NORDIC FEDERATION OF SOCIETIES OF OBSTETRICS AND GYNAECOLOGY – November, 2010

"POLYCYSTIC OVARY SYNDROME THROUGH LIFE"

CARDIOVASCULAR RISK FACTORS

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PCOS

Definition of PCOS is important in assessing cardiovascular disease (CVD)

The different definitions have varying risk factors for CVD and T2DM

1990 – International Conference (NIH):

Both

1. Chronic anovulation
2. Clinical/biochemical hyperandrogenism

2003 – Rotterdam ESHRE / ASRM Consensus Workshop:

2 out of 3:

1. Oligo- and / or anovulation
2. Clinical / biochemical hyperandrogenism
3. Polycystic Ovaries on scan

Androgen Excess Society Guideline – 2006

1.Presence of hyperandrogenism clinical/biochemical,

2. (a) Oligo-anovulation and/or (b) PCOM (scan)

Clinical Features of PCOS

REPRODUCTIVE

Menstrual Irregularity

Hyperandrogenism

Polycystic ovaries

High rates of miscarriage

Endometrial dysplasia

CARDIO-METABOLIC

Insulin resistance

Hyperinsulinaemia

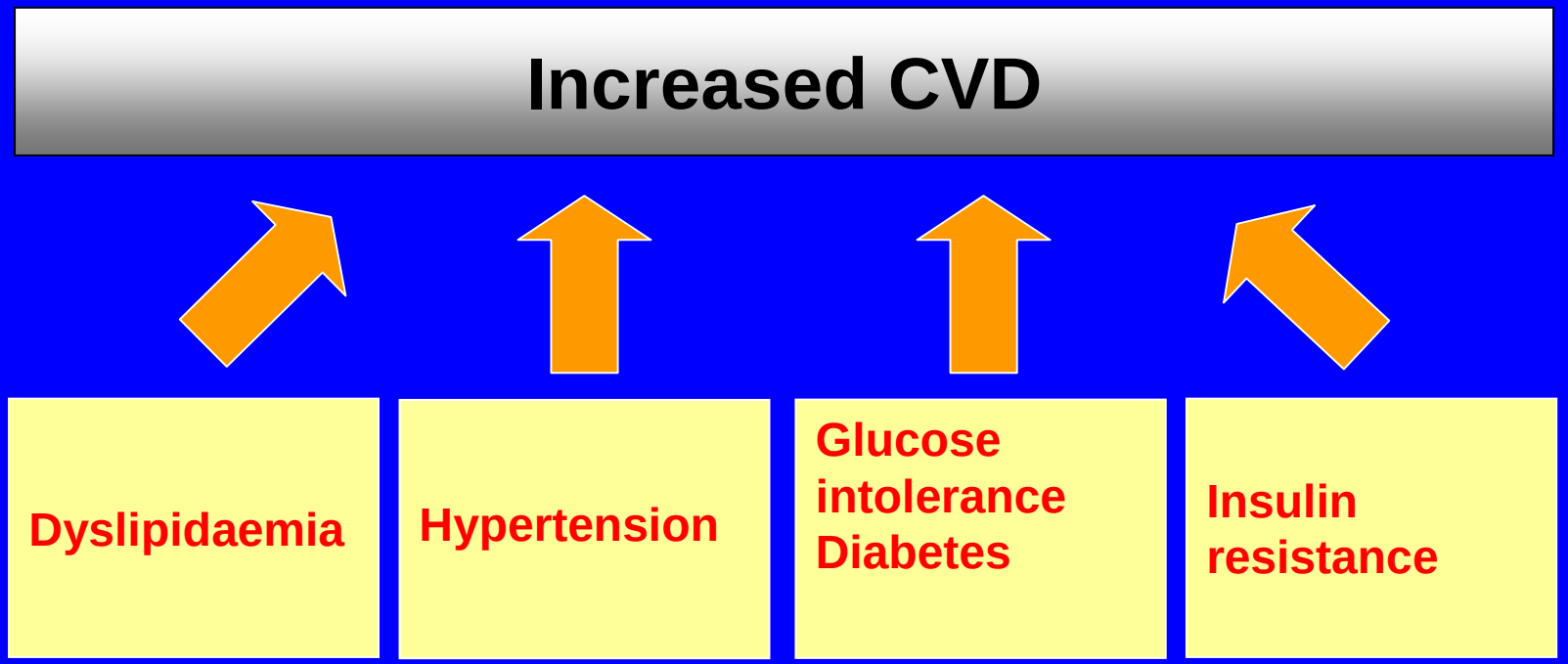
IGT / DM

Dyslipidaemia

Obesity

Sleep Apnoea

Multiple Cardiometabolic Risk Factors Increase Risk of CVD



Dyslipidaemia in PCOS

- Increased small, dense LDL
- Elevated VLDL cholesterol
- Elevated triglycerides
- Decreased HDL cholesterol
- Decreased apolipoprotein A-I

“**Atherogenic Lipoprotein Phenotype**”

Lobo, 2000; Conway, 1992;

Hopkinson, 1998; Bernesi, 2007

Dyslipidaemia in PCOS

- Occurs in both lean and obese PCOS women
- Obesity and IR exacerbate dyslipidaemia

  (85% with IGT/DM + PCOS ***vs.*** 58% with NGT + PCOS)
- Race and Ethnicity
- Androgen levels
  - increased HDL catabolism

Diamanti-Kandarakis, 1998; Ehrmann, 2006.

Hypertension in PCOS

- Particularly systolic hypertension
- ~50% lose physiological nocturnal dip
- Obesity and hyperandrogenism may play a role
- However, not all studies have reported an increased incidence of hypertension in PCOS women

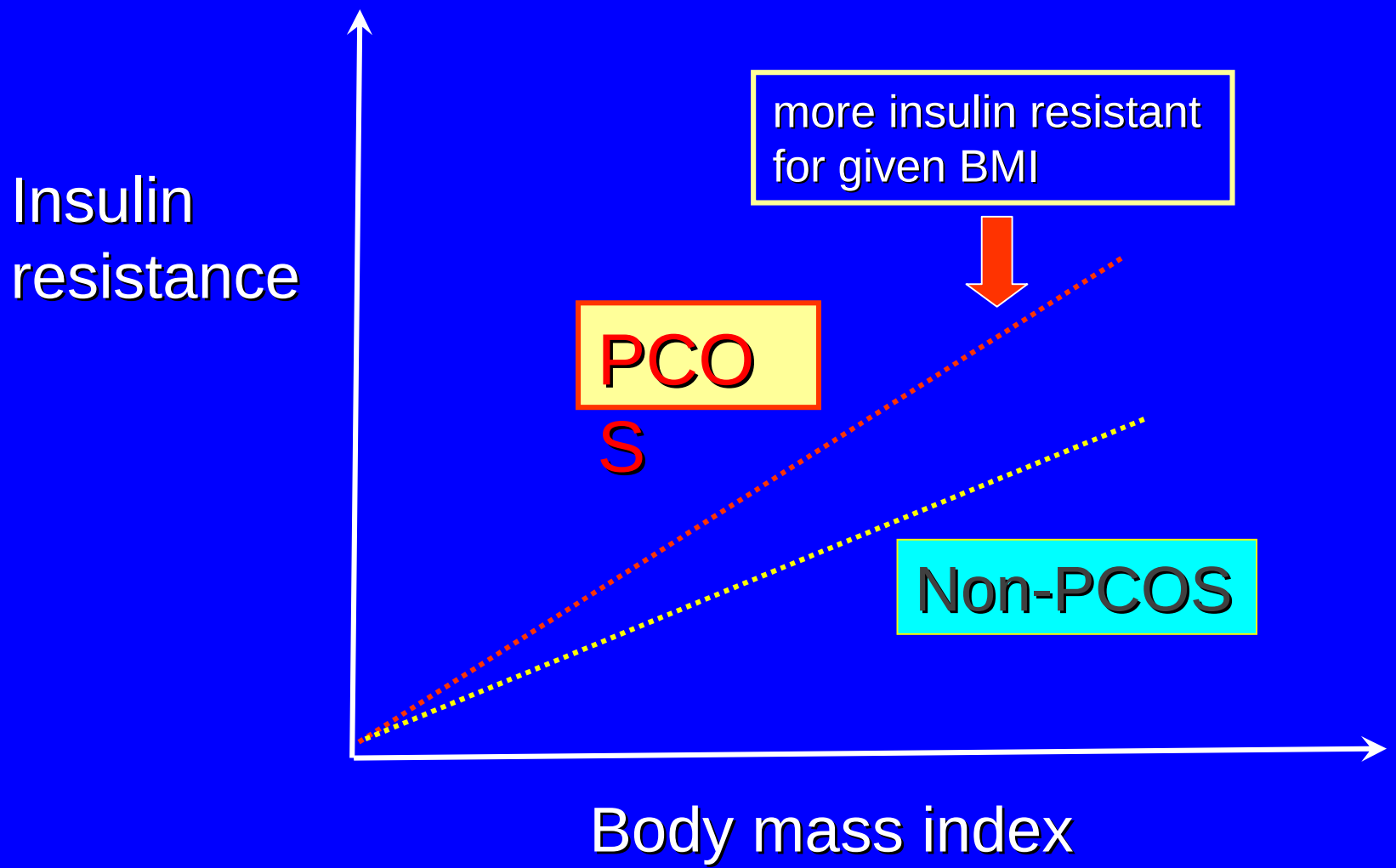
Holte, 1996; Wild, 2000; Orbetzova, 2003; Elting, 2001; Chen, 2007.

Diabetes / IGT - PCOS

- Increased prevalence of impaired glucose tolerance **(IGT : 30-40%)**
- Increased prevalence of type II diabetes mellitus **(7.5-10%)**
- Higher in certain ethnic groups

(Ehrmann 1999; Legro 1999)

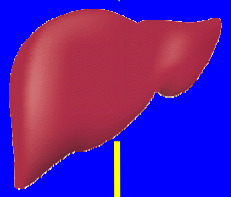
Insulin Resistance and PCOS



Insulin resistance in PCOS

Obesity
fat, muscle

IR → **↑insulin**



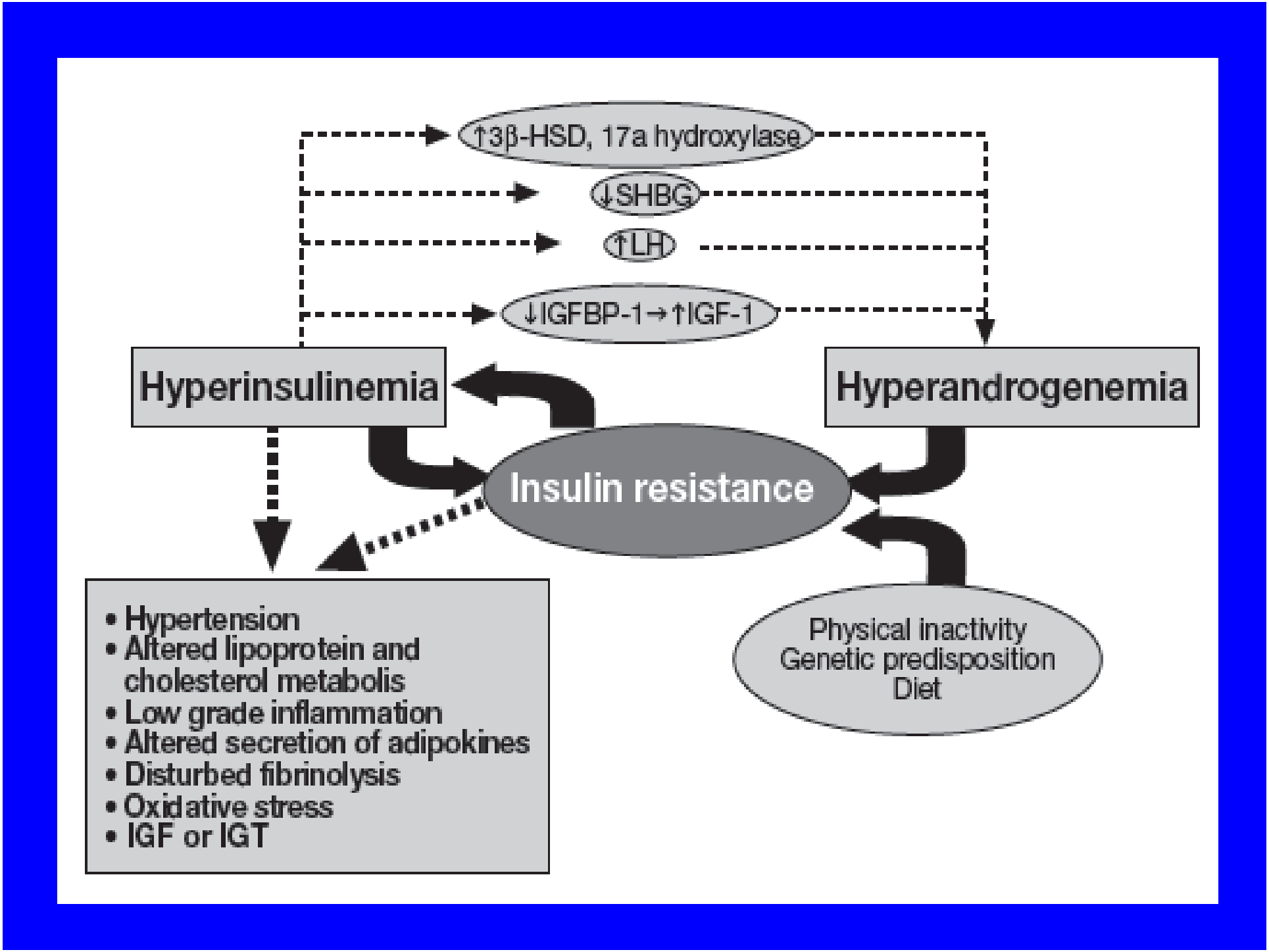
(ovary /adrenal insulin sensitive)

↓ SHBG

↑ androgen

↑ free testosterone

Oligo-ovulation
hirsutism


↑3β-HSD, 17a hydroxylase
↓SHBG
↑LH
↓IGFBP-1→↑IGF-1
Hyperinsulinemia
Hyperandrogenemia
Insulin resistance
• Hypertension
• Altered lipoprotein and cholesterol metabolis
• Low grade inflammation
• Altered secretion of adipokines
• Disturbed fibrinolysis
• Oxidative stress
• IGF or IGT
Physical inactivity
Genetic predisposition
Diet

Insulin Resistance & CV Risk Factors

Obesity is the greatest risk factor

Association Between Weight Gain and PCOS

- 50 - 75% of women with PCOS are moderately obese or overweight

- Obesity is usually the android type (50-60%)

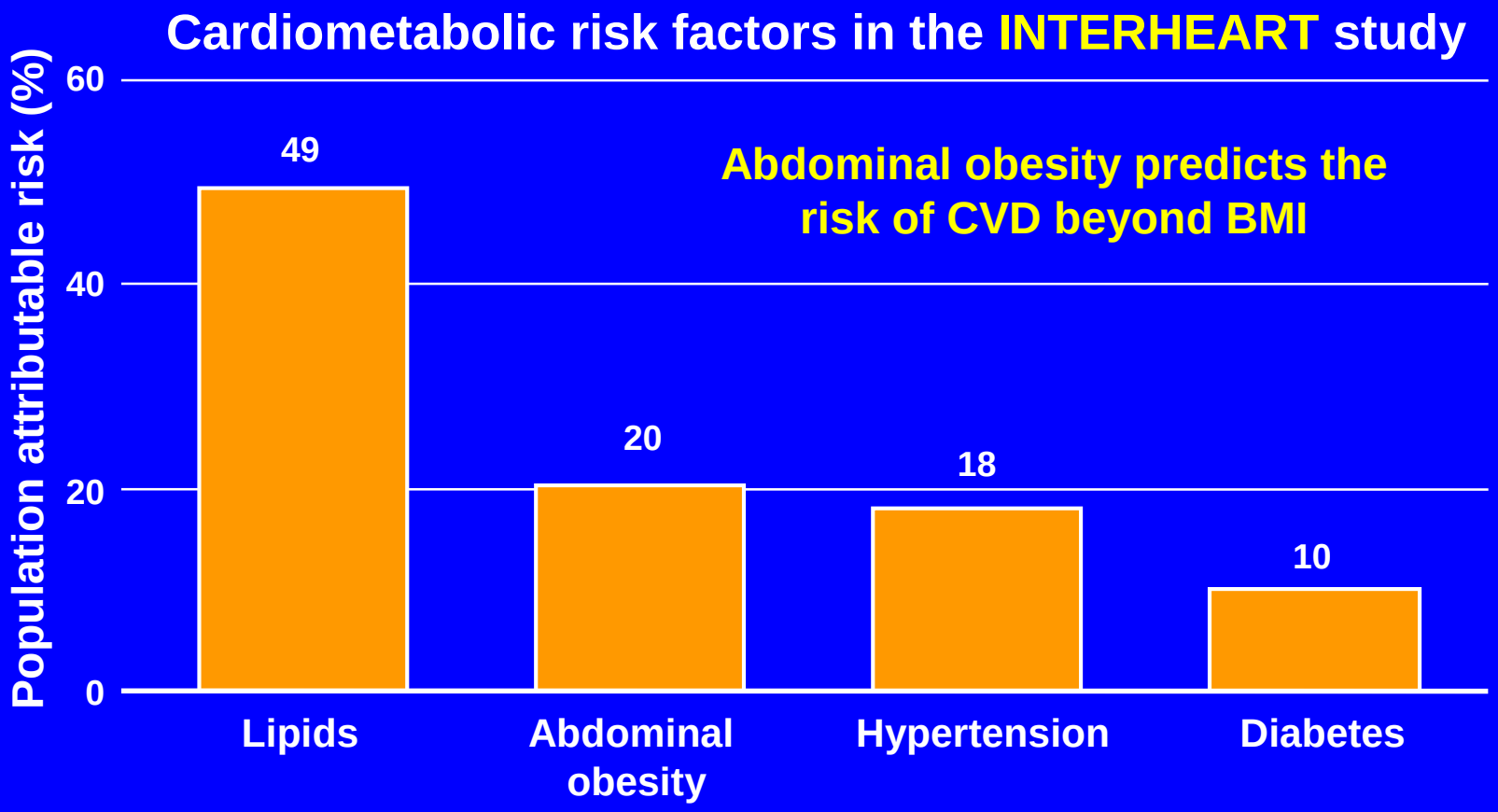
  - worsens insulin resistance and increases the risk for CVD and diabetes

- Weight loss improves symptoms, biochemistry

Evans, 1983; Hollman, 1996;
Ernst, 2002; Horejsi, 2004.

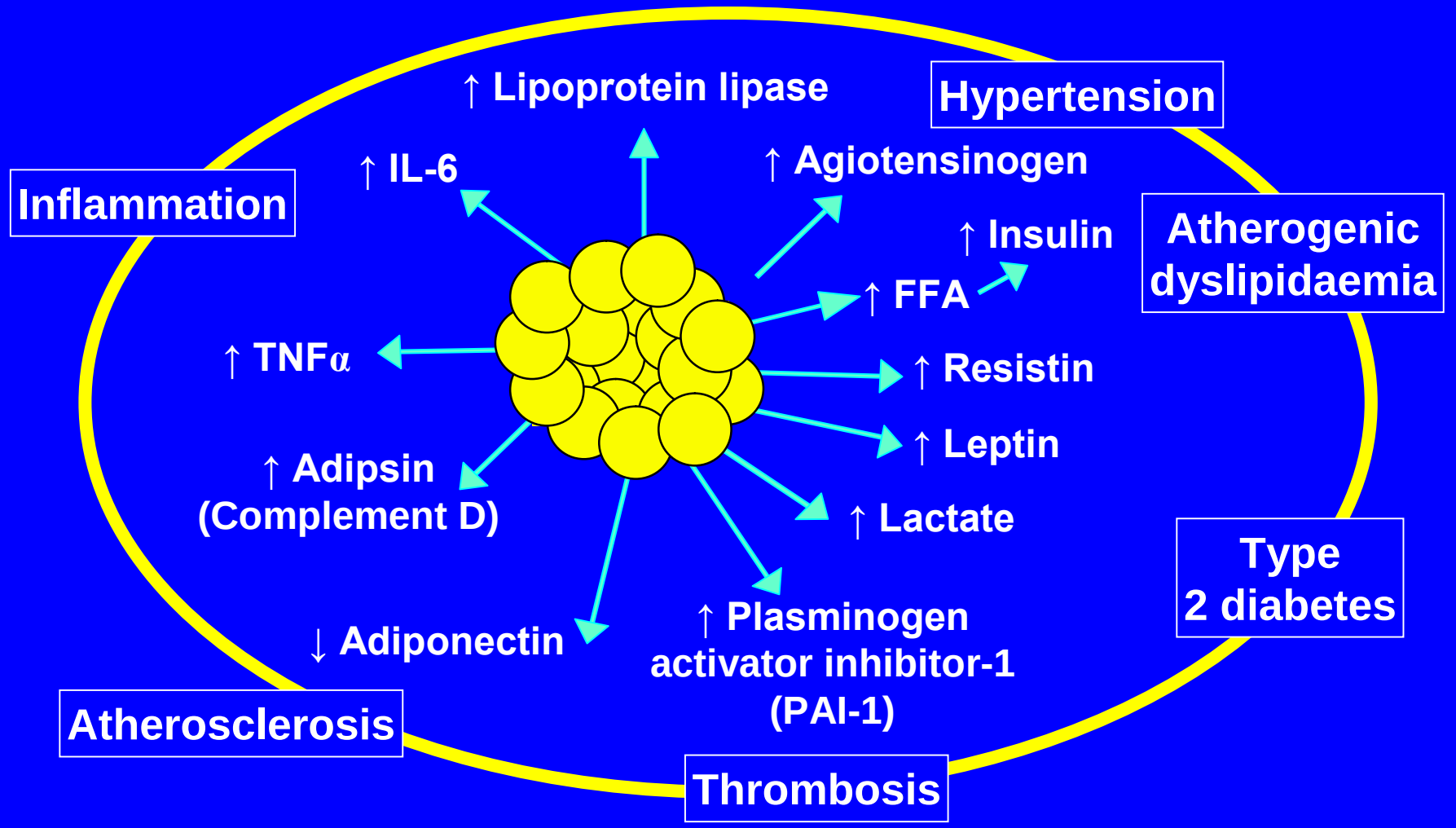
Is Obesity an Independent CV Risk Factor ?

Abdominal obesity: a major underlying cause of acute myocardial infarction (AMI)



Yusuf, *Lancet* 2004

Adverse Cardiometabolic effects of products of Adipocytes



Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

Non-Traditional CV Risk Factors in PCOS

SUBCLINICAL CVD

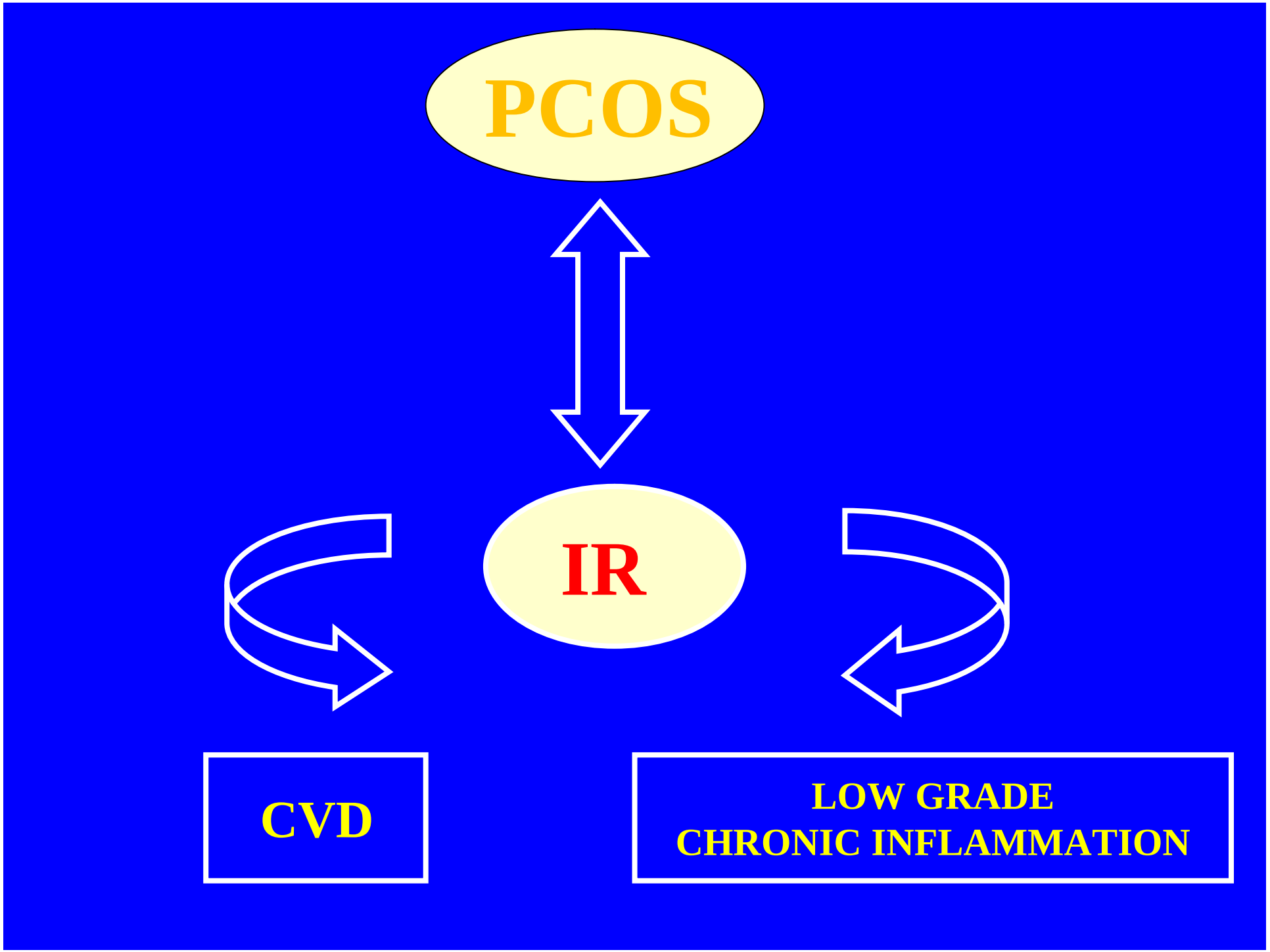
(e.g., ET-1, HCY, PAI-1, ADMA, ADHESION MOLECULES, etc..)

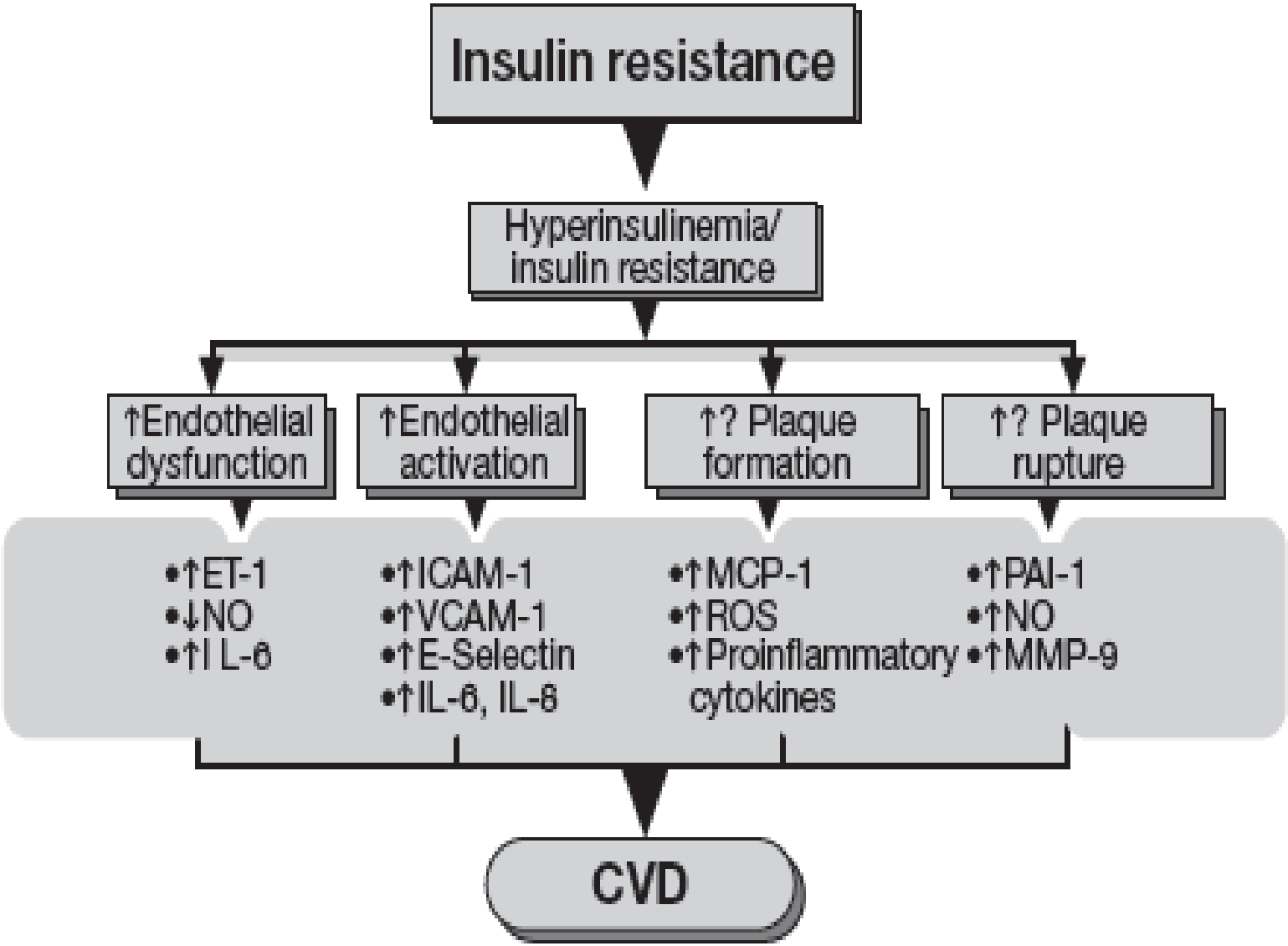
INFLAMMATION

(e.g., CRP, WBC, IL-6, IL-18, TNF-α, AGE, RAGE, ALDOSTERONE, etc..)

Atherogenic risk markers in PCOS

Abdominal obesity	↑ WHR, ↑ FFA, ↑ TNFα, ↑ resistin? ↓ adiponectin
Dyslipidaemia	↑ FFA, ↑ TG, ↑ small dense LDL ↓ HDL, ↓ large less-dense LDL
Inflammation	↑ C-reactive protein (CRP) ↑ Matrix metalloproteinase-9 (MMP-9)
Oxidative stress	↑ Oxidised LDLs and F2-isoprostanes
Endothelial dysfunction	↑ PAI-1, ↑ cellular adhesion molecules
Coagulation	↑ Fibrinogen, ↑ PAI-1, ↓ tPa
Hyperglycaemia	↑ AGEs, ↑ circulating AGE derivatives
Hyperinsulinaemia	↑ Plasma insulin (pre- and early diabetes)


PCOS
IR
CVD
LOW GRADE
CHRONIC INFLAMMATION


Insulin resistance
Hyperinsulinemia/ insulin resistance
↑Endothelial dysfunction
↑Endothelial activation
↑? Plaque formation
↑? Plaque rupture
•↑ET-1
•↓NO
•↑I L-6
•↑ICAM-1
•↑VCAM-1
•↑E-Selectin
•↑IL-6, IL-6
•↑MCP-1
•↑ROS
•↑Proinflammatory cytokines
•↑PAI-1
•↑NO
•↑MMP-9
CVD

PCOS – Metabolic Features

- Insulin resistance
- glucose intolerance / T2DM
- hyperinsulinaemia
- increased VLDL triglycerides
- decreased HDL cholesterol
- truncal obesity

Clustering of Metabolic Risk Factors

↓

METABOLIC SYNDROME

Metabolic Syndrome: Resulting Clinical Conditions

- Type 2 diabetes (RR – X5)
- Hypertension
- Polycystic ovary syndrome (PCOS)
- Nonalcoholic fatty liver disease
- Sleep apnoea
- Cardiovascular Disease (RR – X2)
- Cancer (e.g. Breast, Prostate, Colorectal)

What is the Prevalence of Metabolic Syndrome in PCOS?

Prevalence of Metabolic Syndrome in PCOS?

This depends on a number of factors, including age, BMI, ethnic groups….

but also the diagnostic criteria used for

- Metabolic syndrome (MS)
- PCOS

Metabolic Syndrome: Criteria for diagnosis?

- World Health Organization
- International Diabetes Federation (IDF) - European Association for the Study of Diabetes (EASD)
- National Cholesterol Education Project, Adult Treatment Panel (NCEP-ATP III)
- 5 Others !

Abdominal obesity: required for diagnosing the metabolic syndrome

High waist circumference (>88cm non-Asian;

+ >80cm East/South Asian)

Any two of :

- ↑ Triglycerides (≥ 1.7 mmol/L [150 mg/dL])
- ↓ HDL cholesterol‡
  - Men < 1.0 mmol/L (40 mg/dL)
  - Women < 1.3 mmol/L (50 mg/dL)
- ↑ Blood pressure ≥ 130 / ≥85 mm Hg
- ↑ FPG (≥ 5.6 mmol/L [100 mg/dL]), or diabetes

International Diabetes Federation (2005)

Prevalence of Metabolic Syndrome in PCOS?

Majority of studies have used the NIH and NCEP criteria

	Population	MS
Glueck (2003)	138	46%
Dokras (2005)	129	35% *vs* 4% controls (age adjusted)
Apridonidze (2005)	106	43%
Ehrmann (2006)	394	33%

Prevalence of Metabolic Syndrome in PCOS?

Wide range because of 6 different criteria for MS and 3 potential criteria for PCOS

Furthermore, the possible phenotypes exhibited depends on the criteria to diagnose PCOS are:

a) 1990 NIH 1
b) Rotterdam 4
c) AE-Society 3

COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AES 2006

	Phenotypes			
Characteristics	***A***	***B***	***C***	***D***
Hirsutism/HA	√	√	√	
Ovulatory dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH 1990		√		
Rotterdam 2003	√	√	√	√
AES 2006	√	√	√	

What is the association between the different criteria used to define PCOS and the clinical and biochemical 'phenotype' ?

Characterizing Discrete Subsets of Polycystic Ovary Syndrome as Defined by the Rotterdam Criteria: The Impact of Weight on Phenotype and Metabolic Features

J Clin Endocrinol Metab, December 2006

TABLE 1. Comparison of the PCOS phenotype in subjects with IM/HA, HA/PCOM, and IM/PCOM

	IM/HA (n = 305)	HA/PCOM (n = 77)	IM/PCOM (n = 36)	Control (n = 64)	*P* value, ANCOVA
Age (yr)	28.7 ± 5.6	29.6 ± 6.0	30.2 ± 6.8	30.8 ± 6.1	0.04
Height (m)	1.64 ± 0.07	1.66 ± 0.06	1.66 ± 0.07	1.66 ± 0.08	0.16
Weight (kg)	86.5 ± 24.2[a]	74.9 ± 19.8[b]	67.5 ± 13.5[b]	75.5 ± 22.0[b]	<0.001
BMI (kg/m^2)	32.0 ± 8.6[a]	27.0 ± 6.8[b]	24.7 ± 5.4[b]	27.3 ± 6.8[b]	<0.001
Waist circumference (cm)	100.0 ± 19.7[a]	88.0 ± 15.4[b]	82.2 ± 12.1[b]	87.7 ± 14.5[b]	<0.001
Hip circumference (cm)	112.0 ± 17.8[a]	104.4 ± 14.4[b]	99.7 ± 10.4[b]	104.3 ± 13.8[b]	<0.001
Waist/hip ratio	0.89 ± 0.08[a]	0.84 ± 0.07[b]	0.82 ± 0.07[b]	0.84 ± 0.06[b]	<0.001
SBP (mm Hg)	119.0 ± 13.1	114.7 ± 13.8	111.4 ± 11.2	119.4 ± 13.2	0.08
DBP (mm Hg)	75.3 ± 9.4	71.6 ± 9.8	71.9 ± 10.1	73.0 ± 7.7	0.4
FG Score	14.7 ± 9.1[a]	9.6 ± 6.1[b]	4.2 ± 2.4[c]	3.9 ± 2.0[c]	<0.001
No. with acne (%)	236 (80.3)	48 (66.7)	31 (88.6)	34 (57.6)	<0.001
No. with acanthosis (%)	191 (64.5)	23 (31.5)	15 (42.9)	13 (22.0)	<0.001

J Clin Endocrinol Metab, December 2006

IM – Irregular menses
HA – Hyperandrogenism
PCOM – PCO morphology

TABLE 3. Comparison of the metabolic parameters in PCOS subjects with IM/HA, HA/PCOM, and IM/PCOM

	IM/HA (n = 305)	HA/PCOM (n = 77)	IM/PCOM (n = 36)	Control (n = 64)	*P* value, ANCOVA
Glucose (mg/dl)	87.5 ± 11.7	85.4 ± 8.5	86.1 ± 8.5	86.5 ± 11.6	0.8
HbA1C	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.2	5.3 ± 0.3	1.0
Insulin (μIU/ml)	11.7 ± 10.7[a]	6.6 ± 3.8[b]	9.9 ± 17.6[a,b]	6.5 ± 4.0[b]	<0.02
HOMA	2.62 ± 2.68[a]	1.41 ± 0.90[b]	2.16 ± 3.77[a,b]	1.41 ± 1.00[b]	0.02
Cholesterol (mg/dl)	182.9 ± 34.8	179.4 ± 32.6	175.9 ± 37.0	183.2 ± 37.5	0.9
HDL (mg/dl)	48.8 ± 13.7	50.7 ± 11.9	57.6 ± 16.1	55.0 ± 15.8	0.08
Calculated LDL (mg/dl)	112.2 ± 31.1	110.3 ± 26.3	102.8 ± 29.4	108.1 ± 34.3	0.7
Triglycerides (mg/dl)	113.0 ± 103.8	92.2 ± 53.6	81.9 ± 48.5	100.0 ± 73.7	0.7
No. with IFG (%)	13 (4.5)	0 (0)	1 (2.9)	2 (3.2)	0.3
No. with type 2 diabetes mellitus (%)	1 (0.3)	0	0	1 (1.6)	0.5
Metabolic syndrome					
Total no. (%)	64 (22.2)	8 (10.5)	2 (5.6)	7 (11.1)	0.01
20–29 yr (%)	28 (17.3)	2 (5.7)	2 (15.4)	3 (11.5)	0.4
30–39 yr (%)	31 (29.5)	5 (16.7)	0 (0)	4 (11.4)	0.01
BMI > 30 kg/m^2					
20–29 yr (%)	24 (30.4)	1 (10.0)		2 (25.0)	0.4
30–39 yr (%)	26 (39.4)	4 (30.8)		4 (36.4)	0.8

Conclusions: Subjects with PCOS defined by IM/HA are the most severely affected women on the basis of androgen levels, ovarian volumes, and insulin levels. Their higher body mass index partially accounts for the increased insulin levels, suggesting that weight gain exacerbates the symptoms of PCOS. (***J Clin Endocrinol Metab*** **91: 4842–4848, 2006)**

Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome

Clinical Endocrinology (2007)

	PHO subgroup ($n = 191$)	PH subgroup ($n = 76$)	PO subgroup ($n = 42$)	One-way ANOVA P-value*	Control group ($n = 76$)
BMI (kg/m^2)	29·2 (22·3, 38·3)	23·7 (20·1, 28·0)	23·9 (20·0, 28·6)	< 0·0001	24·0 (19·9, 28·9)
Age§	32·9 (6·3)	34·8 (5·8)	32·1 (5·5)	0·04	36·9 (5·0)
Waist circumference (m)	0·89 (0·73, 1·09)	0·76 (0·68, 0·84)	0·77 (0·67, 0·87)	< 0·0001	0·78 (0·68, 0·89)
Metabolic Syndrome¶ (2005 IDF criteria)	56 (29·3%)	5 (6·6%)	3 (7·1%)	< 0·0001**	3 (3·9%)
LH (U/l)	7·3 (3·7, 14·4)	6·0 (3·8, 9·5)	5·9 (3·6, 9·7)	0·03	4·1 (2·5, 6·8)
FSH (U/l)	5·3 (3·6, 7·9)	6·4 (4·6, 8·9)	6·0 (4·0, 8·9)	0·001	5·9 (3·9, 8·9)
Testosterone (nmol/l)	2·46 (1·73, 3·47)	1·94 (1·35, 2·81)	1·59 (1·11, 2·32)	< 0·0001	1·42 (0·94, 2·18)
Androstenedione (nmol/l)	7·80 (5·27, 11·51)	5·79 (3·78, 8·88)	5·30 (3·50, 8·08)	< 0·0001	4·75 (3·09, 7·28)
SHBG (nmol/l)	33·0 (18·8, 58·1)	50·8 (31·4, 82·2)	51·9 (34·3, 78·6)	< 0·0001	60·6 (40·0, 91·7)
HOMA2-IR	0·61 (0·16, 2·35)	0·31 (0·08, 1·19)	0·24 (0·06, 0·95)	< 0·0001	0·31 (0·11, 0·82)
Fasting insulin (pmol/l)	28·1 (7·1, 111·5)	15·0 (3·9, 57·6)	11·4 (2·9, 44·5)	< 0·0001	9·9 (2·9, 34·2)
HDL cholesterol (mmol/l)	1·2 (0·9, 1·6)	1·3 (1·0, 1·7)	1·3 (1·0, 1·7)	0·005	1·4 (1·1, 1·7)
Triglycerides (mmol/l)	1·2 (0·7, 2·0)	0·8 (0·6, 1·3)	0·8 (0·5, 1·3)	< 0·0001	0·8 (0·5, 1·2)

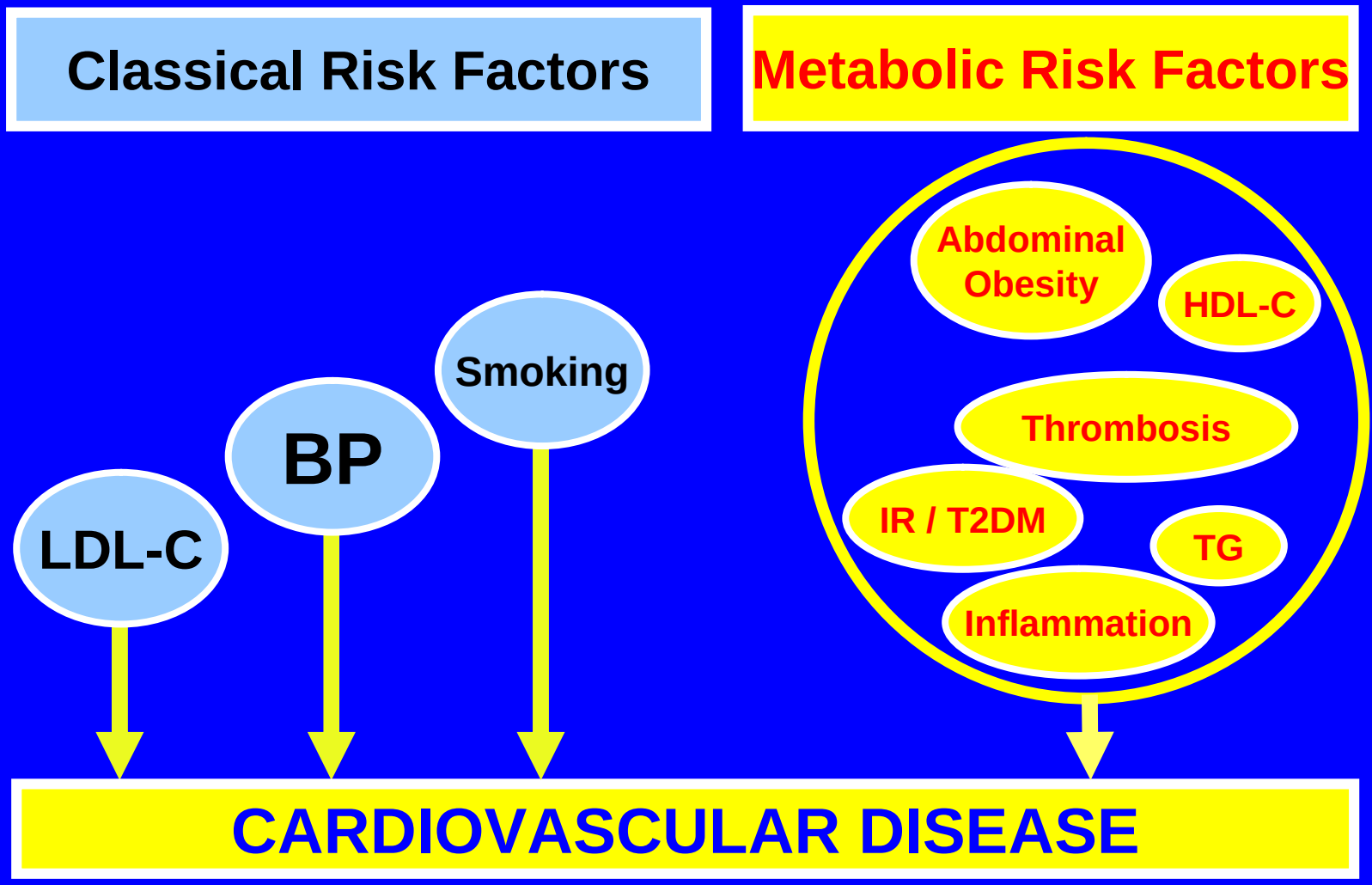
PHO, hyperandrogenaemic and oligomenorrhoeic

PH, hyperandrogenaemic with normal menses

PO, oligomenorrhoeic but normoandrogenaemic

Clinical Endocrinology (2007)

Traditional / Non-Traditional Risk Factors



CVD - PCOS

1) Do women with PCOS have more vascular disease / subclinical vascular disease?

2) Do these Cardio-metabolic Risk Factors Lead to an increase in CV Morbidity & Mortality ?

PCOS & Coronary Artery Disease (CAD)

Increased WHR and hirsutism associated with CAD in women undergoing coronary angiography

Wild RA, et al., Fert Steril: 1990

143 women (<60y), C. Angiography for chest pain

- 42% had PCO
- PCO women had more advanced CAD than women with normal ovaries

Birdsall MA et al., Ann Intern Med, 1997

Atherosclerosis in PCOS

Early studies reported association between hirsutism and significant coronary atheroma (Wild et al, 1985)

Intima-Media Thickness (IMT) – predictor of CVD

- PCOS women have increased carotid IMT (age/BMI matched) (Talbott, 2004)

Coronary artery and aortic calcification

- more in women with PCOS, as compared to matched controls (Talbott, 2004; Shroff, 2007)

Endothelial Dysfunction in PCOS

- Micro- and macro-vascular endothelial dysfunction
- Improvement in parameters of endothelial function following weight loss, and use of insulin sensitisers
- Impaired nitric oxide synthesis in endothelial cells

Kravariti, 2005;
Orio, 2005; Tarkun 2005

Cardiac Dysfunction in PCOS

- Diastolic dysfunction
- Decreased left ventricular ejection fraction
- Young PCOS women (age: ~25yrs) have increased LVMi
- Impaired cardiopulmonary functional capacity – improved by exercise

Prelevic, 1995; 1996; Yarali, 2001; Orio 2004; 2006; Vigorito, 2007.

CVD - PCOS

1) Do women with PCOS have more vascular disease / subclinical vascular disease? **YES**

2) Do these Cardio-metabolic Risk Factors Lead to an increase in CV Morbidity & Mortality ?

CVD - PCOS

“Mortality of Women with Polycystic Ovary Syndrome at Long-term Follow-up”

(Pierpoint T *et al*., J Clin Epid, 1998)

- A total of 786 women diagnosed with PCOS (UK) between 1930 and 1979

- traced from hospital records and followed for an average of 30 years

Conclusion: No increase in CV mortality

PREVALENCE OF CHD, SROKE, DM IN PCOS: A STUDY OF 319 WOMEN WITH PCOS AND 1060 AGE-MATCHED CONTROLS

Odds ratios (OR) and 95% confidence intervals (95% CI) for CHD, stroke/TIA, diabetes, hypertension and high cholesterol for PCOS before and after adjusting for BMI

Outcome	Model	OR	95% CI	*P*
CHD	PCOS	1·5	0·7–2·9	0·3
	PCOS, BMI	1·2	0·5–2·6	0·7
Cerebrovascular disease	PCOS	2·8	1·1–7·1	0·03
	PCOS, BMI	3·4	1·2–9·6	0·02
CHD and/or cerebrovascular disease	PCOS	1·9	1·1–3·3	0·03
	PCOS, BMI	1·7	0·9–3·2	0·09
Diabetes	PCOS	2·8	1·5–5·5	0·002
	PCOS, BMI	2·2	0·9–5·2	0·08
Hypertension	PCOS	1·4	1·0–2·0	0·04
	PCOS, BMI	1·4	0·9–2·0	0·1
High cholesterol	PCOS	2·9	1·6–5·2	<0·001
PCOS, BMI	3·2	1·7–6·0	<0·001	

Wild et al. Clinical Endocrinology 2000

CVD - PCOS

Nurses Health Study: Prospective Cohort study

~82,000 women

- women with irregular menses have an increase risk for non-fatal or fatal CHD (RR: 1.25 and 1.67)
- remained significant after accounting for variables (RR: 1.53)

(Solomon, 2002)

"Postmenopausal Women with a History of Irregular Menses and Elevated Androgen Measurements at High Risk for Worsening Cardiovascular Event-Free Survival:
Results from the National Institutes of Health National Heart, Lung, and Blood Institute Sponsored Women's Ischemia Syndrome Evaluation"

Shaw LJ, *JCEM*: 2008

CVD - PCOS

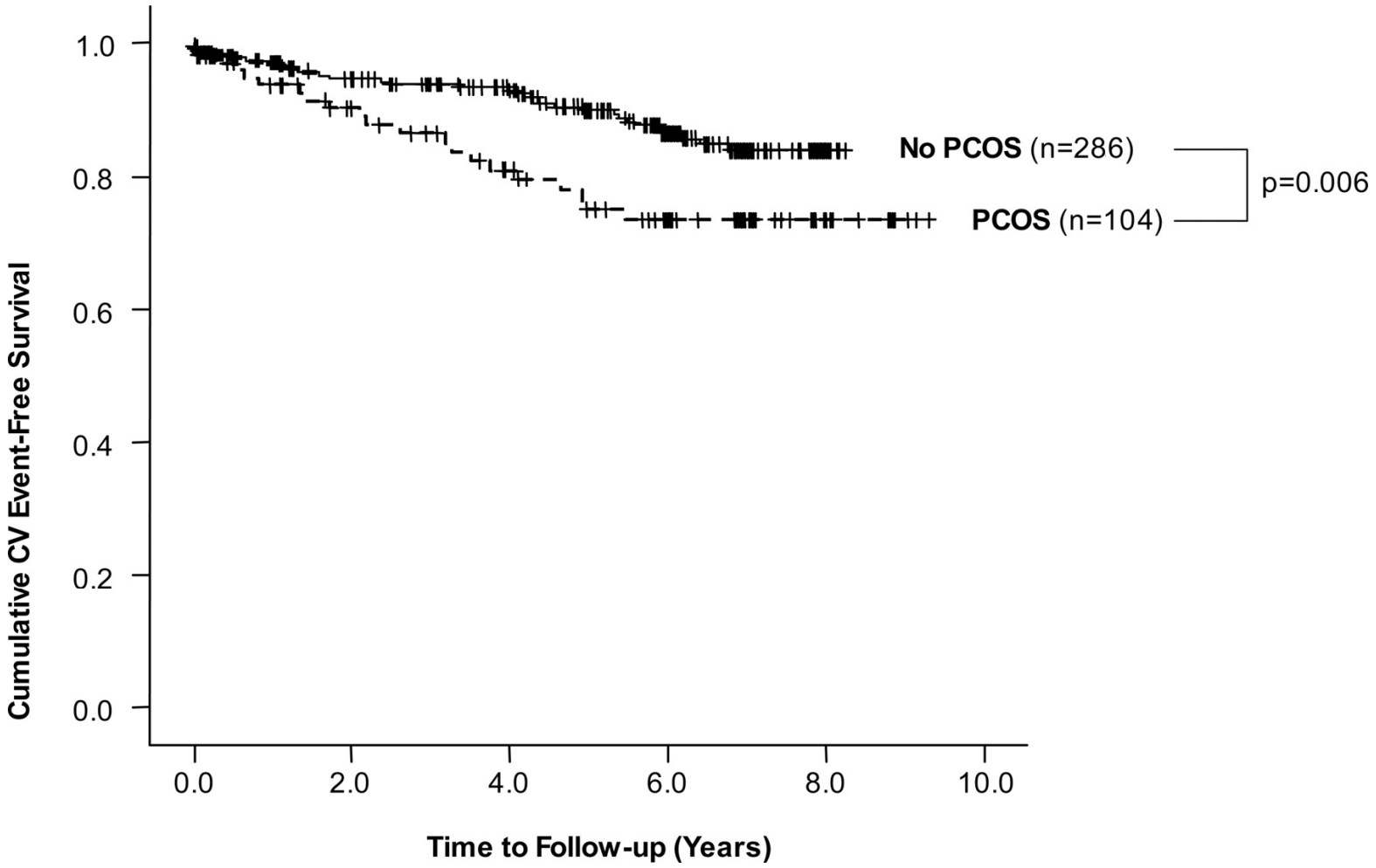
390 post-menopausal women enrolled

104 women had clinical features of PCOS:
- premenopausal history of irregular menses and
- current biochemical evidence of hyperandrogenemia

- Hyperandrogenemia was defined as the top quartile of androstenedione (> or = 701 pg/ml), testosterone (> or = 30.9 ng/dl), or free testosterone (> or = 4.5 pg/ml).

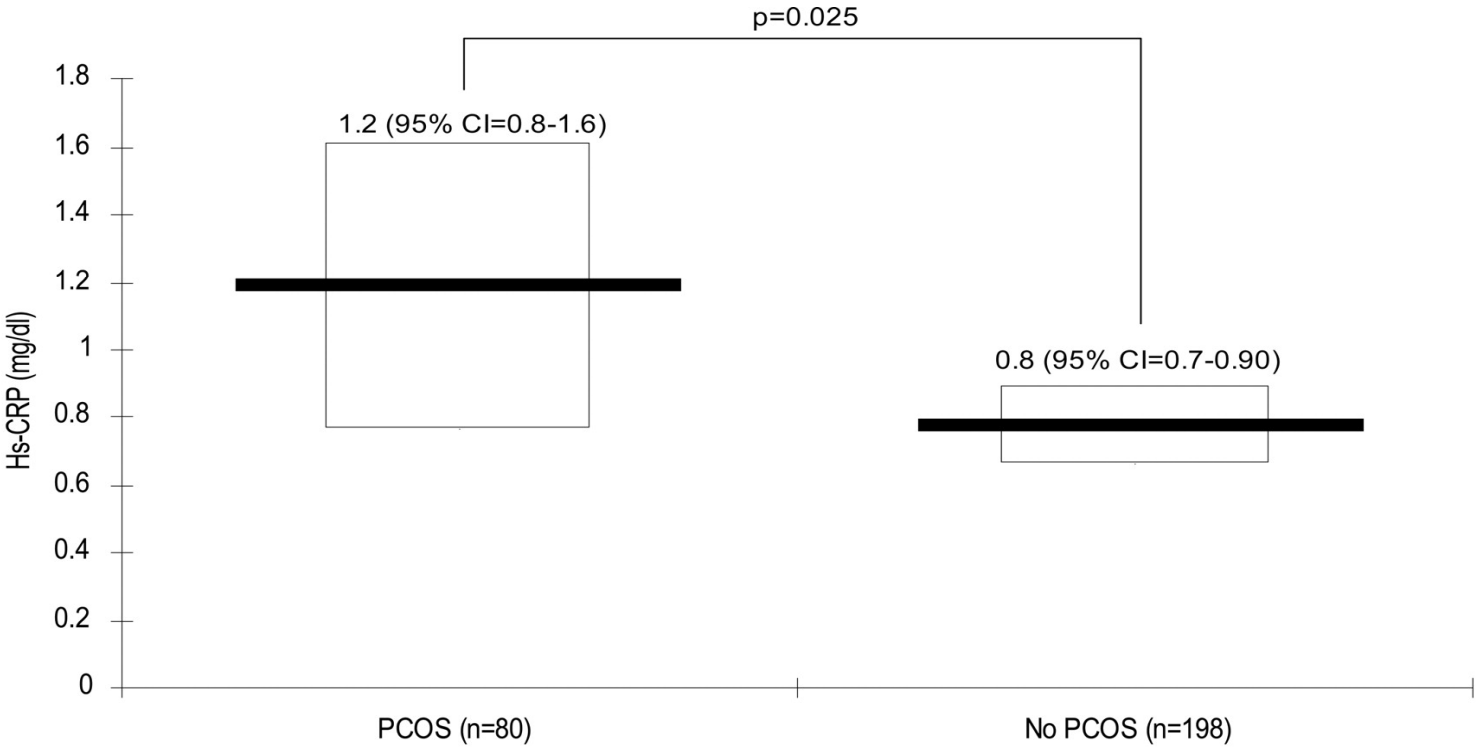
Shaw LJ, *JCEM*: 2008

CUMULATIVE UNADJUSTED CV DEATH OR MI FREE SURVIVAL IN POSTMENOPAUSAL WOMEN



Shaw et al. J Clin Endocrinol Metab 2008

AVERAGE C-REACTIVE PROTEIN (HS-CRP) VALUES FOR POSTMENOPAUSAL WOMEN WITH AND WITHOUT CLINICAL FEATURES OF PCOS



*p value was calculated using a general linear model controlling for statin use, LDL cholesterol, hypertension, metabolic syndrome, history of smoking, and angiographic coronary artery disease severity.

Shaw et al. J Clin Endocrinol Metab 2008

CVD - PCOS

Paucity of data (n=8), particularly prospective studies (n=2); 4 used Rotterdam and/or NIH criteria

Most studies are:
- cross-sectional with small numbers,
- conducted in young subjects, where in CVD would not be expected

“Label of PCOS lost”

Need to take into account ethnic factors..

Assessing CV Risk

Risk:

Obese ? BMI

Smokers

Hypertension

Atherogenic dysplipidaemia

IGT

FH of premature CVD (<55yr M, <65yr F relative)

High Risk:

T2DM

Metabolic Syndrome

Overt vascular disease

Assessing CV Risk

AES recommendations:

- Waist circumference / BMI – each visit
- Lipid profile

LDL <130mg/dl (3.37 mmol/L)

High Risk <70-100mg/dl (1.81 – 2.59mmol/L)

- BP <120/80 mm/Hg
- OGTT
  - BMI >30
  - Lean PCOS with FH of T2DM, >40yr, GDM

Prevention of CVD in PCOS

Lifestyle modification

exercise, diet, cessation of smoking etc..

Pharmacological

- Metformin
- Thiazolidinediones
- Lipid lowering therapies
- Antihypertensives
- Antiobesity agents

Bariatric surgery (BMI >40, when weight loss strategies have failed)

Summary: CV Implications of PCOS

PCOS associated with clustering of traditional and non-traditional cardiometabolic risk factors

Increased prevalence of insulin resistance, IGT, DM

Data on CV mortality inconclusive, but suggestive

Further prospective, multi-centre studies applying a strict and uniform PCOS diagnostic criteria

Thank you

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