A Clinical-Translator’s Point-of-View: At the Interface of Patient Care and Basic Science

Diagnosing Diabetes Mellitus in Adults: Type 1, LADA, Type 2: Rationale and Implications of a β-Cell-Centric Classification of Diabetes

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Diagnosing Diabetes Mellitus in Adults:

Type 1, Type 2, LADA

or

Since Confusion Abounds, Isn’t it Time for A New Classification Schema for the Diagnosis and Treatment of Diabetes Mellitus (DM)

Get us ready for ‘PRECISION MEDICINE’
In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

**Stanley Schwartz**

Research Support: 0  
Employee: 0  
Board Member/Advisory Panel: Janssen, Merck, AZ-BMS, BI-Lilly, Salix, Novo, Genesis Biotechnology Group  
Stock/Shareholder: Saturn EMR Decision Support APP.  
Consultant: NIH RO1 DK085212, Struan Grant PI  
Other: Speaker’s Bureaus: Janssen, Merck, Novo, Salix, BI-LILLY, Eisai, AZ-Int’l, Amgen
Purely Clinical Answer
Empiric, Pragmatic Approach

It doesn’t matter which label is applied 😊

- **Insulin-Dependent**
  - DKA- ketosis prone: insulin needed for survival
- **OR NOT- Everyone else**
  - Use ‘best clinical guess’; ‘label’ patient; Independent of age
  - Treat ‘as needed’ to get glycemic control,
  - (but must work under constraints of current ‘definitions’ for the classification of T2D- per payors/ governments)
'Diagnosis' Has Many Functions

Need To Be More Than Pragmatic!!

- *To plan patient’s care* – MORE tailored patient-centric therapy
- *To prevent* – disease development and progression
- *To predict* – risk of DM
- *To proliferate* – and stimulate new scientific knowledge about DM

AND NEED TO CLASSIFY ACCURATELY
Current DM Classification Failing

(Certainly appropriate with knowledge available when current classification adopted)

BUT WE’VE LEARNED SO MUCH MORE

- Immune destruction of β-cells / and Insulin Resistance is used as basis of distinction between T1D, and T2D and all other sub-types of DM

- Diagnosis is often *imprecise*
  - Flatbush DM - present in DKA - ‘turn out to be T2DM’
  - LADA - Adults who look like ‘typical T1DM’
  - Antibody positive who look like ‘T2DM’
  - T1DM with Insulin Resistance (like T2DM)

*ie:* Complicated by extensive *overlap*
yet distinct differences in etiology and phenotype
Definitions: T1D, ‘LADA’, T2D
May Seem Precise BUT..., Overlapping Phenotypes
In particular:

‘LADA’- Ambiguous classification

- Later age; SPIDDM, ‘Slowly progressive T1D’
  - ‘Slower’ destruction of β-cells than T1D
- Antibody positive T2D = ‘T1.5D’
  - ‘Faster’ destruction of β-cells than in T2D
- T-cell abnormal SPIDDM
  - Antibody negative
- Insulin commonly considered the ‘go to’ drug, even in patients with LADA with retained β-cell function
### Comparing Definitions for T1D, ‘LADA’, T2D

<table>
<thead>
<tr>
<th></th>
<th>IMMUNITY</th>
<th>AGE</th>
<th>GENES</th>
<th>BMI</th>
<th>INSULIN THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1D In children</strong></td>
<td>Strong +++</td>
<td>child</td>
<td>HLA++</td>
<td>low</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>T1D In adults</strong></td>
<td>++</td>
<td>adult</td>
<td>HLA+</td>
<td>normal</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>LADA</strong></td>
<td>+</td>
<td>adult</td>
<td>HLA</td>
<td>normal</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>T2D</strong></td>
<td>weak</td>
<td>adult</td>
<td>?</td>
<td>high</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

Adapted from Leslie et al. Diabetes Metab Res Rev. 2008 Oct;24(7):511-9
### Distinct Etiologies and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>T1D</th>
<th>‘LADA’</th>
<th>T2D</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical Age of Onset</strong></td>
<td>All Ages</td>
<td>Usually Age &gt;30</td>
<td>Adults</td>
<td>Usually Age &lt;25</td>
</tr>
<tr>
<td><strong>% of all Diabetes</strong></td>
<td>10%</td>
<td>10%</td>
<td>75%</td>
<td>5%</td>
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<tr>
<td><strong>Typical BMI</strong></td>
<td>Mostly Normal or Thin</td>
<td>Mostly Normal or Overweight</td>
<td>Mostly Overweight or Obese</td>
<td>Mostly normal</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
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<tr>
<td><strong>Progression to insulin Dependence</strong></td>
<td>Fast (Days/Week)</td>
<td>Latent (Months/Years)</td>
<td>Slow (Years)</td>
<td>Depends on MODY type</td>
</tr>
<tr>
<td><strong>Insulin Resistance</strong></td>
<td>Mostly no; ~10% ,yes</td>
<td>Some</td>
<td>Yes</td>
<td>Depends on MODY type</td>
</tr>
<tr>
<td><strong>Presence of Autoantibodies</strong></td>
<td>Yes (ICA, IA2, GAD65, IAA)</td>
<td>Yes (mostly GAD65), Some not</td>
<td>Some</td>
<td>No</td>
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<tr>
<td><strong>T cell Reponses to islet proteins</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Insulin/ C-peptides</strong></td>
<td>Undetectable or extremely low</td>
<td>Low</td>
<td>Normal to High</td>
<td>Normal</td>
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<tr>
<td><strong>Level at diagnosis</strong></td>
<td></td>
<td>Low</td>
<td></td>
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<tr>
<td><strong>Ketoacidosis</strong></td>
<td>Yes</td>
<td>Yes, many not all</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td><strong>Insulin Secretion</strong></td>
<td>Low/null</td>
<td>Varies</td>
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<td>High</td>
<td>Low</td>
<td>None</td>
<td>None</td>
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<td><strong>TCF7L2 Link</strong></td>
<td>None</td>
<td>In some pop’n, stronger link than T2D</td>
<td>?5%</td>
<td>None</td>
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<td><strong>Other Genes Involved</strong></td>
<td>PTPN22; INS; CTLA4; CCR5; FOXP3; CLEC16a HNF1A; IL2RA; IL6; ITPR3; OAS1; SUMO4</td>
<td>PTPN22; INS</td>
<td>PPARG; JAZF1; KCNJ11; NOTCH2; WFS1; IGF2BP2; FTO; SLC30A8; HHEX</td>
<td>HNF4A; GCK; HNF1A; IPF1; HNF1B; NEUROD1</td>
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<td><strong>Early Treatment</strong></td>
<td>Insulin required, diet &amp; exercise helpful</td>
<td>Non-Insulin or insulin, diet &amp; exercise helpful</td>
<td>Non-Insulin, diet &amp; increased activity</td>
<td>Gene Specific</td>
</tr>
<tr>
<td><strong>Late Treatment</strong></td>
<td>Insulin, diet, exercise</td>
<td>Insulin, pills, diet, exercise</td>
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<td>Gene Specific</td>
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**T1D**
- T1D
- ‘LADA’
- Varies
- Varies
- Varies

**‘LADA’**
- Low/null
- Varies
- Varies
- Varies

**T2D**
- Varies
- Varies
- Varies
- None

**MODY**
- Depends on MODY type
- Depends on MODY type
- Depends on MODY type
- None

**Insulin Resistance**
- Mostly no; ~10% ,yes
- Some
- Yes
- Depends on MODY type

**Insulin Inflammation**
- Chronic Inflammation
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- None

**Insulin Secretion**
- Low/null
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**Islet Inflammation**
- Chronic Inflammation
- Chronic Inflammation
- Chronic Inflammation
- None

**TCF7L2 Link**
- None
- Some Pop’n Greater than T2DM
- ? 5%
- None
Diabetes is a Continuum of $\beta$-Cell Function

So issue is less: ‘What is LADA?’-

Issue is what are mechanisms and rate of destruction of $\beta$-cells in all patients with diabetes - improve therapy!!
Summary

- Current definitions are imprecise and ambiguous
  - Complicated by overlapping characteristics (e.g. T1D with T2D parents, or, T2D with antibodies-no insulin)
  - Don’t take into account newer understandings of causes of DM/mechanisms of hyperglycemia

- **Need to focus on preservation/improvement of** β-cell function
  Insulin is overused in patients with retained β-cell function

- **Multiple mediating pathways of hyperglycemia** are not taken into account in choice of treatment

- Gov’t and payers limit coverage for therapies based on ‘diagnosis’

**THUS….**
Call to Action

- There is a need for a nomenclature for the classification and diagnosis of DM that is in line with up-to-date knowledge of pathophysiology and newer therapies,
- That supports individualized (PRECISION) medicine
- And creates and targets regimens that build upon all available treatment options, for the multiple mediating pathways of hyperglycemia
- Forces, by the logic of the new system, gov’t and insurers to pay for the logical, effective, safe therapies
- Can accommodate future developments
The β-Cell Centric Classification of DM

*Intuitively obvious approach...*

ANSWERS THE CALL TO ACTION

ALL DM = Hyperglycemia

Classify each patient by the specific cause(s) of the β-cell dysfunction in the clinical presentation of their disease

Prescribe personalized treatment

(patient-centric/ PRECISION MEDICINE)

through targeted therapies

aimed at all possible mediating pathways of hyperglycemia

The ‘β-Cell Centric’ Classification will help improve diagnosis and treatment,

especially as our knowledge-base expands
β-Cell Centric Classification of Diabetes: 
Implications for Classification, Diagnosis, Prevention, Therapy, Research

CLASSIFY PATIENT BY CAUSE(s) of Beta-Cell Dysfunction In EACH Individual
Pushback

- What about ‘pure’ Insulin Resistance Syndromes?
The β-Cell: The ‘Final Common Denominator’

- Rare Insulin Resistance Syndromes, e.g. leprechaunism, may not have a specific β-cell genetic defect, but β-cells damage may be part of the disease.

**Fig. 2.** Age-dependent decrease in insulin (A) and increase in glucose (B) levels in a patient with Rabson-Mendenhall syndrome. Insulin and glucose levels were determined by standard procedures. Data were analyzed by linear regression, and significance was determined using ANOVA.

**Fig. 4.** Exponential decline in the insulin/glucose ratio in Rabson-Mendenhall syndrome. The insulin (nanomoles per L)/glucose (millimoles per L) ratio was plotted as a function of age and fitted to an exponential equation. Significance was determined using ANOVA.

(I comment As First Recipient of the Bobby Clarke JDF fellowship😊)

Loss of ‘T1DM’ Designation WILL NOT take away from Focus on ‘the CURE’

New Classification will FACILITATE SEARCH FOR ‘THE CURE’

(focusing on mechanisms that slow the injury/destruction of the b-cell in ‘T1-LADA’, or speed destruction in ‘T2-LADA’ etc)

Actually, ‘Juvenile Diabetes’ Fits better, again 😊
**β-Cell Centric Classification of Diabetes:**

*Implications for Classification, Diagnosis, Prevention, Therapy, Research*

- **Environment**
  - Genetic susceptibility
  - *e.g.* viruses, endocrine disruptors, food AGEs, Gut Biome

- **Epigenetics**

- **Inflammation/Immune Regulation**

- **β-Cell secretion/mass**
  - FINAL COMMON DENOMINATOR

**INSULIN**

**RESISTANCE**

- **Polygenic Monogenic**

**β-Cell Centric Classification**

*Environment=Genetic susceptibility to *e.g.* viruses, endocrine disruptors, food AGEs, Gut Biome*

**Insulin Resistance=Centrally Induced, Peripheral, Stress Hormones, Gut Biome***
Phenotypic Presentation is defined by:

**Slope** = ‘Natural History’ over time, i.e., RATE OF β-cell LOSS. Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved. Complete loss of β-cell mass may never be reached, especially if newer agents better preserve β-cells.

**Severity** = β-cell loss of mass

**Pre-Diabetes** = FBS ≥100, PPG ≥140

**All DM** = FBS ≥126, PPG ≥200

**Age** at presentation = tipping point when the combined gene effect / environmental trigger is exposed as phenotypic hyperglycemia
Phenotypic Presentation is defined by:

**Slope** = ‘Natural History’ over time, i.e., RATE OF $\beta$-cell LOSS. Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved. Complete loss of $\beta$-cell mass may never be reached, especially if newer agents better preserve $\beta$-cells.

**Severity** = $\beta$-cell loss of mass

**Pre-Diabetes** = FBS $\geq 100$, PPG $\geq 140$

**All DM** = FBS $\geq 126$, PPG $\geq 200$

**Age** at presentation = tipping point when the combined gene effect / environmental trigger is exposed as phenotypic hyperglycemia.
The β-cell centric classification allows for individualized care by identifying and treating patient-specific etiologies and mediating pathways of hyperglycemia.

EGREGIOUS ELEVEN

1. One CORE Defect - the β-Cell

1. (at least) 6 treatable Causes of β-Cell Damage / HYPERGLYCEMIA

3. 5 treatable mediators of HYPERGLYCEMIA resulting from β-Cell Damage
A. β-Cell-Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

1. Pancreatic β-cells
   ↓ β-Cell function
   ↓ β-Cell mass
   ↓ Insulin

2. ↓ Incretin effect

3. α-cell defect
   ↓ Glucagon

HYPERGLYCEMIA

4. Adipose
   Increased lipolysis

5. Muscle
   Decreased peripheral muscle uptake

6. Liver
   Increased glucose production

7. Brain
   Increased appetite
   Decreased morning dopamine surge
   Increased sympathetic tone

8. Colon/Biome
   Abnormal-microbiota; possible decreased GLP-1 secretion

9. Immune Dysregulation/Inflammation
   ↓ Amylin

10. Stomach/Small intestine
    Increased rate of glucose absorption

11. Kidney
    Increased glucose re-absorption

INSULIN RESISTANCE
   Upregulation of SGLT-2
Brief Discussions

- Genetics
- Beta-Cell
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment
New β-Cell Centric Construct: *Implications*
Genetics 101 for DM

Phenotype is **DEPENDENT ON** Genotype:
Number of **Genes**- which genes- their nature, how many different ones, the ‘severity/intensity’ of expression!; epigenetics*

i.e: **Genes influence:**

- B-Cell: Insulin secretory dynamics, **sites** of susceptibility of β-Cell to destruction by endogenous/ exogenous **triggers**
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment

(susceptibility to DM COMPLICATIONS)

*Int J Biochem Cell Biol. 2015 May 27. pii: S1357-2725(15)00143-0. doi: 10.1016/j.biocel.2015.05.022. [Epub ahead of print]*

Epigenetic dynamics in immunity and autoimmunity. Zhao M1, Wang Z1, Yung S2, Lu Q.;
Genotyping

- Genotyping should be used for research (cost ~$100) and later as diagnostic markers on custom chips (even LESS)
- Use for Pharmacogenetics should help guide choice of treatment
- Find Gene action/ Function - Leads to understanding mechanisms
  - e.g.: TCF7L2; Potential Therapy re: PARP-1 Inhibitor, other
  - Other Gene/Mechanism/ Therapy
    - low BMR- results in morbid obesity
    - Asian/ Eastern Europeans- store more Visceral Fat at Lower BMI
  - ? PREVENT T2DM- SLC30A8
  - Increase RISK- TBC1D4 (Greenland)

*Trends in Endocrinology and Metabolism* September 2014, Vol. 25, No. 9
Leif Groop. Can genetics improve precision of therapy in diabetes?
Pharmacogenetics:

Which agents most likely to be effective in a given patient

Fig. 1 Summary of the pharmacokinetic, pharmacodynamic and regulatory genes involved in significant gene–drug interaction in response to antidiabetic medication (adapted from Maruthur et al. [10]).
Figure 1. Interplay between genes and environmental/behavioral factors in the development of type 2 diabetes and related vascular complications. Variability in diabetes and obesity-related genes predispose to type 2 diabetes (T2D) and diabetic vascular complications such as coronary artery disease (CAD), diabetic nephropathy (DN), and diabetic retinopathy (DR). Behavioral (e.g., sedentary lifestyle, high-fat diet) and environmental factors (e.g., organic pesticides, chemical exposures, and air pollutants) have complementary effects on the development of type 2 diabetes. Additional genes are associated with CAD and body mass index (BMI) in the general population, without demonstrable effects on the risk of T2D.
Can picture Genomics CHIP for DM as developed for Breast Cancer - multi-gene assay applied to paraffin-embedded breast cancer tissue, which allows physicians to predict subgroups of hormone-receptor-positive, node-negative patients who may benefit from hormonal therapy alone or require adjuvant chemotherapy to attain the best survival outcome.

**Molecular Mammoscan**

*Ex Vivo Functional Pharmacogenomic Assay*

Could put other ‘Markers on same chip, eg:

- Proteinomics,
- Metabolomics
- miRNAs, islet DNA,
- IR markers, inflam.,
- Immune markers

As/when validated
Genetics of ‘LADA’

Typical age of onset

SPIDDM  Antibody + T2DM

<10 yrs

<10 yrs

Type 1 Diabetes

~60 genes

‘LADA’

Late onset type 1 diabetes?

Type 2 Diabetes

~60 genes

40 yrs

We are looking for LADA-Specific Genes

No genes in common

HLA  TCF7L2

We have found ‘typical’ T1DM genes, (Whose defects destroy b-cells) Whose ABSENSE may result in delay of T1DM, Thus = ‘Type 1-Like’ LADA

And Same Genes (or other T1DM –associated genes) May be over-represented/ present in ‘T2DM- Like’ LADA patients

Slow Destruction of B-Cells in T1DM-like LADA; Fast Destruction of B-Cells in T2DM-Like LADA
New β-Cell Centric Construct: Implications

β-cell Issues

- Usual use of Glycemic Criteria- HgA1c, FBS, PPG

- Markers-Usual/Classic= C-Peptide

- New Non-Invasive
  - β-Cell Mass Measures- Nano-particle labeled exendin imaging
  - Circulating DNA Markers of β-Cell Destruction
    Glazer- Hebrew Univ
  - Circulating mRNAs

- Try to Determine Mono-Genetic Causes

NO LOGIC FOR USE OF AGENTS THAT MAY CONTRIBUTE TO APOPTOSIS of β-Cell

STOP USING SU’s, GLINIDES; Minimize INSULIN THERAPY
Be aware of all the Secretory Dynamic Pathways involved, AND GENES INVOLVED
New β-Cell Centric Construct: **Implications**

**Inflammation/ Immune Dysregulation Issues-ALL DM**

β Cells are Destroyed by Innate (macrophages/cytokines) and Adaptive (T-cell/ antibody) Immune Reactions

*β-cells are destroyed via multiple interactions between macrophages, dendritic cells, natural killer cells, and lymphocytes*

Same Processes for T1DM, T2DM -

Same AND Different Triggers

Cytokines, Inflammation, and Metabolic Stress May Play a Role in β-cell Apoptosis in T2DM

*Initiation of a broad inflammatory response involves increased β-cell apoptosis*
Gut Microbiota Trigger Inflammation/Immune destruction of B-Cell in ‘T1DM’

Fig. 1. The role of gut microbiota in the development of T1D. Gut flora can affect islet autoimmunity through mechanisms: (1) expression of autoantigen mimicry to activate autoreactive T cells by antigen-presenting cells to destruct islet beta cells. (2) Generating metabolites, such as acetate, butyrate etc., to induce the differentiation or migration of regulatory T cells to control autoreactivity through GPCR signaling pathway (such as Gpr43). (3) Gut bacteria-derived pathogen-associated molecular patterns (PAMP) activate TLR signaling pathway to initiate the inflammation, which activates autoreactive T cells and/or directly cause injury to beta cells through inflammatory cytokines. (4) Gut bacteria can penetrate the leaky gut and cause inflammation to destruct beta cells.
Pathogenesis and biological interventions in T1DM- LIKE autoimmune diabetes - Insulitis

The class I MHC molecules are hyperexpressed on the β-cell surface in T1D patients making β-cells more susceptible to cytotoxic lymphocyte (CTL)-mediated destruction.

Novel diagnostic and therapeutic approaches for autoimmune diabetes — A prime time to treat insulitis as a disease

http://dx.doi.org/10.1016/j.clim.2014.11.007   Clinical Immunology, 2014    Juha Grönholm, Michael J. Lenardo
Efficacy of Immunotherapy in T1DM: Some Can Delay Decline in C-peptide

Figure 2. Heterogeneity in efficacy of immunotherapies in Type 1 diabetes. Treatment efficacy is determined by the impact of immunotherapy on decline in stimulated β-cell function as defined by C-peptide production in response to glucose. A positive effect implies delayed decline of C-peptide production upon a given immunotherapy (green). Lack of effect (white) denotes immunotherapy not changing the course of decline in β-cell function compared to placebo-treated subjects, whereas a (tendency of) negative effect implies an accelerated loss in β-cell function in response to intervention therapy (orange). GADA: Glutamic acid decarboxylase autoantibodies; T1D: Type 1 diabetes.
Insulin Resistance within the β-Cell Centric Construct

- Insulin Resistance is understood to expose and exacerbate the core β-cell defect
- Genetically-Based
- Exacerbated by Environmental issues: Diet, Activity, Biome
- Includes Multiple Causes of Insulin Resistance

Insulin Resistance Impairs β-Cell Function by:
- Lipo- and gluco-toxicity
- Inflammatory mechanisms
- Adipocytokines effect on β-cell
Insulin Resistance within the β-Cell Centric Construct

- Rare Insulin Resistance Syndromes - e.g.: leprechaunism may not have a specific β-Cell genetic defect, but β-cells may ultimately suffer damage.

Potential Causes of Insulin Resistance and Their Interplay

Central IR
- Loss of dopamine surge in SCN
- Increased appetite
- Increased sympathetic tone

Peripheral IR
- Biome IR
  - Pro-Biotics, Pre-Biotics, Antibiotics
- TZD (Pio-), Metformin

Hyperinsulinemia

Weight Reduction Agents
- Bromocriptine-QR

Inflammation IR
- Anti-Inflammatories
- Immune modulators

Loss of dopamine surge in SCN
Increased appetite
Increased sympathetic tone
Metabolic Derangement, and Insulin Resistance Associated with Microbiome

Lipopolysaccharides (LPS)

Fasting-induced adipocyte factor

Pioglitazone Treats Secondary Adverse Effects of Abnormal Biome
Simplistic Inflammatory and Non-Inflammatory Effects of Insulin Resistance on B-Cell Function
New β-Cell Centric Construct: *Implications*

Environmental Risk Factors in T1D/T2D, ? ‘LADA’

**T1D**

- Seasonality at diagnosis
- Migrants assume risk of host country
- Risk factors from case-control studies
  - Hormones
  - Stress
  - Improved Hygiene
  - Infant/childhood diet
  - Viruses – exposures as early as in utero

**T2D**

- Obesity-Diet
- Lack of Physical Activity
- AGE ingestion

**LADA**

- Coffee
- More Educated
Can Keep Current Terminology
Incorporate the β-Cell Centric Approach with each to determine issues in individual patient or a New Terminology?

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
<th>‘LADA’</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2D</td>
<td>MODY, monogenic</td>
<td>T1D</td>
</tr>
<tr>
<td>Genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mono</td>
<td></td>
<td>+,which</td>
<td></td>
</tr>
<tr>
<td>- poly</td>
<td>+,which</td>
<td>+,which</td>
<td>+,which</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+/-</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Resistance</td>
<td>+/-</td>
<td>+/-</td>
<td>—</td>
</tr>
<tr>
<td>Environment</td>
<td>+,which</td>
<td>+,which</td>
<td>+,which</td>
</tr>
</tbody>
</table>

Easier to get buy-in from many different stakeholders, MDs, etc
Or New Terminology Should Reflect the \textbf{\(\beta\)-Cell Centric Approach};

<table>
<thead>
<tr>
<th>Disease = DIABETES; Phenotype= Hyperglycemia</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Genes</th>
<th>+,which</th>
</tr>
</thead>
<tbody>
<tr>
<td>- mono</td>
<td></td>
</tr>
<tr>
<td>- poly</td>
<td>+,which</td>
</tr>
</tbody>
</table>

- Inflammation: +/-
- Resistance: +/-
- Environment: +,which

Implications for Therapy: Use whatever logically sensible/necessary based on cause of hyperglycemia in each patient.
New approach is Commensurate with Natural History of **ALL DM**

<table>
<thead>
<tr>
<th>Age</th>
<th>0-15</th>
<th>15-40+</th>
<th>15-50+</th>
<th>25-70+</th>
</tr>
</thead>
</table>

**Macrovascular Complications**
- Disability
- MI
- CVA
- Amp
- DEATH

**Microvascular Complications**
- BLINDNESS
- AMPUTATION
- CRF
- Disability
- Risk of Dev. Complications

**INSULIN RESISTANCE**

- Environment
- Inflammation/Immune Regulation
- β-Cell secretion/mass

**IGT**

- ETOH
- BP
- Smoking
- Eye
- Nerve
- Kidney

**ALL DM**
ANOTHER EPIPHANY:

WHAT ABOUT COMPLICATIONS OF DIABETES?

We noticed:
Pathophysiology of Diabetic Complications: Old Conundrum:
why similar HgA1c in different folk give different risks

I
Metabolic Disorder
Glucose, insulin hormones, enzymes, metabolites, etc (i.e., control)

II
Individual Susceptibility
Genetic/ethnic
?Acquired

III
Modulating Factors
Hypertension, diet, smoking, etc.

Delayed Complications
Retinal, renal neural, cardiovascular, cutaneous, etc.

IV
Early

V
Late

Point of metabolic “no return”

Factors Contributing to Cardiometabolic Risk

ARE THE SAME AS THOSE THAT DAMAGE THE Beta-Cell

- Genetics
- Age
- Overweight/Obesity
- Insulin Resistance
  - Lipids
  - BP
  - Glucose

- Insulin Resistance Syndrome

- Abnormal Lipid Metabolism
  - LDL $\uparrow$
  - ApoB $\uparrow$
  - HDL $\downarrow$
  - Triglycerides $\uparrow$

- Smoking, Physical Inactivity
- Hypertension
- Age, Race, Gender, Family History
- Inflammation, Hypercoagulation

diabetes.org/CMR
A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes.

MOST MECHANISMS OF B-cell Damage Overlap with Causes of ALL Complications

ALL COMPLICATIONS (Micro/MacroVascular Damage)

- Inflammation Immune Reg.
- Insulin Resistance - Part of Cardiometabolic Syndrome
- Environment
- Epigenetics
- Inflammation/Immune Regulation
- β-Cell secretion/mass

Provides Logic for Treatment Regimes and CV benefits of DM meds

Endogenous Fuel Excess (glucose/lipids) (Brownlee’s Unified Theory of Complications)

Genes may Be Same Or Different

*Environment=Genetic susceptibility to eg: viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome
Unified Theory of Diabetes and All Its Complications

Most Mechanisms of B-Cell Damage (Hyperglycemia)

Overlap with Causes of Vascular Disease:
Provides Logic for Treatment Regimes and CV Benefits of DM Meds

Endogenous Fuel Excess (glucose/ lipids)
(Brownlee’s Unified Theory of Complications)

Epigenetics - via ROS/ miRNAs

*Environment= Genetic susceptibility to e.g. viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome
Brownlee’s Mechanism’s leads to EPIGENETIC EFFECTS

Endogenous Fuel Excess (glucose/ lipids) (Brownlee’s Unified Theory of Complications)

Why some newer meds for DM Decrease Adverse Outcomes without major drops in HgA1c

Defines Logic for: Varied Risk of Comp. in Individual Patients with similar HgA1c

*Environment=Genetic susceptibility to eg: viruses, endocrine disruptors, food AGEs, Gut Biome; **Insulin Resistance= Centrally Induced, Peripheral, Stress Hormones, Gut Biome
Phenotypic Presentation of Each Complication is defined by:

**Slope** = ‘Natural History’ over time,

i.e. = RATE OF Development of Comp. Slope is not linear, and may be intermittently relapsing, remitting, stabilized, and improved, until ‘point of no return’ when presence and damage irreversible

For All DM

Severity of Complication

end Stage

DEPENDENT on
Genes - which, how many
Environmental Factors - which/how many
Inflammatory/Immune - which factors/how many
IR/ Cardiometabolic Syndrome

Increasing Age/Duration

Age/ at presentation = tipping point when the combined pathophysiologic processes are exposed as phenotypic functional/structural abnormalities
THUS: In Same Context, Need to Change Classification/ Nomenclature of the Complications of Diabetes

• Moreover:

• ‘Microvascular/ Macrovascular’ terminology have lost their meaning given new understanding of Causes of Complications -

• it’s CELLS/TISSUES affected by the pathophysiologic mechanisms

• Complications of ‘T1DM’ and T2DM’ are the same, not different

• MAJOR CORROLARY: Newer DM medications have been found to reduce complications of Diabetes by the common mechanisms causing DM and DM complications

• Diabetes Medications have become the Cardiologist’s Best Friends
Complications are Cellular/Tissue Based: not only ‘vascular’
THUS: In Same Context, Need to Change Classification/ Nomenclature of the Complications of Diabetes

- Moreover:

- ‘Microvascular/ Macrovascular ‘ terminology have lost their meaning given new understanding of Causes of Complications-

- it’s CELLS/TISSUES affected by the pathophysiologic mechanisms

- Complications of ‘T1DM’ and T2DM’ are the same, not different

- MAJOR CORROLARY: Newer DM medications have been found to reduce complications of Diabetes by the common mechanisms causing DM and DM complications

- Diabetes Medications have become the Cardiologist’s Best Friends
### Inferences on Value of Glycemic Control and Other Mechanisms of DM meds in Reducing Complications of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>CV Benefits of DM Meds Driven By Other Mechanisms!!</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Glycemic Hypothesis Proven in Primary</strong></td>
</tr>
<tr>
<td>UKPDS</td>
<td>Reduced</td>
</tr>
<tr>
<td>HgA1c drop</td>
<td>Reduced</td>
</tr>
<tr>
<td>eye</td>
<td>Reduced</td>
</tr>
<tr>
<td>nerv</td>
<td>Reduced</td>
</tr>
<tr>
<td>kidney</td>
<td>Reduced</td>
</tr>
<tr>
<td>MA CE</td>
<td>Reduced</td>
</tr>
<tr>
<td>CV Mort</td>
<td>Reduced</td>
</tr>
<tr>
<td>MI</td>
<td>Reduced</td>
</tr>
<tr>
<td>CVA</td>
<td>Reduced</td>
</tr>
<tr>
<td>CHF</td>
<td>Reduced</td>
</tr>
<tr>
<td>All Cause Mort</td>
<td>Reduced</td>
</tr>
<tr>
<td><strong>PRE V</strong></td>
<td>Prevention despite ‘wrong meds’</td>
</tr>
<tr>
<td>DCCT</td>
<td>~2.0</td>
</tr>
<tr>
<td>VADT</td>
<td>1.5</td>
</tr>
<tr>
<td>ADV.</td>
<td>0.8</td>
</tr>
<tr>
<td>ACCORD</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>OND</strong></td>
<td>Metabolic memory</td>
</tr>
<tr>
<td><strong>ARY</strong></td>
<td>Wrong drugs, wrong process of care</td>
</tr>
<tr>
<td><strong>PRE V</strong></td>
<td>Benefits primarily driven</td>
</tr>
<tr>
<td>BROMO-QR</td>
<td>(pts &lt;7.0)</td>
</tr>
<tr>
<td><strong>VEN</strong></td>
<td>By other mechanisms</td>
</tr>
<tr>
<td>EMPA-Reg</td>
<td>0.6 early</td>
</tr>
<tr>
<td><strong>TI</strong></td>
<td>Besides glycemia, eg:</td>
</tr>
<tr>
<td>IRIS</td>
<td>IR/pr early-DM</td>
</tr>
<tr>
<td><strong>ON</strong></td>
<td>Reduced</td>
</tr>
<tr>
<td>LEADER</td>
<td>0.4</td>
</tr>
</tbody>
</table>
**β-Cell (Islet Cell) Classification Model: Implications for Therapy:**

**Targets for Therapies/ New Guidelines**

Medication Choice Based on

1. Glycemic Efficacy
   
   **BUT ALSO**

2. Number of Targets of Therapy each drug addresses
   
   ( combo therapy efficacy likely depends on number of overlapping mechanisms)

3. Weight loss

4. Proven Reduction in Risk Factors/ CV outcomes—Synergies—eg: SGLT-2, (pioglitazone, bromocriptine QR, metformin, GLP-1)
**Precision Medicine Approach to DM/ CV Therapy: Algorithms should Assess not only Glycemic benefits of agents/classes but CV/weight benefits**

***Implications for New Guidelines***

1. **Pancreatic β-cells**
   - **↓ Insulin**
   - FINAL COMMON DENOMINATOR
   - **Dpp-4 Inhibitors**
   - **GLP-1 RAs**
   - **Metformin**

2. **↓ Incretin effect**
   - **Dpp-4 Inhibitors**
   - **GLP-1 RAs**

3. **α-cell defect**
   - **↑ Glucagon**
   - **Dpp-4 Inhibitors**
   - **GLP-1 RAs**
   - **Pramlintide**

4. **Hyperglycemia**

5. **Liver**

6. **Muscle**

7. **Brain**
   - **GLP-1 RAs**
   - **Dopamine agonist-QR**
   - **Appetite Suppressants**

8. **Colon/Biome**
   - **Probiotics/Prebiotics**
   - **Dpp-4 Inhibitors**
   - **GLP-1 RAs**
   - **Metformin**

9. **Immune Dysregulation/Inflammation**
   - **Dpp-4 Inhibitors**
   - **GLP-1 RAs**
   - **Anti-Inflammatories Immune modulators**

10. **Stomach/Small intestine**
    - **GLP-1 RAs**
    - **Pramlintide**
    - **AGI**

11. **Kidney**
    - **SGLT2 inhibitors**

**Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide**
### Sample Triple Therapy: Anticipated Effects

Table III. Proposed optimal triple therapy with the best risk reduction for patients with type 2 diabetes mellitus presenting with established cardiovascular disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metformin</th>
<th>Pioglitazone</th>
<th>Empagliflozin</th>
<th>Anticipated Effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>All-cause death</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
</tr>
<tr>
<td>Stroke</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>↓↓</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>←</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>Heart failure</td>
<td>←</td>
<td>↑</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>Weight</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>←</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
<td>←</td>
</tr>
<tr>
<td>HDL-C</td>
<td>←</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>←</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

Source: From Schernthaner and Schernthaner.\textsuperscript{42}

↓ = lowered; ↑ = elevated; ← = unchanged; HbA\textsubscript{1c} = glycosylated hemoglobin.
An ‘Evidence-Based Practice, Patient Centeric’ Approach

As a Clinician

Think

Inside a Larger Box 😊

Evidence-Based AND Patient Centric:

EVIDENCE-BASED PRACTICE

Mechanism of Disease +
Mechanism of Drug +
Patient Factors =

Right Drug

Clinical Expertise, Expert Opinions
Patient-Based experience

Evidence-Based Medicine

Randomized, prospective trials – (if exists and if patient fits)


New β-Cell Centric Construct: *Implications*  
Diagnosis Markers

By Virtue of Family History ‘DM”, Physiogomy, hyperglycemia, in prediabetic and diabetic range *

- **Genes**
  - Family History
  - Genotype- HLA, *TCF7L2*, etc

- **β-Cell**
  - FBS, 2hr ppg, HgA1c, ? C-peptide, ?other- β-Cell mass measures

- **Inflammation**
  - Antibodies, Inflammatory Markers, T-Cell function, ?other

- **Insulin Resistance**
  - BMI, Adiponectin, Adipocytokines, ? Other

* Individualized and reliant on cost, insurance coverage, formulary, government
Patient-Centric Diagnosis & Process of Care/Therapy

At Risk Individuals

Traditional Labs/Testing
FBS, RBS, HgA1c

Specific Therapy addressing Genotype

Etiologic Diagnostic Markers:
β-Cell, Insulin resistance, Inflammation, Environment, Genes

Least Number of Meds that Rx most Number of Mechanisms of Hyperglycemia

1. Pancreatic β-cells
↓ Insulin

Final Common Denominator
Dpp-4 Inhibitors *
GLP-1 RAs * WR
Metformin*

2. ↓ Incretin effect
Dpp-4 Inhibitors *
GLP-1 RAs * WR

3. α-cell defect
↑ Glucagon
Dpp-4 Inhibitors *
GLP-1 RAs * WR

Pramlintide*

Hyperglycemia

Genes

Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide
Going Forward: New Focus of Care: **Primary Prevention**? For All DM in New Classification

- **Genetic/antibody screening** 1 effort to identify eligible subjects
- **Potential Immune Modulators** 2
- **Environmental Modulation** 3
  - Especially as we learn more-vaccination, endocrine disruptors, diet, exercise
- Intervention needs to be **extremely safe**
- **Defining risk factors** will facilitate primary prevention studies

Atkinson, Eisenbarth, *THE LANCET* • Vol 358 • July 21, 2001 225
Choice of Therapy

• Based on
  – Treating Causes of \(\beta\)-Cell dysfunction
  – Treating Abnormalities resulting from \(\beta\)-Cell dysfunction
• No Logic for Agents that Decrease \(\beta\)-Cell dysfunction

THUS: SELECT AGENTS THAT CAN PRESERVE \(\beta\)-Cell function/mass

Allows us to Correct a myth

MYTH: “Most Patients with ‘T2DM’ will eventually progress to insulin because of inexorable \(\beta\)-Cell loss”

- But data obtained on SU=apoptosis; Hyperinsulinism with weight gain
- Think of bariatric patients –no insulin after 25 years DM/ 20 years insulin
- Most patients dying with DM have > 20% \(\beta\)-Cell mass- Butler
- Need to remove >80% pancreas in sub-total pancreatectomies to leave patient with DM post-op
Avoid Early Insulin Therapy (except in Ketosis-prone)

Vicious Circle(s) of Hyperinsulinemia - Result in Weight Gain and Hypoglycemia

Figure 1

Blood glucose rises

Patient eats too much
Or simple sugars

Consumption of more calories, diet high in fat and simple carbohydrates and resultant weight gain

Increase in basal doses of insulin to control blood glucose

Undue Basal Or bolus Insulin = Overinsulinized

Hypoglycemia Symptomatic or not!

INCREASED APPETITE

Patient eats too much
Or simple sugars

Blood glucose rises

Consumption of more calories, diet high in fat and simple carbohydrates and resultant weight gain

Increase in basal doses of insulin to control blood glucose

Undue Basal Or bolus Insulin = Overinsulinized

Hypoglycemia Symptomatic or not!

INCREASED APPETITE
Obligatory excess peripheral insulin to get modicum of reduced hepatic glucose production

Endogenous Insulin

Exquisitely controlled levels of insulin released into the portal vein

Fine-tuned, physiologically appropriate insulinemia

Exogenous Insulin

‘Obligatory’ excess peripheral insulin to get modicum of reduced hepatic glucose production

Hyperinsulinemia

Insulin Resistance

Obesity

Weight gain

Dyslipidemia

Chronic Inflammation

Type II Diabetes

Cancer

Atherosclerosis

Hypertension

Hypoglycemia

NOTE:
There is NO perfect Exogenous Insulin: All result in HyperInsulinemia and Potential Hypoglycemia

6-cell Dysfunction
Potential 6-cell Exhaustion
Therapeutic Principles Across Continuum of Care

Right Drug for Right Patient and vice versa

DETERMINE INSULIN DEPENDENCY-(DKA, c-peptide, ?other

DETERMINE Patient Specific Mechanisms of Hyperglycemia

- Treat ? For prevention/ pre-diabetes
- Treat as many of the Egregious 11 Targets as needed,
  least # of agents, lowest sugars/HgA1c as possible
  without undue weight gain or hypoglycemia

• Early Combination Therapy- Patient Centric-
  even 6.5-7.5 HgA1c
  Efficacy, - CV event reduction, Weight Loss
  (Not first-second-third line; Not competition between
  classes)

- Can Modify therapy after 1m-not 3m-use Fructosamie
- Stabilize, preserve β-cells, the CORE DEFECT
- ( NO SU/GLINIDES)-
- Ideally agents will have potential to
  synergistically decrease in CV risk factors / outcomes
Therapeutic Principles Across Continuum of Care

1. Delay Need for Insulin

2. No need for Early Insulin

3. If need Insulin, Continue Non-Insulin RX (Avoids need for Meal-Time Insulin) (Decrease Risk Hypoglycemia 85% - Garber)

4. Get Patients off insulin who had been given early Insulin
Hedge your Bets: Incretins for all patients
DPP4 inhibitors, GLP-1 RAs, [other agents that increase GLP-1 eg: metformin, colsevalam, (TGR-5)]

- **T1DM**: minimize brittle, dawn, unpredictablity, variability, ? CV benefits, Treat those ‘Type 2’ Genes’, ANTI-INFLAMMATORY

- **LADA** = SPIDDM/ Autoimmune T2DM. Same as above - Slow, stabilize disease process, ANTI-INFLAMMATORY

- **T2DM**: Same as above, treats 7 MOA’s of DeFronzo’s Octet, decreases oxidative stress, β-cell inflammation decreases lipo- and gluco-toxicity, ?preserve mass, decreases appetite, treats IR via wt. loss

- **MODY 3**: recent report

FOR ALL DM – potential CV benefit (ANTI-INFLAMMATORY)
Reference list for last slide

LADA

TYPE 1
- Ellis et al, Effect of Sitagliptin on glucose control in Adult patients with Type 1 DM, Diabetic Medicine DOI: 10.1111/j.1464-5491.2011.03331
- Kielgast U., et al Treatment of Type 1 Diabetic Patients with GLP-1 and GLP-1 Agonists, Current Diabetes Reviews, 2009, 5:266-275

TYPE 2
- Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus Diabetologia - Clinical and Experimental Diabetes and Metabolism, 03/04/2014
Aggressive medical therapy in diabetes - SUMMARY

SGLT-2 Inh. Liraglutide
Bromocriptine QR Pioglitazone
Metformin Ranolazine (Incretins)

Hyperglycemia/Insulin resistance

ACE inhibitors
ARBs β-blockers CCBs Diuretics

Hypertension

Statins Fibric acid derivatives Colsevalam PCSK-9 Inh

Dyslipidemia

ASA Clopidogrel Ticlopidine

Platelet activation and aggregation

Atherosclerosis, CV Outcomes, CV Risk Factors, Mortality

DM MEDS MAY BE A CARDIOLOGIST’S BEST FRIEND

Adapted from Beckman JA et al. JAMA. 2002;287:2570-81.
# Treating the ABCs Reduces Diabetic Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose control</strong></td>
<td>Heart attack</td>
<td>↓ 37%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>↓ 51%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>↓ 56%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>↓ 44%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Diabetes-related deaths</td>
<td>↓ 32%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Blood pressure control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease mortality</td>
<td>↓ 35%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Major coronary heart disease event</td>
<td>↓ 55%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Any atherosclerotic event</td>
<td>↓ 37%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lipid control</strong></td>
<td>Cerebrovascular disease event</td>
<td>↓ 53%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Conclusion

• Current classifications of DM are inadequate:
• new classification schema -the β-cell as THE CORE DEFECT in ALL DM,
• The various mediators of β-cell dysfunction offer key opportunities for Prevention, Therapy, Research and Education
• Same Mechanisms of β-cell dysfunction are responsible for DM complications (explains why some DM meds can decrease CV outcomes)
• Patient care should shift from current classifications that limit therapeutic choices to:
  • one that views a given patient’s disease and treatment course based on their individual cause(s) of metabolic dysregulation, e.g. genes, inflammation, insulin resistance- (including gut biome, central (brain) mechanisms), environmental factors, etc.
Conclusion-2

• Defining markers, and Processes of Care = patient-centric, Precision Medicine approaches

• In T1D and LADA, in particular, incretins, insulin sensitivity agents, SGLT-2 inhibitors and others are either underutilized in some cases, and under-evaluated in others

• Convene Organizations eg: ADA/EASD/WHO/IDF/AACE / JDF to Revise Classification of DM

• More research always needed, but,

• in an evidence-based PRACTICE approach to care, we can START NOW
Based on ‘New’ Classification: Recommended Process For Prevention, Diagnosis and Therapy

- Convene ADA/EASD/WHO/AACE Committee: Revise Classification of DM
- Put processes into place. Increase current repositories. JAEB, JDRI to include LADA patients, (but all kinds of hyperglycemic patient types), Large Health Systems (K-P)
- Research into these ideas/approaches
- EDUCATE MDs re :issues

Use Evidence-Based Practice Approaches to DX
Where evidence is incomplete but logic exists, apply appropriate treatment to improve patient care.