Heart disease in women: new targets, new opportunities

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Disclosures relevant to this presentation

Why worry about CV disease in women ?

- Women live longer than m
- Women are le ıe of cardiova se than men
- are less likely to have pertension

What's the big deal?


Slims
because they are bio ally
superior to men
That's right, superior. Women are more resistant to starvation, fatigue, exposure, shock, and illness than men are.
Women have two "X" chromosomes in their sex cells, while men have only one "X" chromosome and a "Y" chromosome... which some experts consider to be the inferior chromosome.
They are also less inclined than men to congenital baldness, Albinism of the eyes, improperly developed sweat glands, color blindness of
the red-green type, day blindness, defective hair follicles, defective iris, defective tooth enamel, double eyelashes, skin cysts,
Virginia Slims.
You've come a long way, baby.

The sex gap in heart disease management

- Women (after menopause) are more likely to have disease risk factors
- Women with heart disease risk factors are less likely to be treated appropriately
- Women with heart disease are less likely to be diagnosed
- Women with heart disease are less likely to be treated
- Women with heart disease are more likely to die of their heart disease and/or complications of revascularization

The evidence basis for ALL of these is in a black box

Have we really come such a long way?

Determinants of sex-specific cardiovascular risk in women

- Cultural/social/behavioural
- Biological
  - higher risk for clotting
  - more small vessel disease
- Cellular/Genetic ?? *(beyond not having a Y chromosome)*
  - role of estrogen unclear…especially post-menopause

Sex-specific regulation of atherosclerotic risk factors: the case of PaM

52 year old post-menopausal female. She runs 5 days a week. She also admits to smoking 6 cigarettes a day and occasionally more when she is stressed. She is entirely asymptomatic.

Her mom was diagnosed with “bad circulation in her legs” at the age of 62 years. Father is 79 years old with no history of heart disease.

PaM: Exam

On examination:

- BMI= 26.8 kg/m^2, WC= 87 cm
- BP = 140/88 (average of repeated measures)
- HR = 64
- Nothing else I could find

PaM: Lab

Lipid Profile:

TC = 6.3

LDL = 4.2

HDL = 0.9

TG = 1.7

Fasting blood sugar: 6.1

Glycated Hgb: 0.062

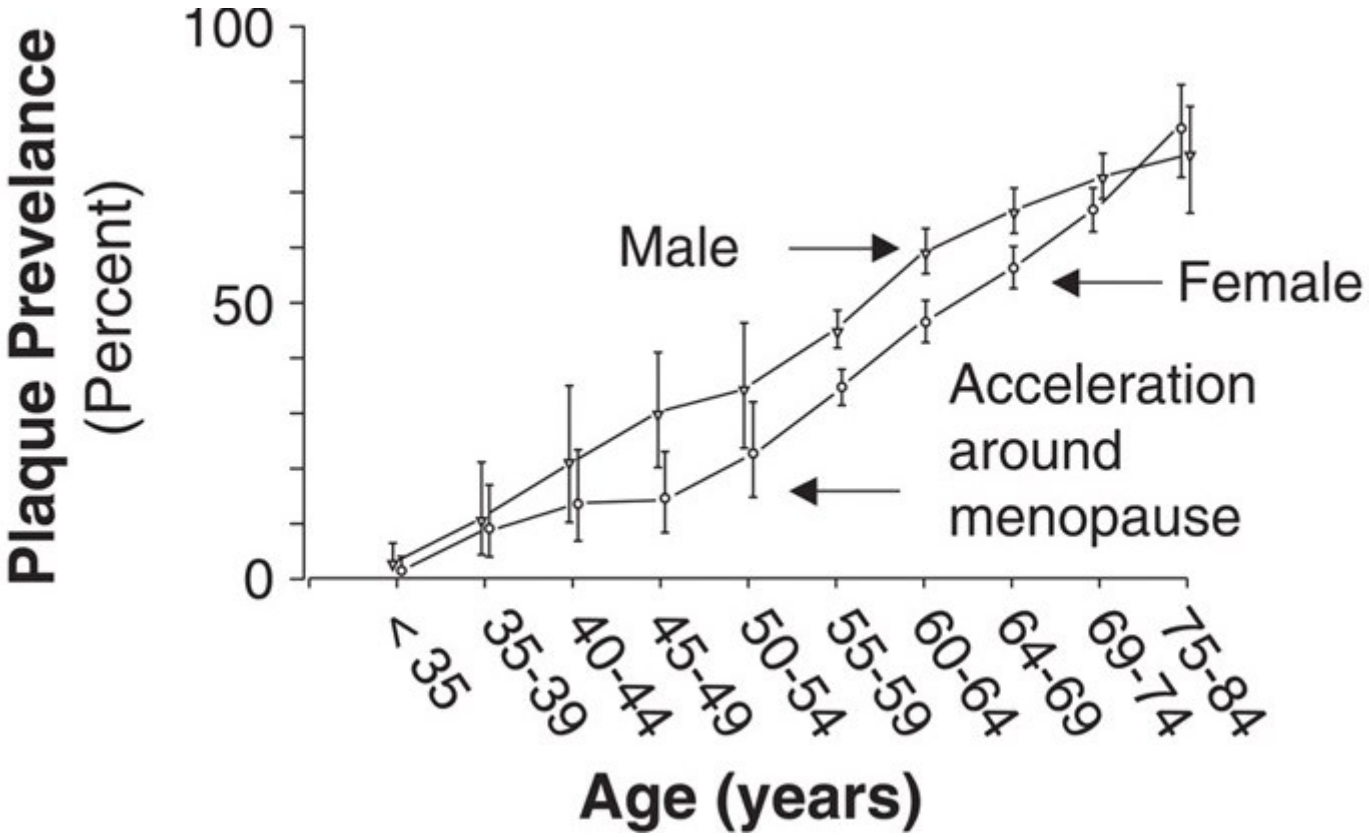
What is PaM's 10 year CV risk?

A) Low (less than 10%/year)

B) Moderate (10-15%/year)

C) High (greater than 15%/year) 17%

Age-dependent incidence of coronary artery disease (CAD) in men and women.



Raghvendra K. Dubey, Bruno Imthurn, Matthias Barton, Edwin K. Jackson.
Cardiovascular Research 66 (2005) 295 – 306

The risk profiles of (*postmenopausal)* women are generally *worse* than males

- Higher BP

  (CDC, http://www.cdc.gov/nchs/data/hus/hus11.pdf)

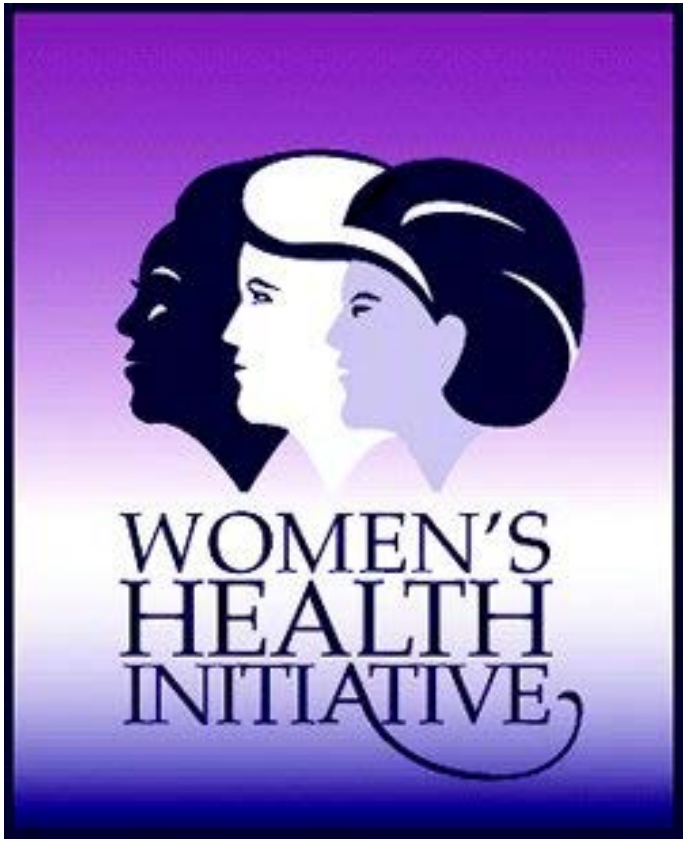
- Higher LDL-C

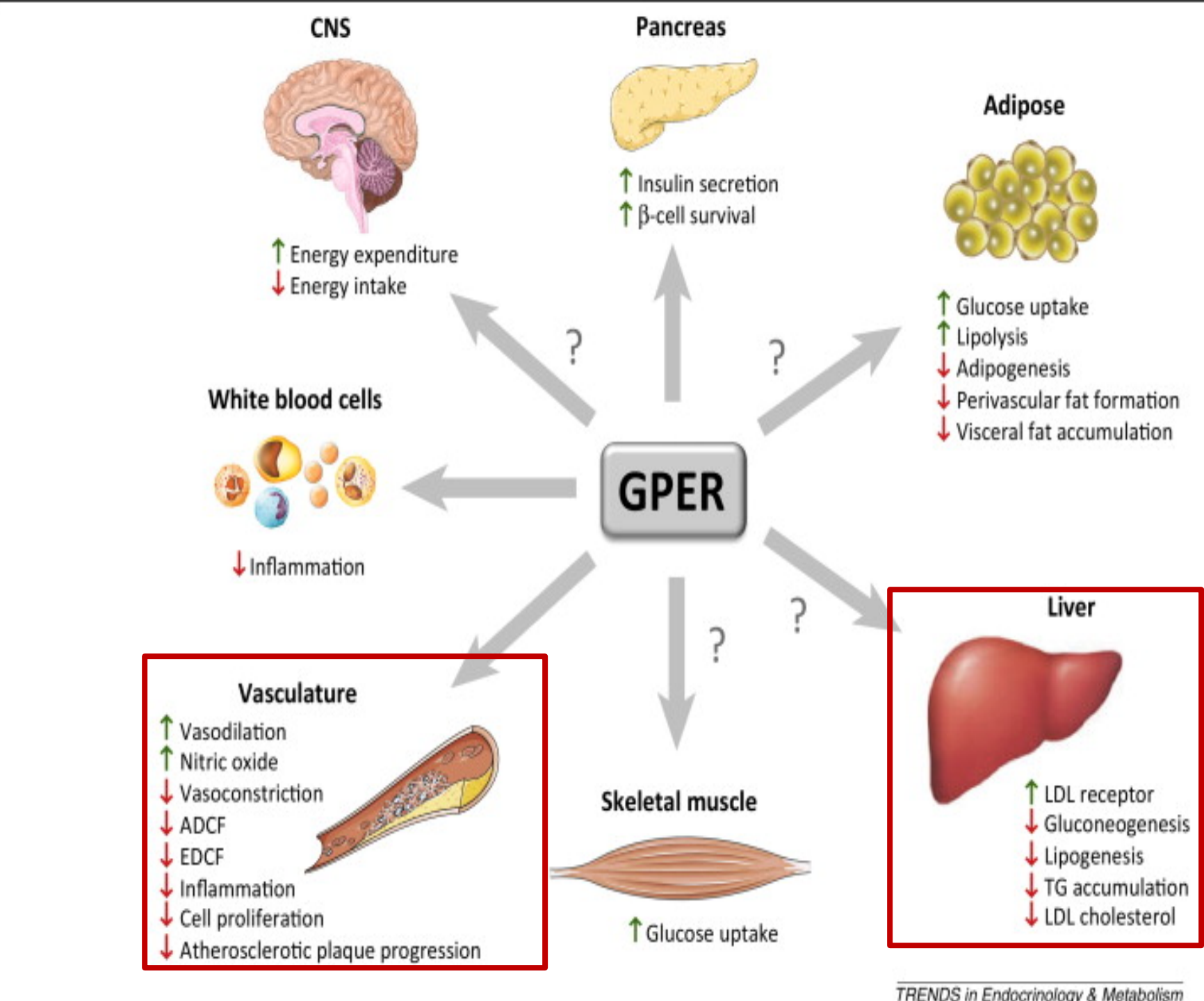
  (JAMA 2003;289:76–9)

- More likely to have multiple risks

  (N Engl J Med. 1990;322(13):882-889)

WHI and HERS studies report tendency to i*ncreased risk* of postmenopausal estrogens





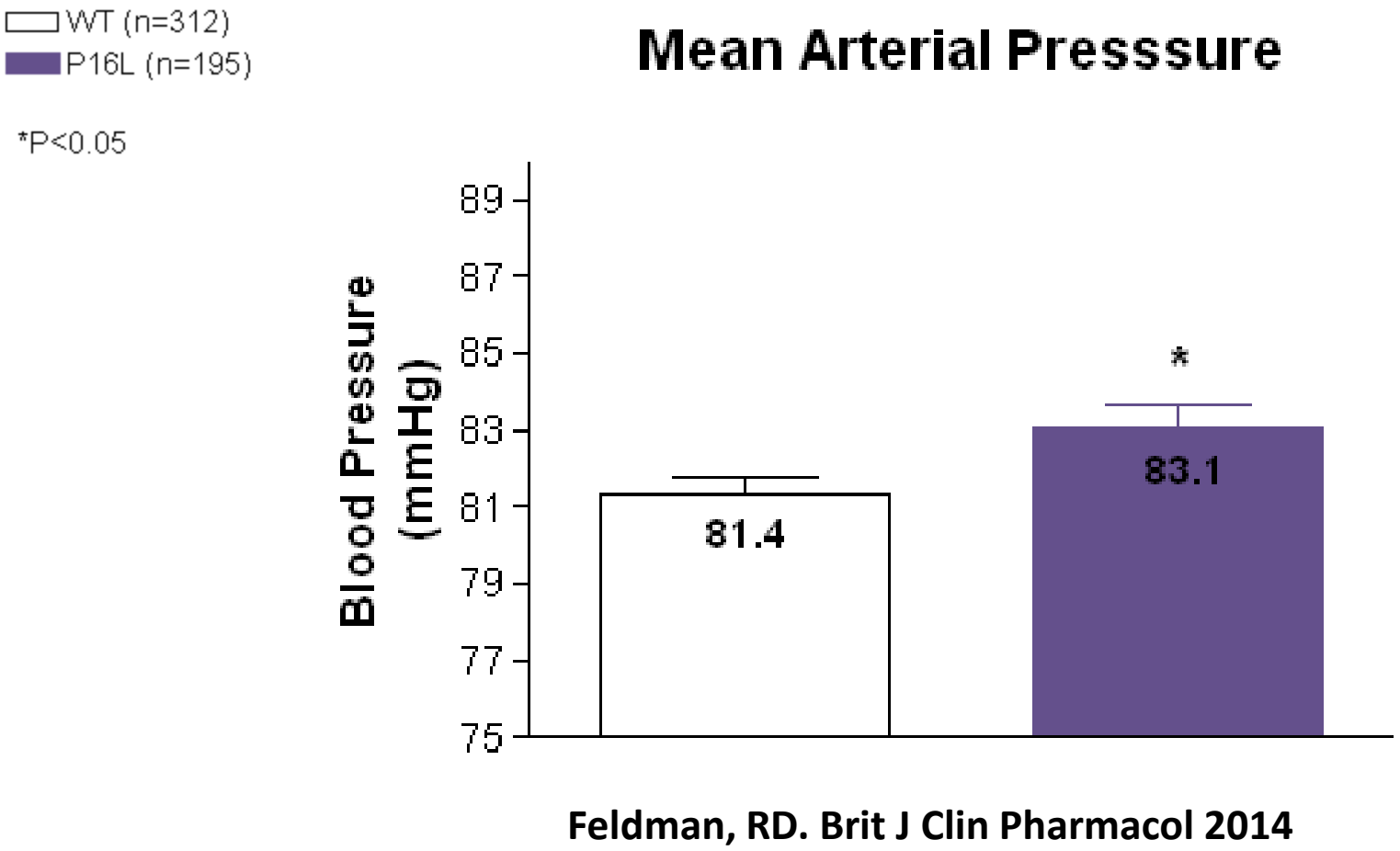
TRENDS in Endocrinology & Metabolism

GPER human genetic variants

- Three missense GPER single nucleotide variants
- P16L GPER variant is most common ,with allelic frequency ~ 20%

How does carrying a *hypofunctional* GPER genetic variant affect blood pressure and the development of hypertension?

Blood pressure is higher in those carrying the GPER genetic variant



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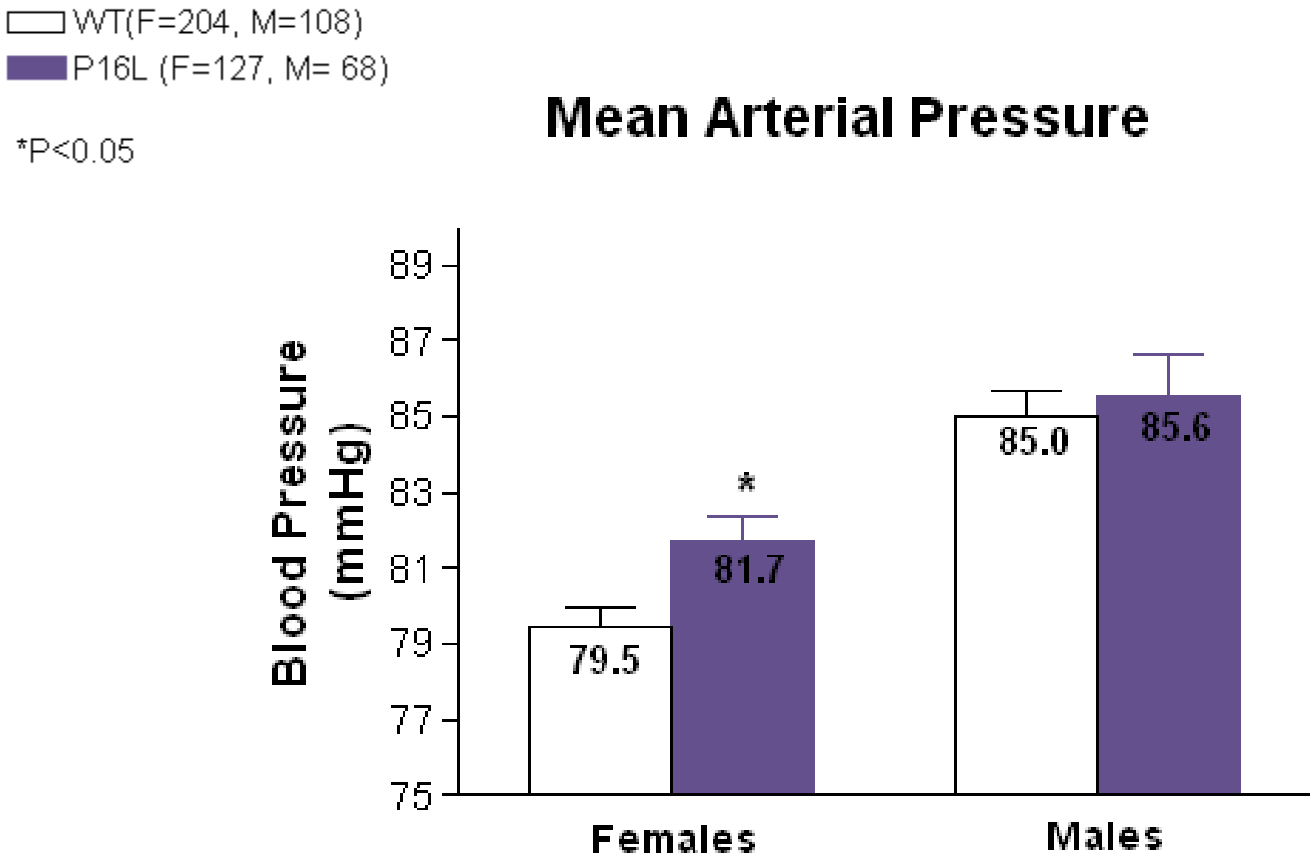
Sex–specific impact of P16L GPER expression on blood pressure



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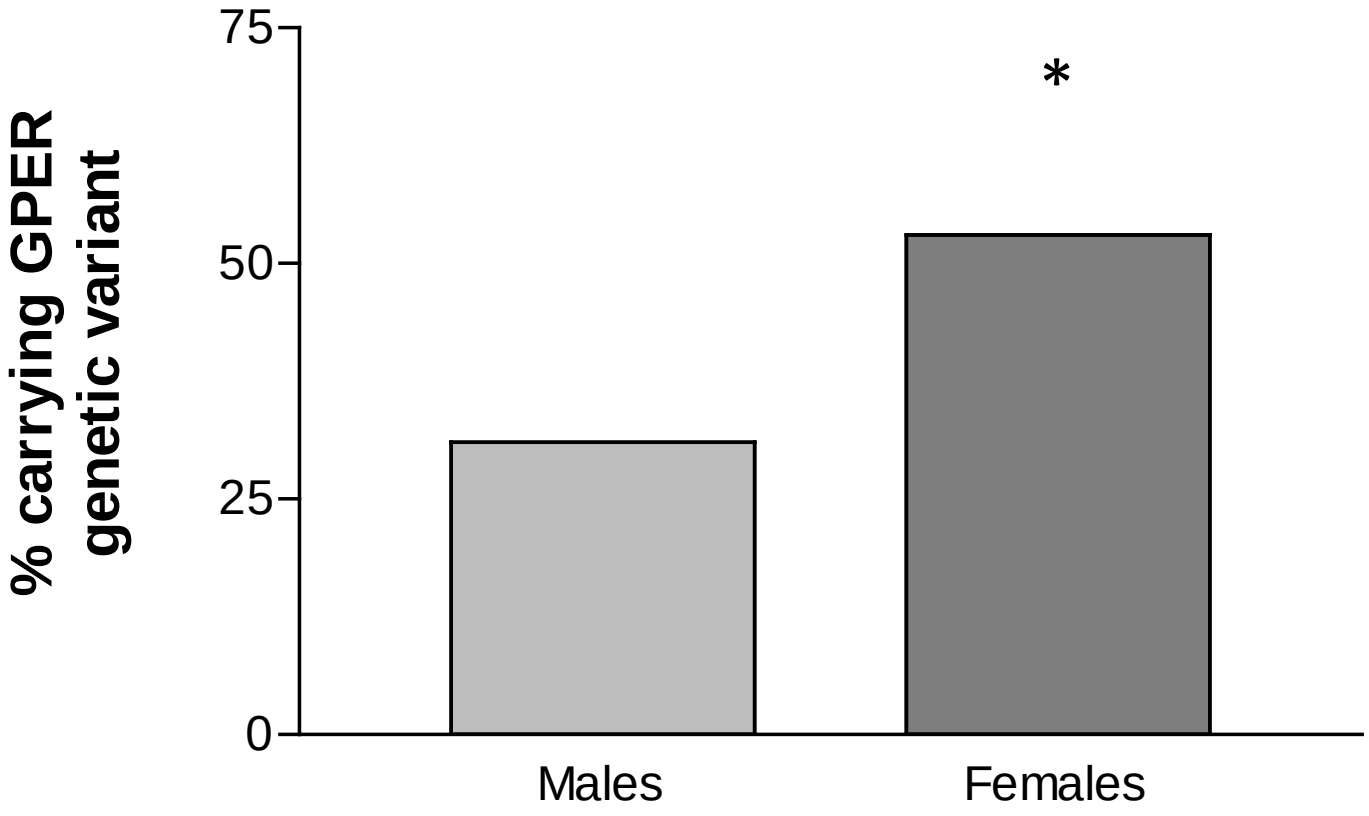
Carrying the P16L GPER genetic variant is a sex-specific risk factor for hard-to-treat hypertension



Feldman, RD. Brit J Clin Pharmacol 2014

How does carrying a *hypofunctional* GPER genetic variant affect cholesterol metabolism?

Carrying P16L GPER is associated with higher plasma LDL and total cholesterol in Hutterites

Whole population (N=415)	CC (N=320)	CT(N=88)		
Triglyceride (mmol/L)	1.37±0.04	1.56±0.09	1	
Total Cholesterol (mmol/L)	5.17±0.05	5.35±0.11	6.23±0.40	0.0071
HDL (mmol/L)	1.37±0.02	1.39±0.04	1.44±0.07	NS
LDL (mmol/L)	3.18±0.05	3.25±0.08	4.25±0.33	0.0034
Apo A1 (g/L)	1.46±0.01	1.49±0.03	1.55±0.10	NS
Apo B (g/L)	1.16±0.02	1.21±0.03	1	

Females (N=235)	CC (N=185)	CT(N=45)	TT(N=5)	P value
Triglyceride (mmol/L)	1.30±0.05	1.29±0.11	1.40±0.20	NS
Total Cholesterol (mmol/L)	5.14±0.07	5.18±0.15	6.69±0.33	0.0016
HDL (mmol/L)	1.48±0.02	1.54±0.05	1.50±0.08	NS
LDL (mmol/L)	3.07±0.06	2.05±0.12	4.56±0.30	0.0002
Apo A1 (g/L)	1.52±0.02	1.58±0.04	1.63±0.12	NS
Apo B (g/L)	1.11±0.02	1.11±0.04	1.50±0.07	0.003

Males (N=180)	CC (N=135)	CT(N=43)	TT(N=2)	P value
Triglyceride (mmol/L)	1.45±0.07	1.86±0.14	0.72±0.03	NS
Total Cholesterol (mmol/L)	5.21±0.09	5.53±0.14	5.09±0.57	NS
HDL (mmol/L)	1.23±0.02	1.23±0.04	1.30±0.15	NS
LDL (mmol/L)	3.32±0.08	3.46±0.12	3.47±0.73	NS
Apo A1 (g/L)	1.38±0.02	1.41±0.03	1.37±0.10	NS
Apo B (g/L)	1.23±0.03	1.32±0.04	1.21±0.19	NS

Husain et al, Arterioscler Thromb Vasc Biol. 2015

Conclusions

- Women have caught up to men in regards to heart disease risk
- Women are more likely to suffer complications of heart disease
- Women are less likely to be treated optimally
- Among multiple molecular determinants the regulation of GPER effects may be important in the development of heart disease in women