

# Statins and diabetes: The missing link

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**Stanford** | Diabetes  
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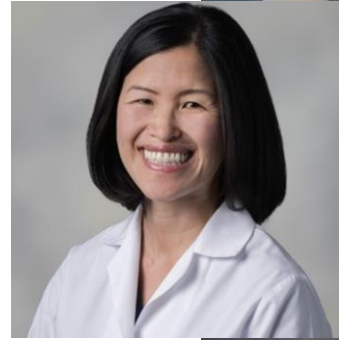


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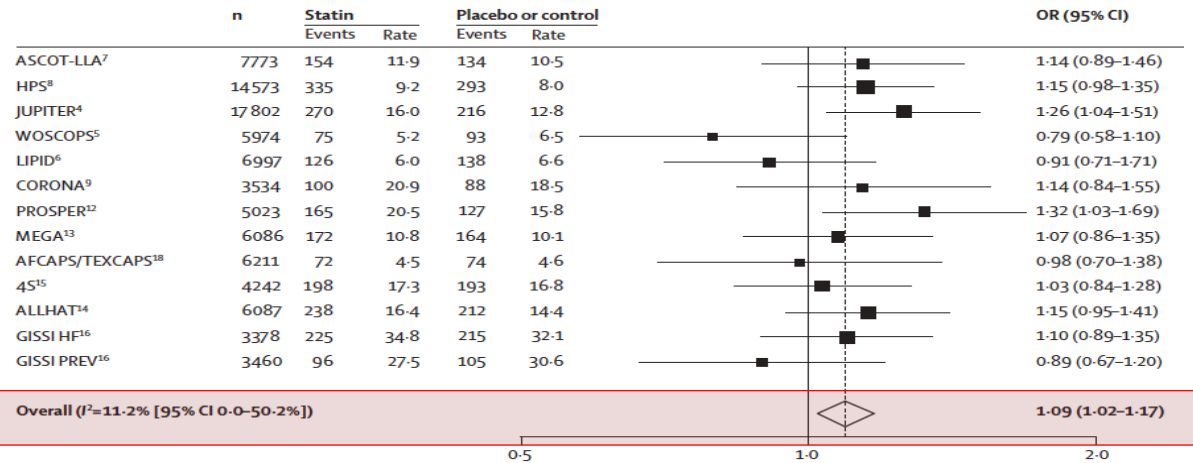
- Jerry Reaven
- Fahim Abbasi
- Sun Kim
- Chelsea Harris
- Vander Harris
- Pragya Tripathi
- Mike Snyder
- Cindy Lamendola



# Lower LDL-C levels are associated with increased risk of T2D and decreased risk of CAD

## Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai,

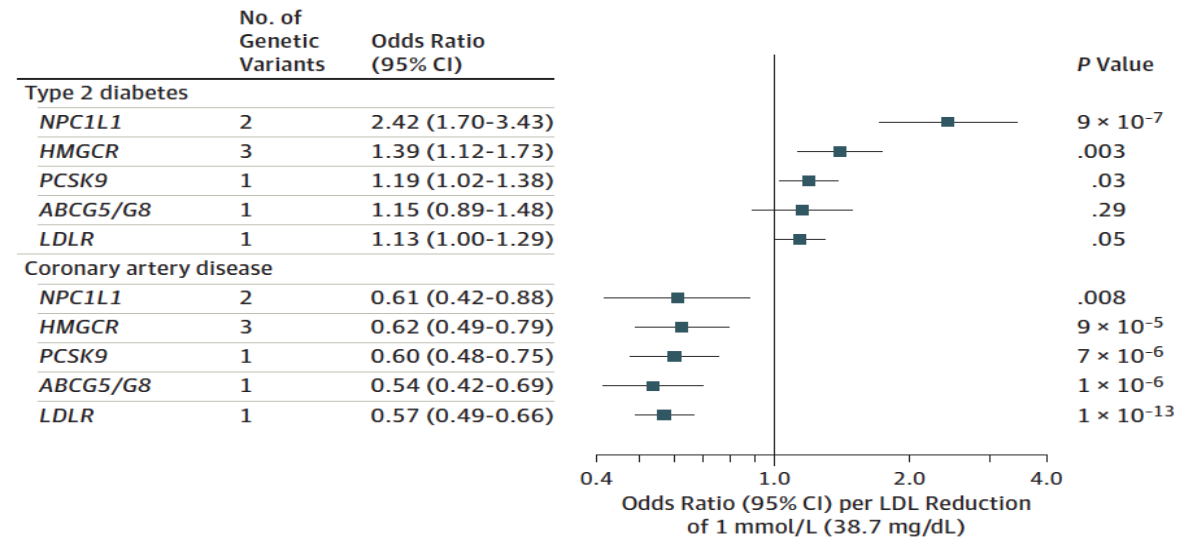


Clinical trial evidence

JAMA | Original Investigation

## Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis

Luca A. Lotta, MD, PhD; Stephen J. Sharp, MSc; Stephen Burgess, PhD; John R. B. Perry, PhD; Isobel D. Stewart, PhD;



Genetic evidence

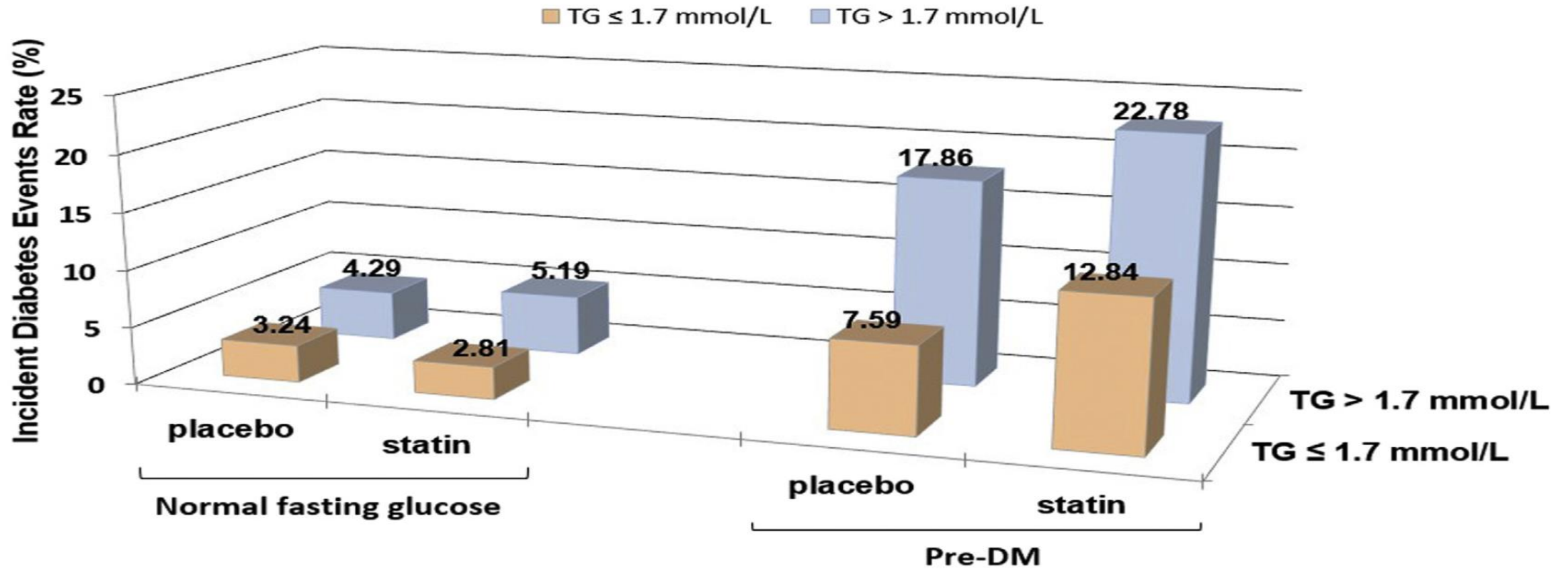
Clinical Chemistry 63:7  
000-000 (2017)

Perspective

## Leveraging Human Genetics to Understand the Relation of LDL Cholesterol with Type 2 Diabetes

Erik Ingelsson<sup>1,2\*</sup> and Joshua W. Knowles<sup>1,2</sup>

# Statins particularly increase the risk of T2D in those with prediabetes and insulin resistance

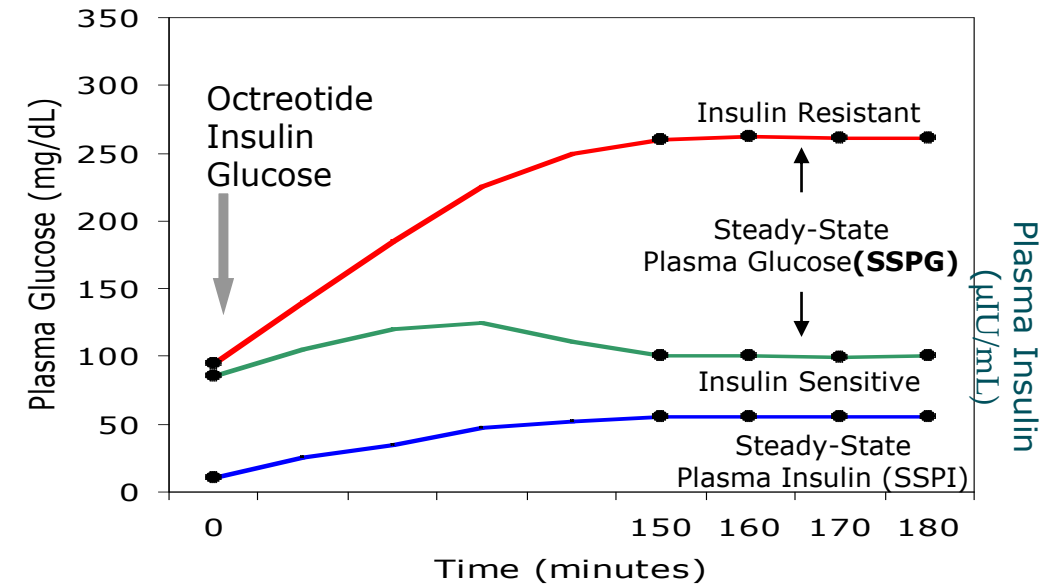


# What is the mechanism of statin-associated diabetes?

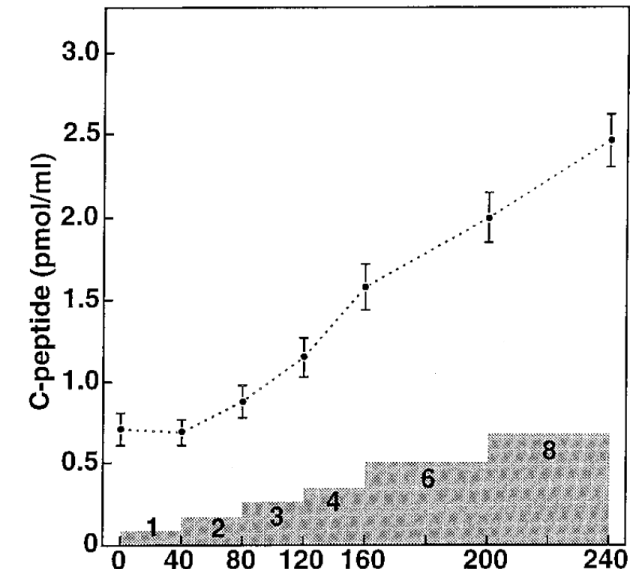
- **Diabetogenic effect of statins:**

- Increased insulin resistance?
- Impaired  $\beta$ -cell compensation?

**Modified Insulin Suppression Test (IST)**  
Gold standard assessment of insulin sensitivity



**Graded Glucose Infusion Test (GGIT)**  
Gold standard assessment of insulin secretion



\* Per 2013 AHA Guidelines

\*\* Statin dosing per AHA Guidelines

# Trial design

## Participants eligible for statin therapy\*

- Primary prevention but statin naïve
- Non-diabetic
- > 5% risk of CVD over 10 years
  - Or hsCRP > 2 mg/L
  - Or LDL  $\geq$  130 mg/dl
- No contraindication to statin

Recruit across a range of insulin sensitivity  
(targeted recruitment of TG > 150 mg/dl, more insulin resistant as a group)

OGTT, Insulin suppression test, Graded glucose infusion, Metabolic and lab characterization, iPOP profiling

**Statin therapy\*\*, 10 weeks**

OGTT, Insulin suppression test, Graded glucose infusion, Metabolic and lab characterization, iPOP profiling

### Primary Outcome Measures:

- Change in insulin sensitivity
  - Insulin Sensitivity: Steady-state plasma glucose concentration (mg/dL) measured during the insulin suppression test (IST)
  - Time Frame: Change from baseline to 9 -10 weeks in insulin sensitivity
- Change in insulin secretion
  - Insulin secretion: Insulin secretion rate AUC (pmol/min x 4 h) measured during the graded glucose infusion test (GGIT)
  - Time Frame: Change from baseline to 9 -10 weeks in insulin secretion

### Secondary Outcome Measures:

- Change in fasting plasma glucose and fasting plasma insulin
  - Fasting plasma glucose and insulin
  - Time Frame: Change from baseline to 8 - 10 weeks in fasting plasma glucose and insulin
- Change in OGTT glucose AUC and insulin AUC
  - OGTT glucose AUC (mg/dL x 2 h) and OGTT insulin AUC (mU/L x 2h)
  - Time Frame: Change from baseline to 8 weeks in OGTT glucose AUC and insulin AUC

### Prespecified Subgroup Analyses

- Determine if significant deterioration of insulin action and/or secretion following statin treatment will be confined to those with baseline insulin resistance.

# Participant Flow

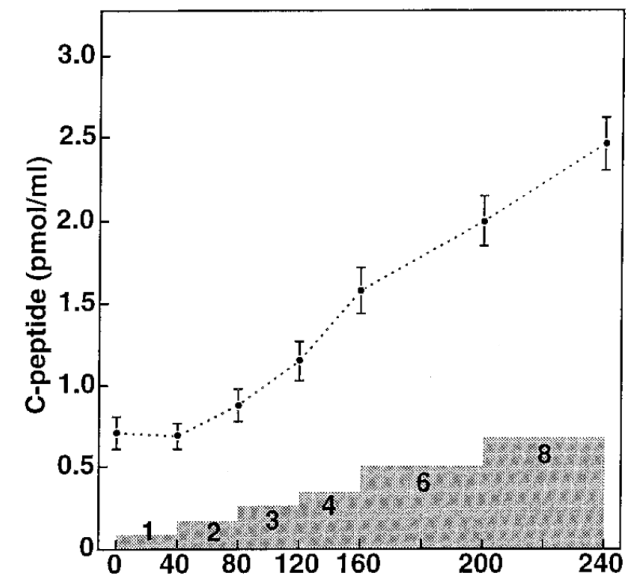
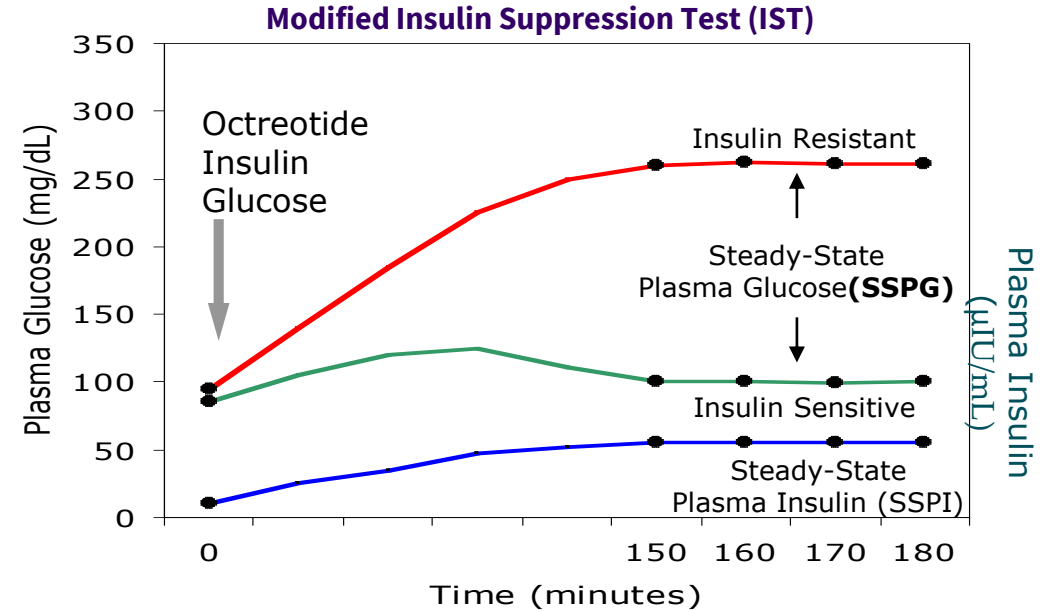
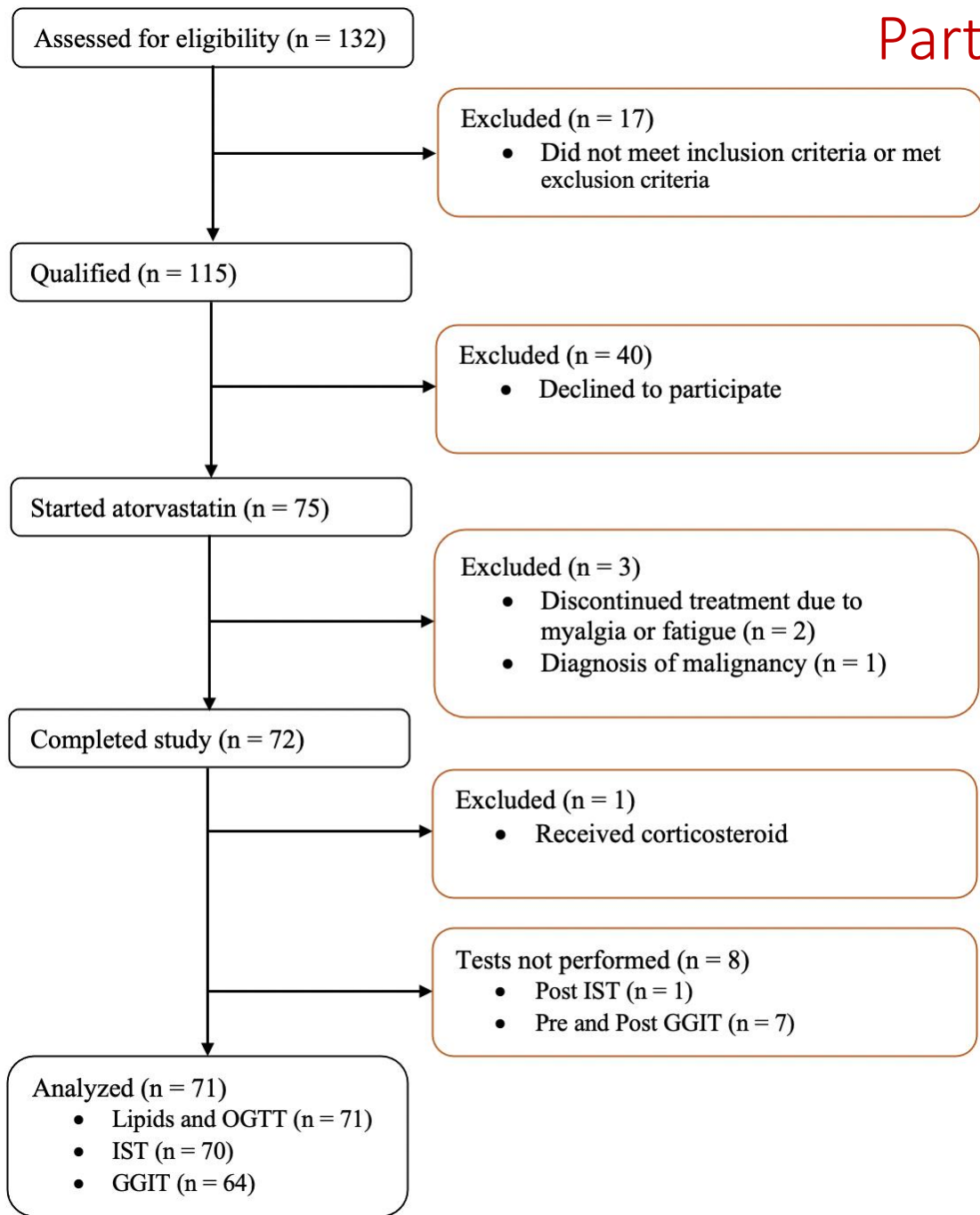


Table 1 – Baseline Characteristics of Study Subjects (n = 71)

Age, years	61 (53 – 64)
Female, n (%)	26 (36.6)
Race, n (%)	
African American	2 (2.8)
East Asian	11 (15.5)
Hispanic	4 (5.6)
South Asian	6 (8.5)
Two or more races	2 (2.8)
White	46 (64.8)
BMI, kg/m <sup>2</sup>	27.8 (24.8 – 30.7)
Waist circumference, cm	99.0 (89.5 – 105.7)
Systolic BP, mm Hg	124 (114 – 132)
Diastolic BP, mm Hg	79 (74 – 84)
Heart rate, bpm	65 (58 – 72)

Data are median (interquartile range) or number (%) of subjects.

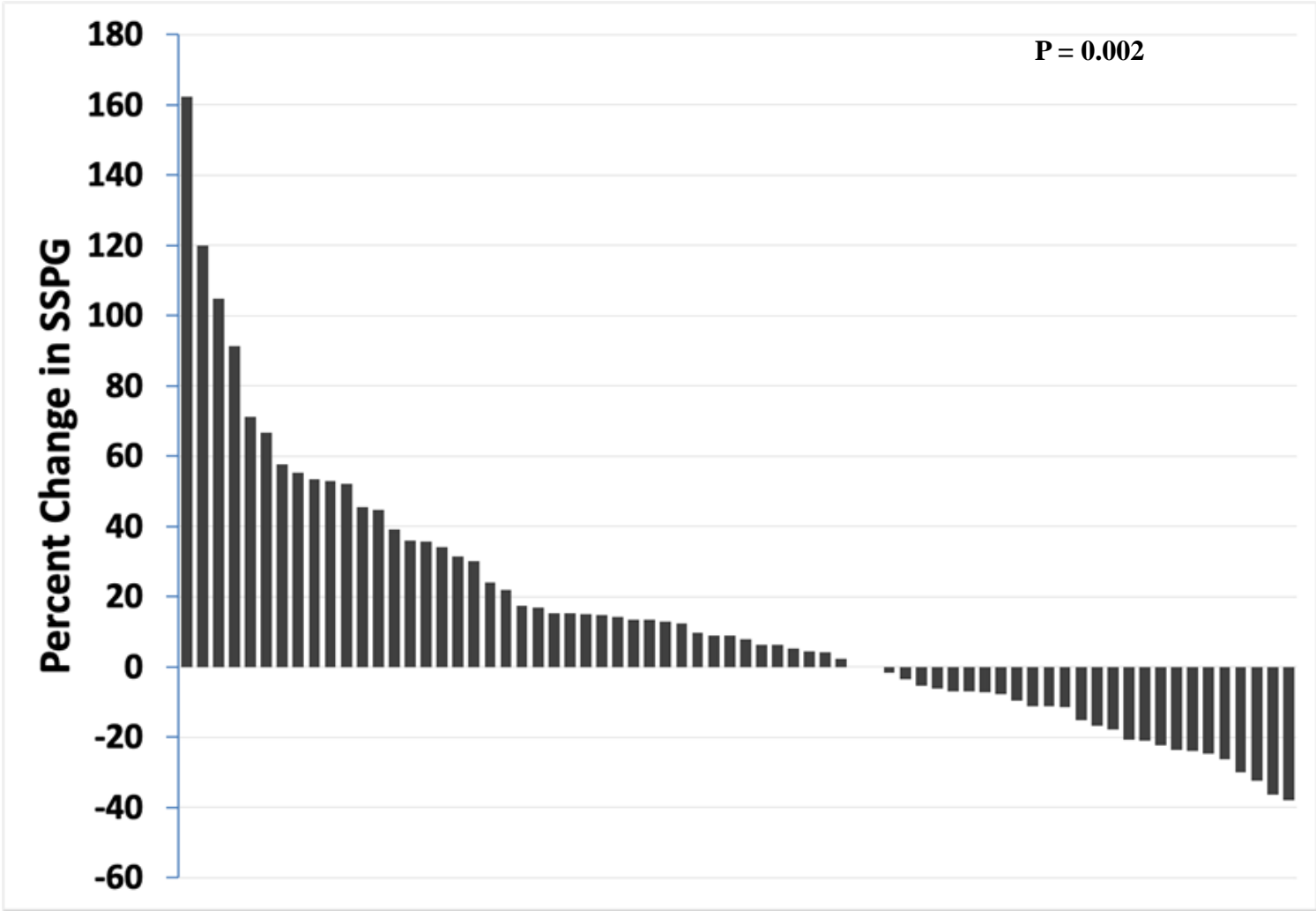


### Effect of Atorvastatin on Weight, Lipids and hs-CRP (n = 71)

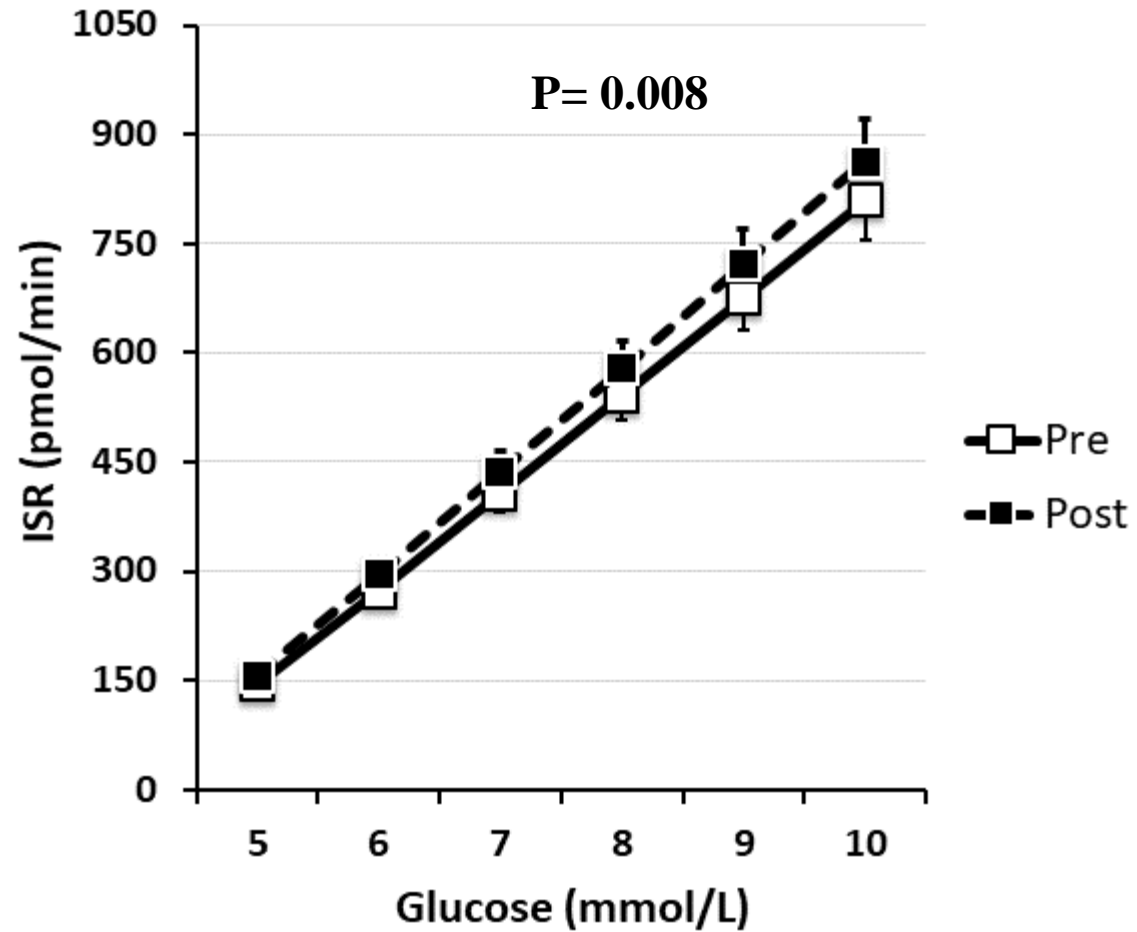
Variable	Baseline	End of Study	P
Weight, kg	83.1 (70.6 – 95.6)	84.7 (68.4 – 93.3)	0.92
Total cholesterol, mg/dL	237 (205 – 256)	149 (125 – 162)	<0.001
LDL cholesterol, mg/dL	156 (130 – 172)	69 (61 – 84)	<0.001
Triglycerides, mg/dL	109 (70 – 150)	78 (59 – 115)	<0.001
HDL cholesterol, mg/dL	51 (43 – 63)	53 (43 – 64)	0.73
hs-CRP, mg/L	1.1 (0.6 – 2.3)	0.7 (0.4 – 1.8)	0.002

Data are median (interquartile range). Triglycerides and hs-CRP were log-transformed for statistical analysis. Means were compared by paired sample t tests. hs-CRP data were analyzed on 69 subjects; HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

# Effect of Atorvastatin Therapy on Insulin Resistance



## Effect of Atorvastatin Therapy on Insulin Secretion (n = 64)



Data are mean (SEM)

## Conclusions

- Short-term, high intensity statin use is associated with an **increase in insulin resistance *and* insulin secretion**
- Study forms the basis for longer-term studies
- Understanding the mechanism of statin–associated T2D will lead to more tailored recommendations and ultimately better outcomes