CME through slides

Insulin Resistance Syndrome

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Journal of the Ceylon College of Physicians, 2003, **36**, 72-81

This lecture on Insulin Resistance Syndrome was delivered at a Diabetic Symposium at the SLMA in March '04. Dr. Rajaratnam agreed to this publication and slides were suitably modified and Abbreviations and References as were added

Abbreviations

ACEI	-	Angiotensin converting enzyme inhibitor
ARB	-	Angiotensin Receptor Blocker
BMI	-	Body mass index
CHO	-	Carbohydrates
CRP	-	C reactive protein
CVD	-	Cardiovascular disease
DM	-	Diabetes mellitus
FFA	-	Free fatty acid
FI	-	Fasting insulin
FPG	-	Fasting Plasma glucose
75GG	-	75 grams of glucose
HT	-	Hypertension
ICAM - 1	-	Intercellular adhesion molecule - 1
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
IMT	-	Intima Medial thickness
IR	-	Insulin resistance
IRS	-	Insulin resistance syndrome
LP(a)	-	Lipoprotein (a)
MCP - 1	-	Monocyte chemo attraction Protein - 1
MMP	-	Matrix Metalloproteinase
MNC	-	Mono nuclear cell
NAFLO	-	Non alcoholic fatty liver disease
NGT	-	Normal glucose tolerance
P CAM	-	Polymorph nuclear cell adhesion molecule
PAI - 1	-	Plasminogen activator inhibitor
PCOS	-	Polycystic ovarian syndrome
PP	-	Post prandial
PPAR	-	Peroxisome proliferating activator receptor
PUA	-	Plasma uric acid
SNS	-	Sympathetic nervous system
SUA	-	Serum uric acid
UA	-	Uric acid
V CAM	-	Vascular cell adhesion molecule - 1
WC	-	Waist circumstance
WHO	-	World health organaisation

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INSULIN RESISTANCE SYNDROME

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WHAT IS IRS?

1. Decreased sensitivity to action of insulin
2. Compensatory increase in insulin secretion
3. Cluster of abnormalities viz CVD, DM,PCOS,NAFLD & others

2

CLINICAL IMPACT OF IRS

1. 25% of american adults
2. Some → type 2 DM
3. Increased risk for CVD
4. 90% of type 2 dm have IR
5. 10% of women have PCOS
6. Epidemic of obesity in children & adolescents

3

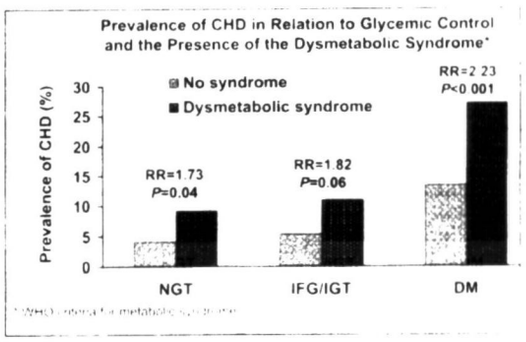

Fig. 2. Insulin resistance (metabolic) syndrome as a risk factor for coronary artery disease. (From Isomaa et al. *Diabetes Care* 2001;24:683.)

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WHO IS AT RISK FOR IRS? - 1

1. Overweight – BMI >25 OR WC>40" IN MEN / 35" IN WOMEN (10 – 15% LOWER IN ASIANS)
2. Sedentary lifestyle
3. Age > 40 years
4. Non caucasian ethnicity (asians)

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CONTINUED...

WHO IS AT RISK FOR IRS? - 2

5. F/H . type 2 DM, HT or CVD
6. H/O glucose intolerance or GD
7. Acanthosis nigricans
8. PCOS
9. NAFLD

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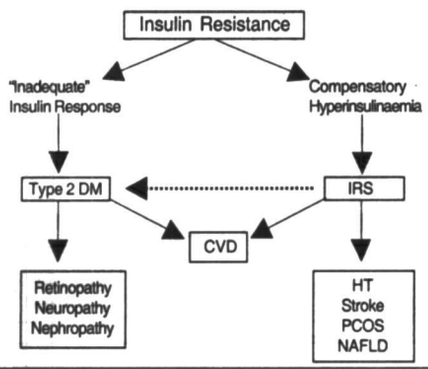
IRS & TYPE 2 DM ARE THEY DIFFERENT ? - 1



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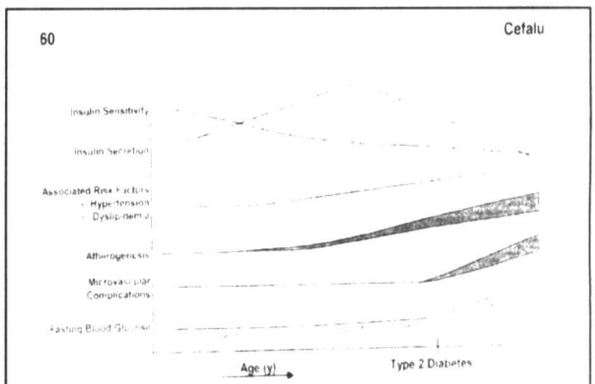

Fig. 2 [illegible] metabolic observations in the natural history of type [illegible]

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IRS & TYPE 2 DM ARE THEY DIFFERENT ? - 2

1. Majority with IR do not become frankly diabetic

   But remain with increased risk for macro vascular disease

2. All diabetics are not IR but increased risk for micro vascular disease

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IRS & TYPE 2 DM ARE THEY DIFFERENT ? - 3

3. IR present many years before onset of DM
4. Detected by IGT on 75 gg
5. Present in offspring of diabetics at a young age
6. IFG denotes beta cell dysfunction
7. CV RISK > 135 mg/dl on 75 gg

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What are the actions of Insulin?

- Metabolic-CHO,Lipid,Proteins
- Mitogenic-growth, differentiation, DNA Synthesis
- Insulin's ability to stimulate glucose uptake
- IRS – Includes glucose, lipid, protein, endothelial and gene functions

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Diseases associated with Insulin Resistance

- Lipoatrophic diabetes
- Leprechaunism
- Rabson-Mendenhall syndrome
- Type 1 DM in obese
- Cushing's disease
- Phaeochromocytoma
- Acromegaly

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Diseases with IR Cont.

- Cirrhosis
- Down's syndrome
- Turner's syndrome
- Klinefelter's syndrome
- Muscular dystrophy
- Friedreich's ataxia
- Laurence Moon Biedl syndrome

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IDIAGNOSIS OF IRS based on

(a) Risk factors

+

(b) 2 or more Metabolic abnormalities

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Diagnosis of IR

(a) Acanthosis and skin tags
(b) Euglycaemic clamp method
(c) Elevated FI > 30miu/ml
(d) FG (mg/dl) / FI (miu/ml) < 4.5
(e) Insulin levels after OGTT-
Fasting > 30miu/ml
One hr > 150 miu/ml
Two hr > 90 miu/ml

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METABOLIC ABNORMALITIES

1. **Plasma Glucose**
   FASTING 110 - 125 mg/dl
   120 MT 75 G G 140 - 200mg/dl
2. **Triglyceride** >150mg/dl
3. **HDLC**
   MEN <40mg/dl
   WOMEN <50mg/dl
4. **Blood Pressure** >130/85mmHg

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COMPONENTS OF IRS - 1

1. SOME DEGREE OF GLUCOSE INTOLERANCE
   - IFG
   - IGT (More sensitive)
2. ABNORMAL URIC ACID METABOLISM
   - Increased PUA (Not very sensitive)
   - Normal level does not exclude IRS
   - Reduced Renal clearance of UA

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CONTINUED...

COMPONENTS OF IRS - 2

3. DYSLIPIDAEMIA

- TG
- HDLC
- LDL C DIAMETER (SMALL DENSE LDL)
- PP TG RICH LIPOPROTEINS

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CONTINUED...

COMPONENTS OF IRS - 3

4. HAEMODYNAMIC CHANGES
   - SNS Activity
   - Renal Sodium Retention
   - BP (50% have IR)

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CONTINUED...

COMPONENTS OF IRS - 4

5. PROTHROMBOTIC FACTORS & ANTI INFLAMMATORY MARKERS
   - PAI-1
   - FIBRINOGEN
   - CRP
   - LEUCOCYTOSIS
   - ICAM – 1 & VCAM – 1
   - MCP-1
   - MMP (DISSOLVES COLLAGEN & MATRIX)

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CONTINUED...

COMPONENTS OF IRS

6. ENDOTHELIAL DYSFUNCTION
   - ↑ MNC Adhesion
   - ↑ P – CAM
   - ↑ P – Asymmetric Dimethyl Arginine (Inhibitor of NOS)
   - ↑ Endothelium – Dependent Vasodilation

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IRS – IS IT GENETIC ?

With parent number

Non-diabetic offspring of biparental

Low birth weight

Mother smoking

Bottle feeding ?

IR gene mutations

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IRS IN ASIANS

- Insulin levels
- Intra abdominal fat (CAD > 10 year followup in men With highest quartile of Visceral obesity)
- IMT with high prevalence of CVD
- Lp(a)
- P Homocysteine
- PAI – 1
- Fibrinogen
- Crp

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Clinical Characteristics

	Asian Indians	*Caucasians*	*P*
AGE (years)	34 ± 3	35 ± 4	NS
Body mass Index (KG/M²)	23.6 ± 0.5	24 ± 1.2	NS
Waist Hip Ratio	0.79 ± 0.02	0.75 ± 0.01	NS
Fat Free Mass (%)	71 ± 3	74 ± 2	NS
Total fat (cm³)	296 ± 40	203 ± 18	0.04
Visceral fat (cm³)	82 ± 20	39 ± 5	0.04
Subcutaneous fat	231 ± 36	195 ± 20	NS

Fig. 4. Markers of insulin resistance in young, "healthy" Asian Indian men. *NS* = no significant difference. (From Raji A et al. *Diabetes*. 2000;50[Suppl 2]:A314.)

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IRS & OBESITY - 1

- Obesity associated with T2DM, CAD & DLA
- Distribution of fat – Truncal or Central vs Gynaeoid
- Visceral > SC

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IRS & OBESITY - 2

- 70% with lowest IR (1st tertile) have normal body mass
- 80% in top tertile of ir are overweight or obese
- 18% in top tertile have normal body mass

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IRS & OBESITY - 3

- Exogenous insulin increases BMI
- Hyperinsulinaemia (endogenous) weight gain ?
- CV risk - IR + Obese > I.S + Obese

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IRS & OBESITY- 4 WHY VISCERAL?

1. ↑11 BETA HSD TYPE – 1 (CORTISOL)
2. ↑ ANGIOTENSINOGEN
3. ↑ DIASTOLIC BP
4. ↑ FPG & 75 GG
5. ↑HT

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IRS and NAFLD - 1

- Synonym – NASH
- Fat in liver cells + inflam cells + Fibrosis
- Commonest cause of elevated isolated liver enzyme (84%)
- Cryptogenic cirrhosis
- Mortality > Hep C cirrhosis

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IRS and NAFLD - 2

- ↑ TG & SUA
- ↓ HDLC (irrespective of BMI)
- Glucose disposal 50% of normal (= DM)
- ↑ Basal FFA
- ↓ Lipolysis suppression with insulin
- ↑ Iron over load

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IRS and NAFLD 3

- HGO not suppressed inspite of hyper I
- ↓ AST, ALT, FI, SUA and TG by weight loss (Increases HDLC)
- PFFA less decreased by insulin
- ↓ Visceral adiposity
- Wt loss, gastroplasty, metformin, glitazones decrease liver enz (no histo improvement)

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IRS & Gestation DM - 1

- ↓ IR
  1. Energy for baby
  2. ↑^{d}FBG &↑ ^{d}FFA
  3. ↑ Maternal Insulin

  12 – 14 weeks – IRI^{s}

  14 – 40 weeks – IRI^{s}

  3rd Trimester - GDM

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IRS & GDM - 2

Causes

1. ↓ Phosphorilation β – Sub Unit of InsR
2. ↑ Phosphorilation of IRS
3. Placental, Lactogen, GH, Progesterone, Cortisol ,PRL

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IRS & GDM - 3

4. ↑FFA
5. ↓PPAR γ Receptor activity
6. ↑TMF α
7. ↑Resistin from Placenta

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Emerging concepts in Management - 1

- Non Glycaemic Targets
  a) Ramipril 10mg/ D < DM 34% over 5 years (HOPE)
  b) Losartan < DM 25% (LIFE)
  c) Pravastatin < DM 30% (WOSCOPS)

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Emerging concepts in Management - 2

- Coagulation Factors
- ↓ PAI – 1 Rosiglit, Metformin, ACEI, ARBs
- ↓ Plasma Fibrinogen – Fenofibrate
- ↓ Platelet aggregation – Aspirin, Clopidogrel, Metformin

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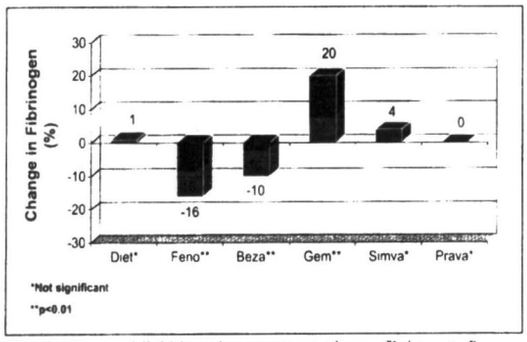

Fig. 6. Effects of lipid-lowering agents on plasma fibrinogen. *Beza* = bezafibrate; *Feno* = fenofibrate; *Gem* = gemfibrozil; *Prava* = pravastatin; *Simva* = simvastatin. (From Branchi A et al. *Thromb Haemost.* 1993;70:241-243.)

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Emerging concepts in Management - 3

- ↓ **Fasting Insulin**
  - Metformin
  - Rosi & Pioglit
  - Atorva, Simva and Prava
  - ACEI, ARBs

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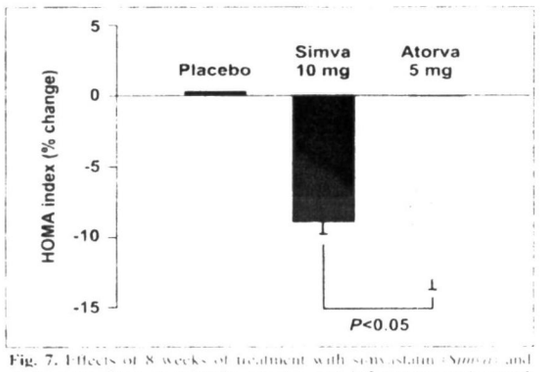

Fig. 7. Effects of 8 weeks of treatment with simvastatin (*Simva*) and atorvastatin (*Atorva*) on insulin resistance in 195 patients with type 2 diabetes. *HOMA* = homeostasis model assessment. (From Paolisso G et al. *Atherosclerosis.* 2000;150:121-127.)

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Emerging concepts in Management - 4

- **Inflamatory Factors**
  - CRP – Rosiglit
    Pravastat
    ARBs

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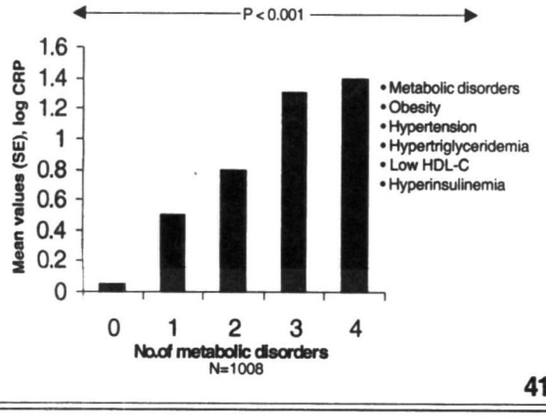

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Emerging concepts in Management - 5

- **Obesity**
  - Lifestyle modification
  - Drugs
    - Sibutramine
    - Orlistat
  - (TC decreased and HDLC increased)

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Emerging concepts in Management - 6

- **Dyslipidaemia**
  - Fenofibrate
  - < TG, TG/HDL, Fibrinogen,
  - Small dense LDL/Large buoyant LDL

Fenofibrate + Statins safe and efficacious
< LDLC , TG and > HDLC

Target TG < 150mg/dl
LDL < 100mg/dl

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Emerging concepts in Management - 7

- **Hypertension**
- Target 130/85
  130/80 if diabetic

ACEI and ARBs – Decrease IR also

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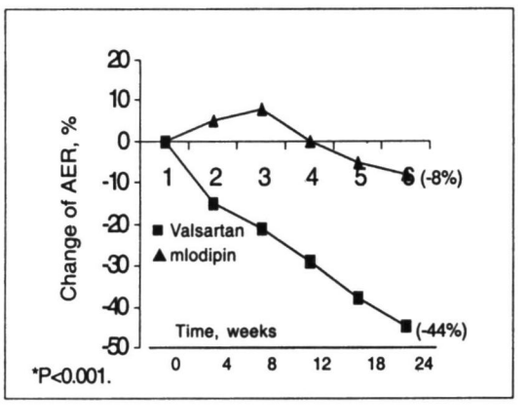

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Emerging concepts in Management - 8

- **Glucose intolerance**
  - Lifestyle modification (Finland - 58%)
  - Metformin 850mg bd (DPP – 30%)
  - Acarbose (STOP – NIDDM – 25%)
  - Troglitazone (TRIPOD – 56%)

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Emerging concepts in Management - 9

- **Endothelial Factors**
  - Microalbuminuria – ACEI, Valsartan, Rosiglit
  - Vasodilatation – ACEI , ARB and statins
    (Alone or incombination – additive)

Endothelial function – Metformin and Glitazones
IMT – Pioglit in type 2 DN
Vascular smooth muscle migration – Gliterzones
Arteriographic regression in CAD – Fenofibrate
(DAIS)

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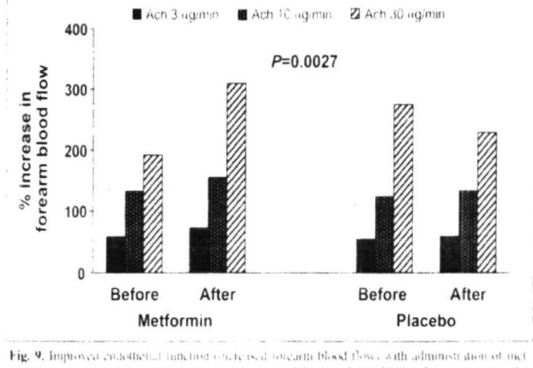

Fig. 9. Improved endothelial function [illegible] forearm blood flow with administration of metformin in patients with type 2 diabetes [illegible] acetylcholine. (From: Mather KJ et al. J Am Coll Cardiol. 2001;37:1344-1350.)

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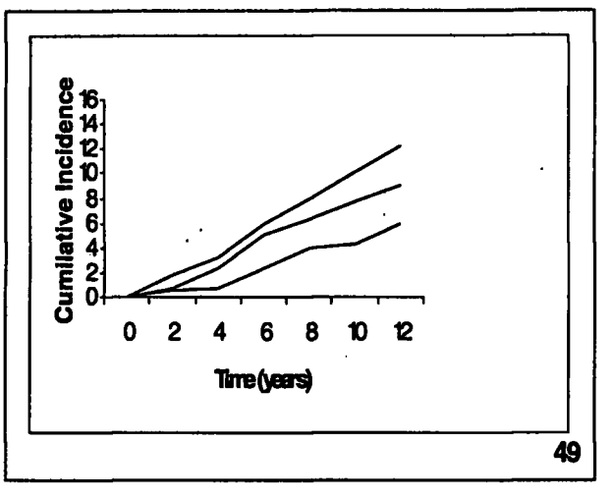

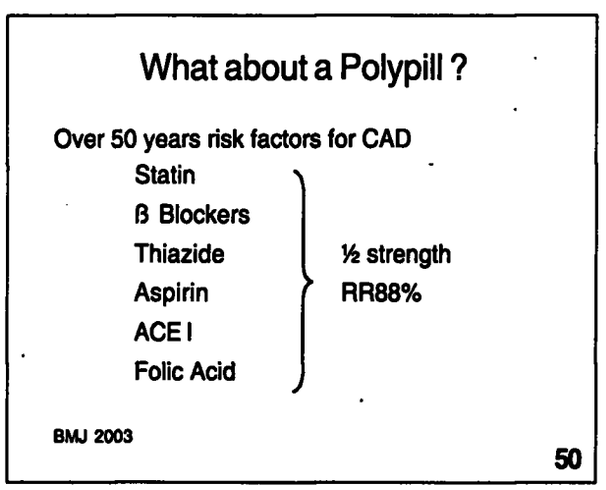

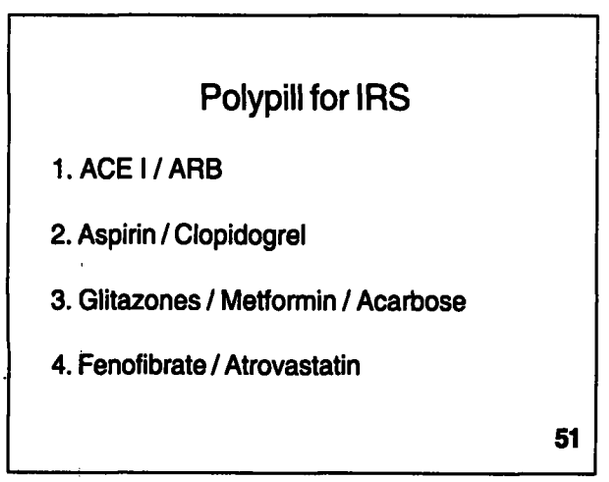

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Slide number, topic and reference given in that order

2 – What is IRS?
Einhorn D. *Endocrine Practice* 2003 Sept/Oct; 9 (Suppl 2): 6.

3 – Clinical impact of IRS.
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5 – Who is at risk for IRS?
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6 – Metabolic Abnormalities.
Endocrine Practice 2003 Sept/Oct; 9 (Suppl 2): 7.

10 – IRS and Type 2 DM Are they different?
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13 – Diseases with IRS.
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19 – Components of IRS.
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24 – IRS and Obesity.
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25 – IRS and Obesity – Why Visceral?
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