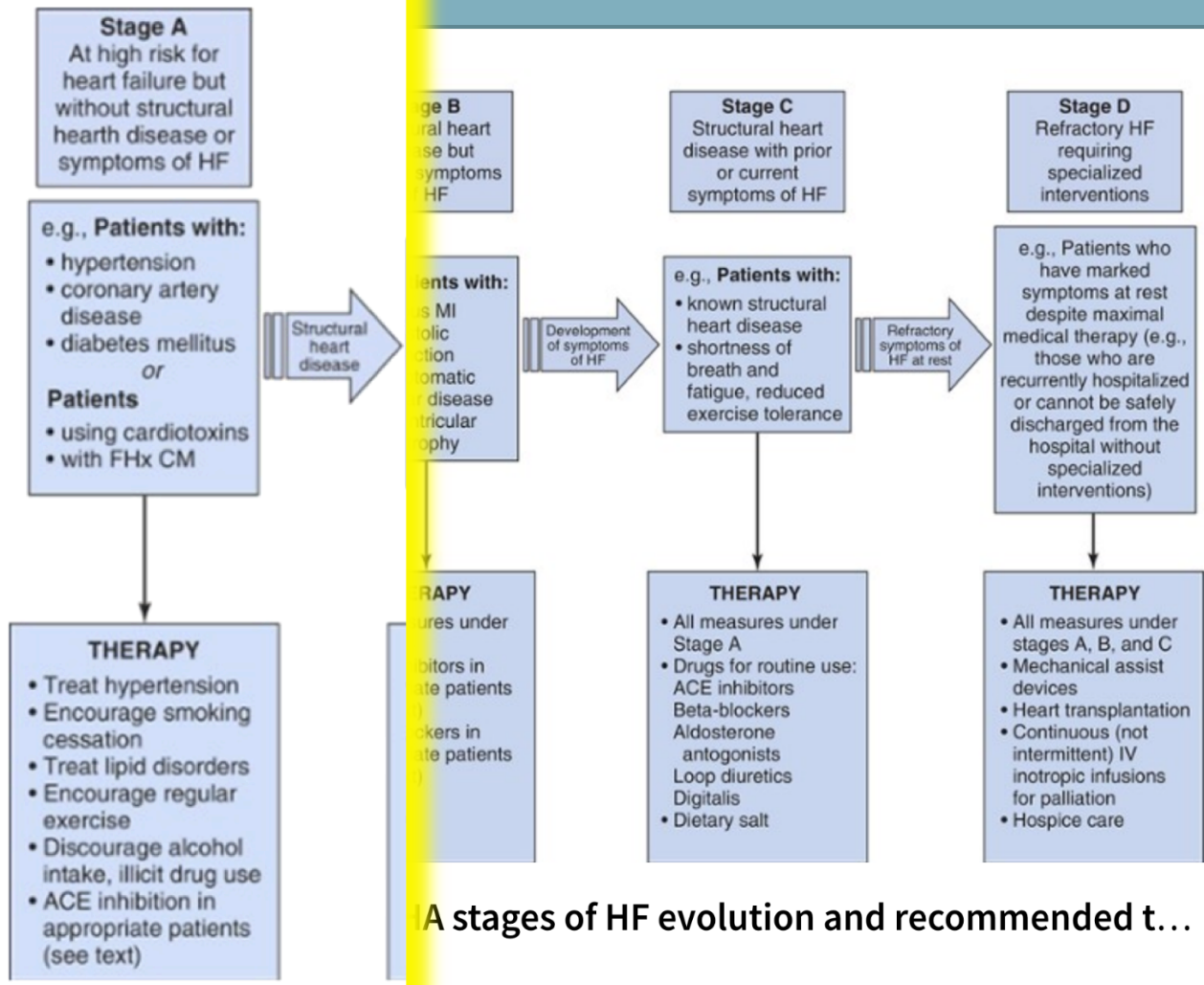


FIGURE 25-1 ACC/AHA stages of HF evolution and recommended t...

# Stage A Heart Failure



A stages of HF evolution and recommended t...

# Cardiomyopathy / CHF

- Systolic and Diastolic dysfunction
  - 60% pt with symptomatic chronic HD have T2DM
  - T2DM & Insulin R are powerful M&M predictors
  - For females with DM CHF risk is 5x normal
- Diastolic dysfunction occurs early
- Diabetic milieu is Toxic
  - FFAs , Endothelial dysfunction, altered Ca<sup>++</sup>
  - ↑ Myocyte injury, fibrosis, microangiopathy
  - ↑ “Lipotoxicity”

# Mechanisms for Cardiomyopathy

- ⦿ Independent of presence of CAD
- ⦿ Cardiac myocytes Normal 2/3 FA use
- ⦿ 1/3 glucose, lactate , ketone use
  
- ⦿ 2 Phases, CMPY early and late
- ⦿ Early changes
  - Myocyte insulin R, endothelial dysfunction
  - ↑ FFA oxidation less efficient ↑ O2 demand
  - Impaired diastolic compliance, lipotoxicity

# Mechanisms for Cardiomyopathy

- Independent of presence of CAD
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- 2 Phases, CMPY early and late
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# ...Mechanisms /Cardiomyopathy

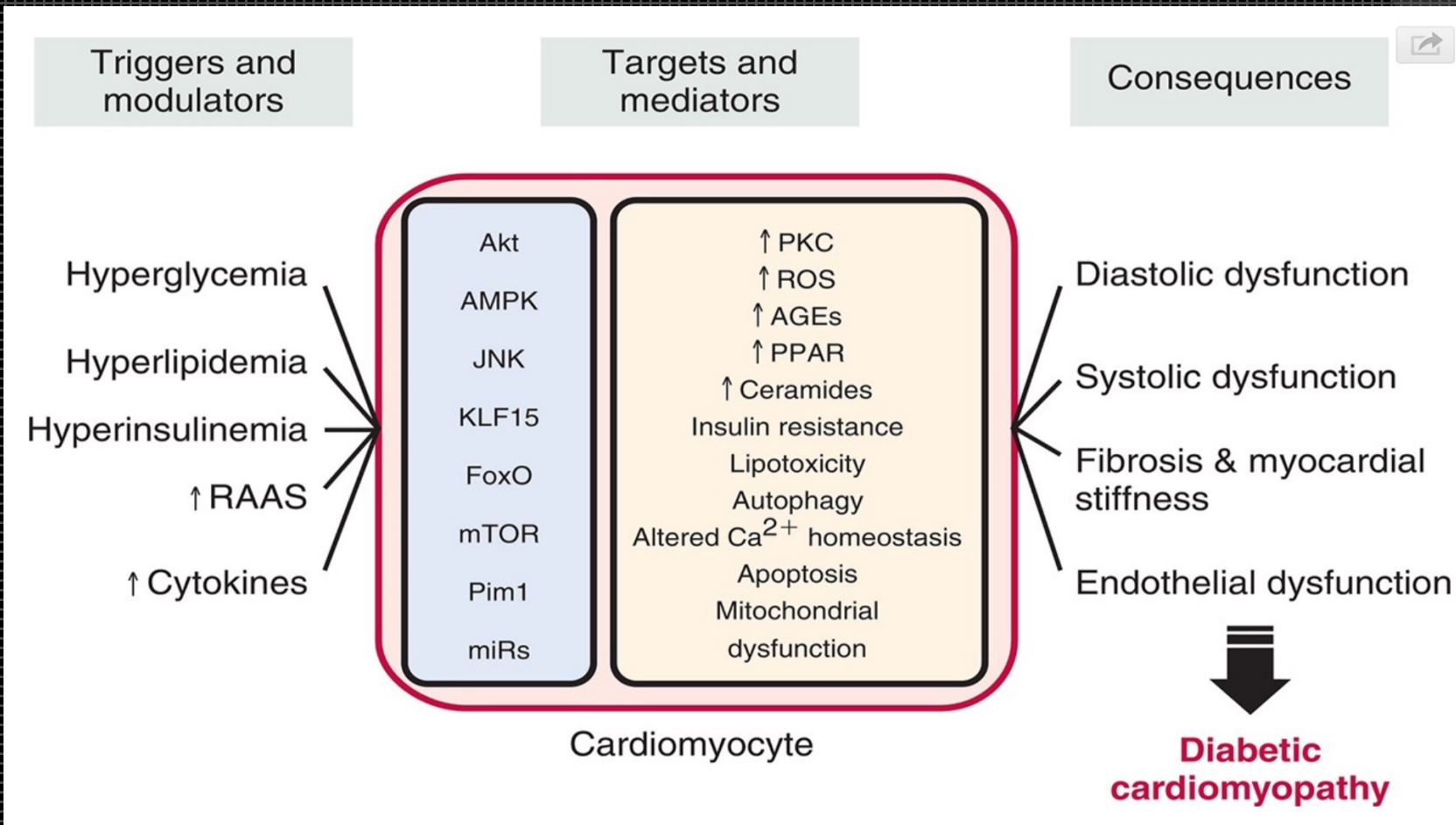
## ⦿ Late phase

- - Myocyte injury, apoptosis
- - CAD, Hypertension, Microangiopathy
- - Cardiac autonomic neuropathy

## ⦿ Changes in structure:

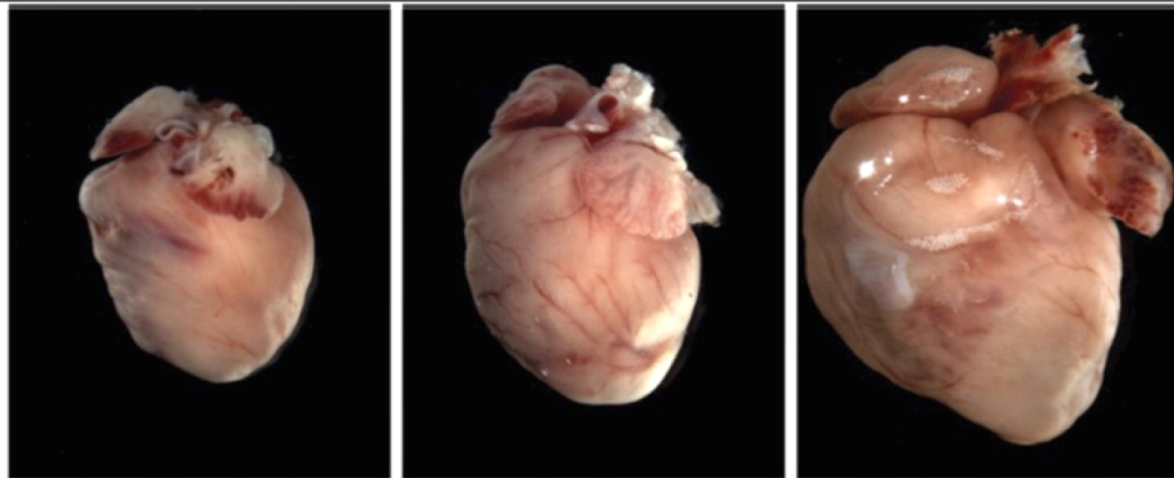
- - Increased dimensions, ↑ wall thickness, mass
- - myocardial microvascular disease

# Triggers, Targets and Outcomes





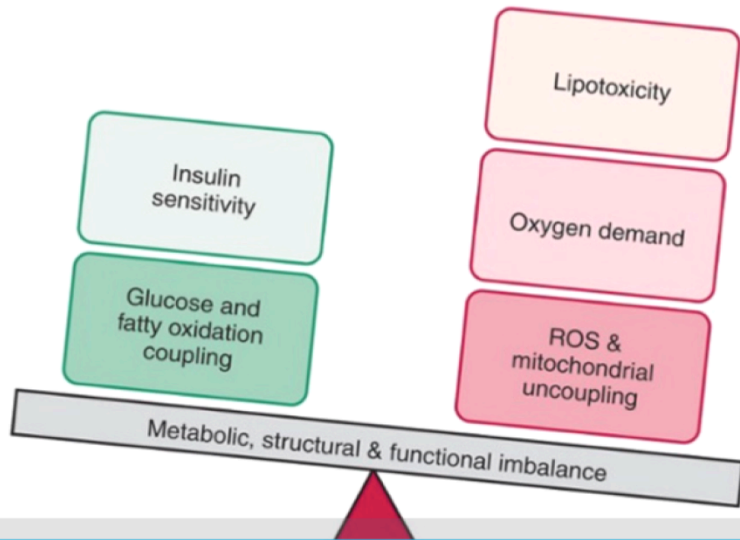
# Is That All?



Normal

Hypertrophy

Diabetic cardiomyopathy





# Is That All?

- NO

- Autonomic cardiac nerves are affected

# CV autonomic Neuropathy

- ⦿ Impairment of autonomic control of CV system in DM
  - - After exclusion of other causes
- ⦿ Poor glycemic control is a contributor, and obesity
- ⦿ In 20 % of diabetics; is a 3.5x predictor of early mortality
- ⦿ Orthostatic Hypotension occurs and predicts mortality
- ⦿ Silent ischemia is present in 30% of CAN
- ⦿ QT prolongation frequent with CAN
- ⦿ Exercise intolerance due to altered SNS
- ⦿ CARTs to diagnose



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# Hypertension

BP is consistently higher in T2DM vs controls

-20% difference in SBP = 45% difference CAD

UKPDS showed 12% ↑ MI risk per 10mmHg ↑ BP

DASH diet / reduce BP 5.5/3.0 mmHg in 8wks!

- low sodium DASH diet can reduce 11.5 / 7.1 mmHg

ACE inhibition slight edge in outcomes vs others

- most patients will require more than one agent

Goals for therapy more strict than non DM

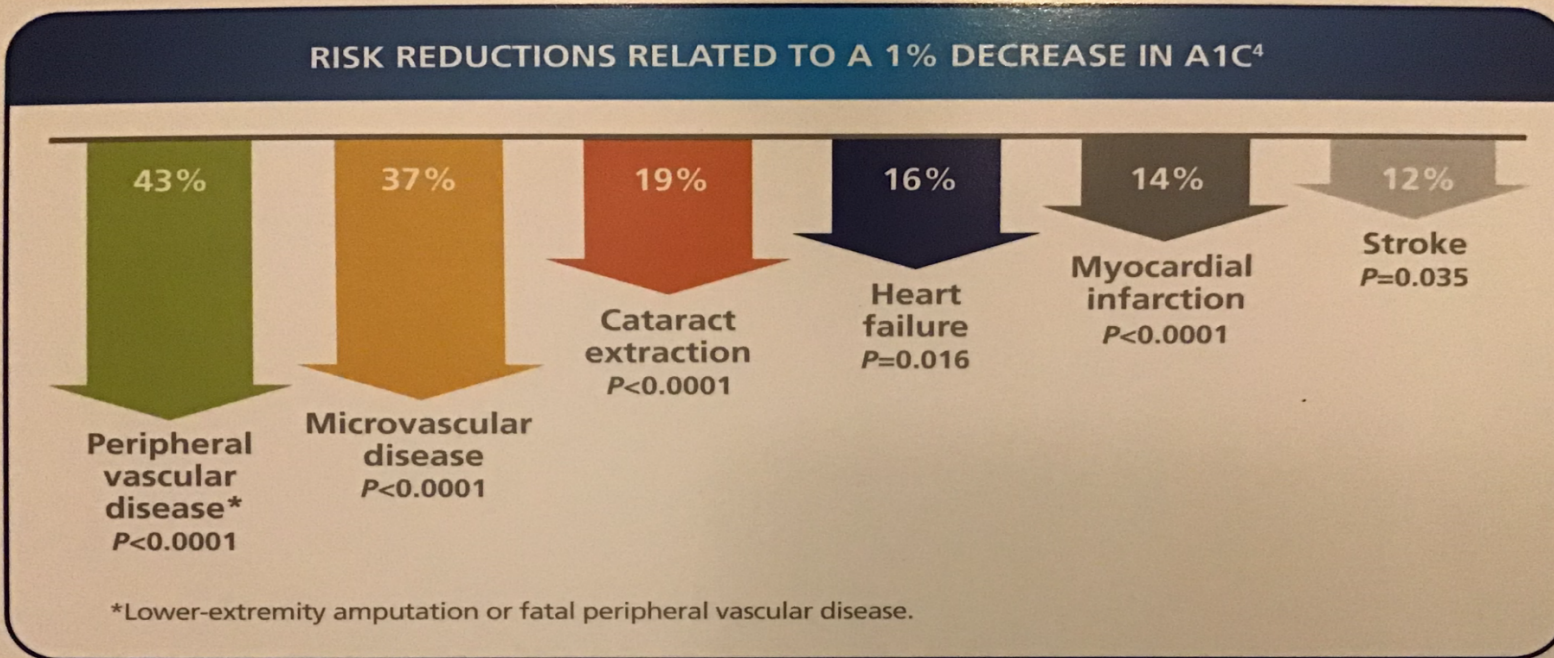
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# Atherosclerotic Complications

- CAD
- MI
- CVA
- PAD
- AAA
- Microvascular

# How Important is A1C Goal?



Prospective observational study in 4585 patients newly diagnosed with type 2 diabetes to evaluate the relation between glycemia over time to the development of macrovascular and microvascular complications, in which 3642 patients had complete data for analyses of relative risk.<sup>4</sup>



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# Cardiovascular Disease

Lifestyle

Diet

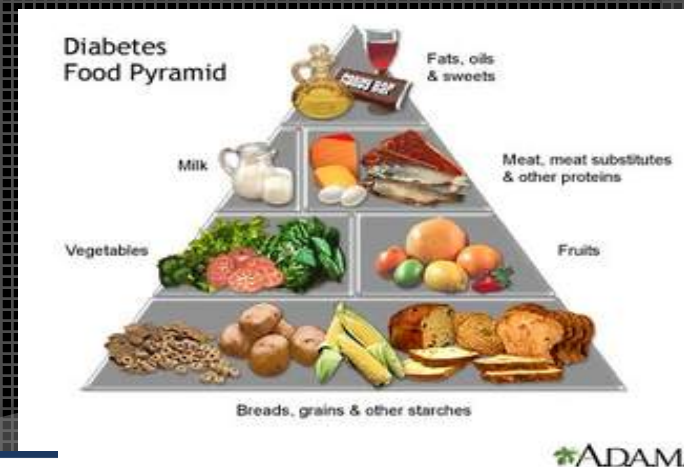


# Is Prevention of T2DM Possible?

- Insulin Resistance is primary process
  - - Visceral fat mass is the key trigger
- Increasing circulating insulin then leads to CV morbidity and ASHD
- Genetic susceptibility is involved
- Sustained lifestyle change can be effective
- RCTs have shown ↓ IGT progress 60%

# Lifestyle Recommendations

- Multiple RCTs have shown: (US DPP)
  - - Physical activity, diet and weight loss key
  - - Can slow risk of progression of IGT by 30-60%
  - - Metformin use in IGT can ↓ progression
  - - Can lower all cause mortality by these methods





## Mediterranean or DASH Diet

Weight vigilance is key

5 portions / day fruit and vegetables

Olive oil or veg oil as main fat PUFA

Fibre + and avoid sugars

Fish > 2x per week esp oily fish

Low fat milk and meat products

Whole grains



## ...Lifestyle Recommendations

- ⊙ Recommendations exercise
  - - 3 days /wk, 45 to 60 min light/ mod
  - - 1 to 3 sets of 8 to 15 reps resistance
- ⊙ Physical activity increase results in
  - - 2 hr post OGTT load ↓ Glu 23 g/dl
- ⊙ Occurs in absence of ↓ weight or waist loss

# DPPS US Multicenter RCTrial

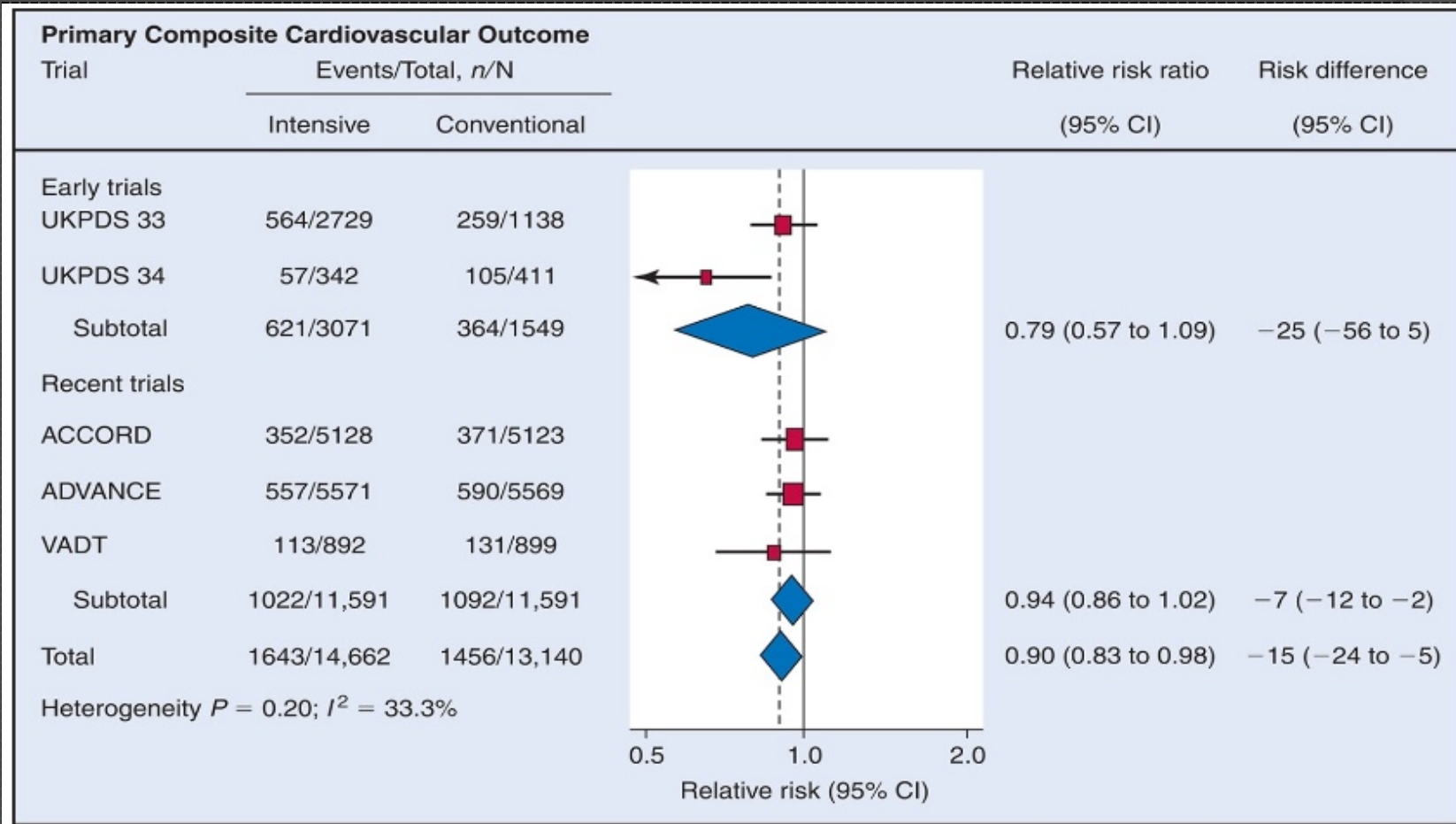
- Compared 3 interventions for IGT
  - Intensive lifestyle change n = 3234 pts
  - Standard lifestyle change + Metformin
  - Placebo
- Intensive group ↓ 58% vs placebo at 2.8 yrs T2DM
  - average wt loss 7 kg at 1 yr
  - at 10 yrs 34% less progression to T2DM
- Metformin Group less benefit, still ↓ 31% at 2.8y
- Similar trial results in Finn and Chinese studies

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# Primary Composite CV Outcomes



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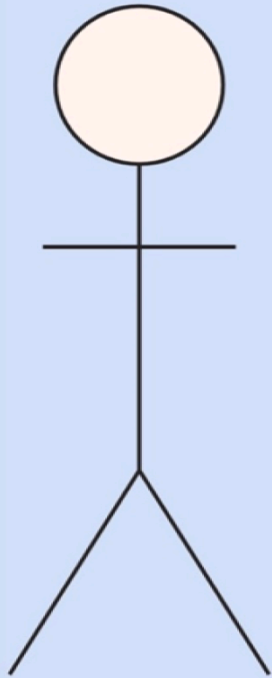
# Goals of Therapy : T2DM

- Improve Beta cell health
- Improve Insulin Resistance
- Improve Incretin effects
- Improve lipids
- Suppress Glucose reabsorption
- Suppress appetite
- Reach lifestyle goals

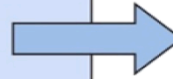


# Why so Important? Cardiac Implications

## Effects of diabetes on the individual



- Retinopathy
- Cardiovascular disease
- Nephropathy
- Neuropathy
- Foot ulcers, peripheral vascular disease, and amputations
- Elevated risk of other conditions including:
  - Tuberculosis and other infections
  - Mental health conditions, including depression
  - Alzheimer disease and general cognitive decline
  - Liver and digestive disease
  - Erectile dysfunction
  - Periodontal disease
  - Sleep apnea
- Lower reported quality of life
- Increased risk of death and lower life expectancy



## Effects on families:



- Loss of productive life years
- Cost of diabetes care
- Lower quality of life
- Disabilities/early death of family member with diabetes can affect the mental health and activities of the entire family



## Effects on society:

- Cost of treating diabetes and its complications
- Increased absenteeism and losses to the workforce

# Why so Important?

Lancet 375: 2215 -22  
2010

⊙ Hazard ratios **No T2DM** vs **T2DM**

⊙ Risk: -2 -1 0 1x 2x

CAD.....

2.0 (1.8 to 2.2)



Death.....

2.31 (2 to 2.6)



MI non.....

1.82 ( 1.6 to 2.1)



All CVA.....

1.8 (1.6 to 2.2)



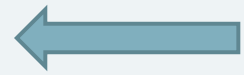
-ischemic....

2.27 (1.95 to 2.7)



Other Vasc...

1.73 (1.5 to 2.0)



# Pharmacotherapeutics

I = insulin

- **Metformin**, increases cell sugar use, I effect and decreases gluconeogenesis
- **Sulfonylureas** Stimulate B cell to make more Insulin, can cause ↓sugar
- **DPP-4** Increase levels of GLP- 1 hormone to increase I release - decrease gluconeogenesis in liver, “gliptins” ex. Linagliptin (Trajenta) , sitagliptin (Januvia) , saxagliptin (Onglyza)
- **TZD** Improves cell ability to use I, can cause fluid retention and liver issues
- **SGLT-2** Allows filtration of glucose to urine without reabsorption, ↓cardiac events
- **GLP analog** Acts like GLP- 1 , potent incretin produced by L cells in ileum
  - “glutides”, ex Semaglutide (Ozempic) , Linagliptide (Trulicity) Injectable, Semaglutide (Rybelsus) Oral
- **Acarbose** Slows absorption of starch from GI tract, limited by GI side effects

# Other Pharmacologic Rx

- ACE inhibition, address RAAS
- Statins
  - - Reduce all ApoB lipoproteins and LDL
  - - ? Of slight increase in progression to DM in non DM
  - - Net benefit in all subgroups with T2DM
- Fibrates
  - - improve all lipids and reduce CVD risk (VA-HIT)
- Antihypertensives
  - - Beware diuretics and non vasodilating BB



# ...Other Pharmacologic Rx

## ● Antihypertensives

- - Beware diuretics and non vasodilating BB
- - Vasodilating alpha B blockers- neutral lipids, FBS
- - \* No B blockers are contraindicated in T2DM

## ● Orlistat

- - Weight loss, may delay onset of DMT2

## ● Acarbose (Precose) and Miglitol

- - may confer reduced CV risk, but S/E ↑

# Surgical Treatments

- ⦿ Can surgical management decrease risk?
- ⦿ Bariatric surgery types:
  - - Roux- en –Y, (RYGB) Sleeve gastrectomy, (LSG)
- ⦿ Lap adjustable G banding, (LAGB)
- ⦿ BilioPancreatic diversion (BPD)
- ⦿ RYGB, LAGB,LSG no malabsorption
- ⦿ Can have 40 to 75% remission of T2DM
- ⦿ Medical/Lifestyle Rx 10 to 20% remission

# “Consumer report” T2DM Guide!

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	○
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	○ ★	★		★
Insulin	●	●	★		★
Glucoside					★

# Consumer report Guide: SUs

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★

# Consumer report Guide: Gliptins

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★

# Consumer report Guide TZDs

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ● Rosi ★
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★

# Consumer report Guide: SGLT-2



Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★



# Consumer report Guide: GLP



Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★

# Consumer report Guide: Insulin

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
Metformin	★ ★	★ ★ ★	★	○	★ ○
SUreas	●	●	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ●
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside					★

# Consumer report Guide : a- Glu

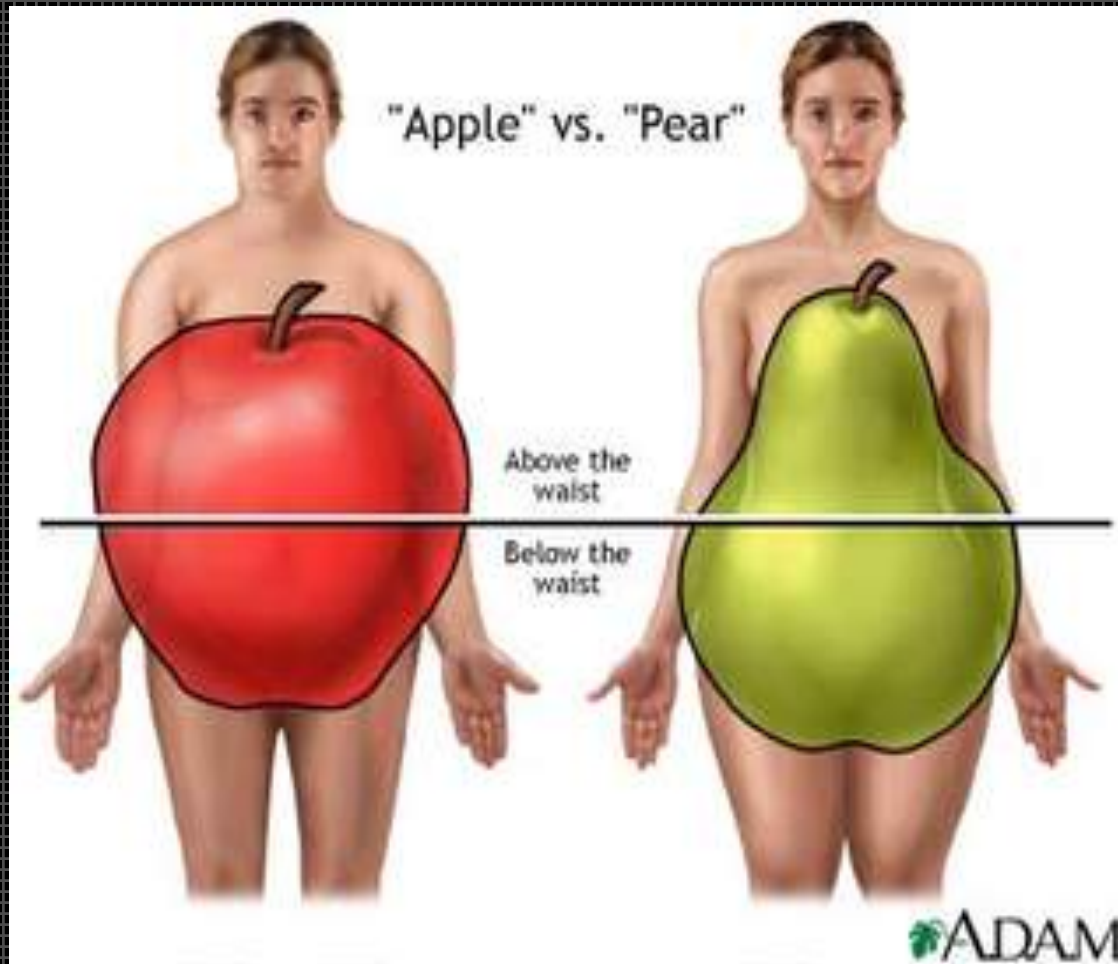
GI side effects >25% D/C

Agent	Weight	Hypo Gly/ Bcell	CHF	Edema	CV/Ischemia
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SUreas	●	● ○	● ●	○	○ ○
DPP-4	★	★ ★ ★	○	★	
TZD pio/ Rosi	●	★ ★ ★	●	●	★ Pio ● Rosi ★
SGLT-2	★ ★	★ ★ ○	★ ★	★ ★	★
GLP analog	★ ★	★	★		★
Insulin	●	●	★	○	★
Glucoside	★				★

# Summary

- DMT2 is a burgeoning health problem
- Has significant cardiovascular risks
- Strongly associated w CHF and mortality
- Associated w hypertension and ASCVD
- Early intervention in IGT important
- Lifestyle intervention is key
- Increasingly, Rx are able to preserve B cells
- Future treatments increasingly targeted

# Don't be an Apple!



Eat one! It has 5 G of soluble fiber