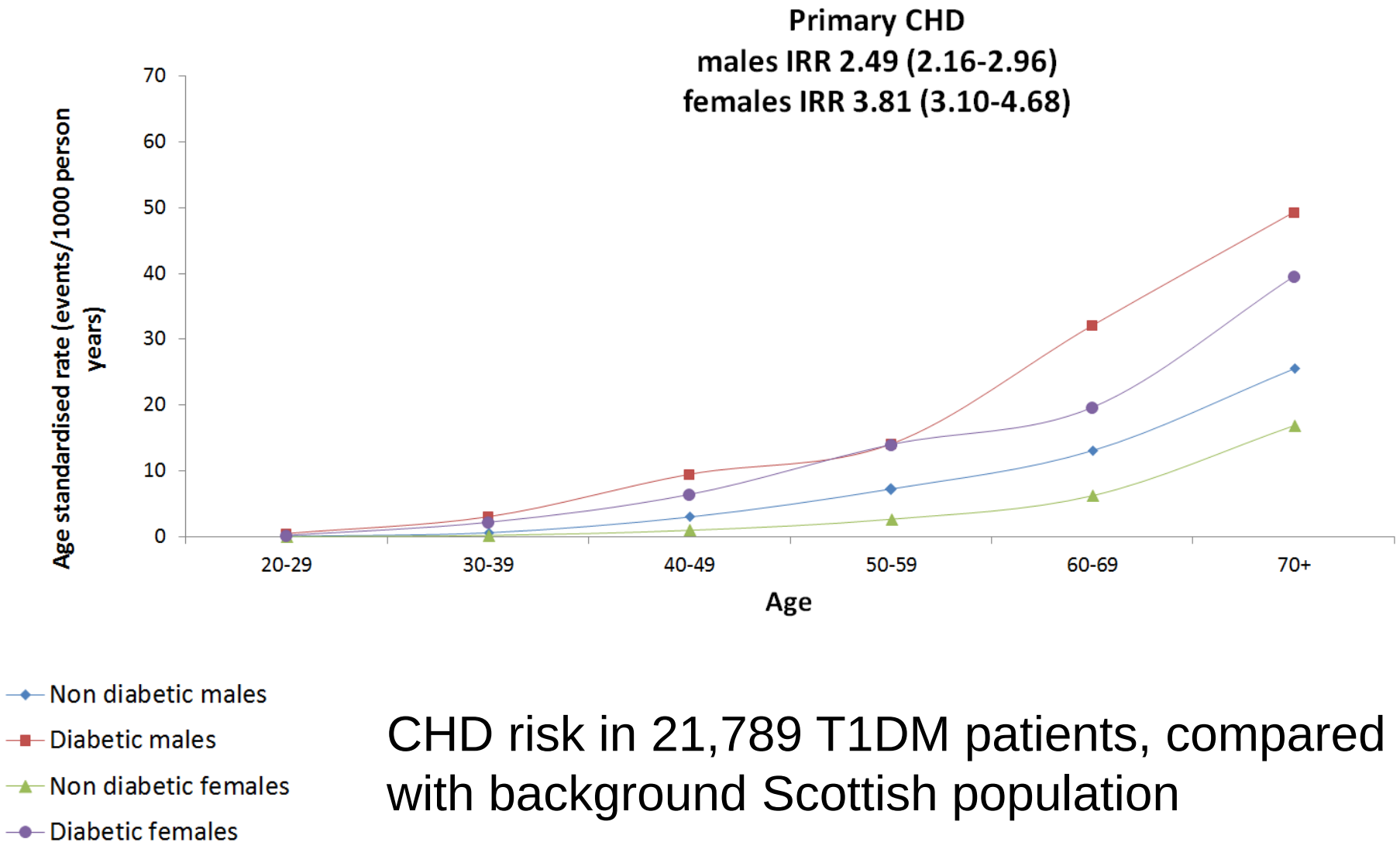

Glucose
Fat
Syringe
Diabetes
Pancreas
Overweig
Obesity
Hea.
Diet
Fat

# DOUBLE DIABETES

# INSULIN RESISTANCE IN TYPE 1 DIABETES

## – where two worlds collide

**Steve Cleland**
**Hampshire Hospitals FT**




CHD risk in 21,789 T1DM patients, compared with background Scottish population

***Livingstone et al, PLOS Med 2012 e1001321***

# T1DM and premature CVD

- T1DM is associated with premature CVD
- DCCT/EDIC results support benefit of intensive HbA1c on CV outcome
- But HbA1c not an independent predictor of CV outcome in prospective cohort studies (Pittsburgh EDC, EURODIAB)

***What factors drive CV risk***?

# Case studies

**Richard**

| | |
|---|---|
| age | 45 yrs |
| T1DM duration | 31 yrs |
| Smoker? | No |
| HbA1c | 64 (8%) |

**John**

| | |
|---|---|
| age | 45 yrs |
| T1DM duration | 31 yrs |
| Smoker? | No |
| HbA1c | 64 (8%) |

# Case studies

## Richard

| | |
|---|---|
| Retinopathy? | BDR |
| MAU? | Yes, ACR 10-15 |
| Neuropathy? | ED |
| CV disease? | Yes, MI 2012 |

## John

| | |
|---|---|
| Retinopathy? | no |
| MAU? | no |
| Neuropathy? | no |
| CV disease? | no |

# Case studies

## Richard

| | |
|---|---|
| Retinopathy? | BDR |
| MAU? | Yes, ACR 10-15 |
| Neuropathy? | ED |
| CV disease? | Yes, MI 2012 |
| | |
| FH T2DM? | Yes, father |
| BP | 143/86 |
| waist | 90cm |
| BMI | 31 |
| Insulin dose /24hrs | 82 |
| HDL chol | 0.9 |

## John

| | |
|---|---|
| Retinopathy? | no |
| MAU? | no |
| Neuropathy? | no |
| CV disease? | no |
| | |
| FH T2DM? | no |
| BP | 136/78 |
| waist | 80cm |
| BMI | 27.5 |
| Insulin dose /24hrs | 57 |
| HDL chol | 1.6 |

# "Double Diabetes"

- *Teupe & Bergis*, Lancet '91
- Observed that T1DM patients with FH of T2DM were more likely to be overweight and required higher insulin doses for a given HbA1c
- The more extensive the FH, the more pronounced the phenotype


PILOT - R.G.BOLINDER
R. O. - R.F.GRAHAM
C. C. - E.W. McLAIN
DOUBLE TROUBLE"

# eGDR – insulin resistance surrogate

- Estimated glucose disposal rate (eGDR)
- Derived from clamp studies

= 24.31 – 12.22(WHR) – 3.29 (hypertension status) – 0.57 (HbA1c)

***Williams et al, Diabetes 2000; 49: 626-632***

# Prospective observational cohorts

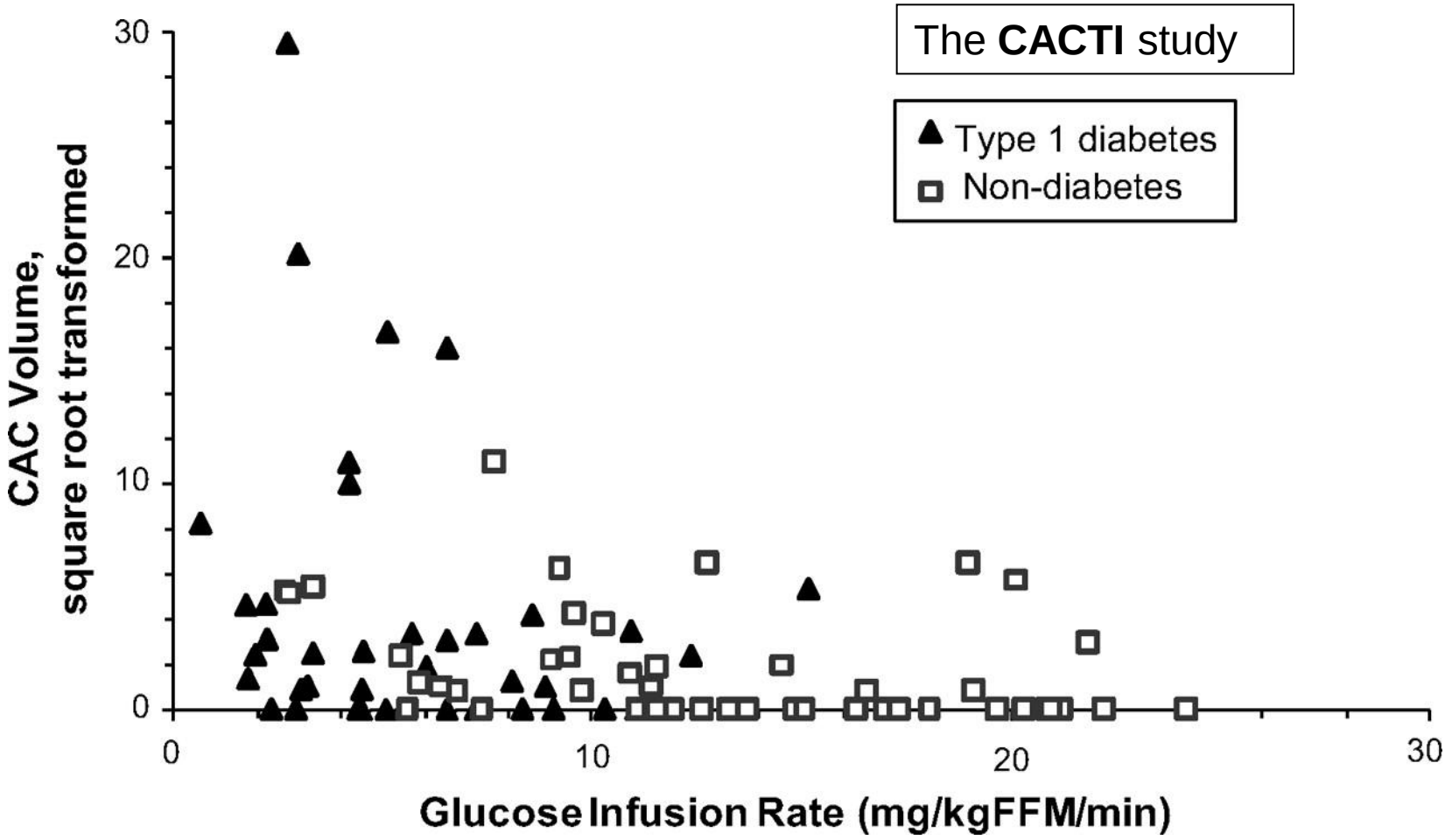
- Pittsburgh EDC (658 T1DM, 119 CHD events)
  - HR 1.62 FH**x1** T2DM,  HR 5.13 FH**x2** T2DM
    - *Erbey et al, Diab Care 1998*
- Pittsburgh EDC (603 T1DM, 42 CHD events)
  - Low eGDR (IR surrogate) predicted events, but not HbA1c
    - *Orchard et al, Diab Care 2003*
- DCCT/EDIC
  - High eGDR predicted fewer CV events (HR 0.70 [0.56-0.88])
    - *Kilpatrick et al, Diab Care 2007*
- DCCT/EDIC & EURODIAB
  - High eGDR predicted less retinopathy & nephropathy
    - *Kilpatrick et al, Diab Care 2007 & Chaturvedi et al, Diab Care 2001*
- EURODIAB (3,250 T1DM)
  - increased incidence of MAU if FH T2DM (HR 1.36, p=0.04)
    - *Roglic et al, Diab Med 1998*

# Clamp studies in T1DM

- The **CACTI** study
- 40 T1DM v 47 controls
- Whole-body IMGU less in T1DM
  - **6.2** v **12.7**mg/kgffm/min, *p<0.0001*
- NEFA suppression significantly less in T1DM
- Within T1DM group:
  - IR (to glucose uptake and NEFA suppression) correlated with CT coronary artery calcification (*p<0.0001*)
  - HbA1c did not correlate with either IR or CAC

***Schauer et al, Diabetes 2011; 60: 306-314***

**Plot of raw data for CAC volume at 6-year follow-up visit as a function of GIR (n = 87).**




***Schauer et al, Diabetes 2011; 60: 306-314***

American Diabetes Association.

# Mechanisms of IR in T1DM?

- Chronic glucotoxicity
- Relative peripheral hyperinsulinaemia
- Relative hepatic hypoinsulinaemia
  - Increased hepatic glucose production
  - Reduced IGF-1 / Increased GH

- Potential for acceleration of IR in context of unhealthy lifestyle / FH T2DM (**'double diabetes'**)

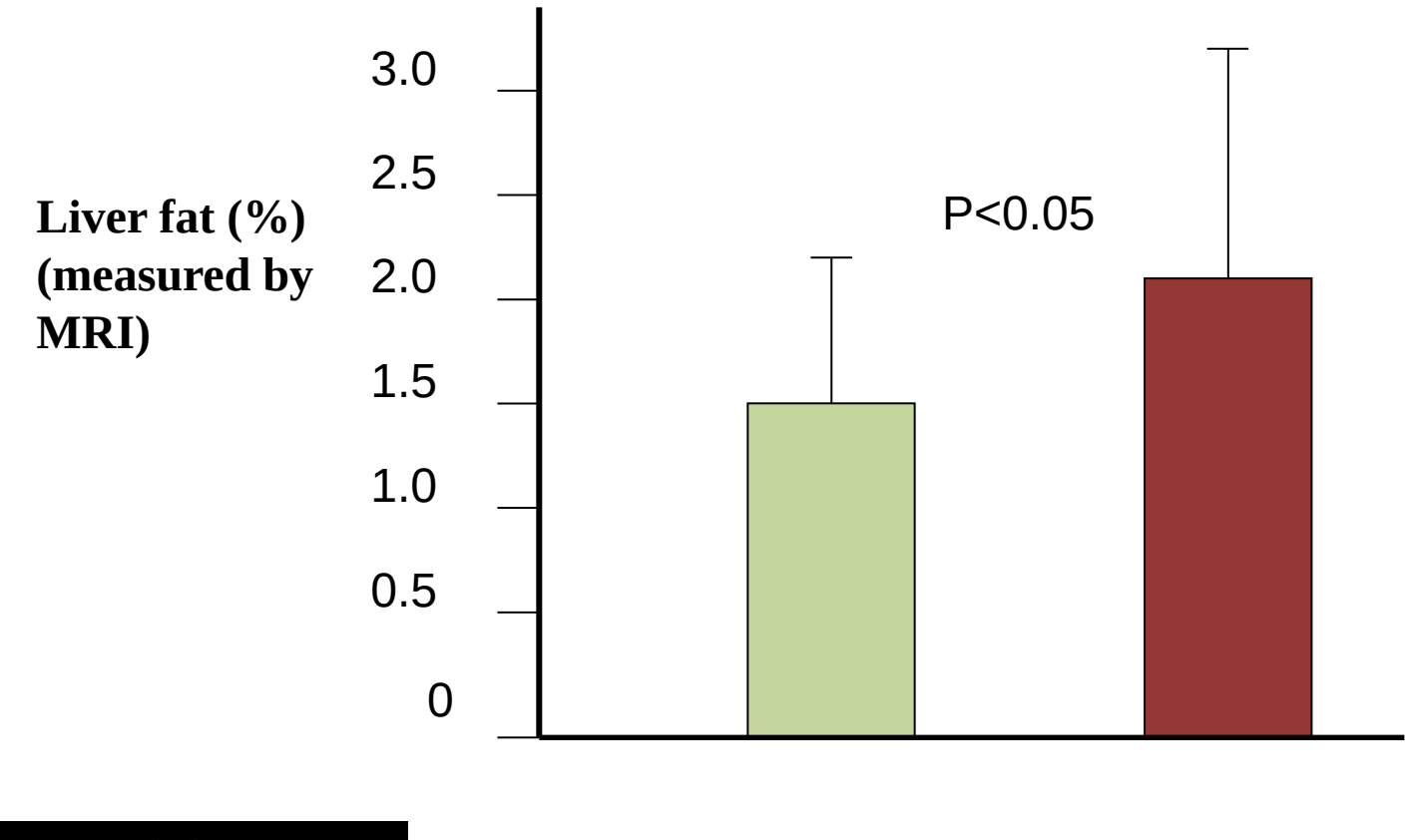
# Glucocentric

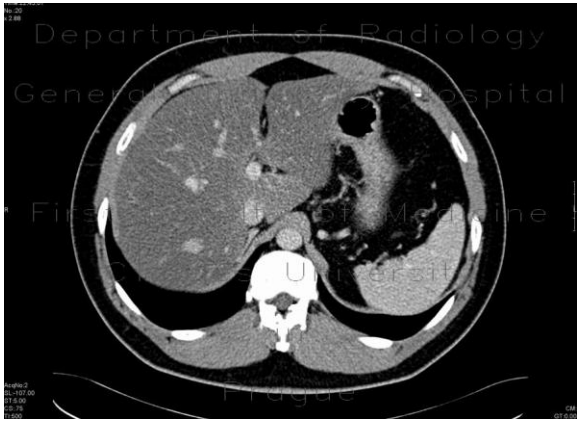
# Lipocentric

**New paradigm for understanding premature CVD in T1DM**

# Hepatocentric

**Where two worlds collide?**



***Perseghin et al, Diabetologia 2005; 48: 2615-2621***

# Fat partitioning implications of hepatic hypoinsulinaemia

- Reduced liver fat
- Reduced NEFA suppression
- Increased ectopic fat
  - Intramuscular triglyceride
    - *Perseghin et al, Am J Physiol 2003; 285: E1174-E1181*
  - cardiac / vascular (eg epicardial fat pad)
    - *Yazici et al, Endocrine 2011; 40: 250-255*

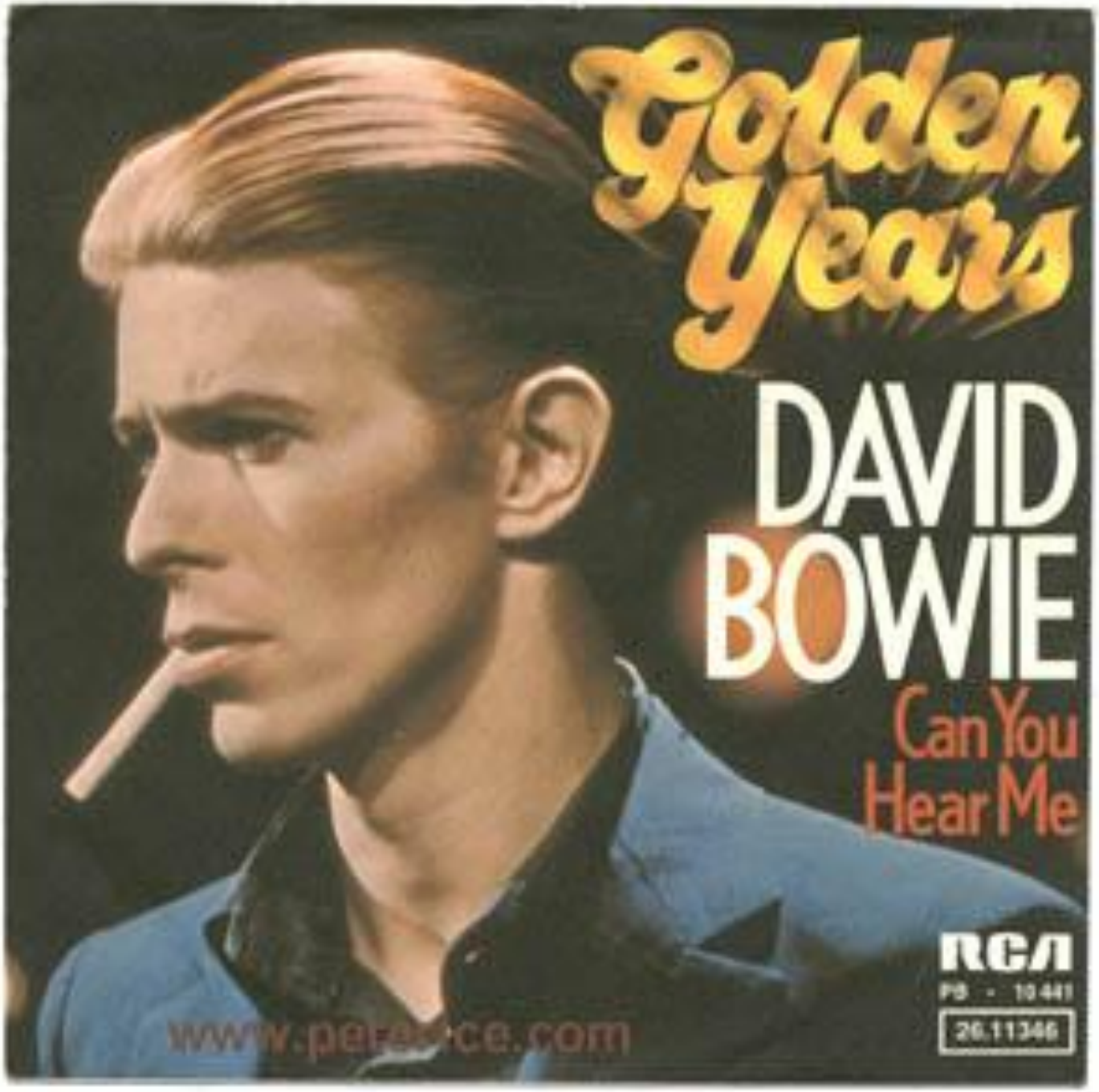
**Implications for premature CVD?**

# The flip side…

# HDL-C in T1DM

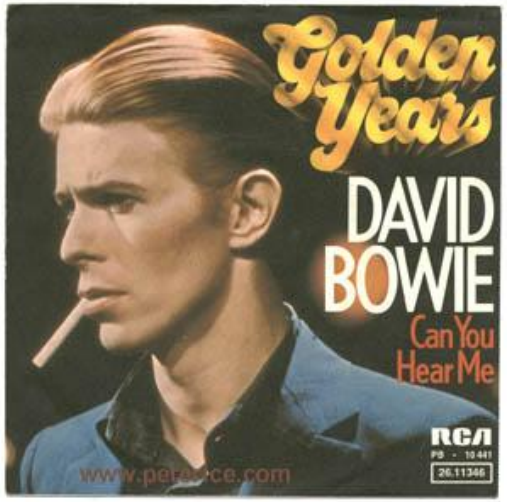
- Mechanisms
  - Reduced hepatic lipase
    - *Ruotolo et al, Diab Care 1994; 17: 6-12*
  - Increased lipoprotein lipase
    - *James et al, Diabetes 1990; 39: 1158-1164*
  - Increased phospholipid transfer protein
    - *Colhoun et al, Diabetes 2002; 51: 3300-3305*

**Confers CV protection??**


Golden Years
DAVID BOWIE
Can You Hear Me
RCA
PB - 10441
26.11346

# Golden Years Cohort

- BMI 25 kg/m$^2$
- HDL 1.84 mmol/l
- Normotensive
- Insulin dose 0.52 U/kg



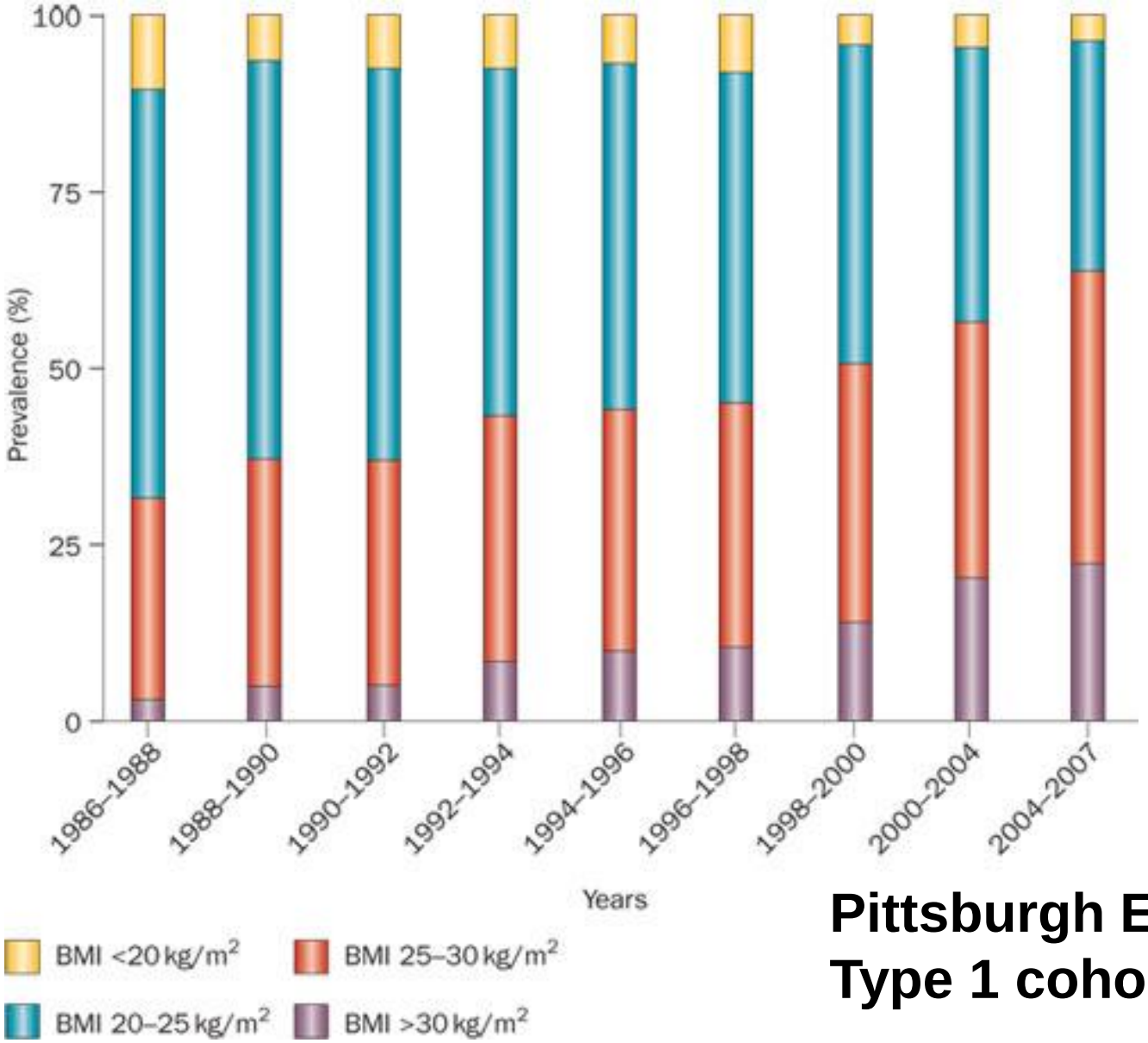

***Bain et al, Diab Med 2003; 20: 808-811***

***Gale, Diabetologia 2009; 52: 559-567***

# Practical Implications?

- Lifestyle and societal / cultural change
- Intensive insulin regimes
- Pancreas transplantation
- Newer liver-targeting insulins
- Thresholds for CV risk reduction
- Metformin use


DIABETES
OBESITY
DIET




**Pittsburgh EDC**
**Type 1 cohort**

***Conway et al, Int J Obesity 2009; 33: 796-805***

# DCCT intensive insulin group

| Quartiles of weight gain | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| HbA1c | 7.3 | 7.2 | 7.1 | 7.3 |
| BMI | 24 | 25 | 27 | 31 |
| Systolic BP | 113 | 117 | 115 | 120 |
| TG | 0.79 | 0.82 | 0.91 | 0.99 |
| LDL chol | 2.74 | 2.79 | 2.92 | 3.15 |
| HDL chol | 1.40 | 1.34 | 1.29 | 1.27 |

***Purnell et al, JAMA 1998; 280: 140-146***

# 5 yrs post pancreas transplant

| | Systemic drainage SPKT (n=14) | Portal drainage SPKT (n=15) |
|---|---|---|
| cholesterol | 3.99 | 5.49*(p=0.016) |
| HDL-C | 1.39 | 1.38 |
| LDL-C | 2.12 | 4.05 *(p=0.017) |
| TG | 0.76 | 1.05 |

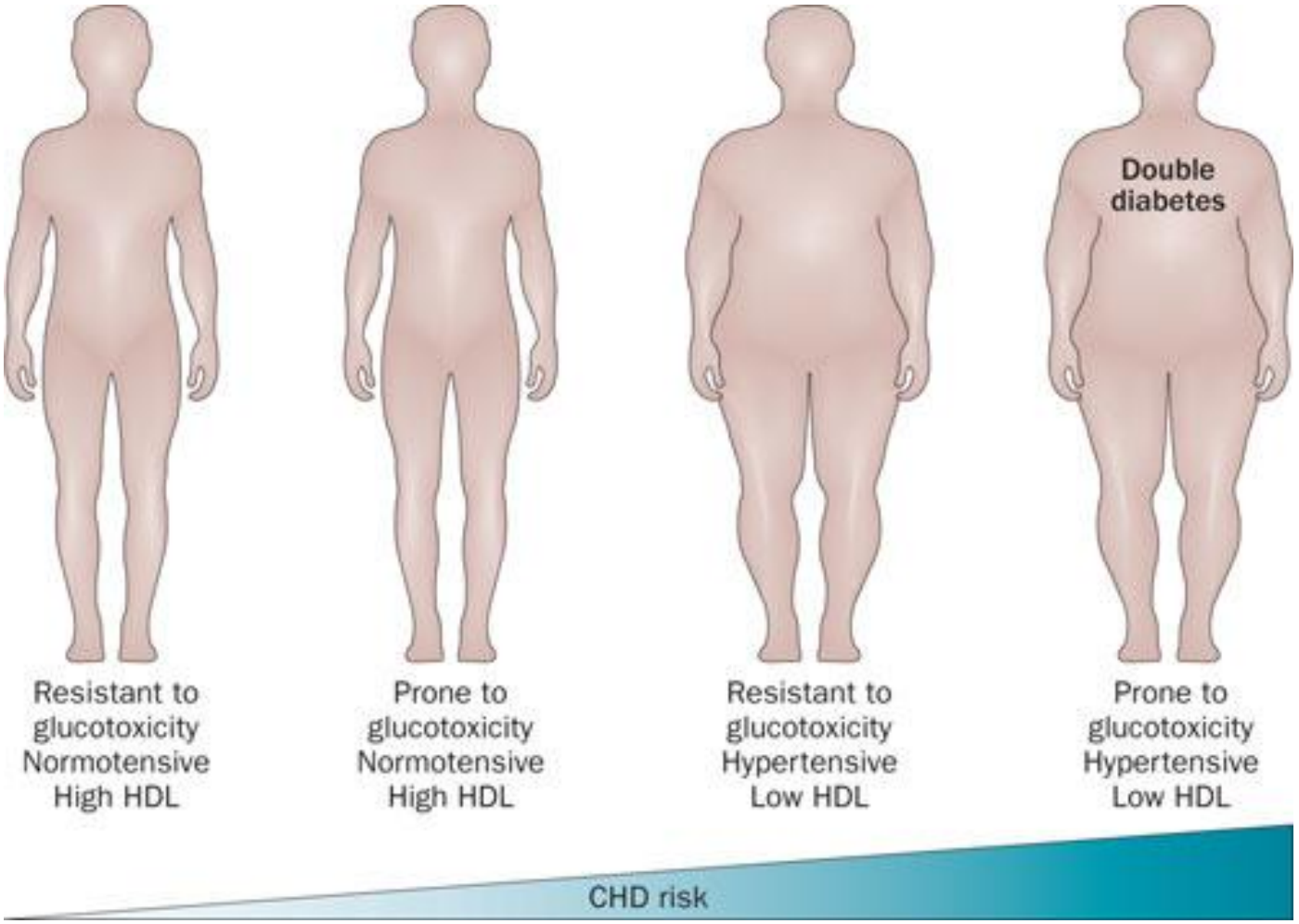
***Effects of new liver-targeted insulins on lipids and fat partitioning?***

***Petruzzo et al, Diab Med 2006; 23: 654-659***

# Therapeutic implications?

- Lower threshold for CVD primary prevention?
  - Anti-hypertensives
  - Statins
- Consider metformin?
  - REMOVAL trial ongoing
- Consider easing intensive insulin regime if double diabetes supervenes?


DOUBLE
WHAMMY


Double diabetes
Resistant to glucotoxicity Normotensive High HDL
Prone to glucotoxicity Normotensive High HDL
Resistant to glucotoxicity Hypertensive Low HDL
Prone to glucotoxicity Hypertensive Low HDL
CHD risk

*Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks?*

**S. J. Cleland, B. M. Fisher, H. M. Colhoun, N. Sattar & J. R. Petrie**

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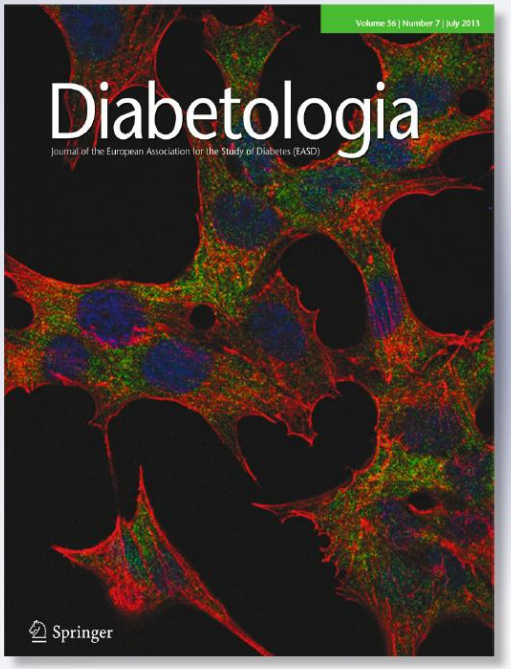


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***Cleland et al, Diabetologia 2013; 56: 1462-1470***


DOUBLE
TROUBLE