FunDia

Diabetes made fun

The DHOL

The drums of diabetes are beating

- D diabetes
- H hypertension
- O obesity
- L lipidemia

Definition

a disease in which
the body’s ability to produce or respond
to the hormone insulin is impaired,
resulting in abnormal metabolism of carbohydrates
and elevated levels of glucose in the blood.

ADA

A complex chronic illness

Requiring continuous medical care

With multifactorial risk reduction strategies

Beyond glycemic control

Diagnosis

- Fasting glucose
- 2 hour plasma glucose: post load or post challenge
- A1C
- Random plasma glucose + symptoms

- Max diagnosis is with 2 h PG; least with A1C
- Repeat test if symptoms are absent
- Max variation with 2 h PG, minimum with A1C

Doing an OGTT

- Equivalent of 75 g of anhydrous glucose

When to Suspect that a Patient with Diabetes Has a Hemoglobinopathy

- an A1C result is different than expected
- an A1C result is above 15%
- results of self-monitoring of blood glucose have a low correlation with A1C results
- a patient’s A1C result is radically different from a previous A1C result following a change in laboratory A1C methods

False A1C

- Falsely low A1C result can occur in
- anemia
- heavy bleeding

- Falsely elevated A1C result can occur in
- iron deficiency anemia

Classification

- Type 1
  - Autoimmune
  - Idiopathic
- Type 2
  - Prediabetes
    - IFG
    - IGT
- GDM
- Others

Other non type 2 DM

- Monogenic diabetes
  - Neonatal diabetes
  - MODY - Maturity onset diabetes of the young
- Cystic fibrosis related diabetes
- Corticosteroid induced diabetes
- Pancreatic diabetes
- Type 1.5 diabetes
- Type 3 diabetes
- LADA - Latent autoimmune diabetes of adults

D/D of type 2 diabetes

Targets of therapy

Targets of therapy

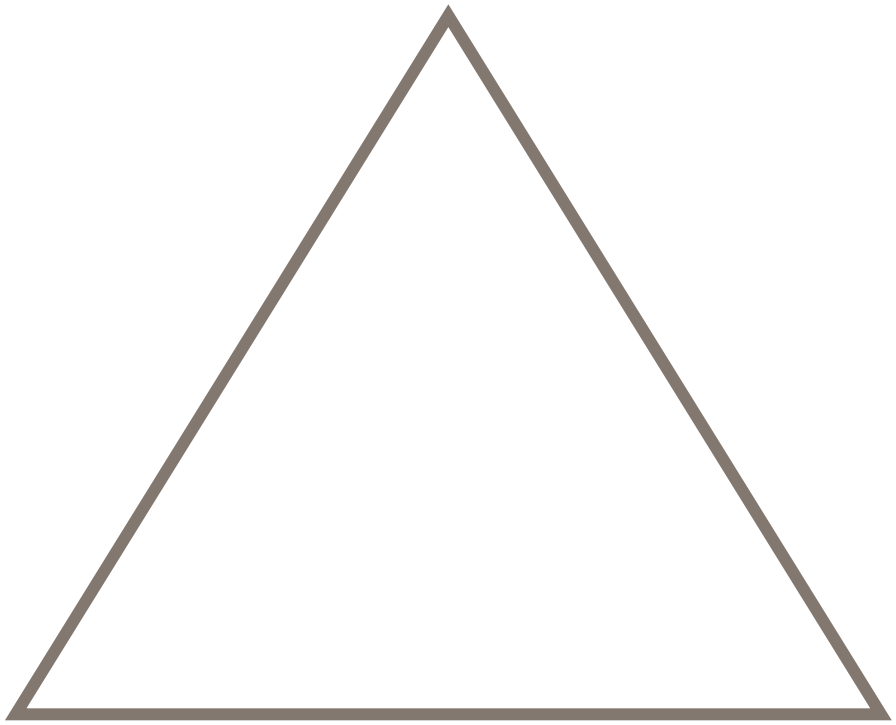
- A1C
- Premeal glucose
- Postmeal glucose

- Others??

Monitoring

- A1C
- GLUCOSE
  - Frequency
  - By whom?
  - What time?
- Flash, CGMS

‘Glycaemic triad’ of diabetes management



THE THERAPUTIC PENTAD AND PENTUPLETS

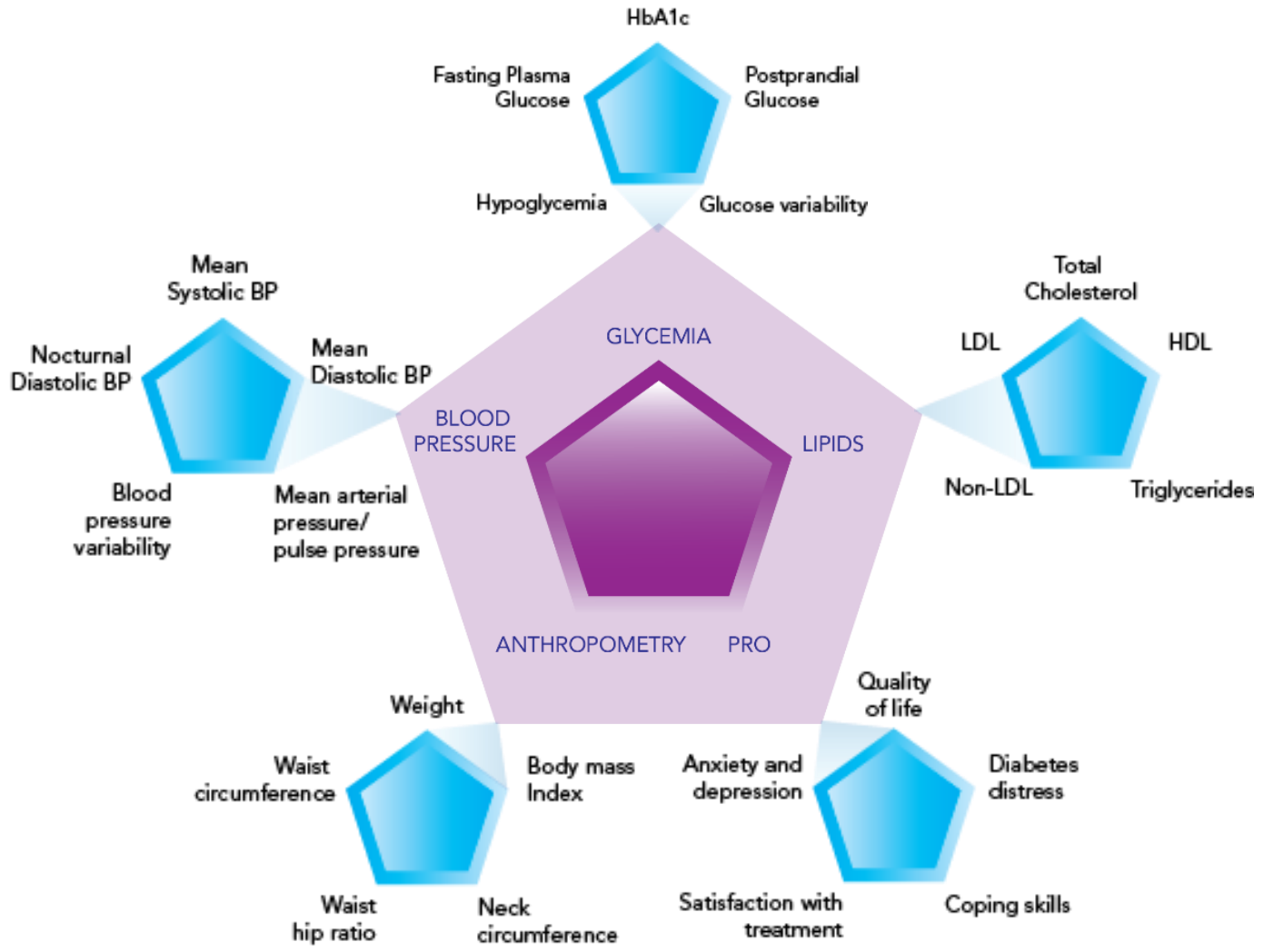
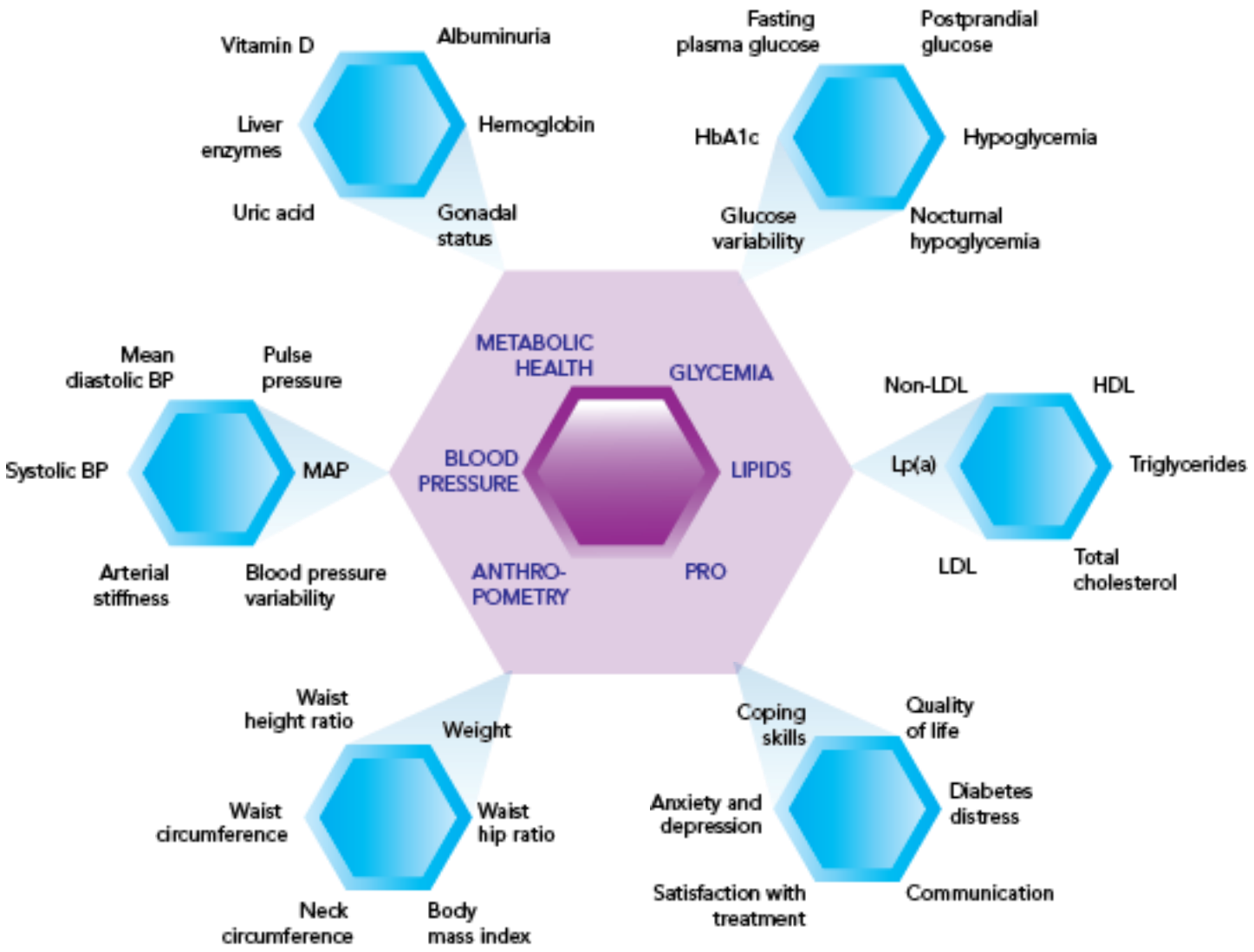


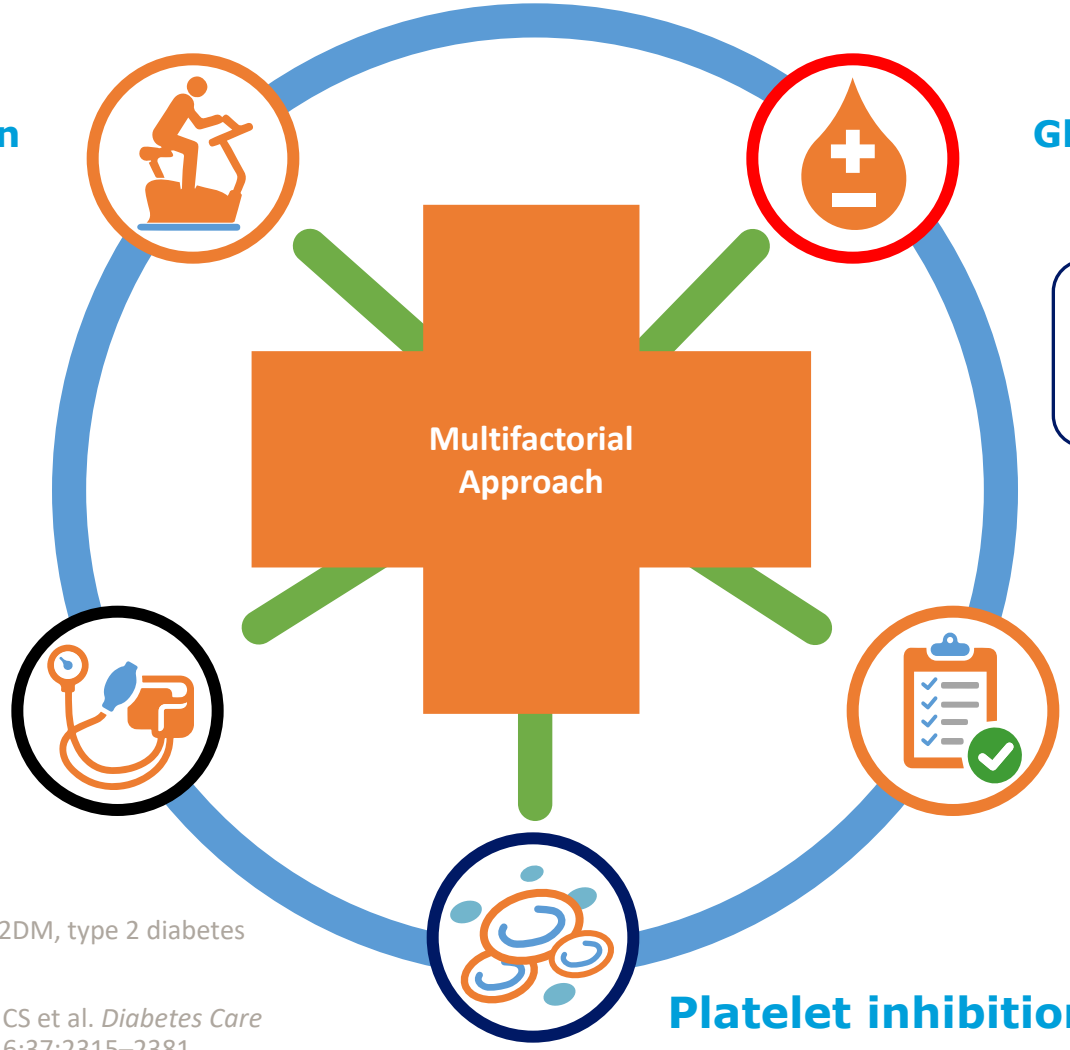
Figure 1: The therapeutic pentad and pentuplets. BP: Blood pressure, PRO: patient reported outcomes
HDL-C: High-density lipoprotein-cholesterol, LDC-C: Low-density lipoprotein-cholesterol

THE THERAPEUTIC HEXAD AND HEXUPLETS



Management approach

Multifactorial approach in managing T2D patients with CVD



Lifestyle modification

Glycaemic control

- Generally, HbA_{1c} <7.0%
- On an individual basis, <6.5–6.9% or above 7%

Blood-pressure control

Management of dyslipidaemia

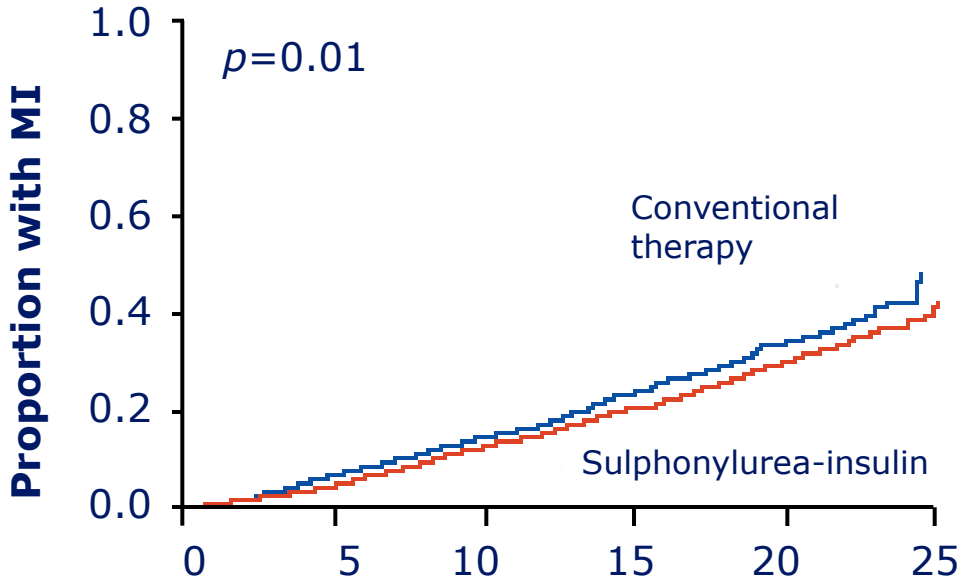
Platelet inhibition

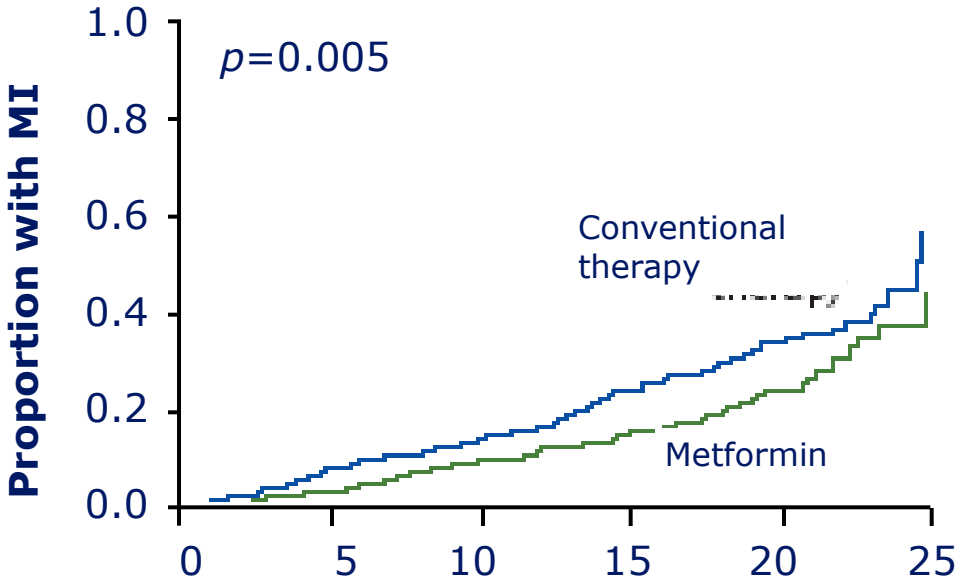
CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; T2DM, type 2 diabetes mellitus

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

CV benefits of intensive glycaemic control

10 years from the UKPDS





Years since randomisation

No. at risk

Conventional:	1138	1013	857	578	221	20
SU/insulin:	2729	2488	2097	1459	577	66

No. at risk

Conventional:	411	360	311	213	95	4
Metformin:	342	317	274	214	106	16

Impact of intensive vs. conventional glucose-lowering therapy

Study (HbA$_{1c}$ intensive vs. conventional)	**Microvascular complications**		**CV complications**		**CV mortality**	
UKPDS 33[1,2] (7.0% vs. 7.9%)	↓	↓	↔	↓	↔	↓†
ACCORD[3,4] (6.4% vs. 7.5%)	↓	↓	↔	↔	↑	↑
ADVANCE[5,6] (6.3% vs. 7.0%)	↓	↔	↔	↔	↔	↔
VADT[7,8] (6.9% vs. 8.4%)	↓	N/R	↔	↓	↔	↔

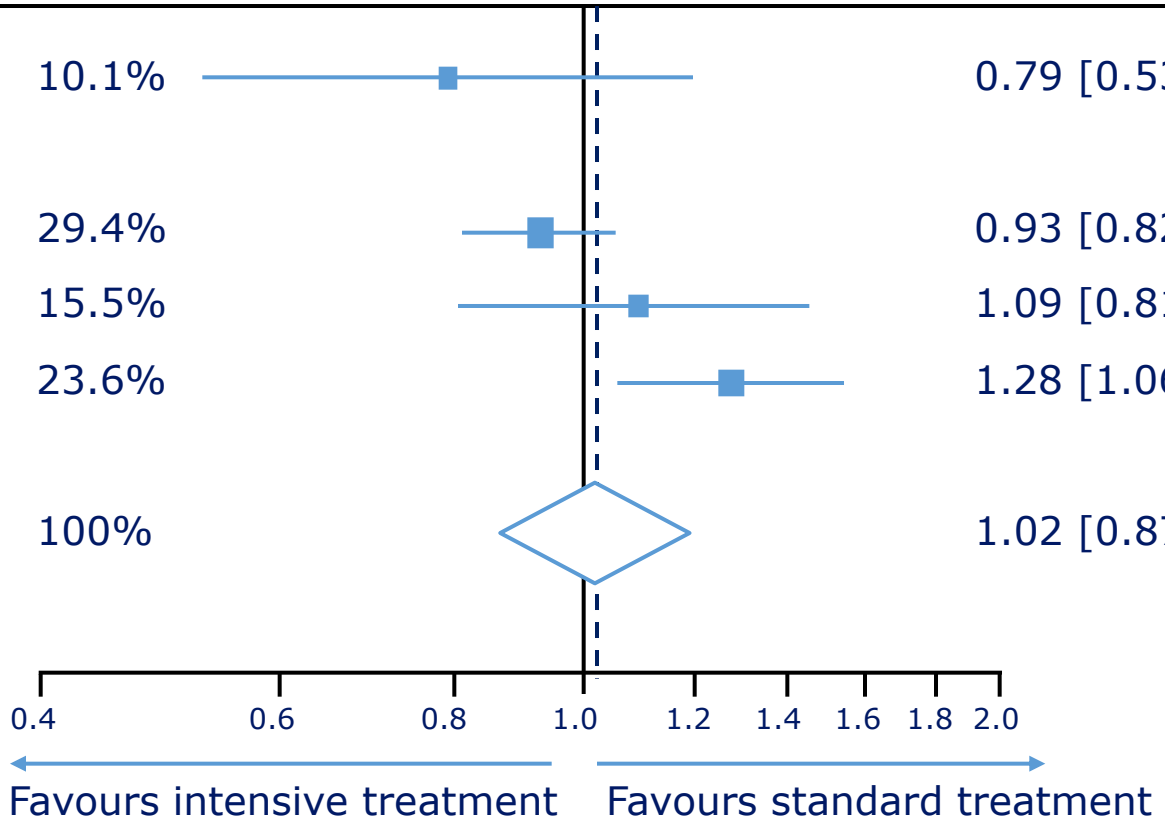
Initial trial Long-term follow-up

*Significant improvement in end-stage renal disease was observed but no other difference in other microvascular end points. †Diabetes-related mortality
ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; HbA$_{1c}$, glycosylated haemoglobin; N/R, not reported; UKPDS, UK Prospective Diabetes Study; VADT, Veteran's Affairs Diabetes Trial

1. UKPDS Group. *Lancet* 1998;352:837–853; 2. Holman et al. *N Engl J Med* 2008;359:1565–1576; 3. Gerstein et al. *N Engl J Med* 2008;358:2545–2559;
4. ACCORD study group *Diabetes Care* 2016;39:701–708; 5. Patel et al. *N Engl J Med* 2008;358:2560–2572; 6. Zoungas et al. *N Engl J Med* 2014;371:1392–1406; 7. Duckworth et al. *N Engl J Med* 2009;360:129–139; 8. Hayward et al. *N Engl J Med* 2015;372:2197–2206

Intensive glycaemic control has no overall impact on all-cause mortality

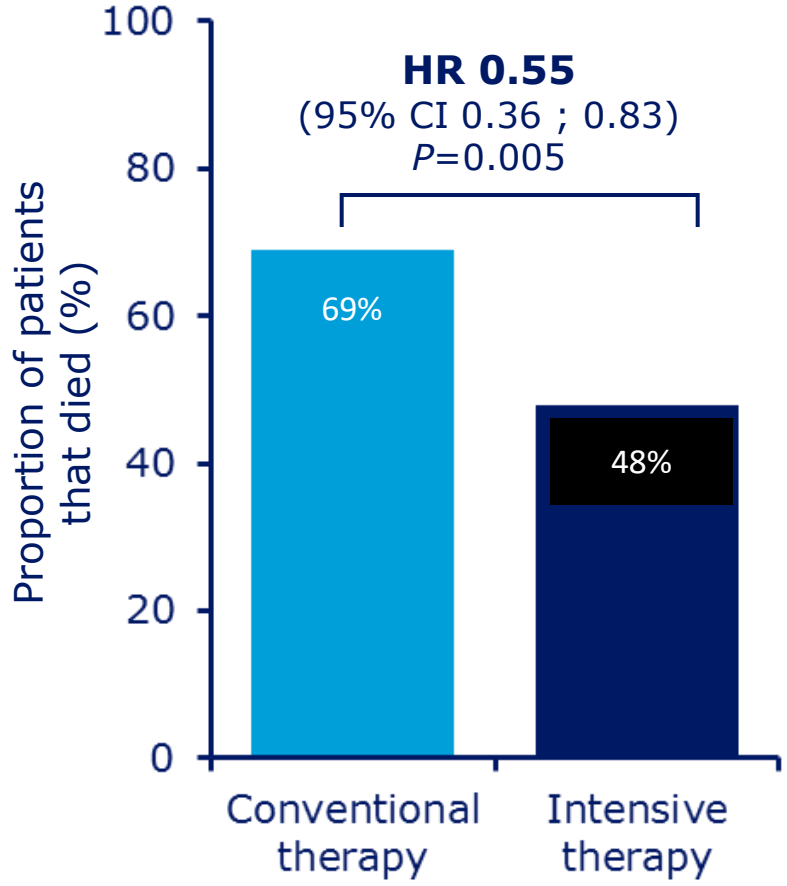
	Intensive treatment/ standard treatment		Weight of study size	Odds ratio [95% CI]
	Participants	Events		
UKPDS	3071/1549	539/302	10.1%	0.79 [0.53; 1.20]
ADVANCE	5571/5569	498/533	29.4%	0.93 [0.82; 1.05]
VADT	892/899	102/95	15.5%	1.09 [0.81; 1.47]
ACCORD	5128/5123	257/203	23.6%	1.28 [1.06; 1.54]
Overall	17267/15773	1573/1319	100%	1.02 [0.87; 1.19]

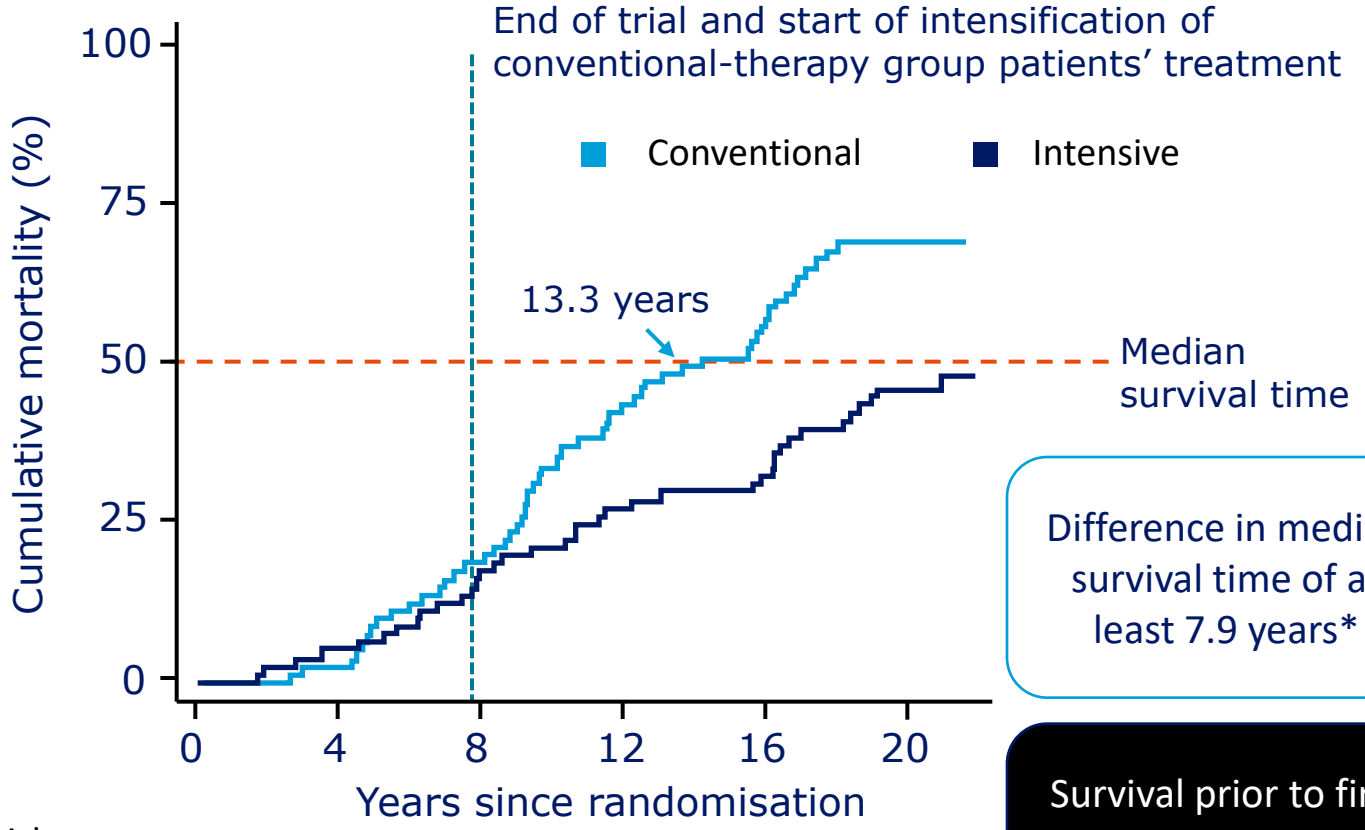


CI, confidence interval.

1. Ray KK, et al. *Lancet*. 2009;373:1765–72.

Mortality at 21-year follow-up
STENO – 2 Trial





No. at risk						
Intensive	80	76	66	58	54	43
Conventional	80	78	65	45	34	24

Difference in median survival time of at least 7.9 years*

Survival prior to first CVD event is 8.1 years

*no formal calculation possible as <50% mortality in intensive therapy groupCI, confidence interval; HR, hazard ratio

Gæde P et al. *Diabetologia.* 2016; 59: 2298–2307. doi: 10.1007/s00125-016-4065-6.

Metabolic karma

THE THERAPUTIC PENTAD AND PENTUPLETS

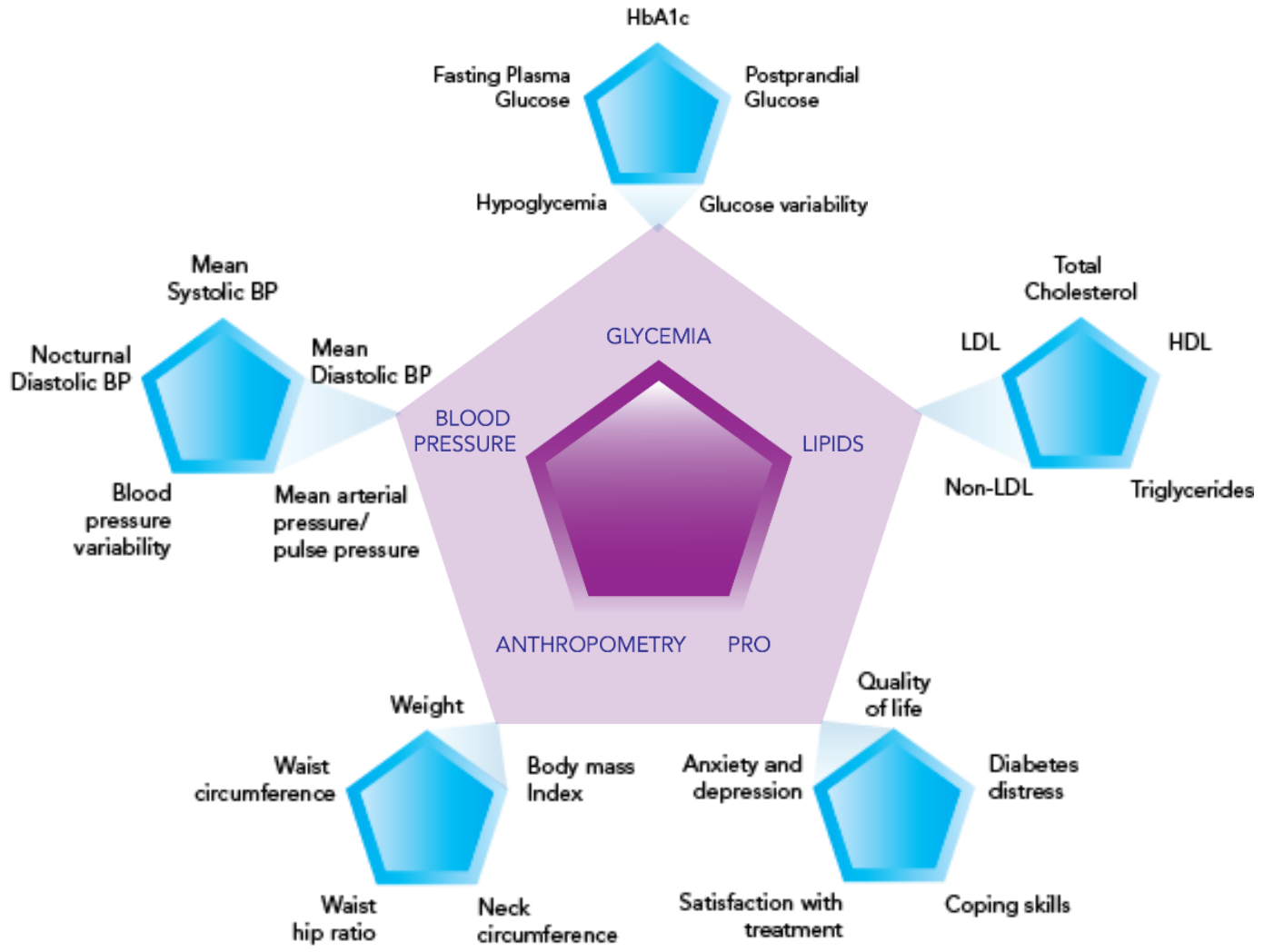
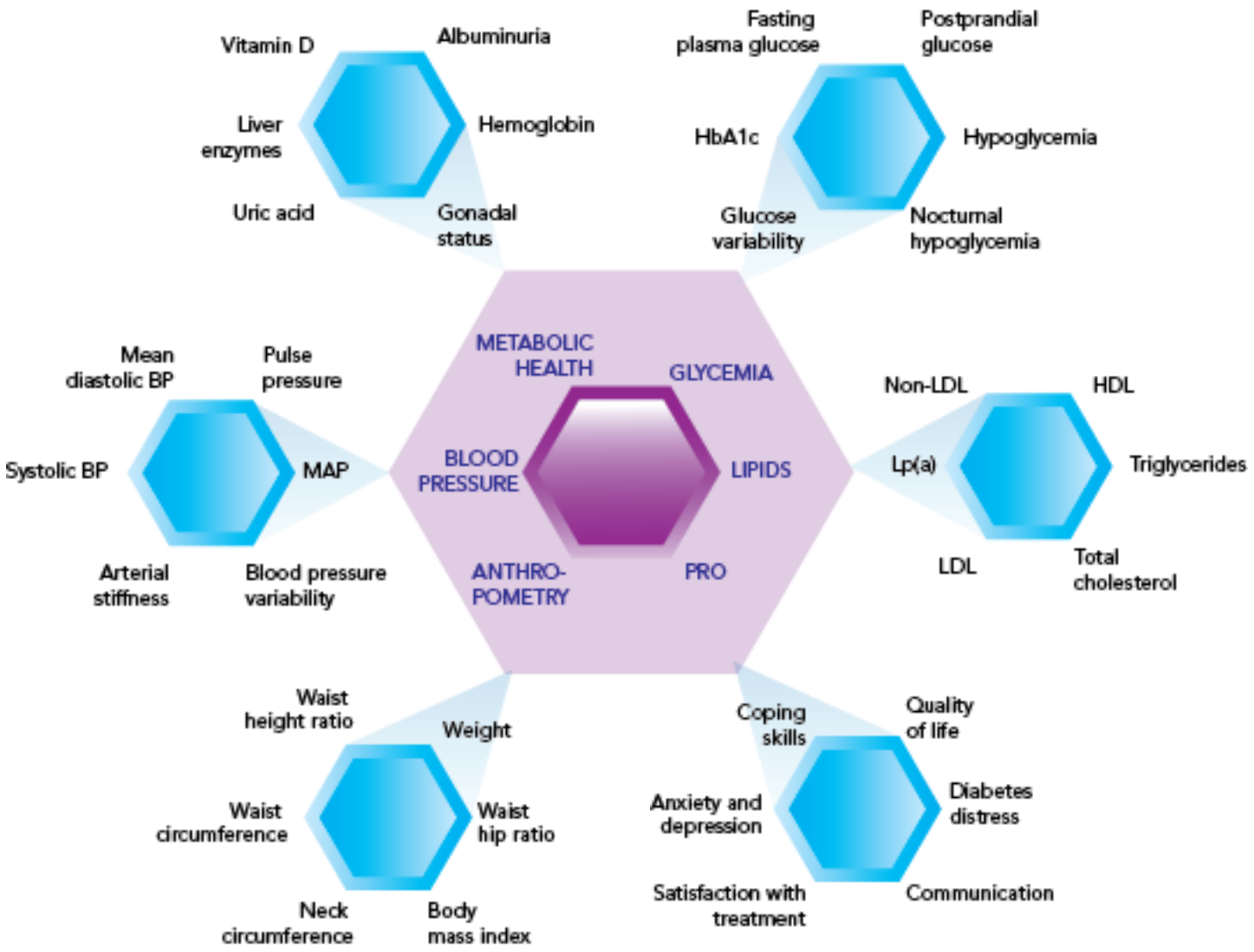


Figure 1: The therapeutic pentad and pentuplets. BP: Blood pressure, PRO: patient reported outcomes
HDL-C: High-density lipoprotein-cholesterol, LDC-C: Low-density lipoprotein-cholesterol

THE THERAPEUTIC HEXAD AND HEXUPLETS



Aagey maro, jorey maro

The 5D approach to refractory diabetes

D Diagnosis to be reviewed

D Disease, comorbid, to be excluded

- Medical/Endocrine/Surgical

D Distress

- Psychological/Psychiatric

D Diet and lifestyle

D Drug and drug regimen choice

D

D for dialogue

The 7I approach to refractory diabetes

- Infection
- Injury
- Inflammation
- Invasive tumour
- Irritability, psychogenic
- Iatrogenic cause
- Intervention, needed/planned

I

I for interaction

I for initiate

Increase

Intensify

Interchange

Váro-centric Diabetes Management

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While efficacy and safety are proven for all modern glucose-lowering drugs, their tolerability may vary. This is especially true in terms of weight gain. This communication proposes a váro-centric model of diabetes care. This approach helps choose appropriate glucose-lowering therapy, based upon weight (body mass index). The váro-centric model suggests a weight-centric approach to selection of drugs. While respecting the tenets of patient-centred care and good clinical sense, it serves as a clinical and teaching tool for rational prescription in diabetes.

PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.
2.	Weight loss should be considered as a lifelong goal in all patients with prediabetes and T2D who also have overweight or obesity, utilizing behavioral interventions and weight loss medications as required to achieve chronic therapeutic goals.
3.	The A1C target must be individualized.
4.	Glycemic control targets include fasting and postprandial glucoses.
5.	The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.
6.	Minimizing risk of hypoglycemia is a priority.
7.	Minimizing risk of weight gain is a priority.
8.	Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.
9.	This algorithm stratifies choice of therapies based on initial A1C.
10.	Combination therapy is usually required and should involve agents with complementary actions.
11.	Comprehensive management includes lipid and blood pressure therapies and related comorbidities.
12.	Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.
13.	The therapeutic regimen should be as simple as possible to optimize adherence.
14.	This algorithm includes every FDA-approved class of medications for diabetes.

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Heavyweight AACE

1. lifestyle therapy, including medically supervised weight loss therapy, is the key…
2. weight loss therapy should be considered as a life long goal
7. minimizing risk of weight gain is a priority
8. ….total cost of care includes weight gain

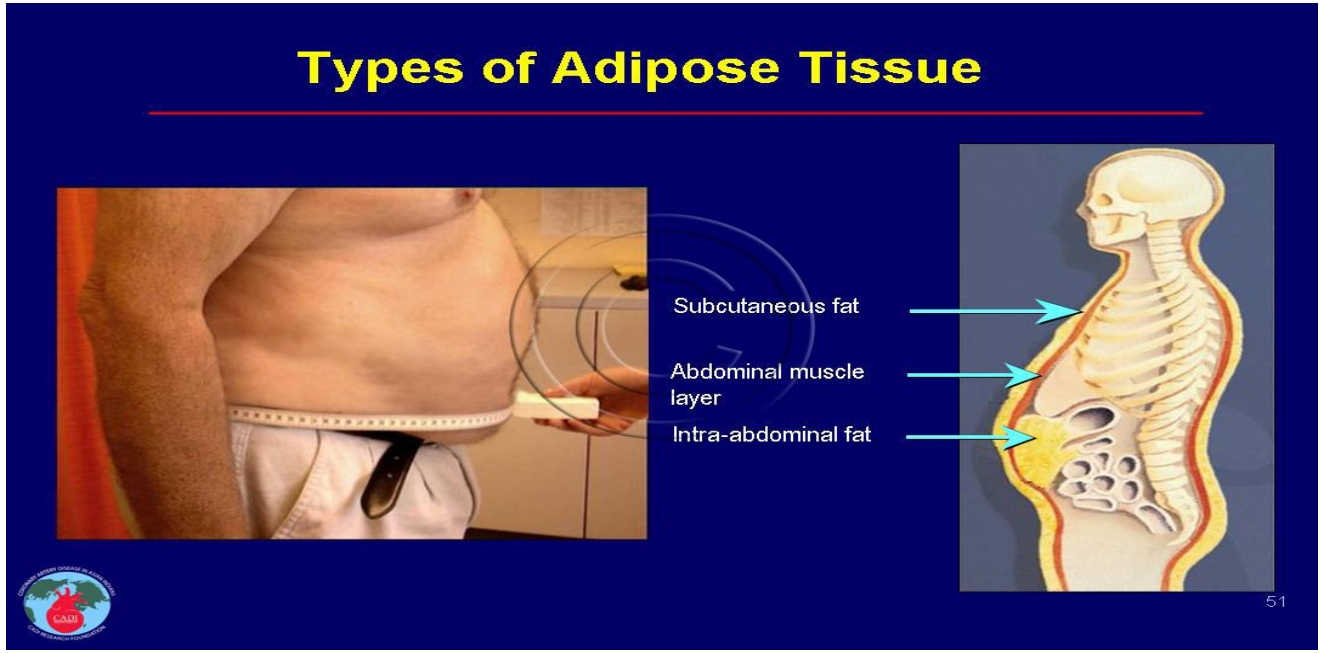
Q

Is this weight reducing centricity appropriate for South Asia?

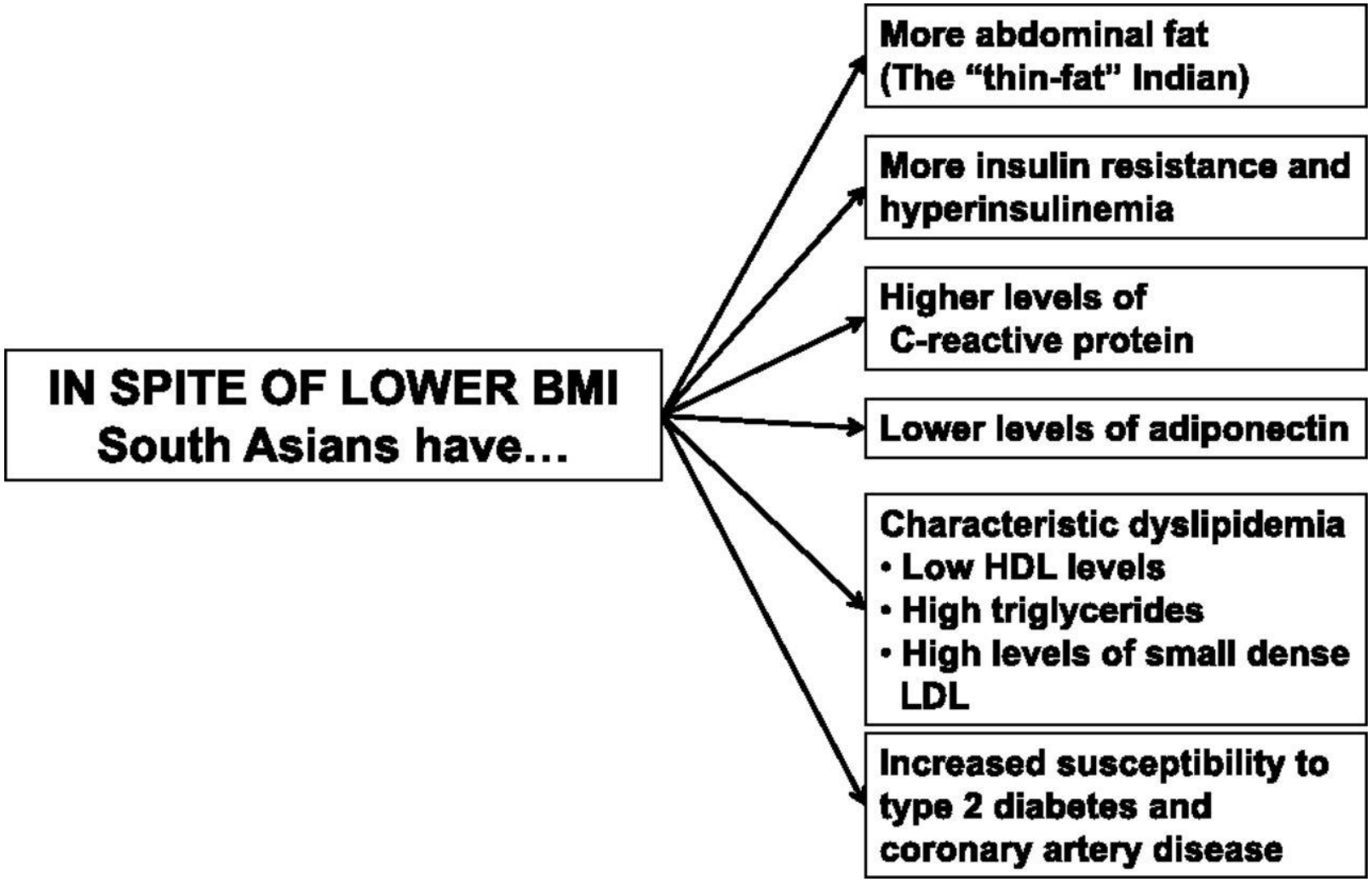
The Asian phenotype

Central obesity

Obesity at lower BMI



The South Asian ("Asian Indian") phenotype.



Ranjit Unnikrishnan et al. Diabetes 2014;63:53-55

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American Diabetes Association

Wide spectrum of phenotypes in the clinic

- Malnourished
- Lean
- Thin built with central obesity
- Normal weight, normal built
- Overweight
- Obese
- Morbidly obese

Metabolic syndrome: the DHOL beats loud

Diabetes	D
Hypertension	H
Obesity	O
Lipids: HDL	L
Lipids: Triglycerides	L

Lean type 2 diabetes

- Mohan V, Vijayaprabha R, Rema M, Premalatha G, Poongothai S, Deepa R, et al. Clinical profile of lean NIDDM in South India. Diabetes Res Clin Pract. 1997;38:101–8.
- Das S, Samal SC, Baliarsinha AK, Tripathy BB. Lean (underweight) NIDDM – Peculiarities and differences in metabolic and hormonal status- A pilot study. J Assoc Physicians India. 1995;43:339–42.
- Sinharoy K, Mandal L, Chakrabarti S, Paul UK, Bandyopadhyay R, Basu AK. A study on clinical and biochemical profile of low body weight type 2 diabetes mellitus. J Indian Med Assoc. 2008;106:747–50.
- Unnikrishnan AG, Singh SK, Sanjeevi CB. Prevalence of GAD65 antibodies in lean subjects with type 2 diabetes. Ann N Y Acad Sci. 2004;1037:118–21.
- Barma PD, Ranabir S, Prasad L, Singh TP. Clinical and biochemical profile of lean type 2 diabetes mellitus. Indian journal of endocrinology and metabolism. 2011 Jul;15(Suppl1):S40.
- Chaudhary P, Laloo D, Salam R. Prevalence of lean type 2 diabetes mellitus in recently diagnosed type 2 diabetes mellitus patients. Indian journal of endocrinology and metabolism. 2013 Oct;17(Suppl 1):S316-7.

The catabolic diabetic

- C cachexia
- A asthenia
- Tab tuberculosis
- O osmotic symptoms
- L lean
- I infections
- SM stigmata of malnutrition

Somatotypes

- Ectomorph: lack of fat/muscle
- Mesomorph: muscle+
- Endomorph: body fat+

Somatotypes, WH Sheldon

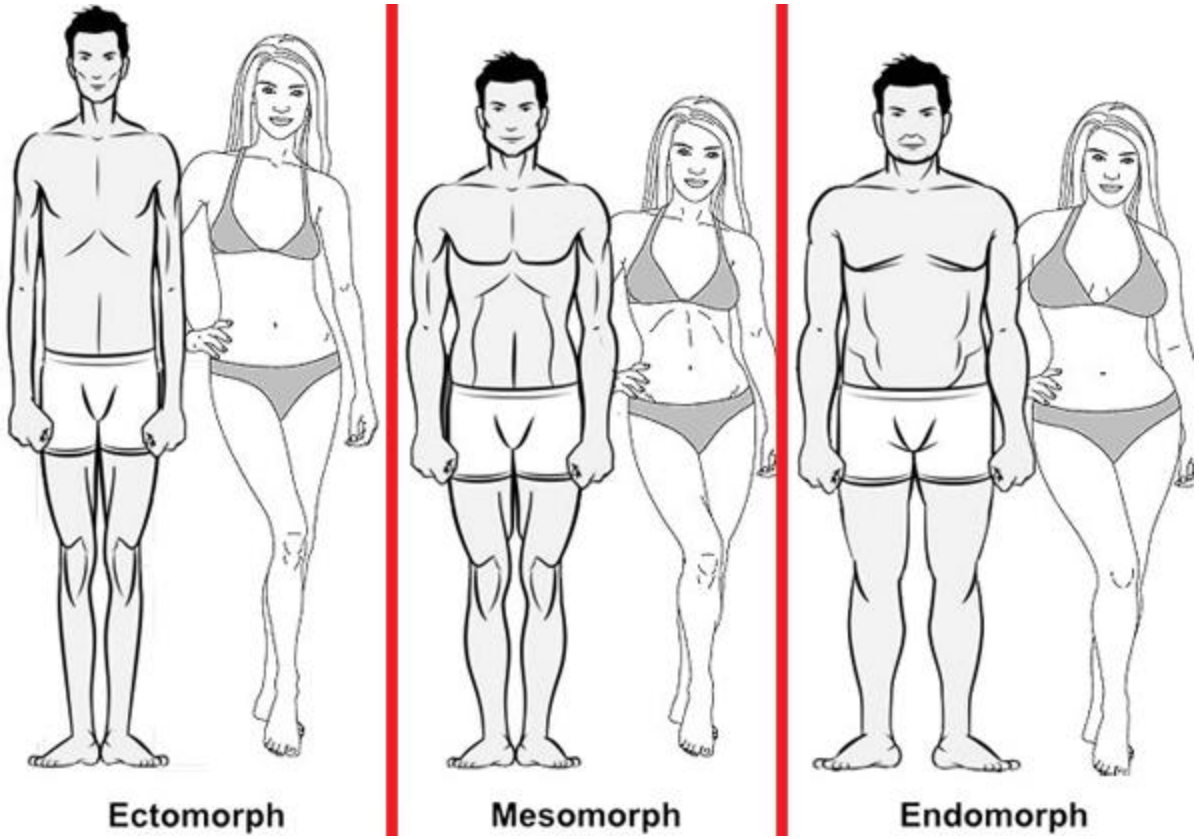


Table-1: Metabolic score based on IDF definition of Metabolic syndrome.

	Parameter	Score
Central obesity Ethnicity specific values for other groups)	Waist circumference ≥ 94cm for Europid men ≥ 80cm for Europid women	One
TG level:	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality	One
HDL cholesterol:	< 40 mg/dL (1.03 mmol/L*) in males and < 50 mg/dL (1.29 mmol/L*) in females, or specific treatment for this lipid abnormality	One
Blood pressure:	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension	One
Fasting plasma glucose (FPG)	≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes	One

TG- Triglyceride; HDL- High Density.

Table-2: Metabolic score based on the presence of various components.

Score classification		Classification	Alternate
High metabolic score	>4	MCD	DMS+
Moderate metabolic score	3	MCD	DMS+
Low metabolic score	< 2	MUD	DMS-

MUD: Metabolically uncomplicated diabetes; MCD: Metabolically complicated diabetes;
DMS: Diabetes with metabolic syndrome.
Maximum possible score =5.
Minimum possible score =2, in a person with diabetes.

scores, principal components, or sum of standardized residuals.[9] The problems of misclassification and low statistical power of binary scores can be overcome by this approach, but any cutoff level used will have limited sensitivity and/or specificity, At the same time, mis-allocation may occur even if a continuous score is used.

Discrete variables of metabolic syndrome, on the other hand, can be calculated [or rather, counted] in a convenient manner, which is feasible even in a busy practice. We can rate every component as being present

Table-3: Effect of antidiabetic agents on various metabolic parameters.[12-32]

Parameters	Abdominal Obesity	TGs	HDL	Glycaemic control	Blood pressure
Biguanides	No effect	Slight decrease	Slight decrease	Reduction	No effect
Sulfonylureas	Weight gain	Mild Reduction	No effect	Marked reduction	No effect
Thiazolidinediones	Weight gain	Mild increase	No effect	Reduction	No effect
Glucagon like peptide-1 receptor agonists	Marked Reduction in weight	Reduction	Mild increase	Marked reduction	Reduction
DPP-4 inhibitors	Weight Neutral	No effect	No effect	Mild reduction	No effect
SGLT-2 inhibitors	Reduction in weight	Mild reduction	Mild increase	Mild reduction	Reduction
Alpha glucosidase inhibitors	No effect	Mild reduction	No effect	Mild reduction	No effect
Insulin	Mild increase	Mild reduction	Mild increase	Marked reduction	No effect

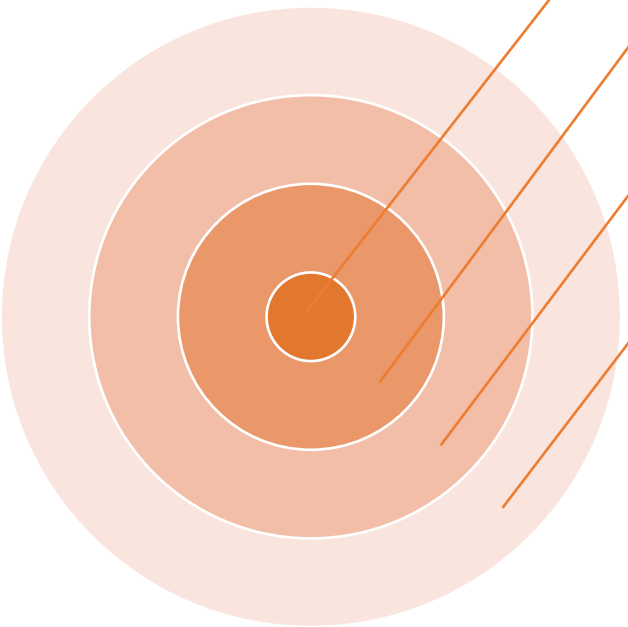
DPP-4 inhibitors= dipeptidyl peptidase 4 inhibitors

SGLT2 inhibitors = sodium glucose cotransporter 2 inhibitors.

ASCVD: cardio-centric choice of therapy

- Liraglutide
- Empagliflozin

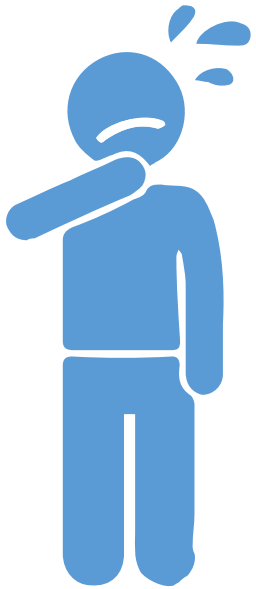
The spectrum of CVD



Subclinical CVD	Atypical CVD
• Without signs and symptoms • ECG, ABI measurements can lead to identification	• Angina equivalents • Erectile dysfunction • Postprandial abdominal pain • Pain in the shoulder

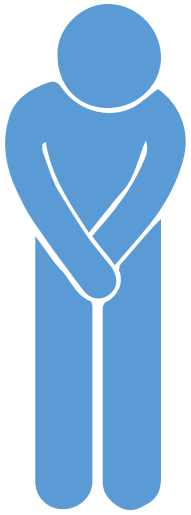
The sound of silence

Dyspnea



Palpitation

Erectile dysfunction



Fatigue

Stern. *Circulation* 2005;111(24):e435-7.

The ABCDE equivalents of ACS

- Atypical site pain
- Breathlessness
- Clamminess of skin/diaphoresis
- Dry mouth

@

- Exertion/exercise

The ABCDE equivalents of chronic CVD

- Arrhythmias
- Biochemical abnormalities, e.g, dyslipidemia, albuminuria
- Claudication
- Dizziness
- Erectile dysfunction

Table-2: Assessment of cardiovascular phenotype.

Variable	Clinical Assessment	Lab Assessment
Heart rate	Resting pulse rate	ECG
Blood pressure	Resting blood pressure	Ambulatory blood pressure monitoring
Weight	Waist hip ratio, body mass index	Fat distribution
Lipid status	Xanthomas, xanthelasmae	Lipid profile
Myocardial health	NYHA class, evidence of fluid overload	Ejection fraction, tissue Doppler index
Coronary health	h/o angina, angina equivalents	Angiography
Cerebrovascular health	Carotid bruit	Angiography, Carotid intima medial thickness
Peripheral arterial health	Ankle brachial index	Angiography
Cardiac autonomic function	Heart rate and blood pressure variability	Cardiac autonomic function tests

Table-3: Choice of glucose-lowering therapy based on cardiovascular phenotype.

Variable	Robust indication	Notes
Resting pulse rate	-	GLP1RA may cause tachycardia
Blood pressure		Delayed/erratic absorption of oral/subcutaneously administered drugs may occur in hypotensive patients
♦ Hypertension	GLP1RA, SGLT2i	
♦ Hypotension/shock	Intravenous insulin	
Weight		
♦ Overweight	GLP1RA,SGLT2i, detemir, metformin, AGI Pioglitazone, insulin	AGIs, metformin improve outcomes Thiazolidinediones increase weight as well as cause fluid retention
♦ lean		
Lipid status	GLP1RA,pioglitazone	SGLT2i, rosiglitazone have mixed effects
Myocardial health	SGLT2i (empagliflozin)	Saxagliptin increase risk of hospitalization for heart failure
Coronary health	SGLT2i (empagliflozin), AGI (acarbose)	Older sulfonyureas abolish ischemic preconditioning

Abbreviations: AGI = alpha-glucosidase inhibitors, GLP1RA = glucagon-like peptide 1 receptor agonists, SGLT2i = sodium glucose cotransporter inhibitors.

Gluco-phenotype

The clinical and biochemical attributes,
which allow characterization of the glycaemic status,
understanding of the etio-pathogenesis of dysglycaemia,
and planning of therapeutic strategies,
in an individual.

past present future

Gluco-phenotype

may be classified as

predominant insulin deficiency or insulin resistance;

non-obese or obese;

predominant fasting, prandial or combined hyperglycaemia;

with or without acute/modifiable precipitating factors.

“Glycemic personality”

- More human-centric
- Severity and style of hyperglycemia
- Utility and urgency of glucose lowering
  - Short term
  - Long term

- Relative risk of hypoglycaemia
- Expected efficacy of various glucose lowering strategies

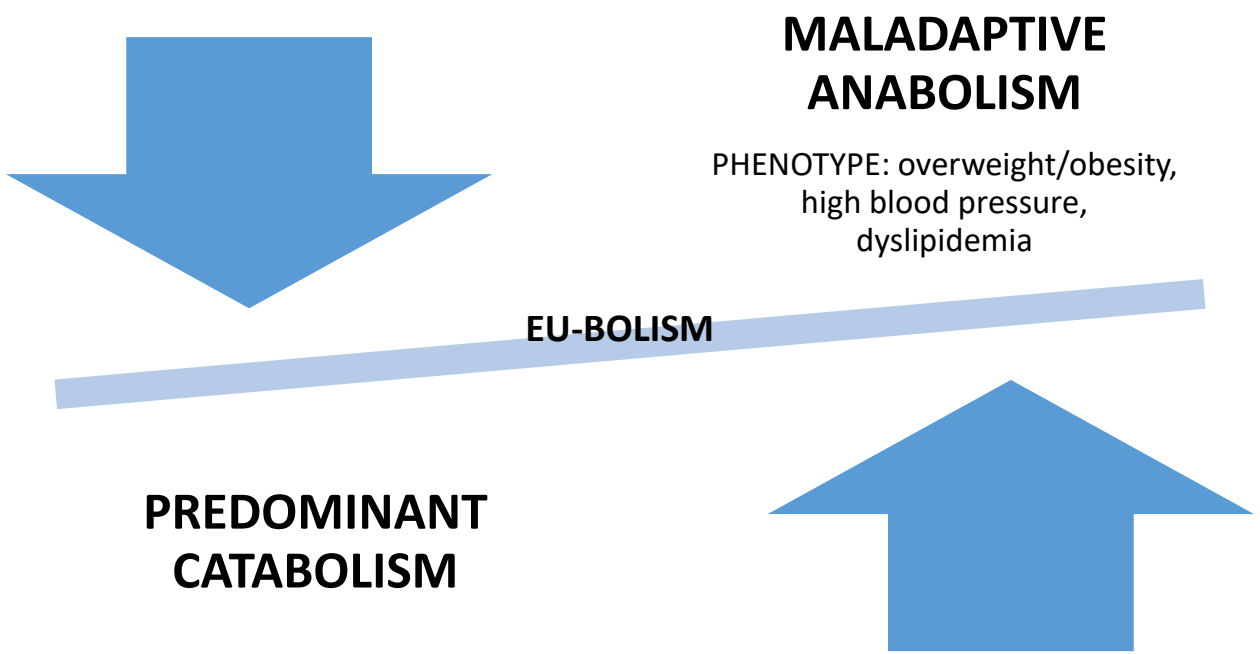
The need for simplicity

E efficient/effective for the patient

E easy to understand for the doctor

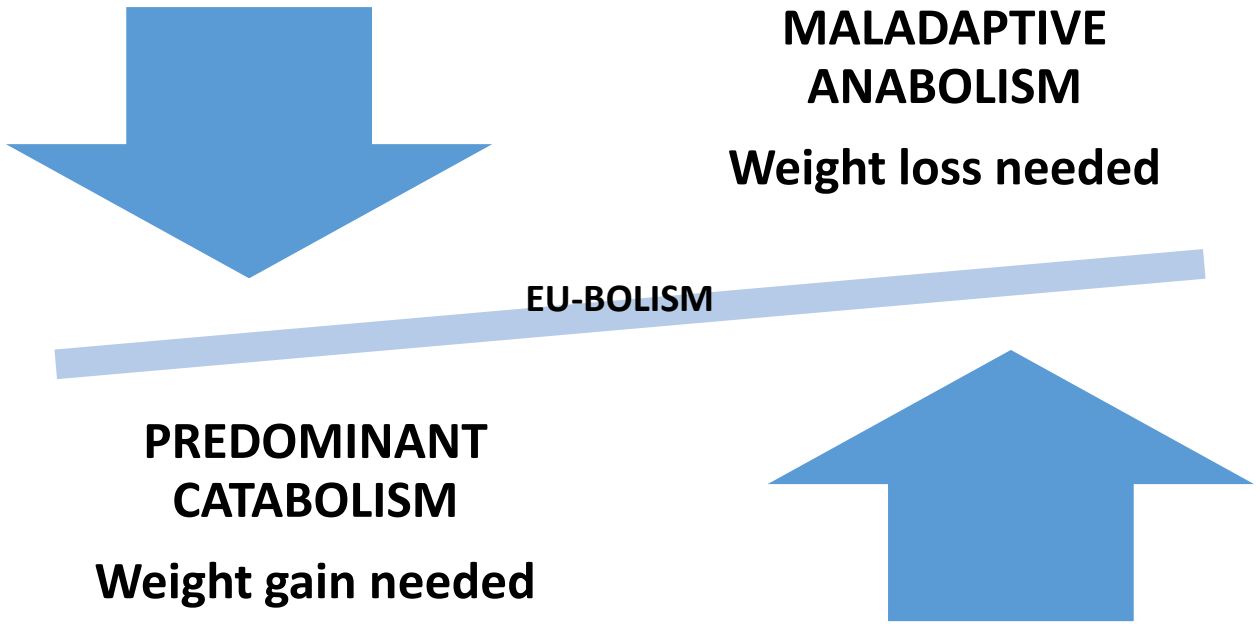
E error free for both

Metabolic fulcrum, and metabolic triage

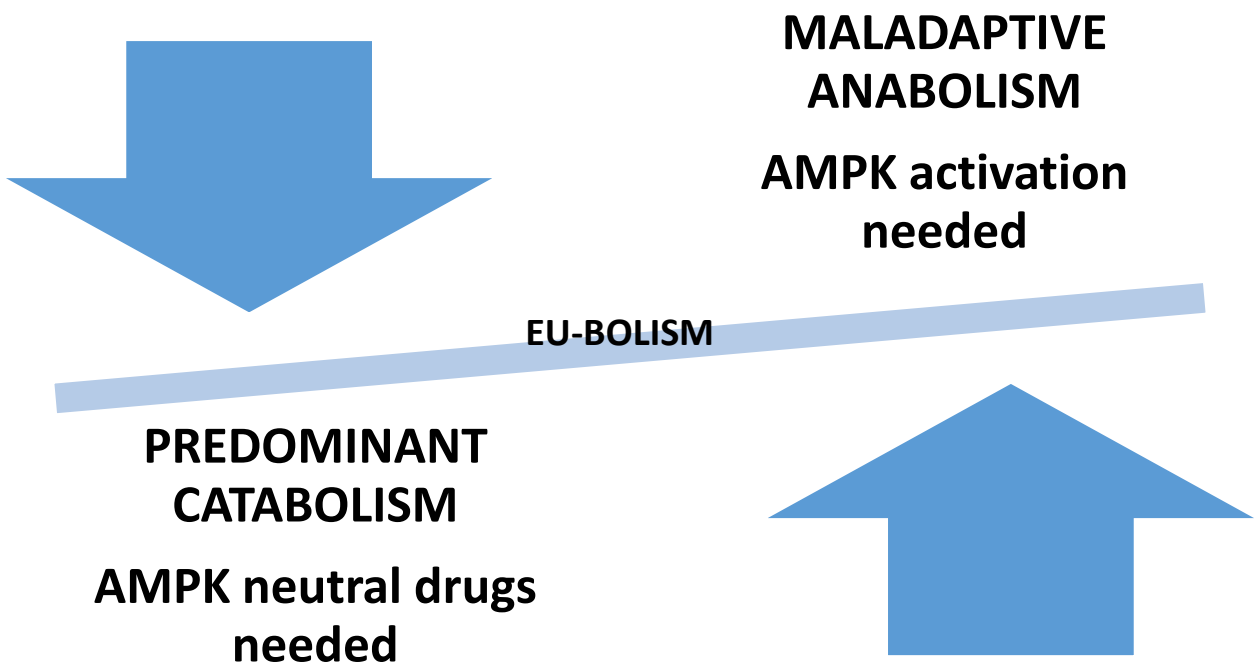


Kalra S, Gupta Y. **Choice of Glucose-lowering Therapy— A Metabolic Fulcrum-based Approach**. **US Endocrinology, 2015**;11(2):79–80

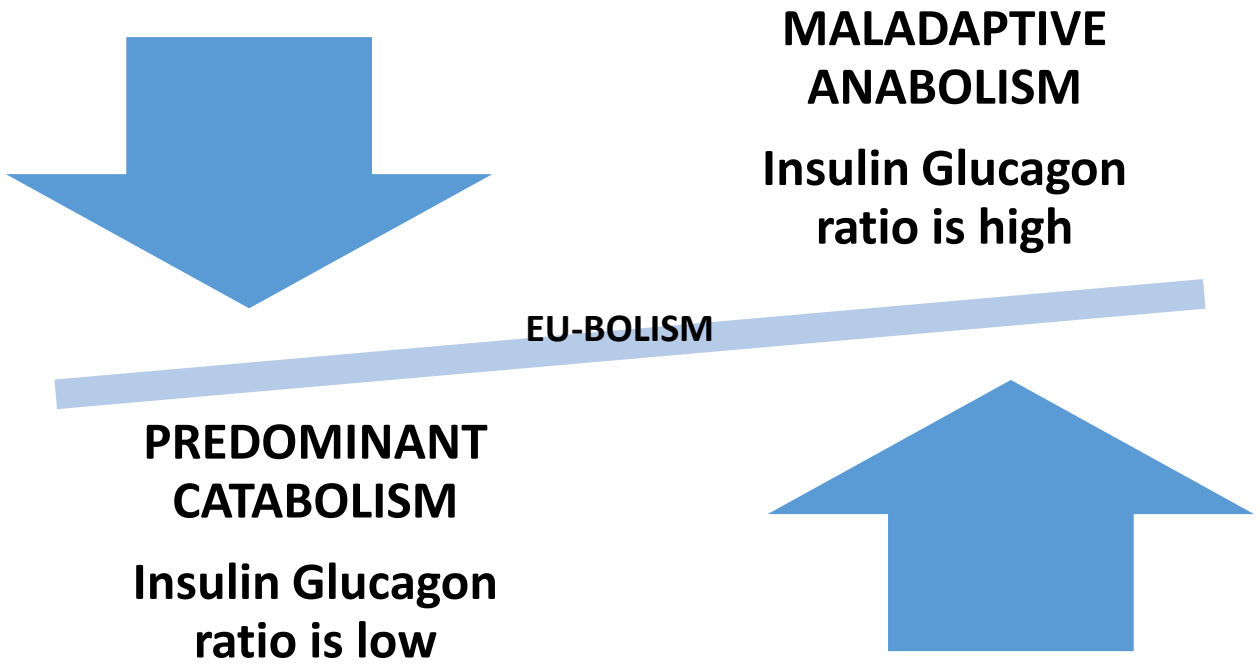
Metabolic fulcrum, phenotypic justification



Metabolic fulcrum, biochemical justification



Metabolic fulcrum, endocrine justification



Metabolic fulcrum, and metabolic triage

PREDOMINANT CATABOLISM

PHENOTYPE: thin built, cachexia, osmotic symptoms

PATHOPHYSIOLOGY: predominant insulin deficiency

CHOICE: insulin, insulin secretagogues

EU-BOLISM

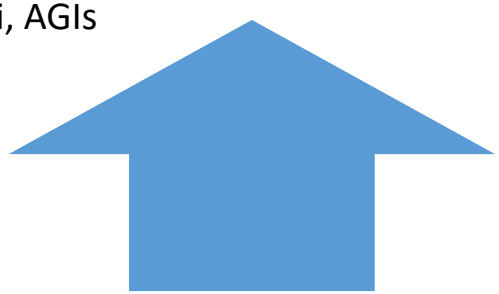
CHOICE: DPP4i, AGIs

MALADAPTIVE ANABOLISM

PHENOTYPE: overweight/obesity, high blood pressure, dyslipidemia

PATHOPHYSIOLOGY: predominant insulin resistance

CHOICE: GLP1RA, SGLT2i



Kalra S, Gupta Y. **Choice of Glucose-lowering Therapy— A Metabolic Fulcrum-based Approach**. **US Endocrinology, 2015**;11(2):79–80

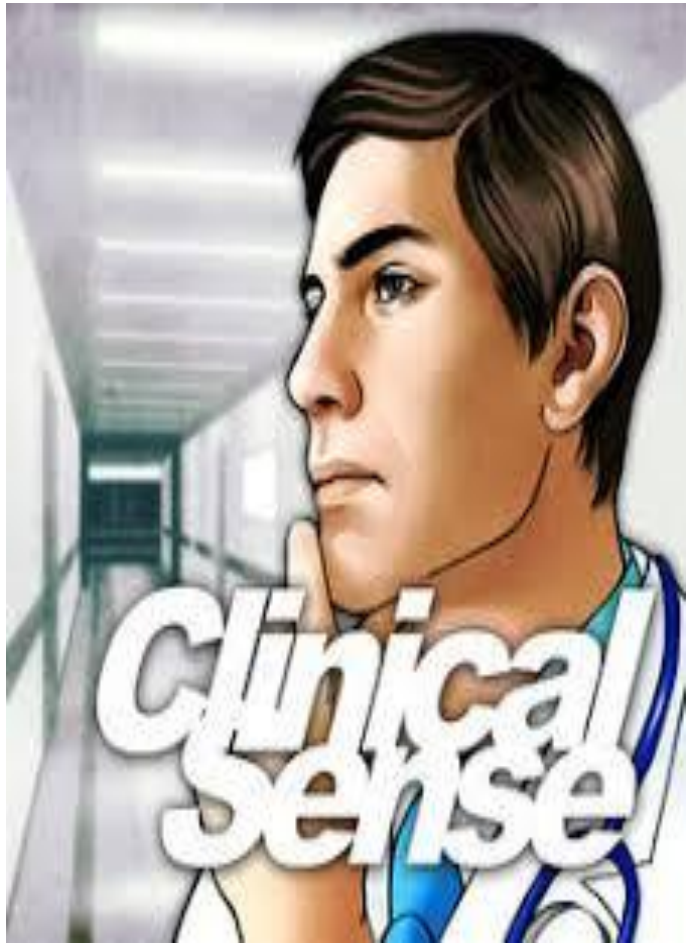
INSULIN SECRETAGOGUES	INSULIN SENSITIZERS	NUTRIENT LOAD REDUCERS
DIRECTLY ACTING • Sulfonylureas • Meglitinides	DIRECTLY ACTING • Metformin • Pioglitazone	ABSORPTION INHIBITORS • AGIs • Colesevelam • Orlistat
INDIRECTLY ACTING, via incretin pathway • GLP1RA • DPP4i	INDIRECTLY ACTING, via counter-regulatory hormone pathways • Pramlintide • Bromocriptine	EXCRETION ENHANCERS • SGLT2i

Figure: Taxonomy of non insulin glucose lowering drugs.

Table-2: Choice of first injectable after metformin inadequacy: Simple algorithm.

	Weight	Lean	Obese/overweight
Hyperglycaemia	Only fasting	Basal insulin	GLP1RA
	Fasting + post prandial	Dual action insulin	Insulin+ GLP1RA

Good clinical sense



"the presence of sensory faculties,
their usage and interpretation,

by which one is able to

practice good clinical medicine“

Kalra, Gupta 2015