Polycystic Ovary Disease and the Risk for Diabetes and Cardiovascular Disease

(*or: A Disorder for the Internist*)

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Disclosure

- Has no financial relationships to disclose
- Will be discussing the use of Metformin in the treatment of PCOS

Polly O.

- 21 year-old woman c/o hirsutism and irregular menses
- Menarche: age 12; never had regular menses; menstruates 3-4 times per year
- Hirsutism affecting the upper lip, chin, cheeks, nipples, and linea alba
  - Shaves twice weekly
- No nipple discharge, headaches, visual problems
- Does not desire fertility at this time

Polly O.

- PMH: Unremarkable
- Meds: None
- Allergies: None
- SHx: G0P0; sexually active but does not use contraception; no smoking, drug or EtOH use
- FMHx: Father had MI at age 49 and has DM2; mother A+W; sister has hirsutism but normal menses
- ROS: Negative

Polly O.

- PE remarkable for:
  - Hirsutism as described in HPI
  - Acanthosis nigricans on nape of neck
  - No galactorrhea
  - Clitoris normal in size
- Labs:
  - Total testosterone 90 ng/dl; free T: 7.8 pg/ml
  - DHEA-sulfate 425 µg/dl
  - PRL nl; TSH nl; 17-hydroxyprogesterone nl
  - HDL cholesterol 29 mg/dl;
  - OGTT: glucose 156 mg/dl at 2 hours

Polly O.

- What other lab tests should be drawn?
- What is this patient's risk for developing type 2 diabetes?
- What is this patient's risk for developing premature cardiovascular disease?

Q1: True Or False: An Obese Woman with PCOS Is as Insulin-resistant as a Patient with Type 2 Diabetes?

A. True

B. False

Answer: A. True

Q2: What Percentage of Obese Women with PCOS Have Glucose Intolerance ?

A. <10%

B. 10-20%

C. 30-50%

D. >70%

Answer: C. 30-50%

Q3: The Best Screening Test for Glucose Intolerance in Women with PCOS Is:

A. Random Glucose

B. Fasting Glucose

C. Hemoglobin A1c

D. 2-Hour OGTT

Answer: D. 2-Hour OGTT

Q4: What Percentage of PCOS Women Fulfill at Least 1 of the 5 NCEP-ATPIII Criteria for the Metabolic Syndrome?

A. 5-10%

B. 20-30%

C. 60-70%

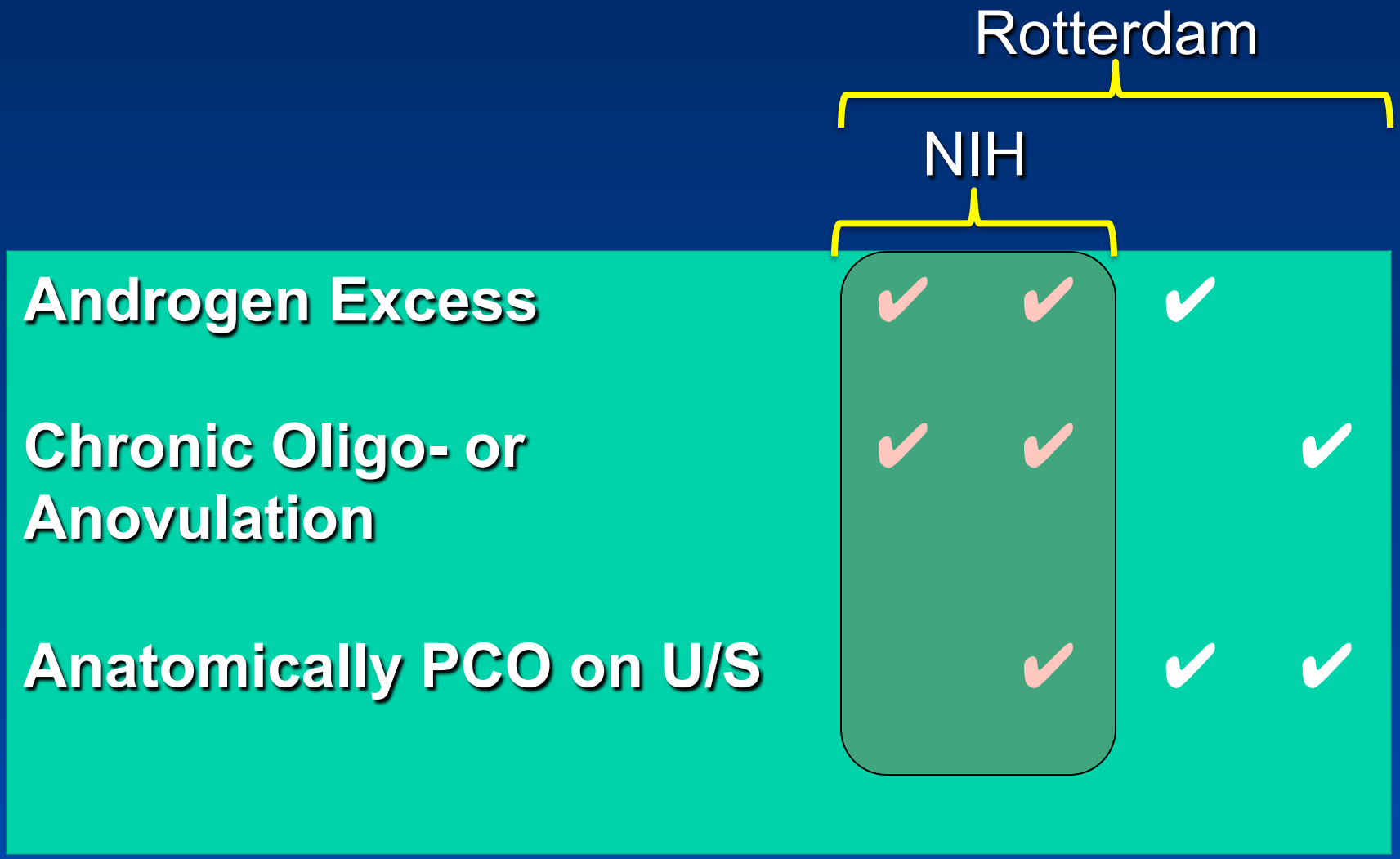
D. >90%

Answer: D. >90%

PCOS

- Chronic oligo/anovulation *and/or* hyperandrogenism *and/or* polycystic ovaries on ultrasound (need 2 out of 3)
  - R/O ↑prolactin, thyroid dysfunction, adrenal hyperplasia
- Affects 6% to 10% of women of childbearing age (in *Qatar* : 18% or 104,000 women)
- Most common cause of female infertility (approximately 50% to 60%)
  - ✓ Anovulation
  - ✓ Early (first trimester) miscarriage
- May be most common endocrinopathy in young women
- *Insulin resistance* a prominent feature

Criteria for PCOS



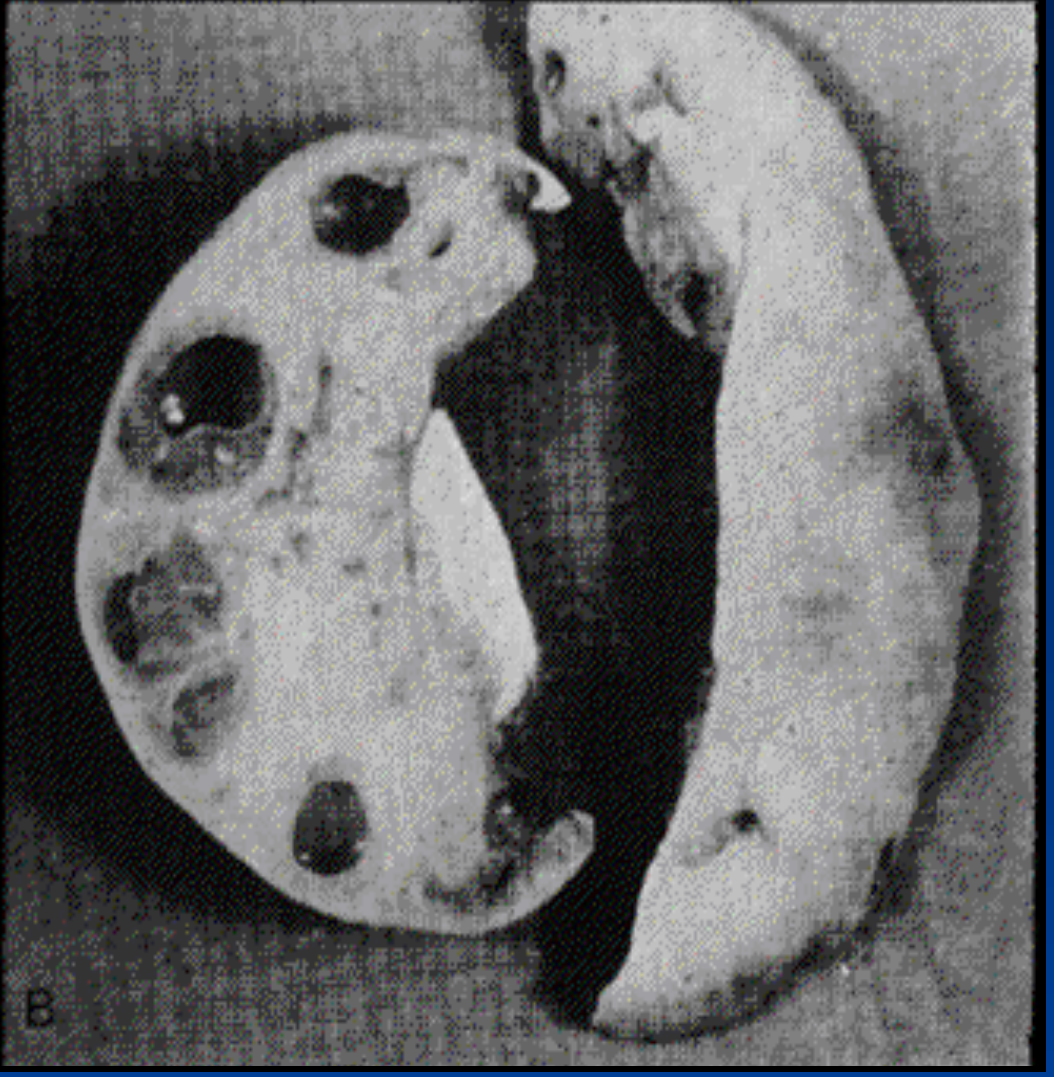
Testing for PCOS

To establish diagnosis:

- Testosterone (total and free)
- DHEA-sulfate
- Prolactin, TSH, 17α-hydroxyprogesterone

Once diagnosis established:

- 2 hour 75 gm dextrose OGTT
- Lipid panel

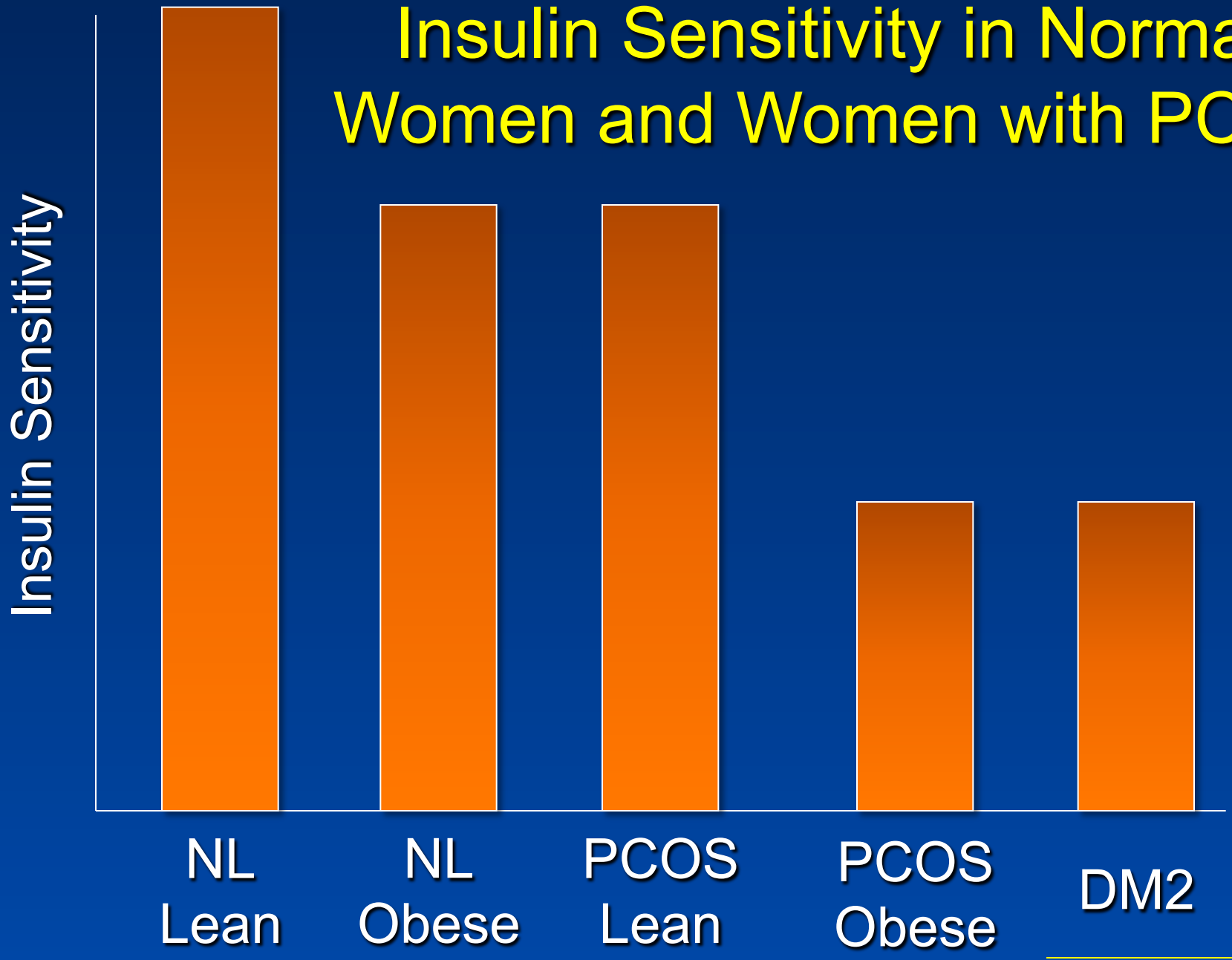


Typical Woman with PCOS! ⟶

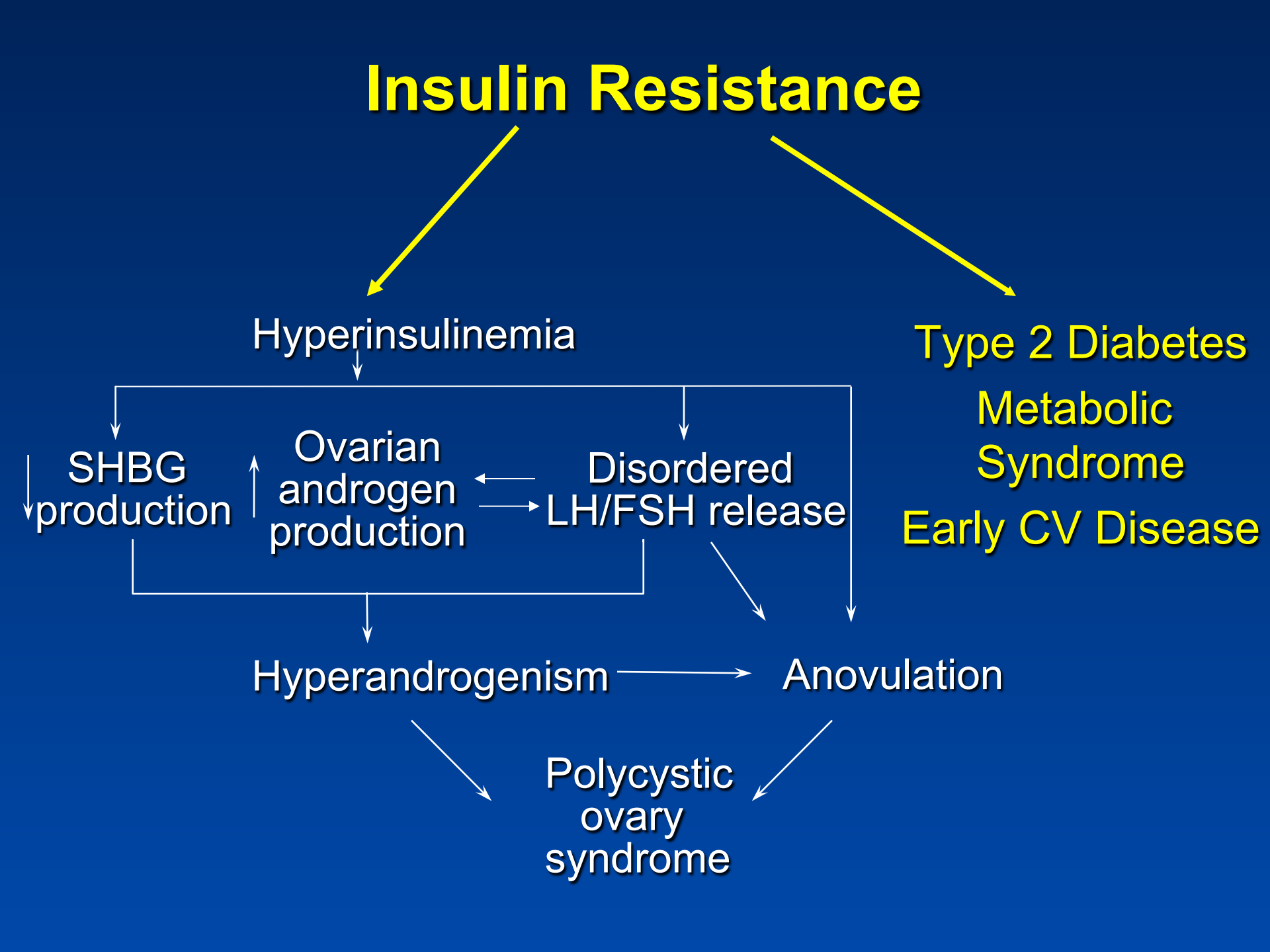
Insulin Resistance and PCOS

- *Hyperinsulinemic insulin resistance* appears to be a universal feature of women with PCOS
- PCOS is associated with a unique form of insulin resistance that is intrinsic to the syndrome
- Hyperinsulinemic insulin resistance occurs in both obese and nonobese women with PCOS

Insulin Sensitivity in Normal Women and Women with PCOS



Adapted from Dunaif et al.

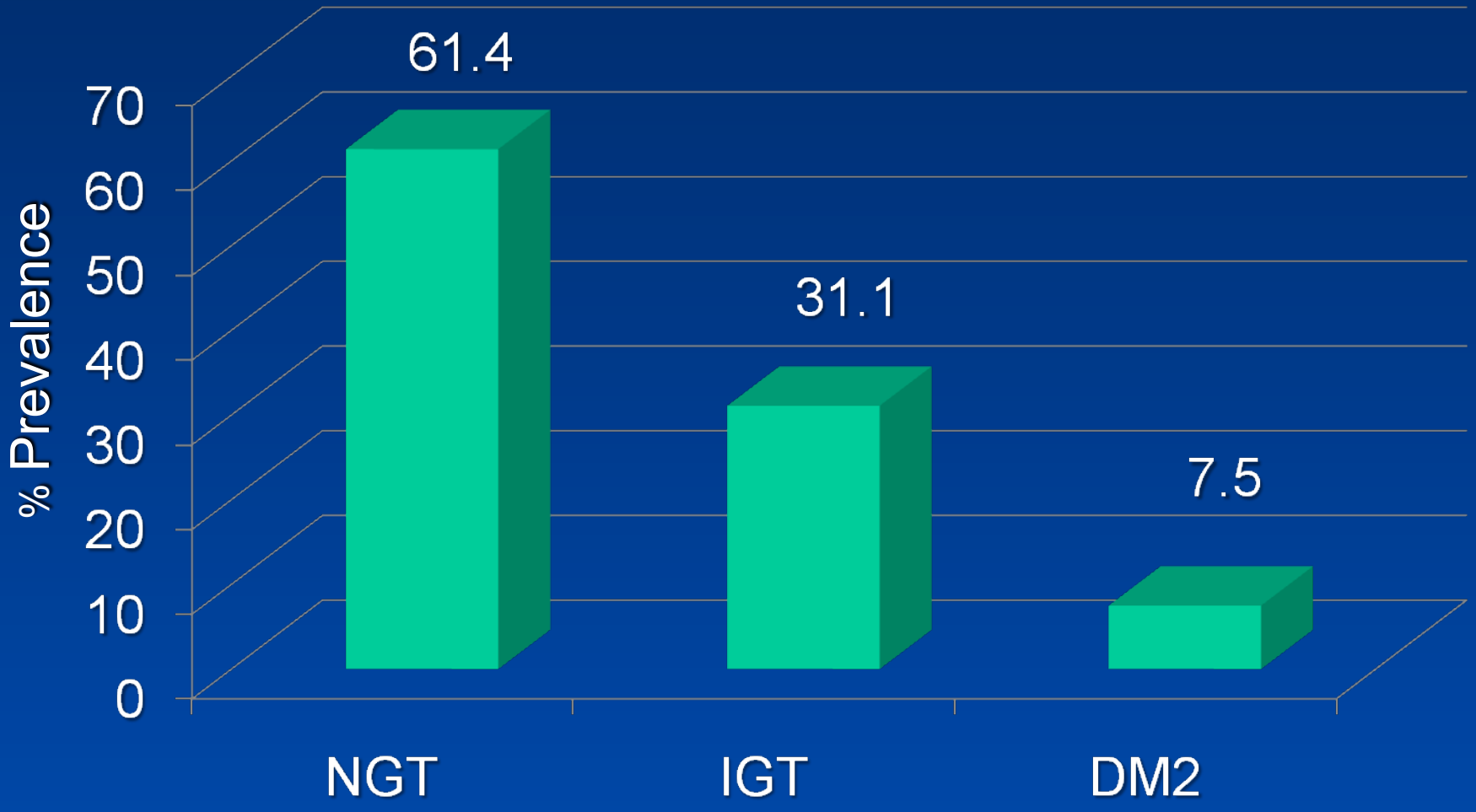

Insulin Resistance
Hyperinsulinemia
Type 2 Diabetes
Metabolic Syndrome
Early CV Disease
SHBG production
Ovarian androgen production
Disordered LH/FSH release
Hyperandrogenism
Anovulation
Polycystic ovary syndrome

PCOS: Topics to Be Discussed

I. Prevalence of glucose intolerance

Glucose Tolerance (by OGTT) in 254 Women with PCOS 14-44 Years Old

Legro RS et al. 1999



PCOS and Type 2 Diabetes

Nurses' Health Study II (NHSII):

- 101,073 women followed for 8 years
- Conversion rate to DM2 was 2-fold higher in oligomenorrheic women, independent of weight

JAMA 2001;286:2421

PCOS and Type 2 Diabetes

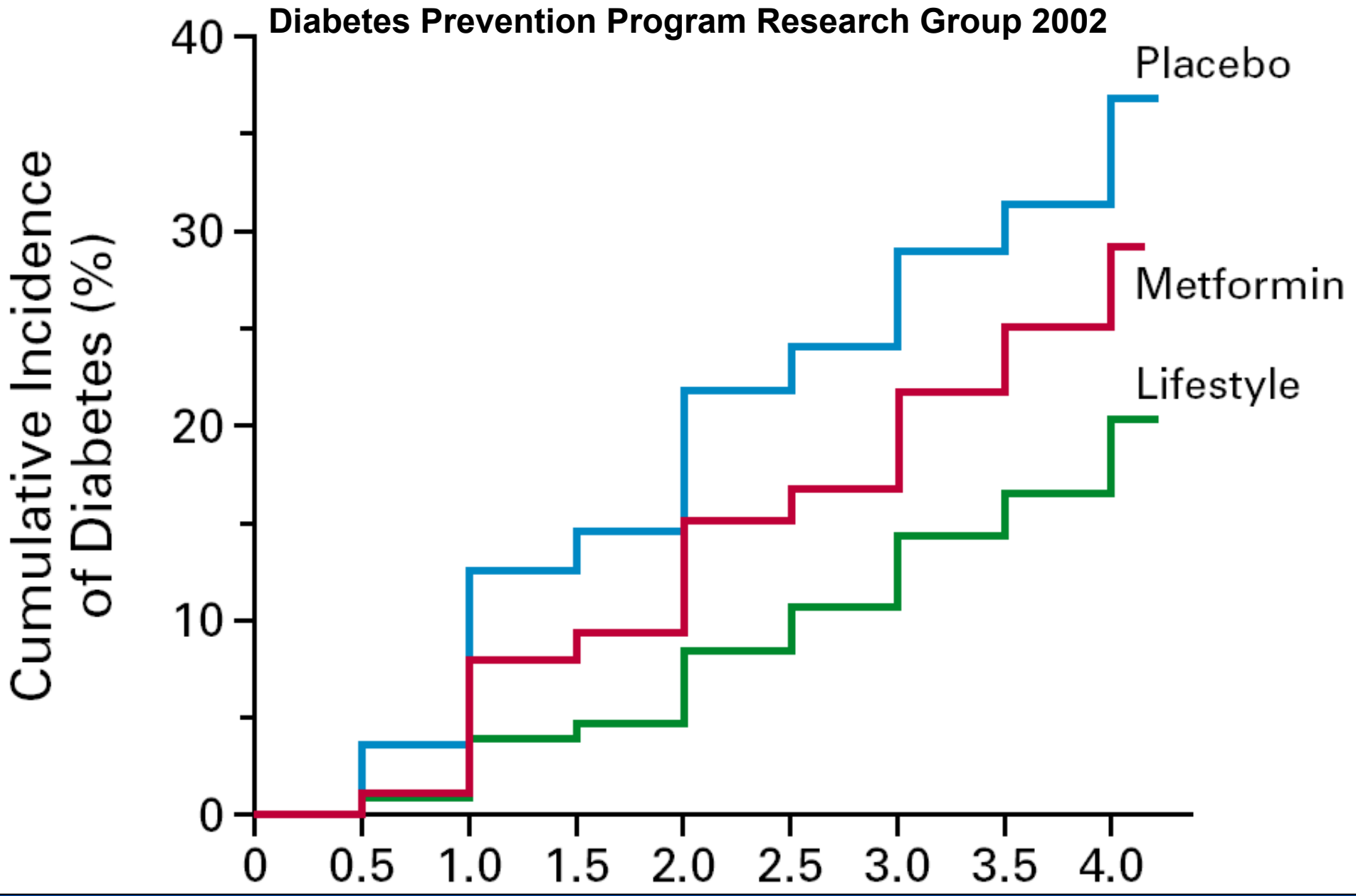
- *10-fold increased prevalence of Type 2 diabetes in young women with PCOS*
- *30-50% of obese women with PCOS develop IGT or DM2 by the age of 30*
- At any one time in ***Qatar***:
  >30,000 women with PCOS have IGT
  >10,000 women with PCOS have T2DM

PCOS: Topics to Be Discussed

I. Prevalence of glucose intolerance

II. Prevention of glucose intolerance

Cumulative Incidence of Diabetes



TRIPOD Study
(Troglitazone in Prevention of Diabetes)

- 266 Latina women with recent gestational diabetes
- Randomized to:
  - Placebo
  - Troglitazone (400 mg daily)

Results

After median of 30 months annual conversion to DM 2 was:

Placebo: 12.1%

Troglitazone: 5.4 %

Buchanan TA et al. Diabetes 2002;51:2796-2803

Metformin and Prevention of Glucose Intolerance in PCOS

(Sharma, Wickham & Nestler, *Endocrine Practice* 2007;13:373-379)

- Retrospective chart review study of clinical practice
- All women started on metformin within 5 past years
- Inclusion criteria
  - OGTT at baseline
  - No diabetes at baseline
  - At least one year follow up with repeat OGTT

Metformin and Prevention of Glucose Intolerance in PCOS

(Sharma, Wickham & Nestler, *Endocrine Practice* 2007;13:373-379)

- Study Group: 50 women with PCOS
- At baseline
  - 39 women (78%) had NGT
  - 11 women (22%) had IGT
- Average duration of follow up
  - 43 months for NGT group
  - 29 months for IGT group

Metformin and Prevention of Glucose Intolerance in PCOS

(Sharma, Wickham & Nestler, *Endocrine Practice* 2007;13:373-379)

At follow up:

- No woman developed DM!
- IGT Group
  - 5 of 11 women (45%) continued IGT
  - 6 of 11 women (55%) reverted to NGT
- NGT Group
  - 2 of 39 women (5%) converted to IGT
  - 37 of 39 women (95%) continued NGT

Metformin and Prevention of Glucose Intolerance in PCOS

(Sharma, Wickham & Nestler, *Endocrine Practice* 2007;13:373-379)

- Annual conversion rate from NGT or IGT to DM2: 0%
- Annual conversion rate from NGT to IGT: 1.4%
- NGT to IGT conversion rate was significantly ($P<0.015$) lower than rates reported by:
  - Legro at al.: 16%
    (JCEM 2005;90:3236-3242)
  - Ehrmann et al.: 19%
    (Diabetes Care 1999;22:141-146)

PCOS: Topics to Be Discussed

I. Prevalence of glucose intolerance

II. Prevention of glucose intolerance

III. PCOS and CV risk

Evidence for CV Disease in PCOS

- Prevalence of risk factors

CV Risk Factors in PCOS

All linked to insulin resistance

- Obesity
- Hypertension
- Vascular dysfunction
- ↓ HDL, ↑ triglycerides
- ↑ PAI-1
- ↑ Endothelin-1
- ↑ C-reactive protein

NCEP 2001 ATP III: Metabolic Syndrome

(must meet 3 of 5 criteria)

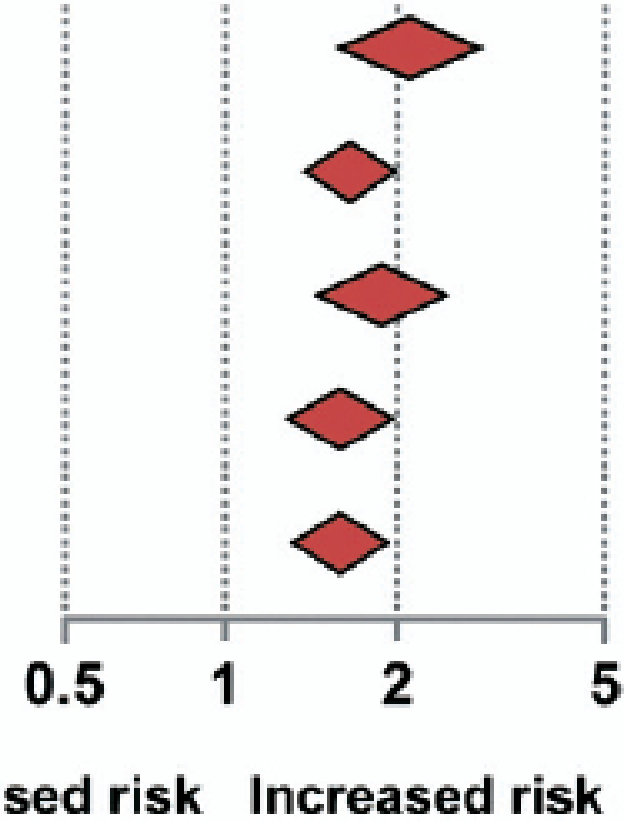
- Waist circumference
  - Men: > 40 inches (102 cm)
  - *Women: > 35 inches (88 cm)*
- Triglycerides: ≥ 150 mg/dl
- HDL
  - Men: < 40 mg/dl
  - *Women: < 50 mg/dl*
- Blood pressure: ≥ 130/85 mmHg
- Fasting plasma glucose: ≥ 110 mg/dl

Metabolic Syndrome and Cardiovascular Risk

- Meta-analysis of longitudinal studies to assess association between metabolic syndrome and risk of cardiovascular events and mortality
- 37 studies: 43 cohorts, total of 172,573 persons

Gami AS et al. J Am Coll Cardiol. 2007;49:403-413.

Outcome	Studies (N)	RR	95% CI
CV event	11	2.18	1.63-2.93
CHD event	18	1.65	1.37-1.99
CV death	10	1.91	1.47-2.49
CHD death	7	1.60	1.28-2.01
Death	12	1.60	1.37-1.92



- Overall RR for CV event or mortality: 1.78 (CI 1.58-2.00)
- Association remained after adjusting for traditional CV risk factors: 1.54 (CI 1.32-1.79)

Gami AS et al. J AM Coll Cardiol. 2007;49:403-413.

Metabolic Syndrome: Sex Differences

Seven studies provided separate risk estimates for women and men

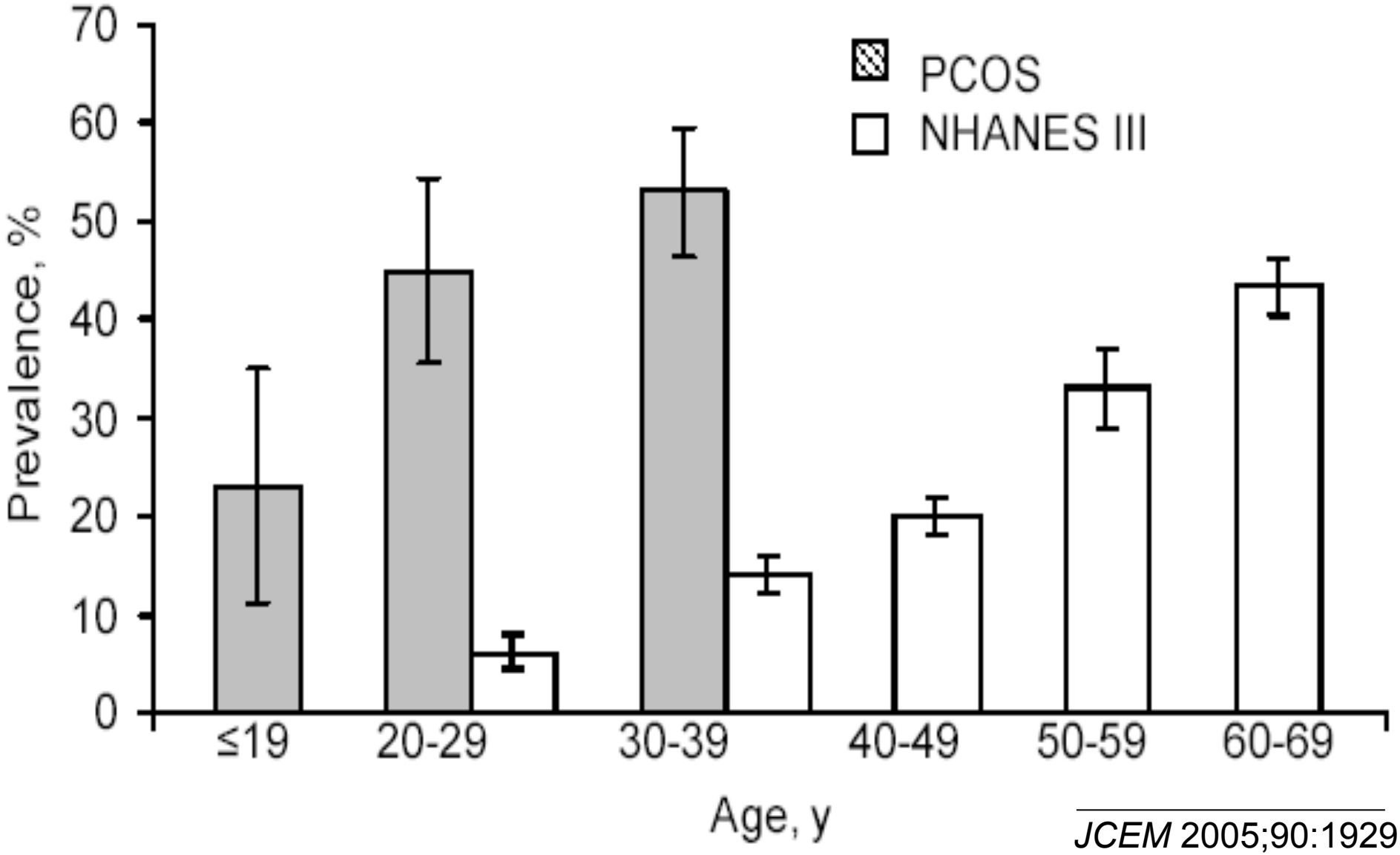
Risk of CV events and death 30% higher in women

- Women: RR 2.63
- Men: RR 1.98

P=0.09

Gami AS et al. *J Am Coll Cardiol* 2007;49:403

Prevalence of MBS in 106 Women with PCOS



JCEM 2005;90:1929

Prevalence of MBS in 106 Women with PCOS Stratified by Age and BMI vs NHANES II Women

Age Group (yr)	BMI Group (kg/m^2)	PCOS (%)	U.S. Women (%)
20-29 (N=29)	Total in the age group:	44.8	5.9
	<25	0	0.8
	25-30	16.7	8.3
	>30	58.6	27.5
30-39 (N=49)	Total in the age group:	53.1	14.6
	<25	23.1	1.1
	25-30	40.0	14.4
	>30	61.8	43.4

Prevalence of MBS Abnormalities in 106 Women with PCOS

No. of MBS Factors	Prevalence (%)	N
0	9	10
1	23	23
2	26	27
3	30	32
4	11	12
5	2	2
Total	100	106

Prevalence of Components of the Metabolic Syndrome in 106 Women with PCOS

Low HDL cholesterol	68%
High BMI (WHR)	67%
High blood pressure	45%
Elevated triglycerides	35%
Impaired fasting glucose	4%

Worldwide Prevalences of MBS in Women with PCOS

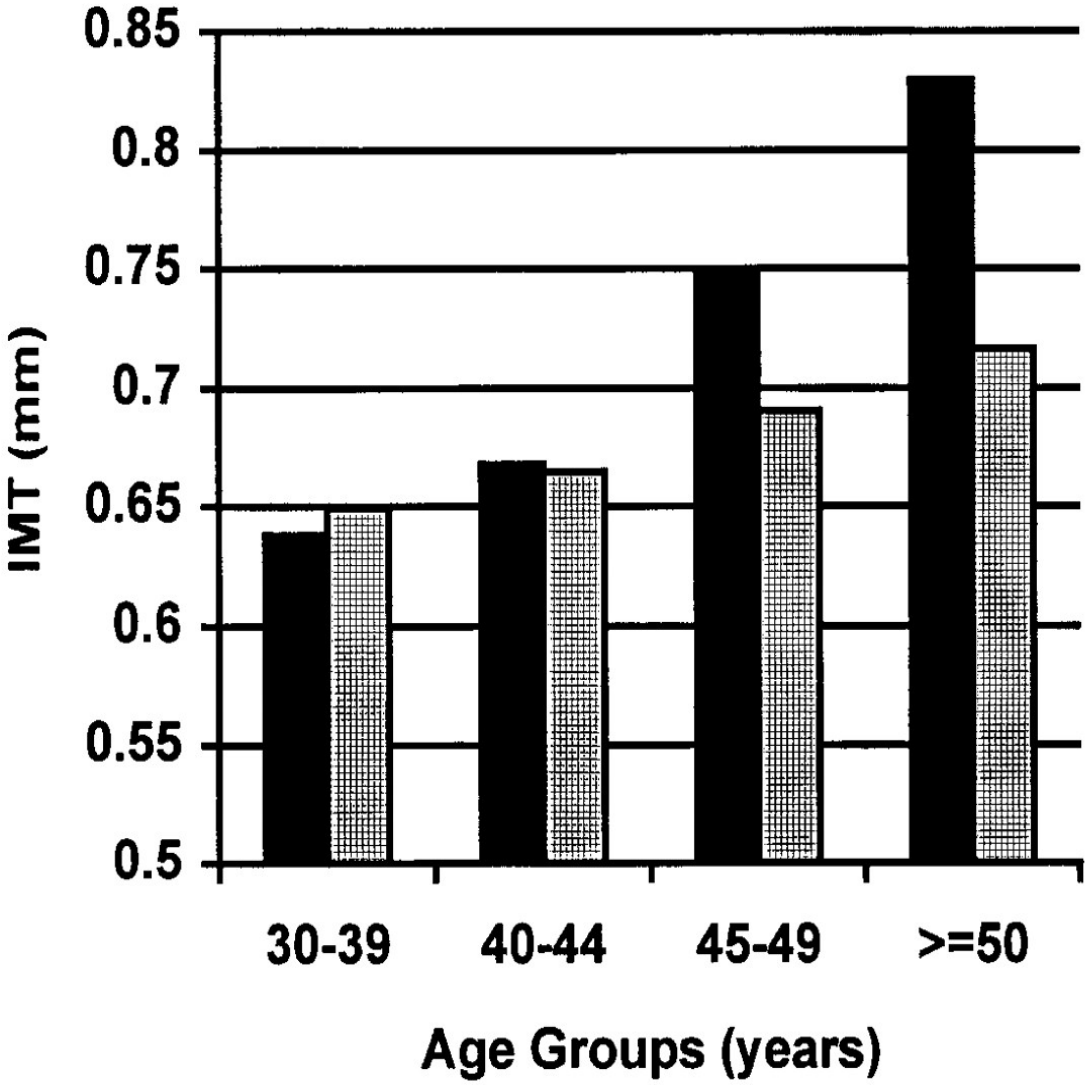
	Country	MBS in PCOS
Aprodonidze et al.	USA	43%
Dokras et al.	USA	47%
Ehrmann et al.	USA	33%
Soares et al.	Brazil	28%
Vural et al.	Turkey	12% (0% in controls)
Rabelo et al.	Puerto Rico	44%
Vrbikova et al.	Czech Republic	2% (0% in controls)
Cheung et al.	China	25% (3% in controls)
Park et al.	Korea	15% (4% in controls)
Weerakiet et al.	Thailand	35%
Bhattacharya	India	46%

Evidence for CV Disease in PCOS

- Prevalence of risk factors
- Imaging and functional identification of underlying atherosclerosis

Carotid Intima Media Thickness in Normal and PCOS Women

Talbott E et al., Arterioscler Thromb Vasc Biol. 2000; 20:2414



(Cases = solid, Controls = hatched) (PCOS X age interaction p =.031)

Prevalence of Coronary Calcifications in Women 30-45 Years Old

(Christian RC et al. JCEM 2003;88:2562-2568)

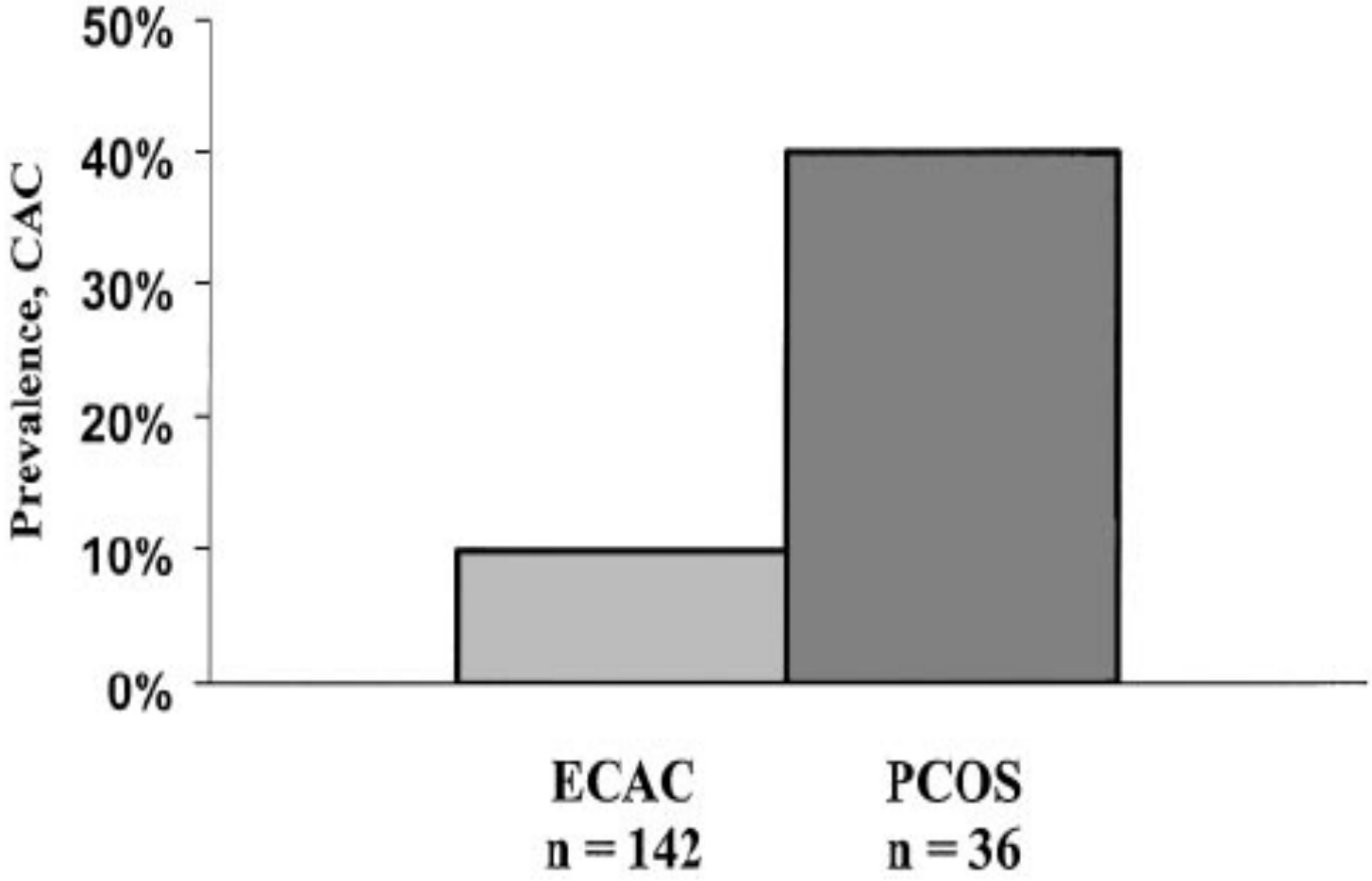
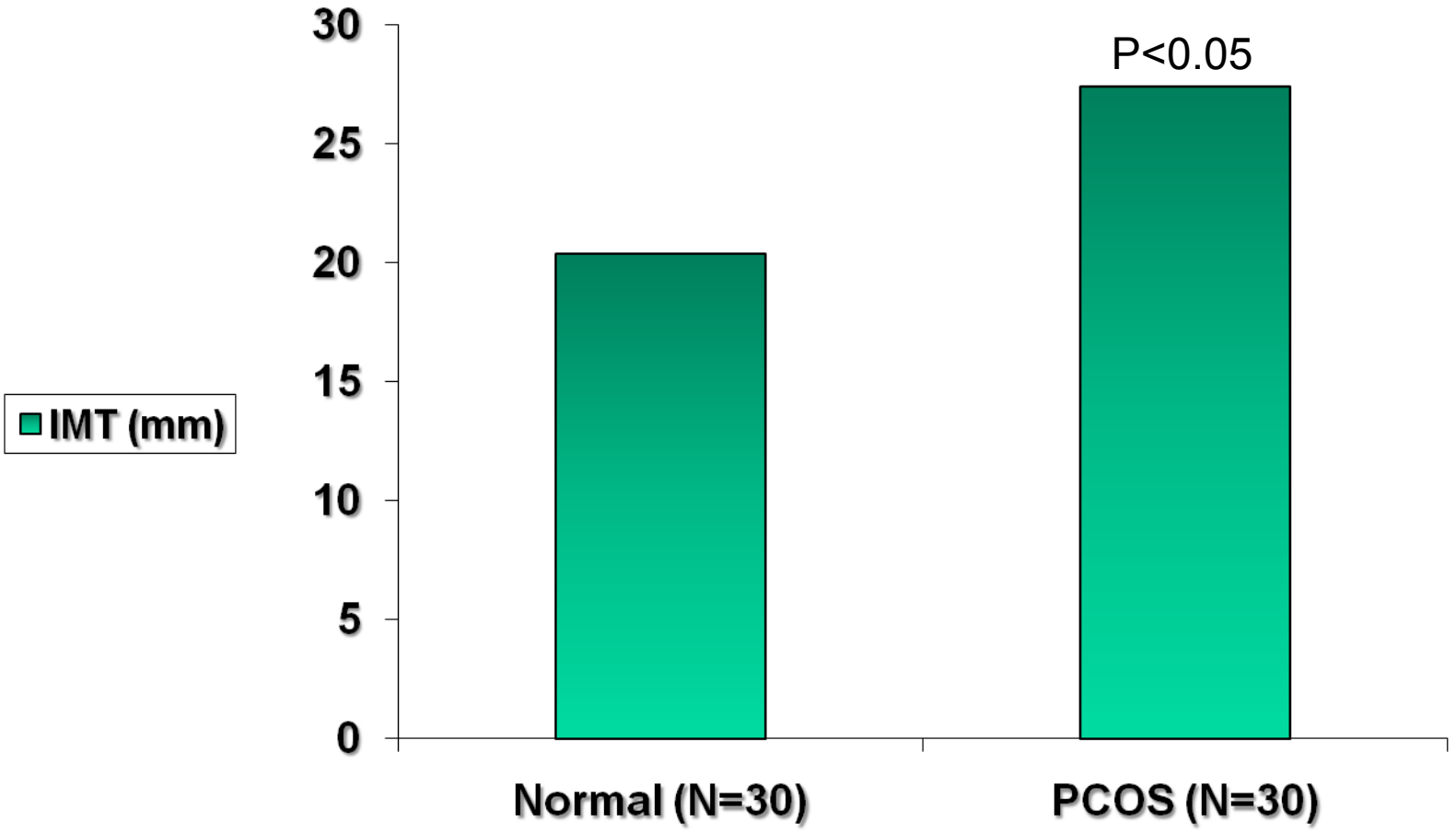


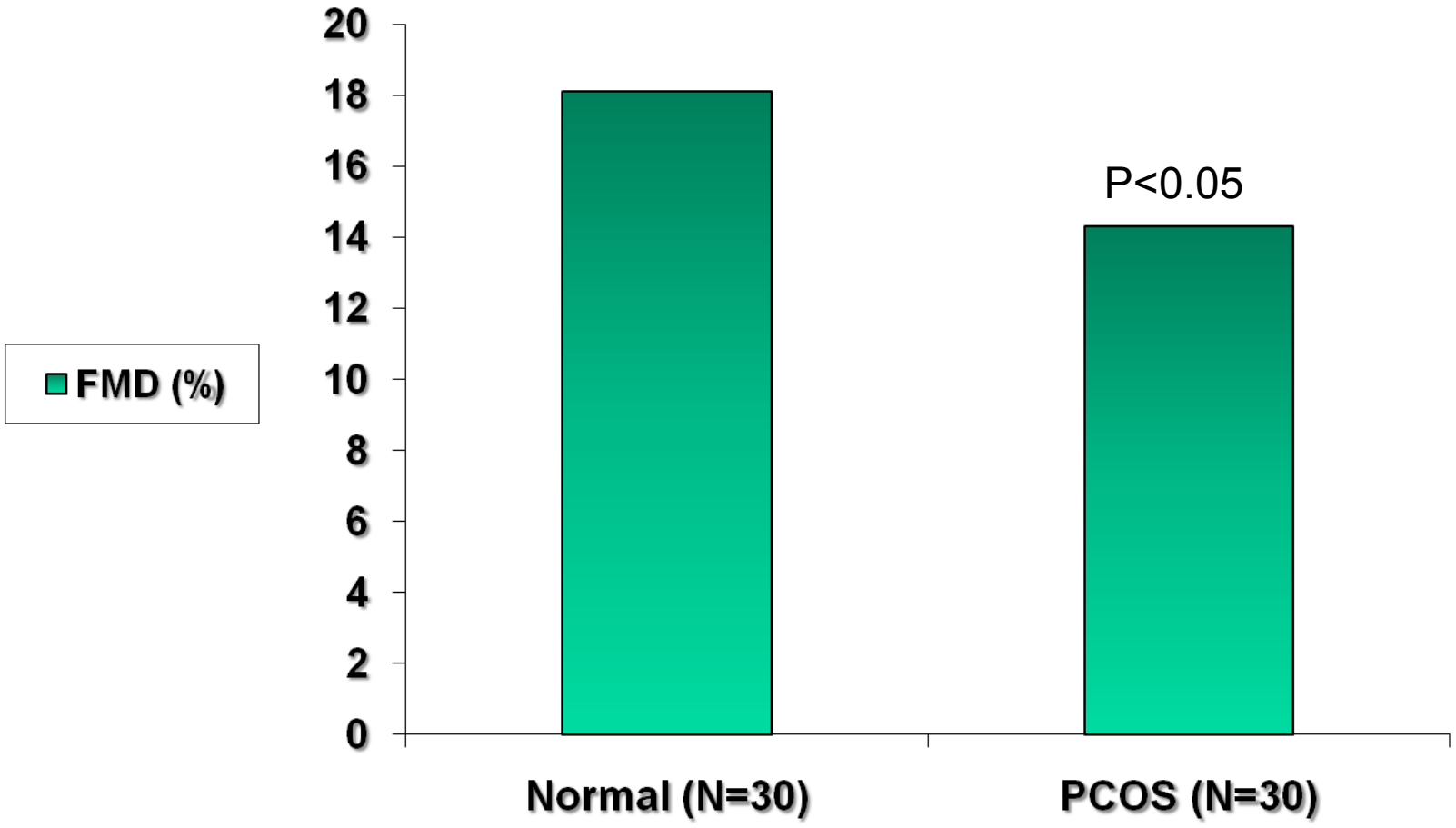
FIG. 2. Prevalence of CAC in ECAC study women *vs.* PCOS women. OR = 5.89; 95% CI = 2.46–13.97; $P = 0.001$.

Intima-Media Thickness in Young (22 year-old) and Normal Weight (BMI: 22 kg/m^2) Women with PCOS



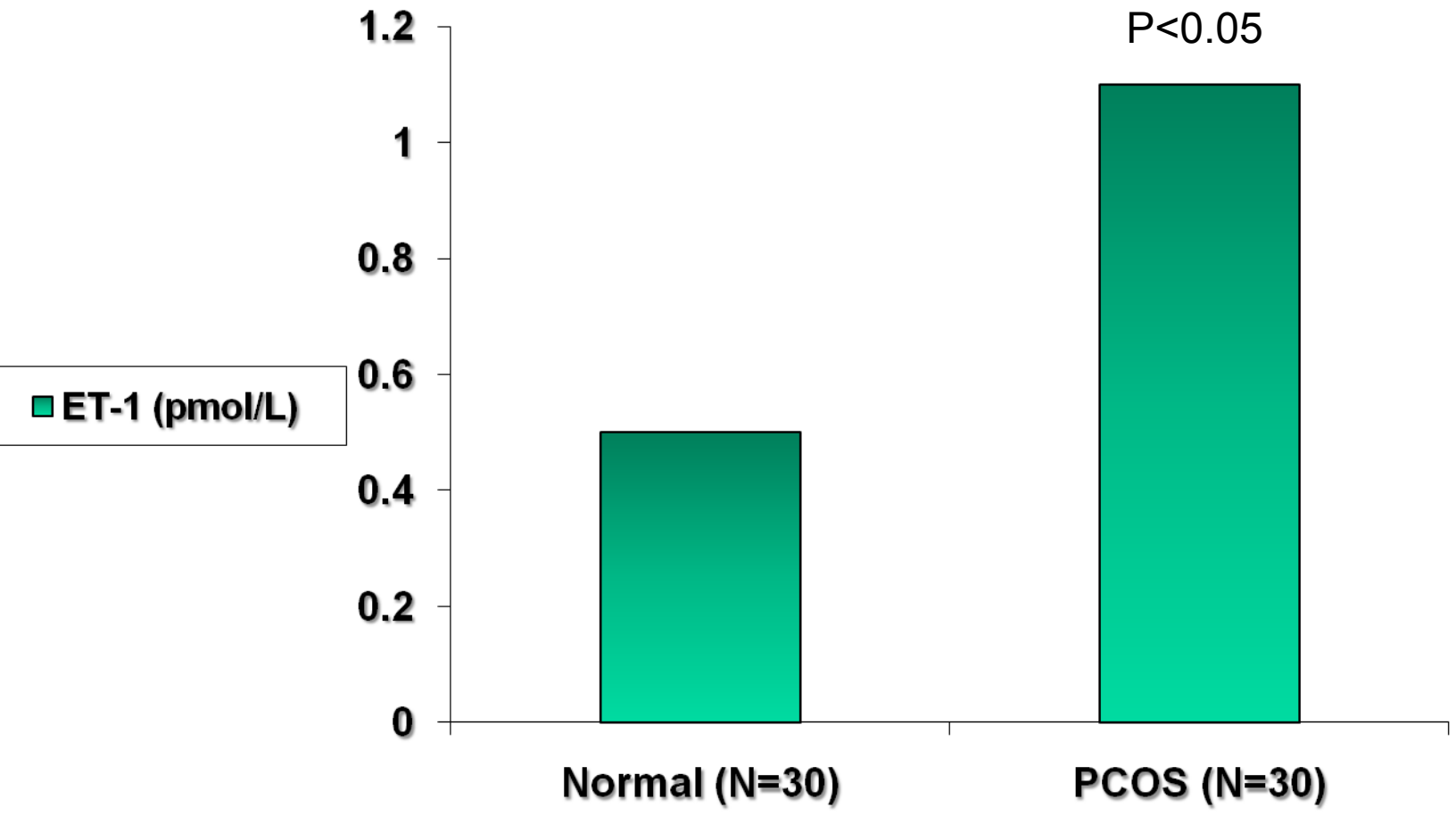
Orio F et al. *J Clin Endocrinol Metab* 2004;89:4588-4593

Flow-Mediated Dilation in Young (22 year-old) and Normal Weight (BMI: 22 kg/m^2) Women with PCOS



Orio F et al. *J Clin Endocrinol Metab* 2004;89:4588-4593

Endothelin-1 in Young (22 year-old) and Normal Weight (BMI: 22 kg/m^2) Women With PCOS



Orio F et al. *J Clin Endocrinol Metab* 2004;89:4588-4593

Evidence for CV Disease in PCOS

- Prevalence of risk factors
- Imaging and functional identification of underlying atherosclerosis
- Outcome studies (epidemiological & longitudinal)

The Controversy!

Diabetes and Cardiovascular Events in Women with Polycystic Ovary Syndrome; A 20 Years Retrospective Cohort Study

(Mani H et al. *Clin Endocrinol (Oxf)* 2013;78:926)

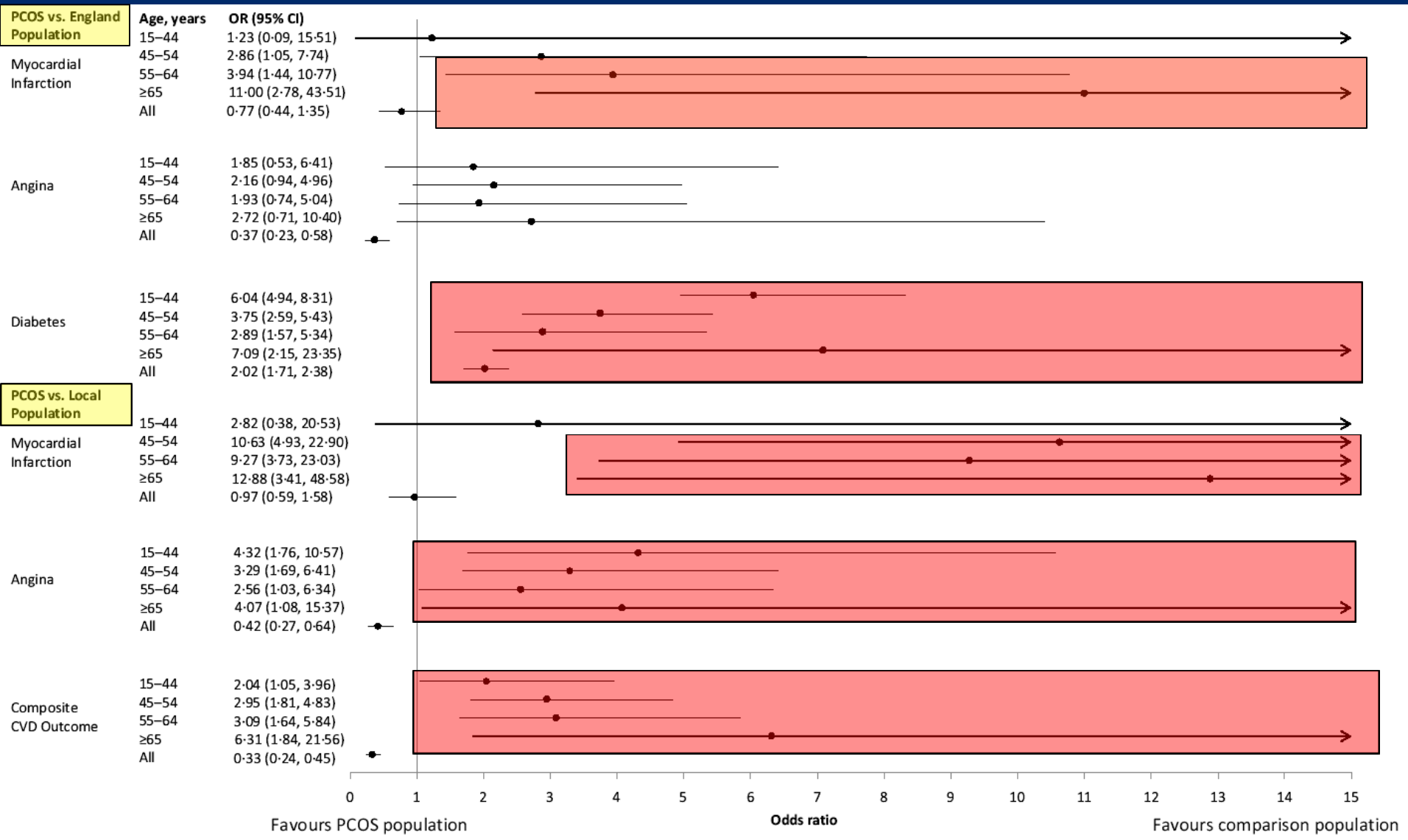
Design: Retrospective cohort study (total follow-up >12,000 person-years)

Participants: 2301 women with PCOS (mean age = 29.6 years) attending a specialty clinic in Leichestershire, U.K.

Conclusion: We have shown a *high incidence and age group-specific prevalence of T2DM, MI and angina* in the women with PCOS, with *over a quarter having had MI or angina in those >65 years*.

CV Events in 2301 Women with PCOS Over 20 Years

(Mani H et al. *Clin Endocrinol* 2013;78:926)

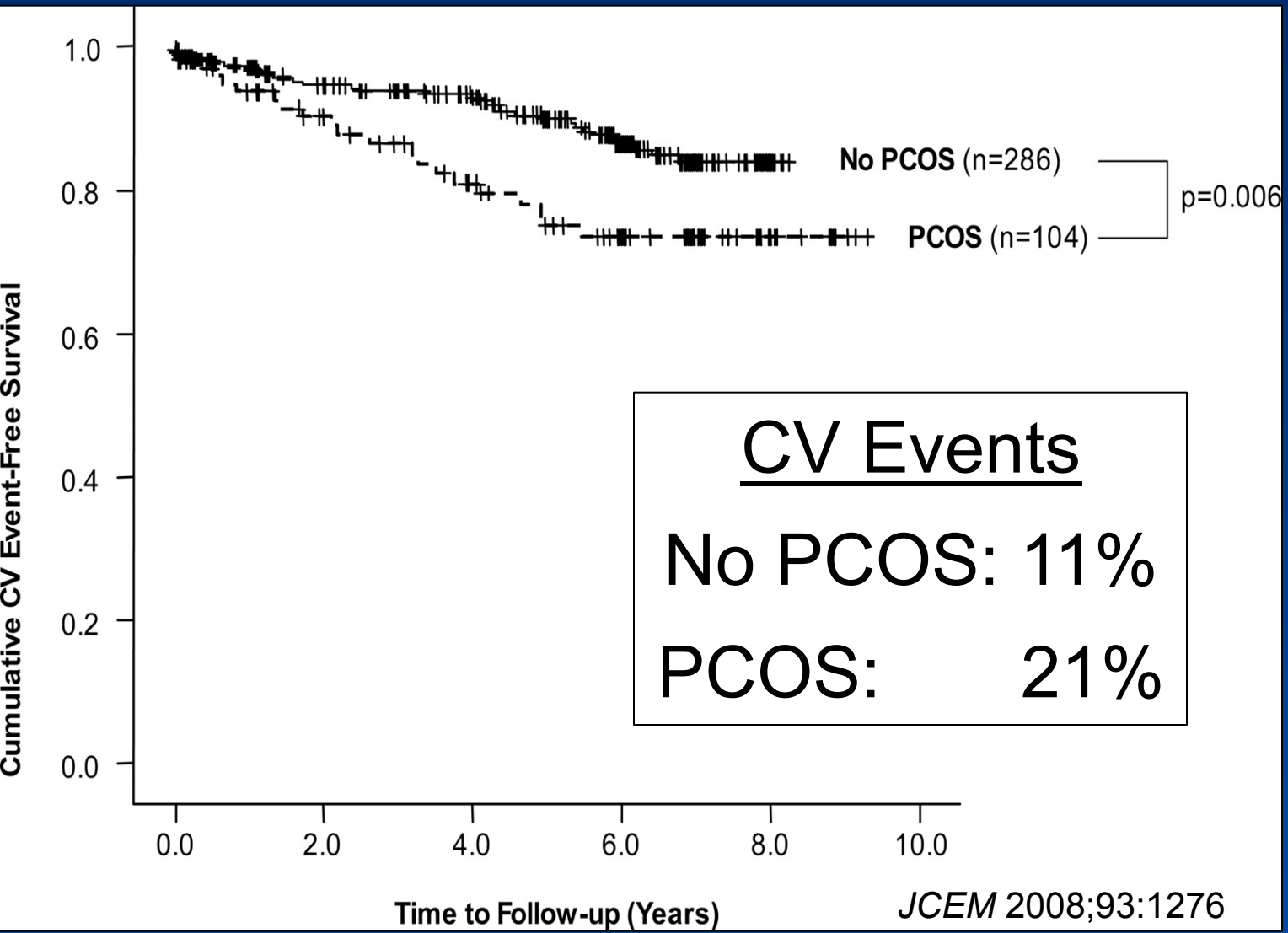


PCOS and Cardiovascular Disease

- Nurses Health Study: 82,439 women followed for 14 years. In women with very irregular menses:
  - RR for CHD was 1.5 (CI: 1.3-1.9)
  - RR for fatal MI was 1.9 (CI: 1.3-2.7)

J Clin Endocrinol Metab 2002;87:2013

WISE Study: Cumulative CV Death or MI Free Survival in Postmenopausal Women with and without PCOS



CV Events

No PCOS: 11%

PCOS: 21%

Age of PCOS at baseline: 63 yrs

JCEM 2008;93:1276

PCOS: Topics to Be Discussed

I. Prevalence of glucose intolerance

II. Prevention of glucose intolerance

III. PCOS and CV risk

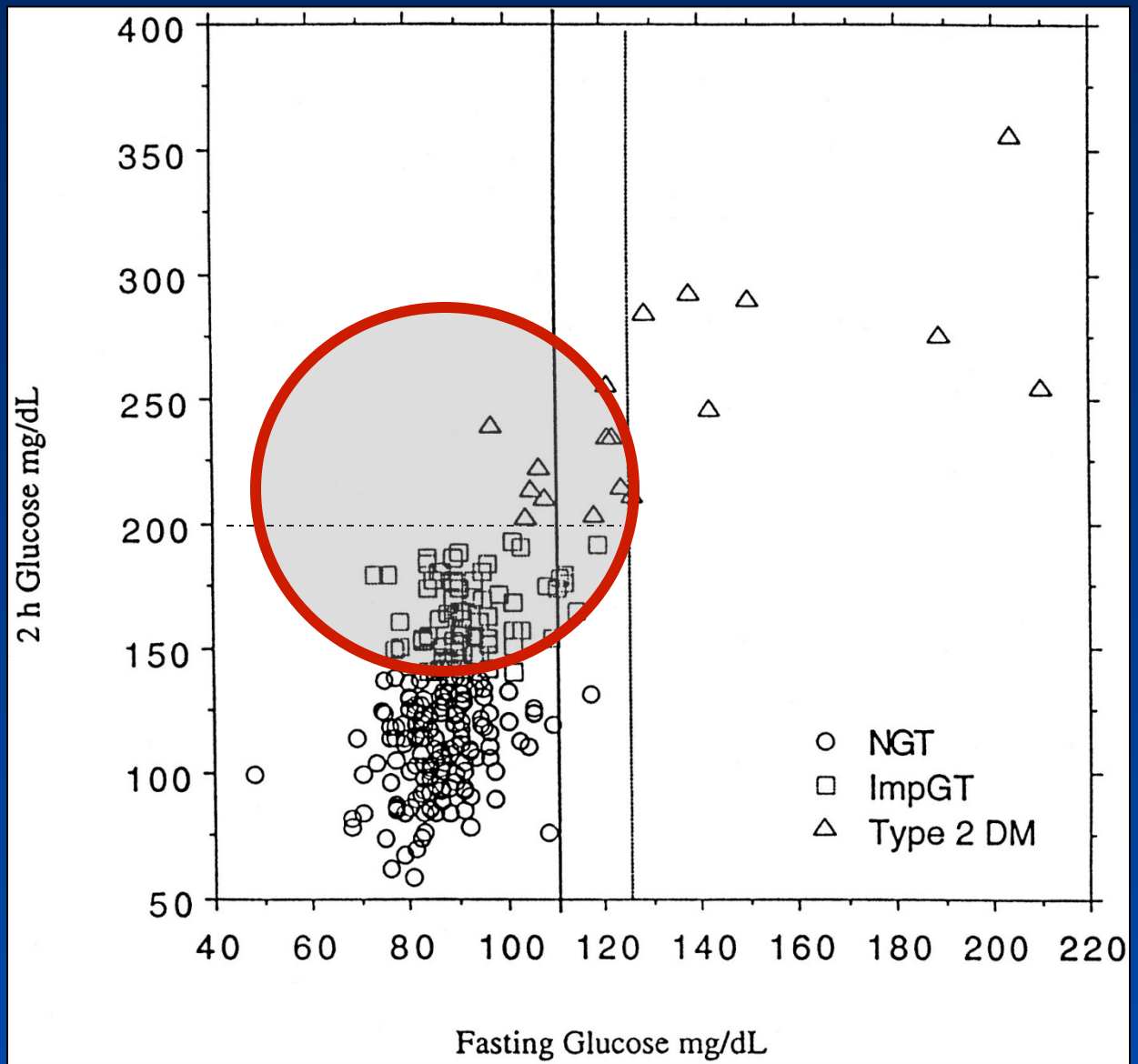
IV. Implications for Evaluation and Treatment

Evaluation of Women With PCOS: General Health Issues

- Check for
  - Glucose intolerance (OGTT)
  - Hypertension
  - Dyslipidemia
  - Risk factors for heart disease

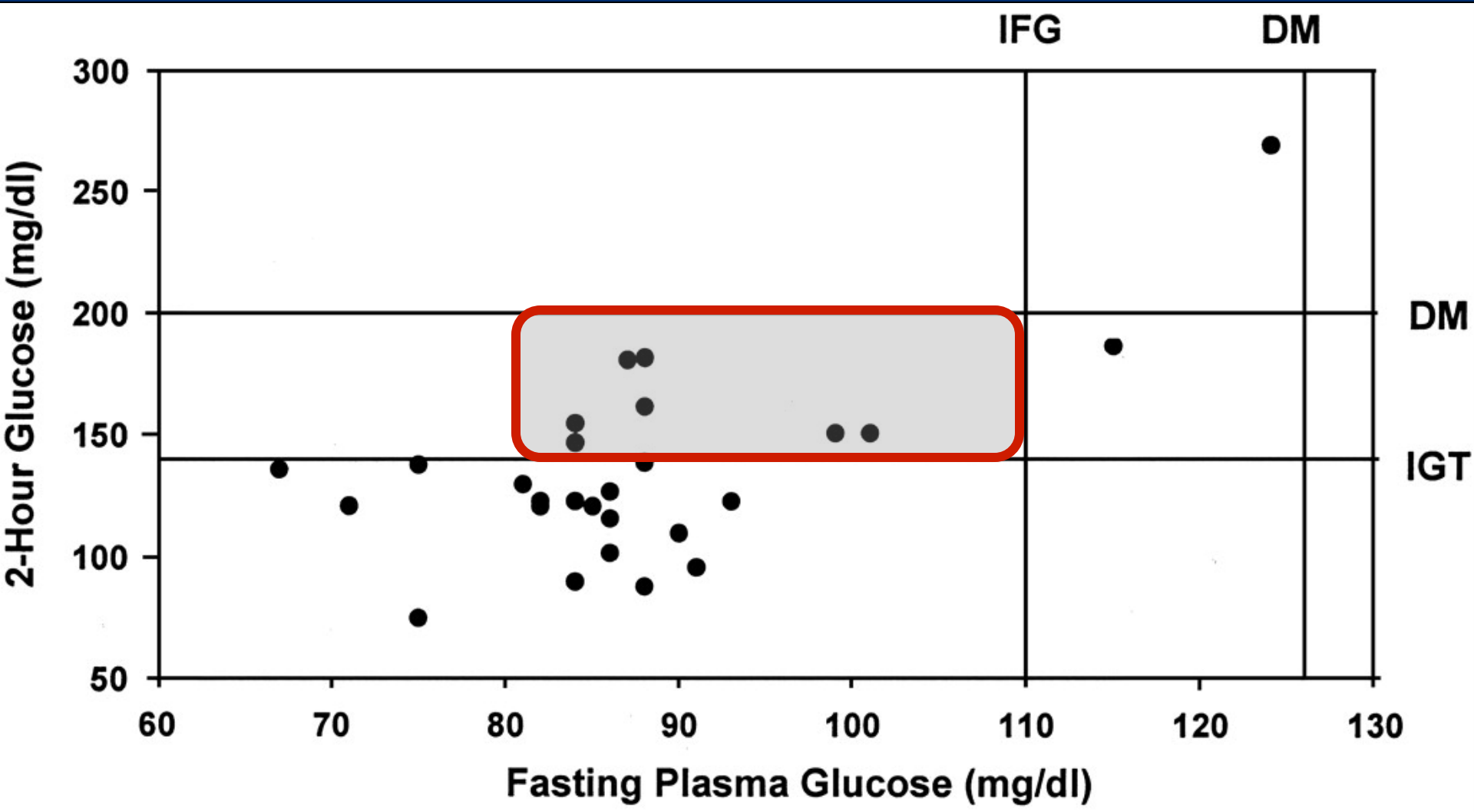
Scattergram of Fasting and OGTT Glucose Levels in 254 Women with PCOS

(Legro RS et al. *J Clin Endocrinol Metab* 1999;84:165-169)



Glucose Tolerance in Adolescents with PCOS

(Palmert MR et al. *J Clin Endocrinol Metab* 2002; 87:1017-1023)



Androgen Excess and PCOS Society 2007 Guidelines

"…an *OGTT is recommended as the standard screening tool* for IGT in these patients [PCOS women], and should initially be performed at diagnosis….

[The] panel recommends screening PCOS women with NGT *at baseline and at least once every 2 years* or earlier if additional risk factors are identified. [W]omen with PCOS who have IGT should be screened annually using an OGTT."

J Clin Endocrinol Metab 2007;92:4546

Evaluation of Women With PCOS: General Health Issues

- Check for
  - Glucose intolerance (OGTT)
  - Hypertension
  - Dyslipidemia
  - Risk factors for heart disease

Traditional and Novel Goals of Therapy in PCOS

Traditional

- Improve menstrual cyclicity
- Decrease risk for endometrial cancer
- Reduce serum androgens
- Improve symptoms
  - Hirsutism
  - Acne

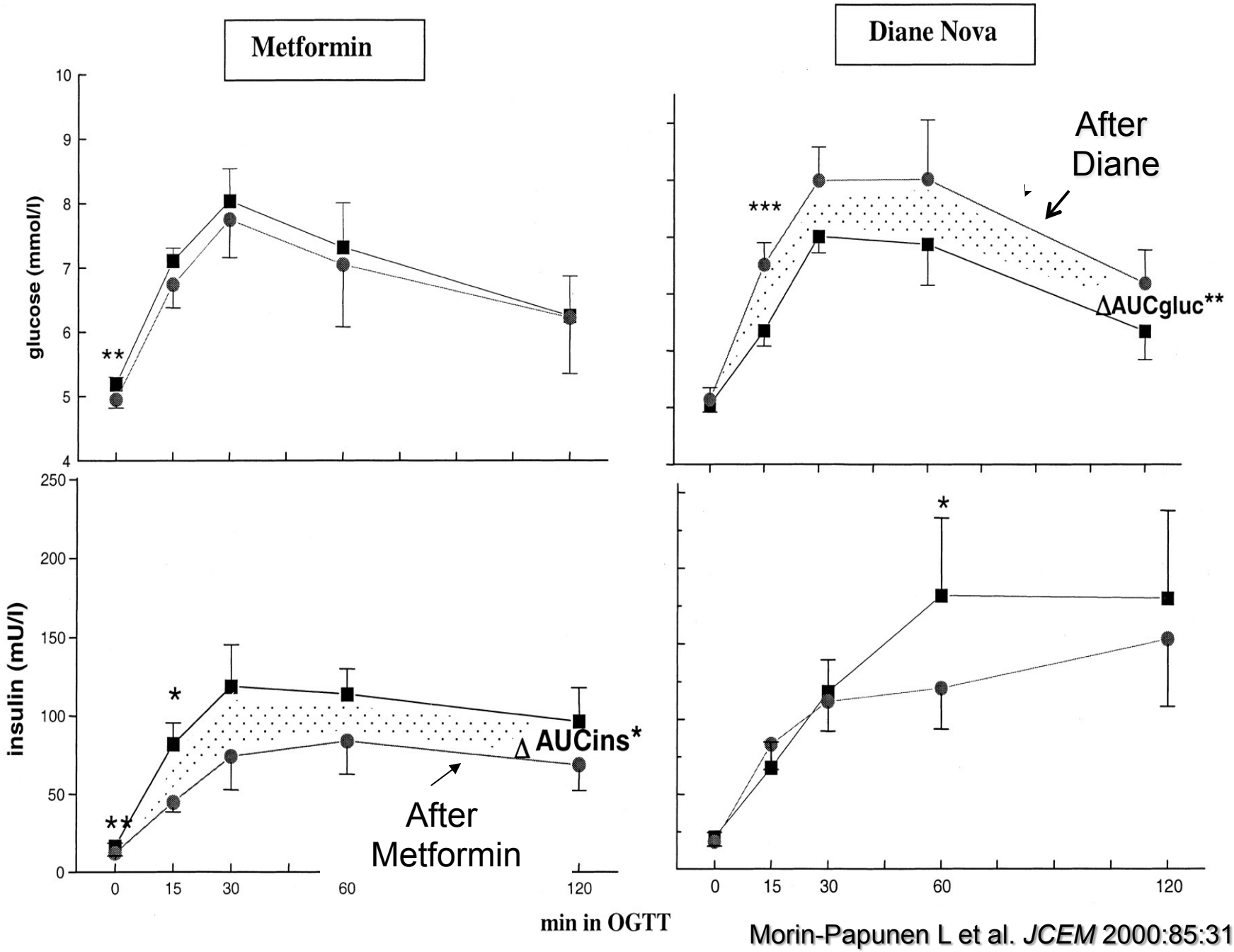
Novel

- Prevent glucose intolerance and diabetes
- Prevent atherosclerosis and acute cardiac events

Therapeutic Options

- Weight loss
  - Diet
  - Surgery
- Diet modification
- Medication to enhance insulin sensitivity
  - Metformin

35 µg Ethinyl Estradiol/2 mg Cyproterone Acetate versus Metformin in PCOS



Morin-Papunen L et al. *JCEM* 2000:85:3161

Long-Term Therapy: OCP versus Insulin-Sensitizing Drug

OCP in PCOS

- May worsen insulin resistance
- May induce glucose intolerance
- May increase serum triglycerides
- May increase risk for DM2
- Increases risk for cardiovascular disease

Insulin Sensitizing Drug in PCOS

- Improves insulin sensitivity
- Improves glucose tolerance
- May reduce serum triglycerides
- Reduces plasma PAI-1
- Reduces Endothelin-1
- Reduced CRP

Insulin Sensitizing Drug in IGT or GDM

- Prevents progression to DM2
- May decrease CV disease

Disclosure:
Dissent with Endocrine Society Guidelines

- Endocrine Society Guideline: Use metformin only if glucose intolerance (impaired glucose tolerance or diabetes) is present
- Large long-term studies are lacking
- *However*:
  - Women with PCOS (esp. if obese):
    - Markedly high risk for developing impaired glucose tolerance or diabetes
    - Increased risk for CV disease

Disclosure:
Dissent with Endocrine Society Guidelines

- Metformin reduced progression to diabetes in the Diabetes Prevention Program (DPP)

- Metformin exerts beneficial effects on multiple cardiovascular risk factors in women with PCOS

Disclosure: Dissent with Endocrine Society Guidelines

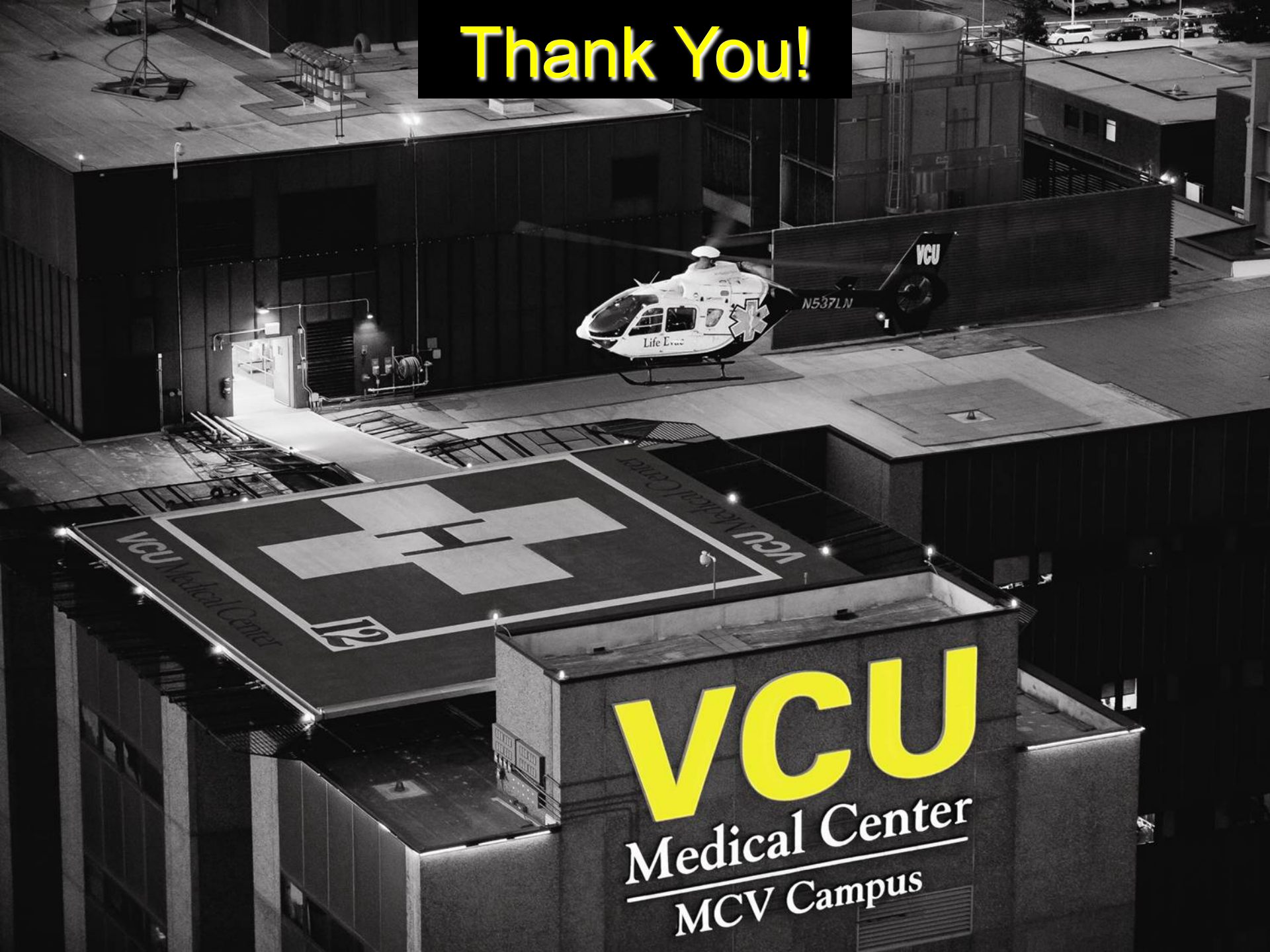
Expert Opinion:

- Metformin may be used, alone or in combination with hormonal contraception, for the long-term treatment of PCOS in women with normal glucose tolerance:
  - *Improved ovulation, menstrual cyclicity, and fertility*
  - *Reduction in androgen levels*
  - *May retard progression to glucose intolerance*
  - *May retard development of CV disease*

Summary: Clinical Pearls

- *PCOS is a GENERAL HEALTH ISSUE*
  - Evaluation
    - Screen for glucose intolerance (*use OGTT!*), dyslipidemia (*check HDL!*), hypertension, CV risk factors
  - Novel Goals of Therapy
    - Decrease risk for type 2 diabetes
    - Decrease risk for early CV disease
  - Long-Term Treatment
    - Metformin may reduce risks for DM2 and CV disease (*couple it with diet and exercise!*)

Johannes Vermeer
ca. 1665-1667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