OCHSNER'S 2021 FRANK RIDDICK INSTITUTE DIABETES SYMPOSIUM

Moving Goalposts; The evolution of therapeutic targets and goals in diabetes care; Beyond HBA1c.

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DISCLOSURES STATEMENT

- While I am a clinical trialist that runs several industry and govt sponsored clinical trials all funds from these trials are paid directly to the Ochsner medical foundation.
- Nothing presented during this presentation has any relationship to any of the therapeutic medications nor devices in any of my ongoing or completed clinical trials.
- There are no personal nor family related/affiliated disclosures of any relevance nor bearing to any of the material presented here.

Thank you very much

Presentation Objectives

- To review the history of HBA1c as a therapeutic target for Diabetes care.

- To discuss the changes in HBA1c goals and targets in diabetes.

- To highlight the limitations of HBA1c as a therapeutic target in Diabetes care.

- To discuss the role and place of non-HBA1c goals and targets in diabetes therapeutics.

- To highlight the evolution of emerging non-HBA1c goals and targets in diabetes therapeutics.

THE ASCENDANCY OF HBA1C; A TRIP DOWN MEMORY LANE

DCCT/EDIC: Overview

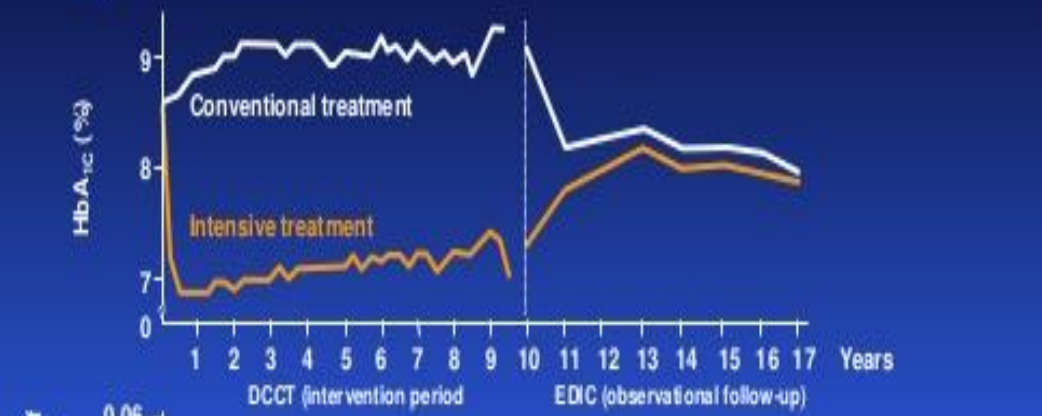
- **The DCCT** was designed to test the glucose hypothesis and determine whether the complications of type 1 diabetes could be prevented or delayed (**1982–1993**)
- **The EDIC** observational follow-up study determined the durability of the DCCT effects on the more-advanced stages of diabetes complications including cardiovascular disease (**1994–present**)

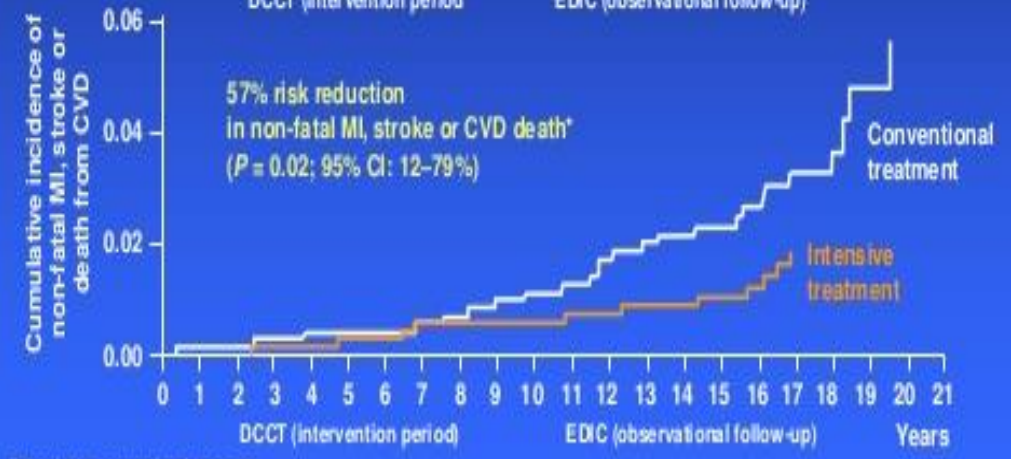
AIMS: determine whether conventional therapy and intensive treatment program prevent or delay the appearance of early background retinopathy (primary prevention) and would prevent the progression of early retinopathy to more advanced forms of retinopathy (secondary intervention)

DCCT : Diabetes Control and Complications Trial;
EDIC : Epidemiology of Diabetes Interventions and Complications

Nathan *et al. Diabetes Care* 2014;37:9–16

DCCT/EDIC: glycaemic control reduces the risk of non-fatal MI, stroke or death from CVD in type 1 diabetes





*Intensive vs conventional treatment

Adapted from DCCT. *N Engl J Med* 1993;329:977–986. DCCT/EDIC. *JAMA* 2002;287:2563–2569. DCCT/EDIC. *N Engl J Med* 2005;353:2643–2653.

THE ASCENDANCY OF HBA1C; A TRIP DOWN MEMORY LANE

UKPDS Objective and Study Design

CardioVasculaire GeneesKunde.nl

- UKPDS
  - Investigated the advantages of intensive glucose control with metformin[1]
  - 20-year prospective interventional trial from 1977 to 1997[1]
    - Intensive treatment with sulfonylurea or insulin
    - Intensive treatment with metformin
    - Conventional treatment with diet
  - 5102 patients with newly diagnosed type 2 diabetes recruited between 1977 and 1991[1]
  - Median follow-up: 10 years, range: 6-20 years[2]
  - Results presented at the 1998 EASD meeting in Barcelona[2]
- UKPDS 10-year posttrial monitoring from 1997 to 2007[2]
  - Annual follow-up of survivor cohort (n=3227)
    - Clinic-based for first 5 years
    - Questionnaire-based for last 5 years
- Median overall follow-up: 17 years, range: 16-30 years[2]

UKPDS=United Kingdom Prospective Diabetes Study.

1. UKPDS Group. *Lancet* 1998;352(9131):854-865.
2. Holman et al. *N Engl J Med* 2008;359(15):1577-1589.

UK Prospective Diabetes Study

An intensive glucose control policy HbA$_1$ 7.0 % vs 7.9 % reduces risk of

any diabetes-related endpoints	12%	p=0.030
microvascular endpoints	25%	p=0.010
myocardial infarction	16%	p=0.052

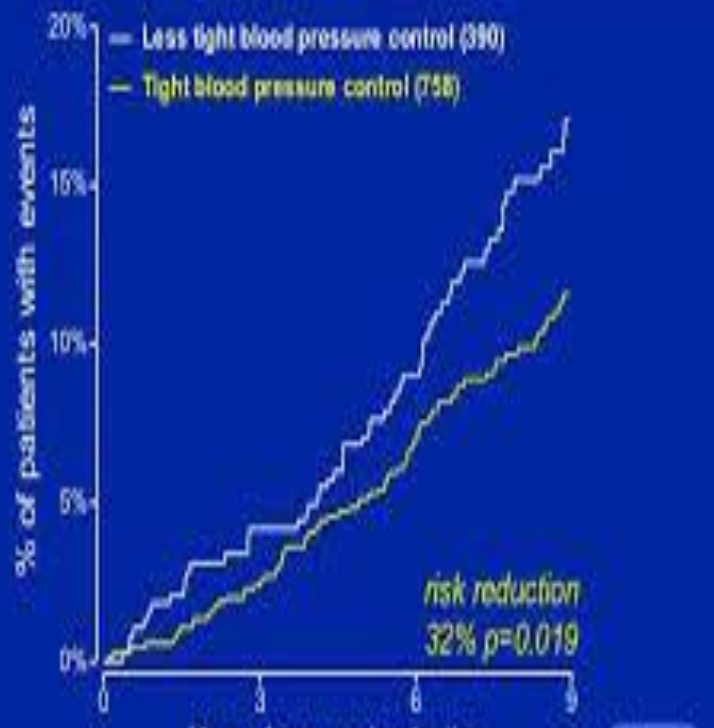
A tight blood pressure control policy 144 / 82 vs 154 / 87 mmHg reduces risk of

any diabetes-related endpoint	24%	p=0.005
microvascular endpoint	37%	p=0.009
stroke	44%	p=0.013

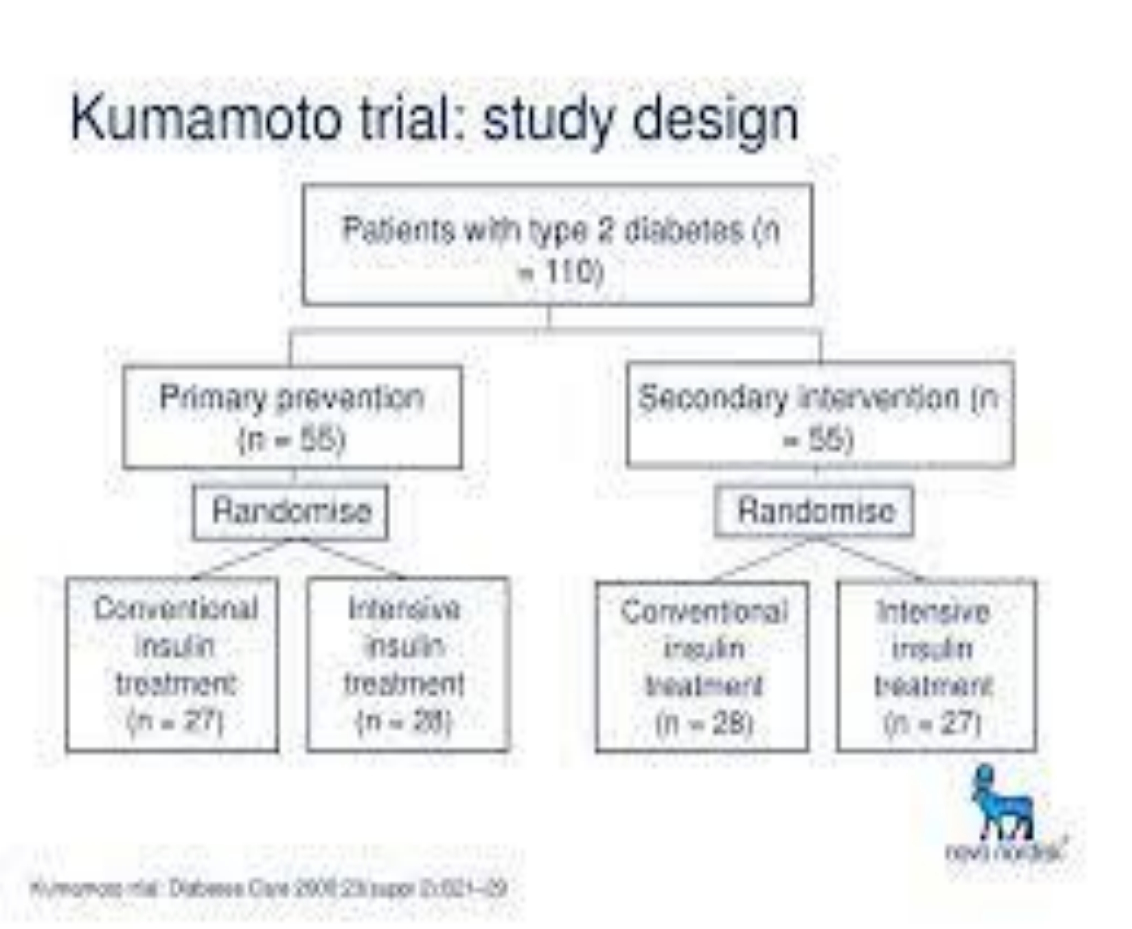
ukpds

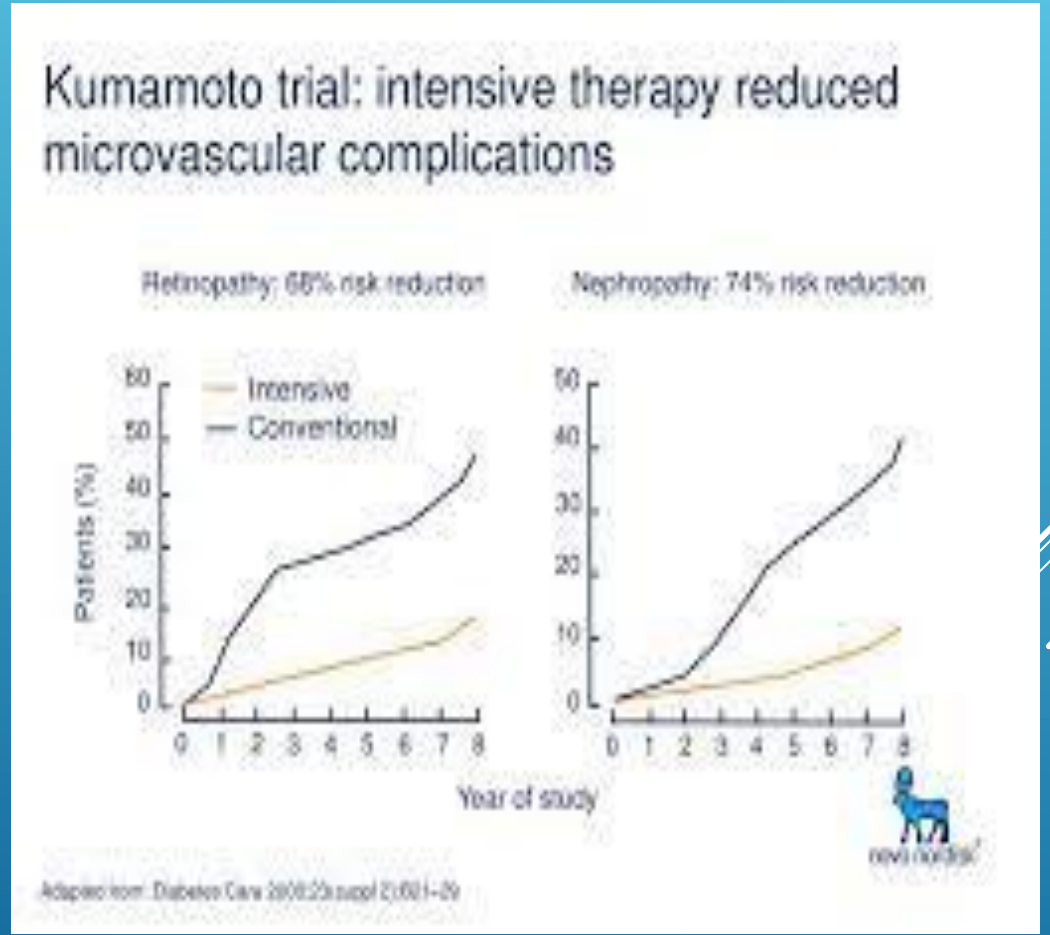
Microvascular Endpoints (cumulative)

Diabetes-related deaths



THE ASCENDANCY OF HBA1C; A TRIP DOWN MEMORY LANE





The ascendancy of HBA1c; a trip down memory lane

Intensive Diabetes Therapy & HbA1c: Reduced Incidence of Complications

HbA1c	DCCT 9 → 7.2%	Kumamoto 9 → 7%	UKPDS 8 → 7%
Retinopathy	63%	69%	17% to 21%
Nephropathy	54%	70%	24% to 33%
Neuropathy	60%	Improved	-
Cardiovascular Dx	41%	-	16%

Diabetes Control and Complications Trial (DCCT) Research Group. N Engl J Med 1993; 329, 977-996
Ohkubo Y et al. Diabetes Res Clinc Pract. 1995;28:103-117
UK Prospective Diagets Study (UKPDS) group. Lancet 1993;352:837-853
Slide modified from D. Kendall, IDC

HealthPartners
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International Diabetes Center

ITS ALL ABOUT HBA1C (AND GETTING IT UNDER 7.0 BY ANY MEANS NECESSARY) ISN'T IT?

- We are strongly admonished to ensure we score but it is not that simple nor straightforward anymore;
- Which ball are we playing with and in which sport? What goal are we aiming to score?

HBA1C > 7.0 AS THE TARGET FOR DIABETES CARE GOALS

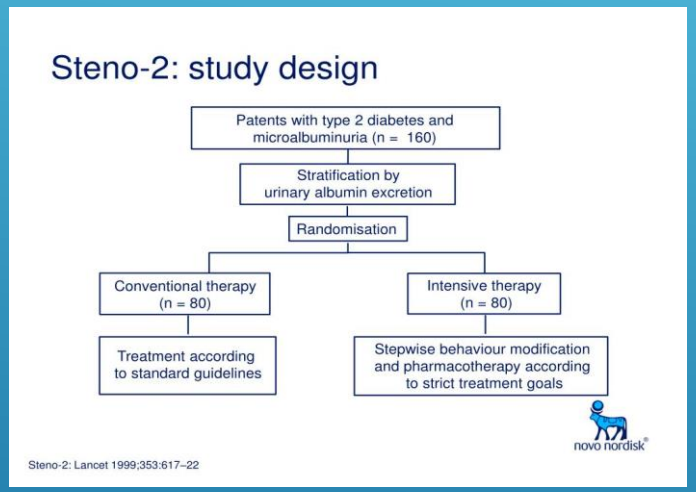
- The Ascendancy of HBA1c > 7.0 quickly became universal as the goal for diabetes care in clinical settings, public health settings and for antidiabetic medication pharmaceutical and medical device certifications. It is now also widely used in quality of care measures, reimbursement and compensation decisions.

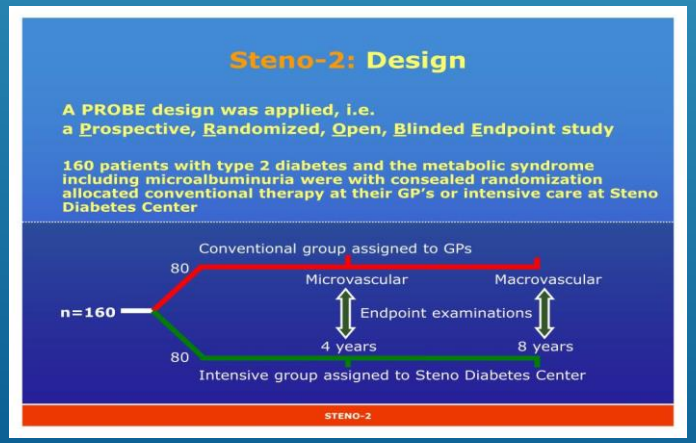
But what are the problems and caveats that have seen this goal now undergo widespread revision and tweaks?

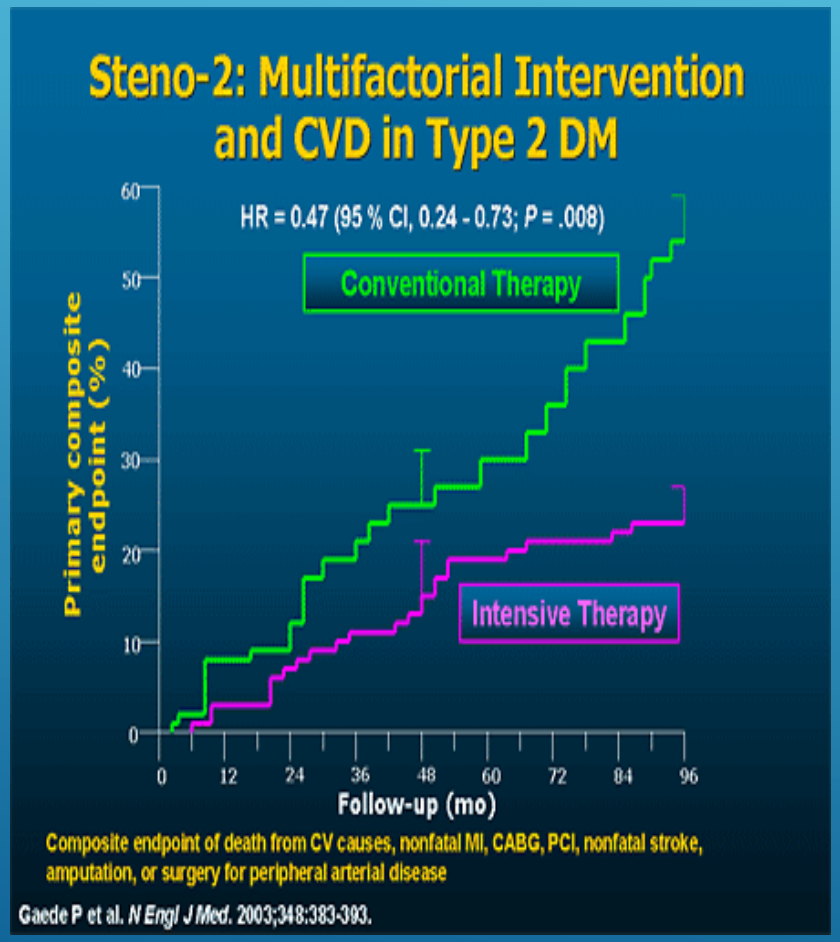
- 1. Diabetes is more than a glucocentric state; it is a cardio-metabolic syndrome
- 2. Diabetes is not one disease but several different conditions with the only commonality being the shared chronic hyperglycemia associated with metabolic derangements of protein, lipid and glucose metabolism.
- 3. Even among patients with the same “type” of diabetes it is now clear that demographic and comorbidity factors significantly impact goal setting.
- 4. HBA1c as an outcome surrogate has many important limitations and caveats that are now better understood and appreciated.
- 5. Clinical therapeutic and diagnostic tools have improved substantively since the age of the DCCT, UKPDS and Kummato trials.
- 6. As the prevalence of Diabetes has skyrocketed worldwide with its associated macrovascular comorbidities and mortality the importance of cardiovascular and all cause mortality outcomes has progressively gained ascendancy.
- 7. The burden of the lifestyle and mental health related impacts of diabetes have progressively highlighted quality of life indices and measures in evaluating and establishing diabetes care goals.

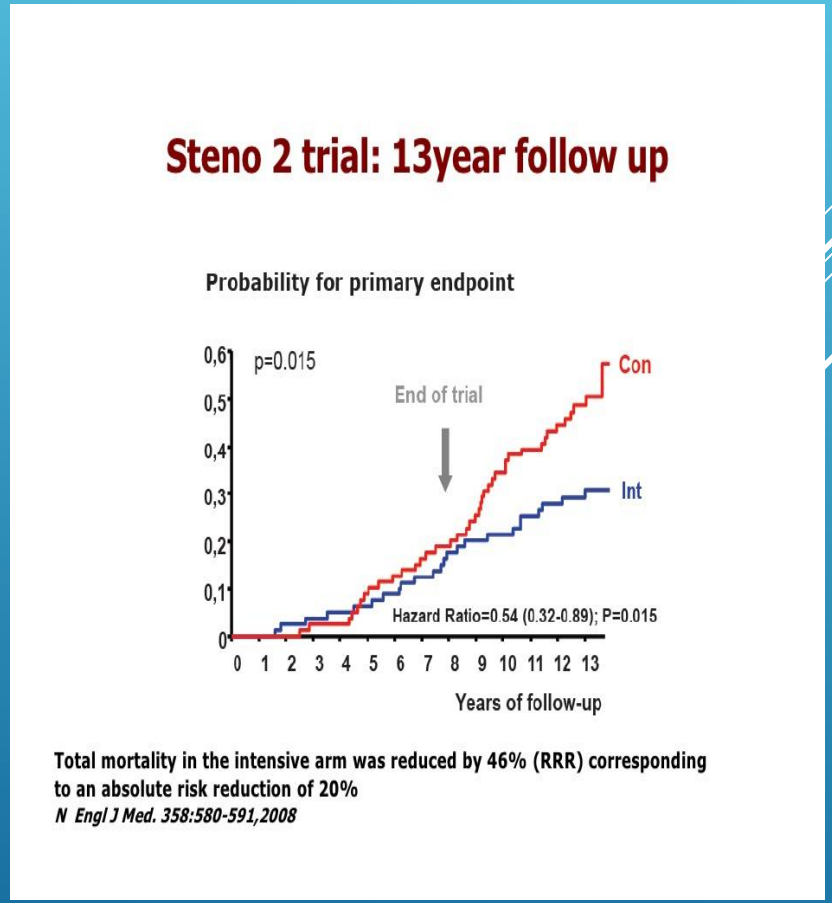
DIABETES IS MORE THAN A GLUCOCENTRIC STATE; IT IS A CARDIO-METABOLIC SYNDROME

- It has taken years of prospective data accumulation but it now clear that the dominant cause of mortality in both type 2 as well as type 1 diabetes is atherosclerotic cardiovascular disease acute events including coronary and cerebrovascular events.









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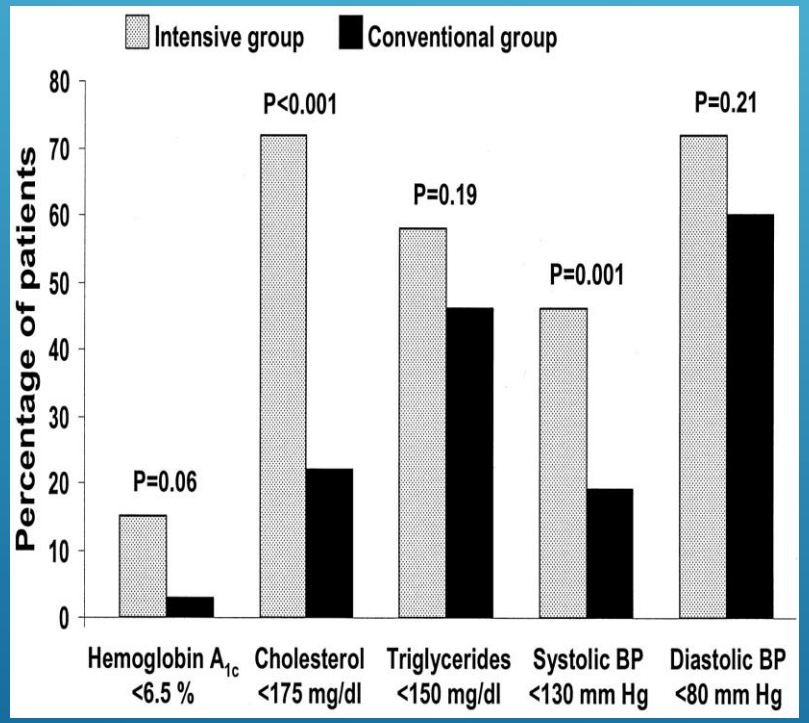

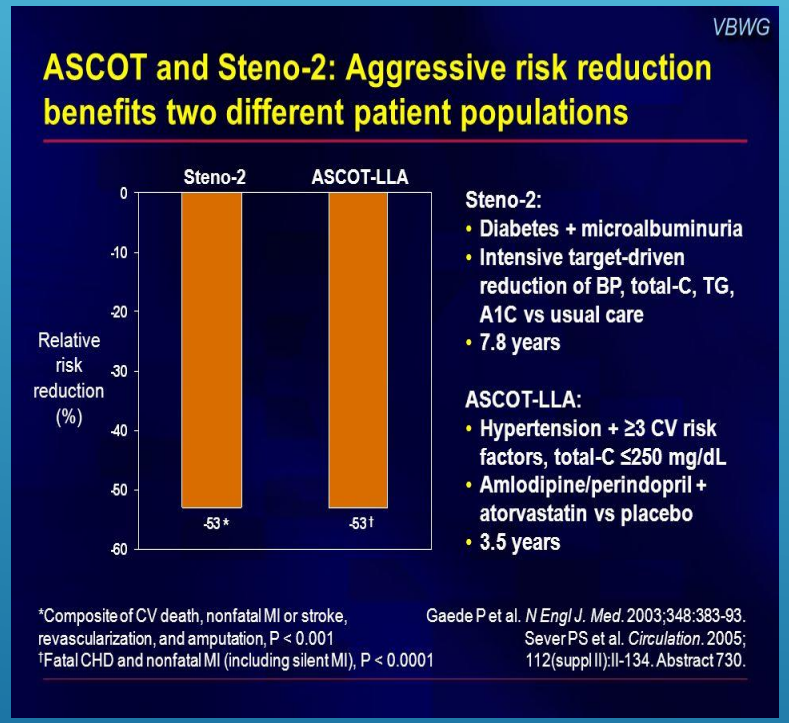

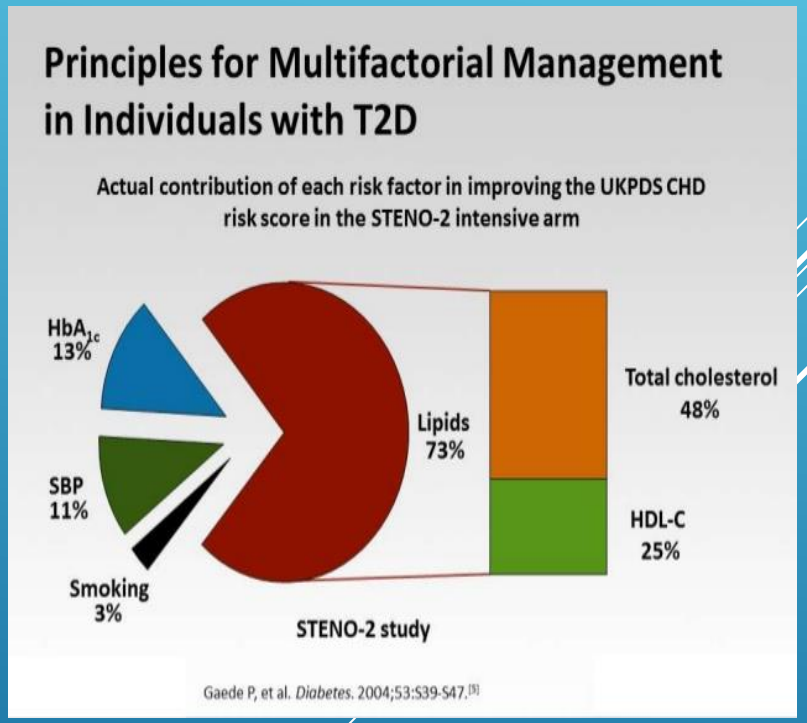

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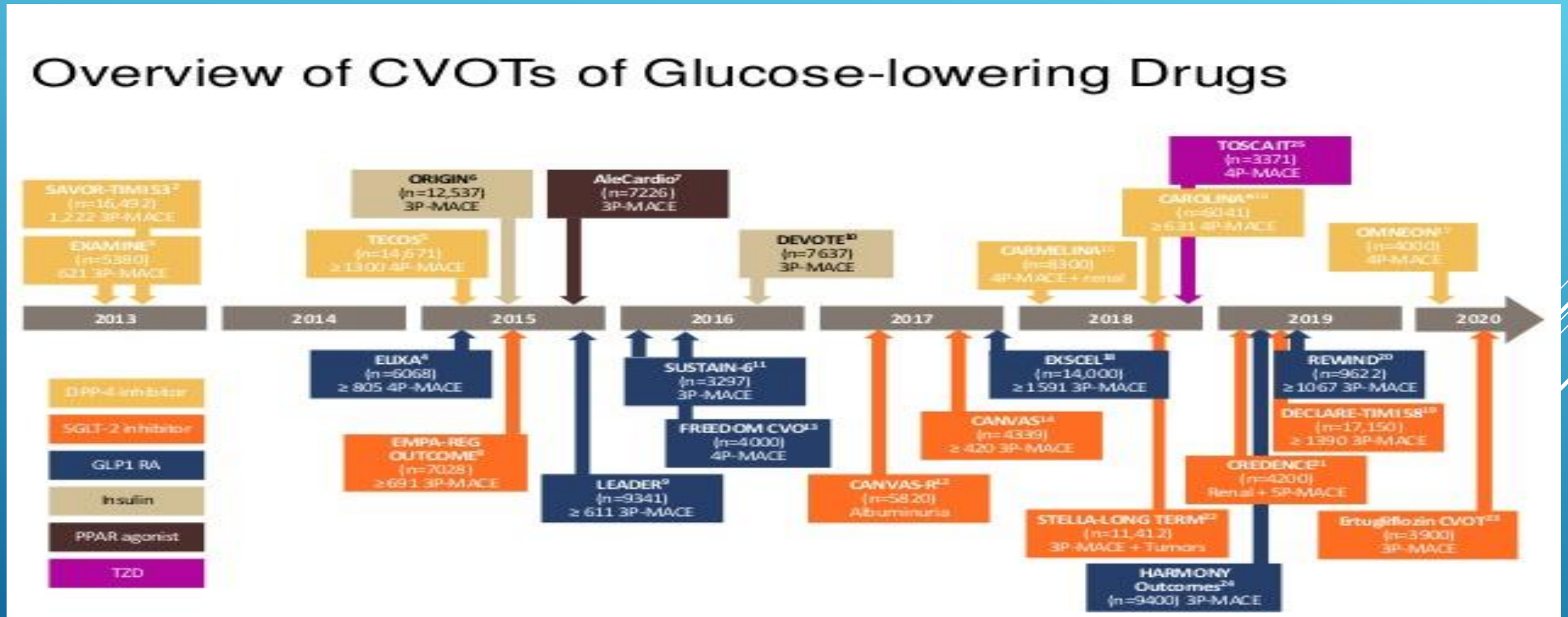

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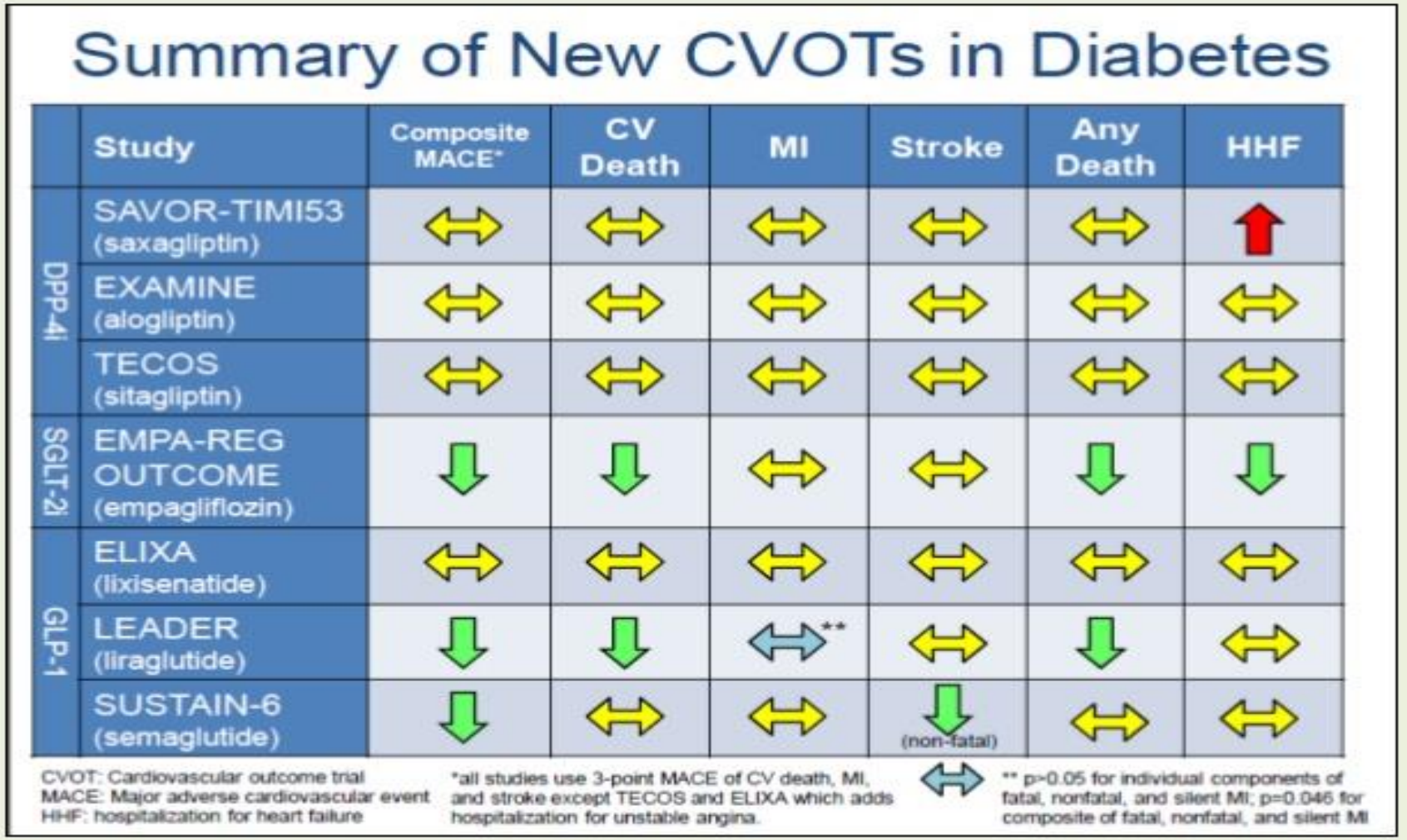

DIABETES IS NOT ONE DISEASE BUT SEVERAL DIFFERENT CONDITIONS

Etiologic classification of diabetes mellitus

Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated
B. Idiopathic
Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
Other specific types
A. Genetic defects of beta cell function
1. Chromosome 12, HNF-1-alpha (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4-alpha (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1-beta (MODY5)
6. Chromosome 2, NeuroD1 (MODY6)
7. Mitochondrial DNA
8. Others
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
E. Drug or chemical induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. Beta-adrenergic agonists
8. Thiazides
9. Atypical antipsychotics
10. Dilantin
11. Alpha interferon
12. Others
F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others
G. Uncommon forms of immune-mediated diabetes
1. "Stiff man" syndrome
2. Anti-insulin receptor antibodies
3. Others
H. Other genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others
Gestational diabetes mellitus
Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

- The equivalent of DCCT and UKPDS studies have not been done on the various unique "other" forms of diabetes and likely will never be done.
- The heterogeneity of diabetes is increasing.
- Just as the treatment methods for different forms of diabetes are distinctive the therapeutic goals are not always the same as for non-syndromic diabetes.
- One size certainly does not fit all.

DIABETES IS NOT ONE DISEASE BUT SEVERAL DIFFERENT CONDITIONS

The special case of gestational diabetes and diabetes in pregnancy (pre-gestational diabetes)

Modified White's classification of diabetes in pregnancy

Class	Description
A	Abnormal GTT before pregnancy at any age or of any duration treated only by diet therapy
B	Onset at age 20 years or older and duration of less than 10 years
C	Onset at age 10 to 19 years or duration of 10 to 19 years
D	Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia)
R	Proliferative retinopathy or vitreous hemorrhage
F	Nephropathy with over 500 mg/day proteinuria
RF	Criteria for both classes R and F
H	Evidence of arteriosclerotic heart disease
T	Prior renal transplantation
Gestational diabetes	
A1	Diet-controlled gestational diabetes
A2	Insulin-treated gestational diabetes

Classes B through T require insulin treatment.

GTT: glucose tolerance test.

Adapted from:

1. *Hare JW, White P. Gestational Diabetes and White Classification. Diabetes Care 1980; 3:394.*
2. *White P. Pregnancy complicating diabetes. Am J Med 1949; 7:609.*

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Diagnostic criteria for the 100-gram three-hour GTT to diagnose gestational diabetes mellitus

	Plasma or serum glucose level Carpenter/Coustan	
	mg/dL	mmol/L
Fasting	95	5.3
One hour	180	10.0
Two hours	155	8.6
Three hours	140	7.8

100-gram oral glucose load is given in the morning to a patient who has fasted overnight for at least 8 hours. Glucose concentration greater than or equal to these values at two or more time points are generally considered a positive test, but in 2017, an American College of Obstetricians and Gynecologists practice bulletin stated that clinicians may reasonably consider one elevated value diagnostic of a positive test.[1]

GTT: glucose tolerance test.

References:

1. *Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 180: Gestational diabetes mellitus. Obstet Gynecol 2017; 130:e17.*

Data from: VanDorsten JP, Dodson WC, Espeland MA, et al. National Institutes of Health consensus development conference statement: Diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements 2013; 29:1.

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IADPSG and ADA criteria for a positive two-hour 75-gram oral glucose tolerance test for the diagnosis of gestational diabetes

Two-hour 75-gram oral glucose tolerance test	
Fasting	≥92 mg/dL (5.1 mmol/L)
OR	
One hour	≥180 mg/dL (10.0 mmol/L)
OR	
Two hour	≥153 mg/dL (8.5 mmol/mol)

The diagnosis of gestational diabetes is made at 24 to 28 weeks of gestation when one or more plasma glucose values meets or exceeds the above values.

IADPSG: International Association of the Diabetes and Pregnancy Study Groups; ADA: American Diabetes Association.

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- Priorities in pregnancy related diabetes; prevention of neonatal hypo and hyperglycemia, prevention of fetal macrosomia, prevention of maternal and fetal morbidity and mortality.
- Glycemic goals are geared towards these and thus are glucocentric and not HBA1c driven nor concerned with macrovascular disease risk surrogates.

DIABETES IS NOT ONE DISEASE BUT SEVERAL DIFFERENT CONDITIONS

The special case of gestational diabetes and diabetes in pregnancy (pre-gestational diabetes)

The glycemic goals for diabetes in pregnancy therefore are;

- **American College of Obstetricians and Gynecologists (ACOG; 70 to 110 mg/dL [3.9 to 6.1 mmol/L])**
- **The Endocrine Society Clinical Practice Guidelines (72 to 126 mg/dL [4 to 7 mmol/L])**

- **Intrapartum glucose levels above 140 to 180 mg/dL (7.8 to 10.0 mmol/L)**

have been shown to be associated with neonatal hypoglycemia.

- **Recommended serum glucose goals (ADA) thus of fasting 70-90mg/dl, 1hr PP >140mg/dl and 2 hr PP >120mg/dl.**
- **American College of Obstetricians and Gynecologists (ACOG) recommends the following targets: fasting <90 mg/dL, preprandial <105 mg/dL, 1-h postprandial <130–140 mg/dL, and 2-h postprandial <120 mg/dL.**
- **These goals and targets are materno-fetal outcome driven and irrespective of type of diabetes be it type 1, type 2, gestational or other forms of diabetes in pregnancy.**

EVEN AMONG PATIENTS WITH THE SAME "TYPE" OF DIABETES DEMOGRAPHICS AND COMORBIDITIES SIGNIFICANTLY IMPACT GLYCEMIC GOAL SETTING.

ACCORD, ADVANCE and VADT Study Design

	ACCORD	ADVANCE	VADT
Major Endpoints	CV death, Non-fatal MI/Stroke	CV death, Non-fatal MI/Stroke, macrovacs event	CV death, Non-fatal MI/Stroke, CHF macrovacs event
Study	RCT	RCT	RCT
design	Glucose Intensive vs Standard Arm 2x2 BP control +/-fenofibrate v placebo	Glucose Intensive vs Standard Arm 2x2 Perindopril +indamide v placebo	Glucose Intensive vs Standard Arm 2x1 All received BP and Lipid Rx

ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572.
VADT Study Results ADA Scientific Session San Francisco, 2008
In Press, Diabetes Obesity and Metabolism, 2008

Therapeutic Approach: ACCORD, ADVANCE and VADT

	ACCORD	ADVANCE	VADT
Protocol	Provider Directed Formulary-based Poly-pharmacy	Stepped Approach: SU, Met, TZD, Insulin	Stepped Approach: Met BMI ≥27; SU BMI <27, TZD, Insulin
Meds (Inten v Std)			
Metformin	95 v 87 %	74 v 67 %	75 v 71%
TZD (Rosi)	91 v 58 %	17 v 11%	85 v 78%
Oral Hypoglycemic	87 v 74 %	94 v 84 %	55 v 45%
Insulin	73 v 58 %	41 v 24 %	90 v 74%
Exenatide	12 v 4 %	- - -	- - -
Follow-up intensive group	Q mo x 4, then q 2 mo	Q mo x 4, then Q 3 mo	-

ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572.
VADT Study Results ADA Scientific Session San Francisco, 2008

ACCORD, ADVANCE and VADT Demographics

	ACCORD	ADVANCE	VADT
# Participants	10,251	11,140	1,791
population	North America	Europe /Asia	US
Male	62%	58%	97%
Age group mean age	40-79 62.2	>55 yrs 66	>40yrs 60.5
Non-Hispanic White Ethnic Representation	27% Hispanic, African Am	37% Asian	38% Hispanic, African Am, Native Am

ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
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ACCORD, ADVANCE and VADT Baseline Clinical Characteristics

	ACCORD	ADVANCE	VADT
Weight	93.5	78 kg	97.2
BMI	32.2	28	31
Duration DM	10	8	11.5
Baseline A1c	8.3	7.5	9.4
Prior CVD	35%	32%	40%

ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572.
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Even among patients with the same "type" of diabetes demographics and comorbidities significantly impact glycemic goal setting.

Outcomes: Summary of ACCORD, ADVANCE and VADT

	ACCORD*	ADVANCE	VADT
A1C (%) (Intensive vs. Std)	6.4 vs.7.5 †	6.4 vs. 7.0 †	6.9 vs. 8.4 †
Nonfatal MI (%) (Intensive vs. Std)	3.6 vs 4.6% †	2.7 vs.2.8	6.3 vs. 6.1
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Hazard Ratio)	4.5 vs. 5.2	2.1 vs.1.7
Microvascular	-	nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take home	↓ risk MIs, but ↑ risk death in intensive arm	Glucose control has no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08)
† significant difference between intensive and standard group
ACCORD Study Group, *NEJM* 2008, 358:2545-2559.
ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572.
VADT Study Results ADA Scientific Session San Francisco, 2008
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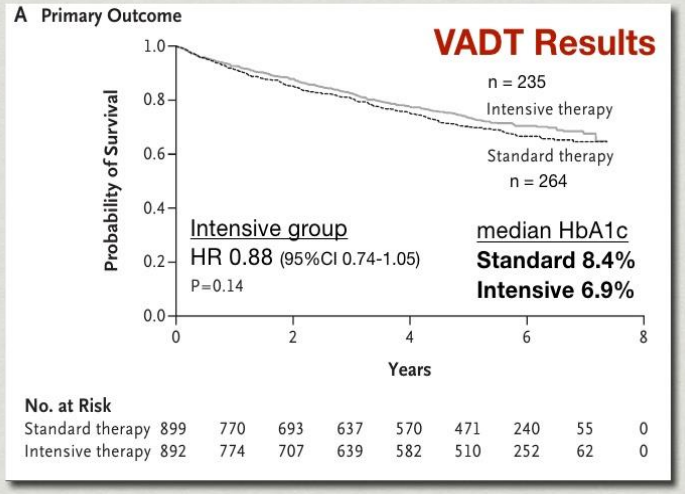
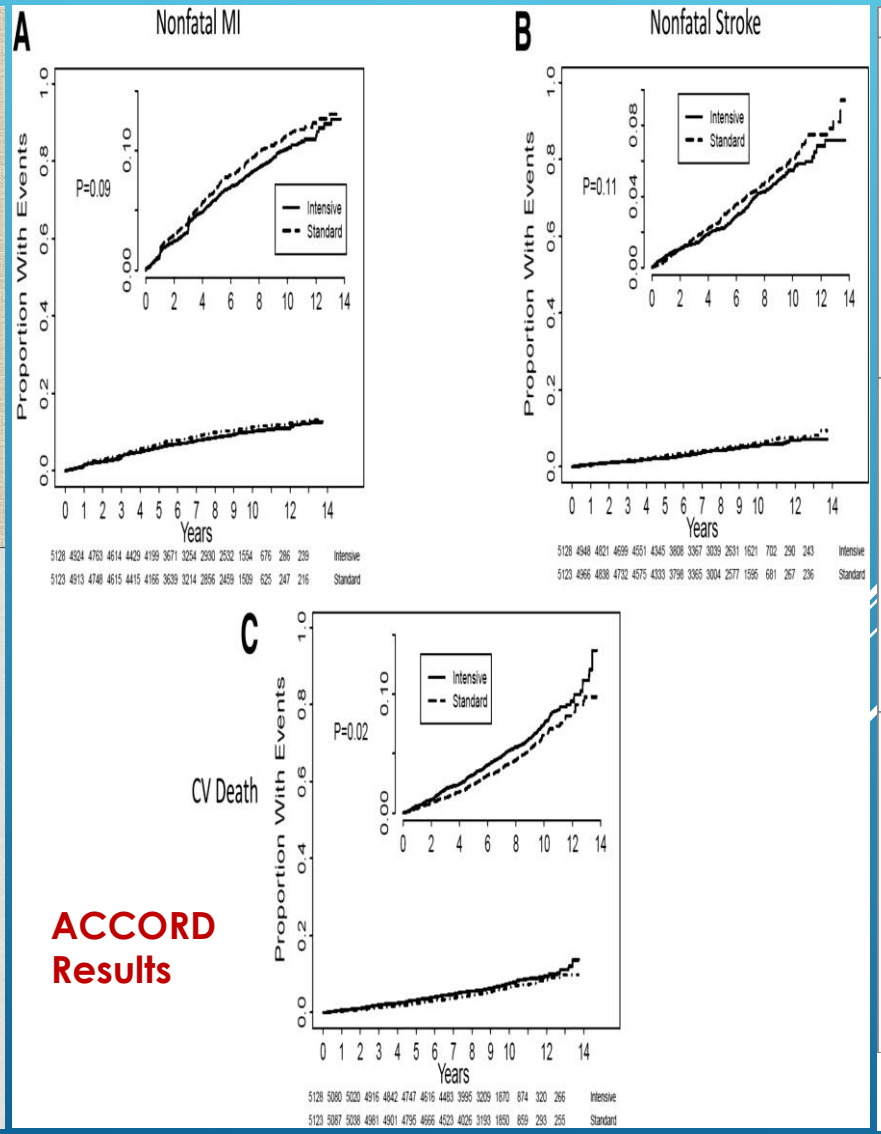
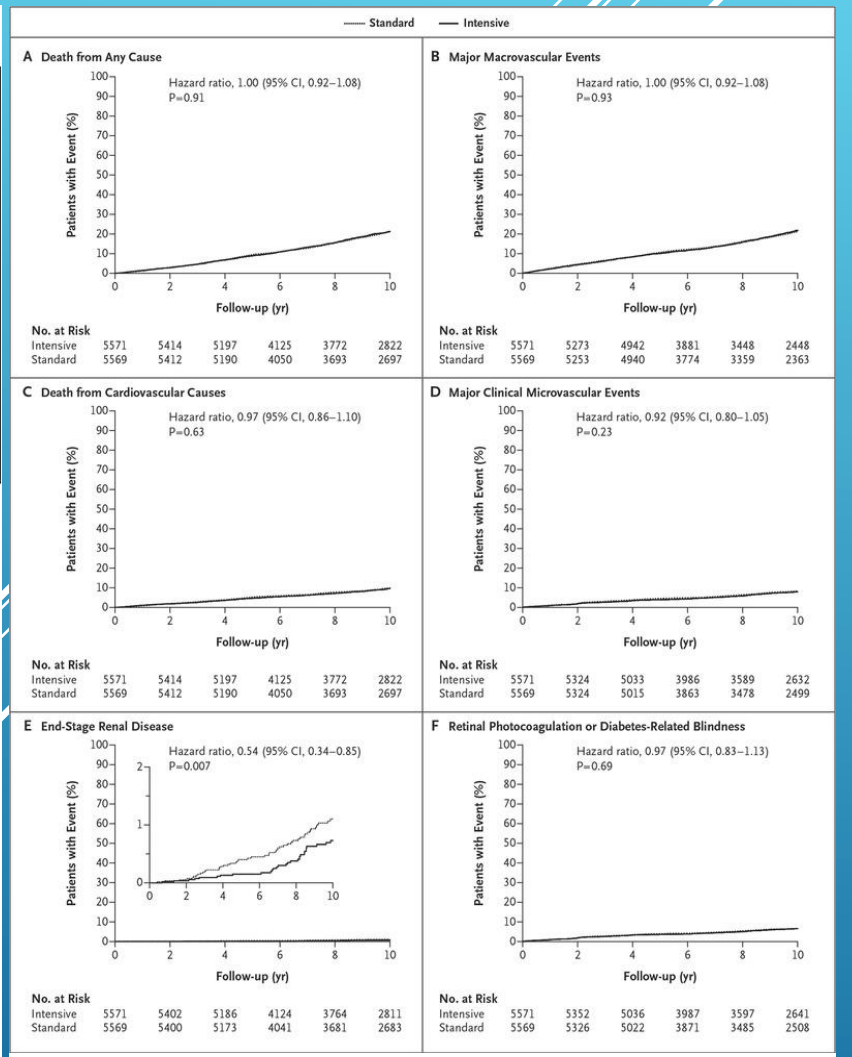


Duckworth et al NEJM 2009;360:129-39

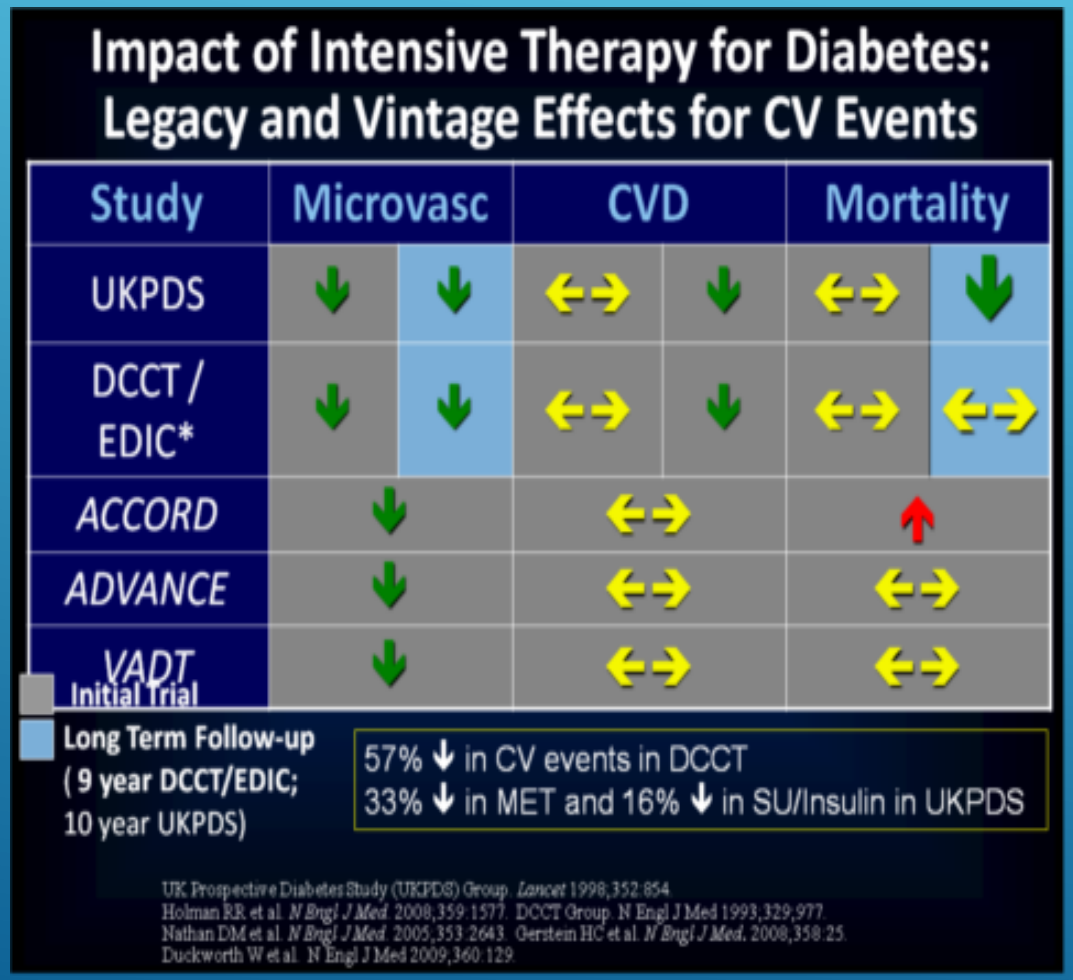


ACCORD Results



ADVANCE Results

EVEN AMONG PATIENTS WITH THE SAME "TYPE" OF DIABETES DEMOGRAPHICS AND COMORBIDITIES SIGNIFICANTLY IMPACT GLYCEMIC GOAL SETTING.



The fall out from the trio of ACCORD, ADVANCE and VADT trials;

- With HBA1c less is not neccesarily better. Aggressive HBA1c pursuit (<6.5) adds nothing as far As ASCVD benefit and can actually be dangerous.

- In the cohort of patients with type 2 diabetes >60 yr with already established ASCVD or at high risk HBA1c of <8.5 provides similar ASCVD benefit to <7.0 with less risk.
- These studies have informed the change in target HBA1c targets in geriatric patients, patients with established ASCVD/high risk of same and patients with already established advanced Triopathy
- Unclear whether this applies to similar profile type 1 diabetes patients but subgroup analyses of EDIC data suggests that it probably does.

EVEN AMONG PATIENTS WITH THE SAME "TYPE" OF DIABETES DEMOGRAPHICS AND COMORBIDITIES SIGNIFICANTLY IMPACT GLYCEMIC GOAL SETTING.

Table 7—Summary of A1C recommendations for nonpregnant people with diabetes*

Youth (<18 years)	<7.5%
Adults	<7.0%
Older adults	
Healthy†	<7.5%
Complex/intermediate	<8.0%
Very complex/poor health	<8.5%

*Targets must be individualized based on a patient's circumstances. †No comorbidities, long life expectancy.

Major Comorbidities or Physiologic Age	Microvascular Complications		
	Absent or Mild	Moderate	Advanced
Absent >10-15 years life expectancy	6.0-7.0%	7.0-8.0%	7.5-8.5%
Present 5-10 years of life expectancy	7.0-8.0%	7.5-8.5%	7.5-8.5%
Marked <5 years of life expectancy	8.0-9.0%	8.0-9.0%	8.0-9.0%

https://www.qualityandsafety.va.gov-ChoosingWiselyHealthSafetyInitiative%2FHypoglycemiaSite%2FClinicians_Toolkit_for_Shared_Decision_Making.

What about the Fasting glucose vs postprandial glucose conundrum and controversy?

Do We Have Evidence that Targeting Postprandial Hyperglycemia Reduces CV Risk?

STOP-NIDDM Trial: Acarbose in IGT patients (n=1368)
Myocardial Infarctions **0.09** (0.01-0.72) P=0.0226
Any cardiovascular events: **0.51** (0.28-0.95) P=0.0326

Acarbose Meta-analysis in Diabetes: (n=2180)
Myocardial Infarctions **0.36** p=0.012

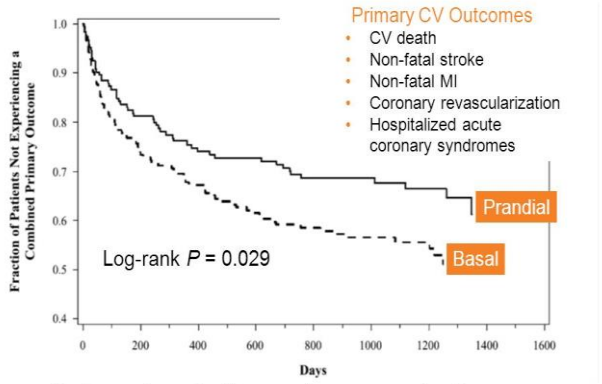
NAVIGATOR Trial : Nateglinide in IGT, n=9306, 6 years
CV Outcomes: **0.94** (0.82-1.09) P=0.43

Heart2D Trial (Prandial (Lispro TID) vs Fasting (Glargine or NPH bid))
21 days post-MI

A1c	7.7%		7.8%
Fasting Glucose	8.1		7.0
Post-prandial	7.8		8.6
Glucose variability	18% lower	HR CV **0.98**	

Chiasson JL et al. JAMA 290:486-494, 2003. Hanefeld M. Eur. Heart J. 25:10-6, 2004. Navigator Study Group. N. Engl. J. Med. 362:1463-76, 2010 Raz I et al. Diabetes Care 32:381-6, 2009

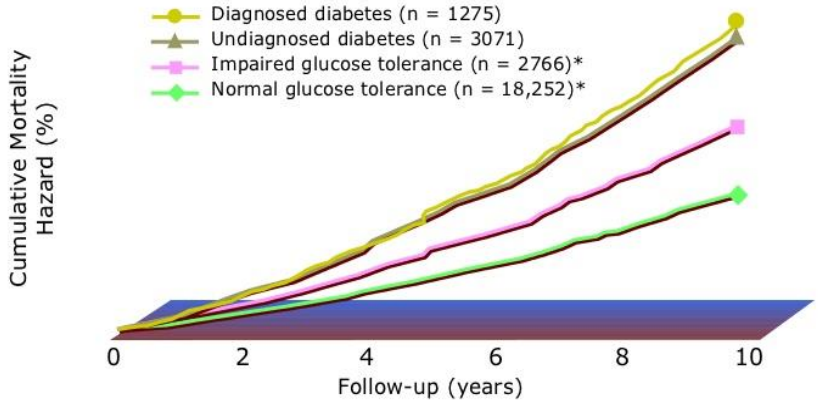
Fewer Older T2D Experienced a Cardiovascular Event on Prandial Insulin Therapy vs. Basal Therapy



Raz, Ceriello, et al. Post Hoc Subgroup Analysis of the HEART2D Trial Demonstrates Lower Cardiovascular Risk in Older Patients Targeting Postprandial Versus Fasting/Premeal Glycemia. Diabetes Care (34), Jul 2011

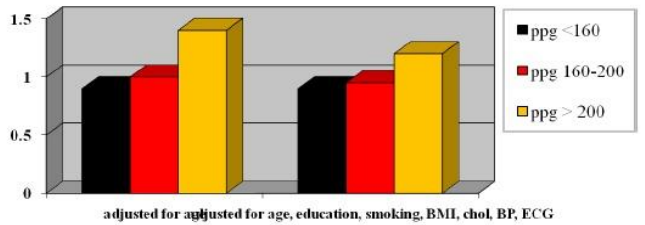
DECODE: IGT Increases Mortality Risk

Collaborative Analysis of Diagnostic Criteria in Europe
N = 25,364 aged ≥30 years



Long-Term Problems

22-yr CVD Mortality Risk by Baseline post-challenge glucose



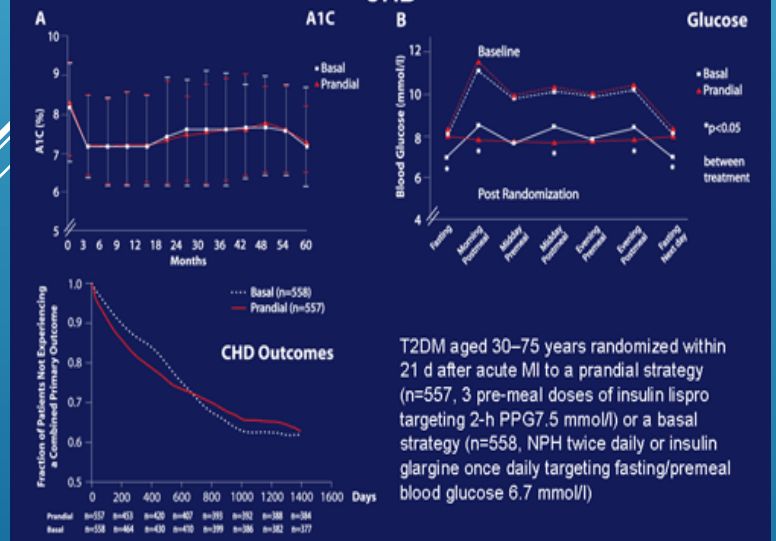
Source: Chicago Heart Study, Lowe et al, Diabetes Care, 1997; 20: 163-170.

RESEARCH DESIGN AND METHODS

- Patients (aged **30–75 years**) with type 2 diabetes , duration of ≥3 months
- Entered within 18 days of an AMI
- Within 21 days of hospital admission for the recent AMI, randomly assigned into one of two treatment groups

Heart 2D Trial design

HEART2D: Treating T2DM After Acute MI with Prandial vs. Basal Strategies Achieved No Difference in Risk for Future CHD



T2DM aged 30–75 years randomized within 21 d after acute MI to a prandial strategy (n=557, 3 pre-meal doses of insulin lispro targeting 2-h PPG7.5 mmol/l) or a basal strategy (n=558, NPH twice daily or insulin glargine once daily targeting fasting/premeal blood glucose 6.7 mmol/l)

Raz I, et al. *Diabetes Care* 2009;32:381–386.

medicalquery@torrentpharma.com

WHAT ABOUT THE FASTING GLUCOSE VS POSTPRANDIAL GLUCOSE CONUNDRUM AND CONTROVERSY?

0021-972X/06/$15.00/0
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doi: 10.1210/jc.2005-1005

Postprandial Blood Glucose Is a Stronger Predictor of Cardiovascular Events Than Fasting Blood Glucose in Type 2 Diabetes Mellitus, Particularly in Women: Lessons from the San Luigi Gonzaga Diabetes Study

F. Cavalot, A. Petrelli, M. Traversa, K. Bonomo, E. Fiora, M. Conti, G. Anfossi, G. Costa, and M. Trovati

Diabetes Unit, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga Hospital (F.C., M.Tra., K.B., E.F., M.C., G.A., M.Tro.), and Department of Public Health, University of Turin (A.P., G.C.), 10043 Orbassano, Turin, Italy

Objective: The influence of postprandial blood glucose on diabetes complications is intensively debated. We aimed to evaluate the predictive role of both fasting and postprandial blood glucose on cardiovascular events in type 2 diabetes and the influence of gender.

Methods: In a population of 529 (284 men and 245 women) consecutive type 2 diabetic patients attending our diabetes clinic, we evaluated the relationships, corrected for cardiovascular risk factors and type of treatment, between cardiovascular events in a 5-yr follow-up and baseline values of hemoglobin A1c (HbA1c) and blood glucose measured: 1) after an overnight fast, 2) after breakfast, 3) after lunch, and 4) before dinner. Continuous variables were categorized into tertiles.

Results: We recorded cardiovascular events in 77 subjects: 54 of 284 men (19%) and 23 of 245 women (9.4%). Univariate analysis indicated that cardiovascular events were associated with increasing age, longer diabetes duration, and higher HbA1c and fibrinogen in men, and higher systolic blood pressure, albumin excretion rate, HbA1c, and all blood glucose values in women. Smoking was more frequent in subjects with events. When all blood glucose values and HbA1c were introduced simultaneously in the models, only blood glucose after lunch predicted cardiovascular events, with hazard ratio of the third tertile *vs.* the first and the second tertiles greater in women (5.54; confidence interval, 1.45–21.20) than in men (2.12; confidence interval, 1.04–4.32; $P < 0.01$).

Conclusions: Postprandial, but not fasting, blood glucose is an independent risk factor for cardiovascular events in type 2 diabetes, with a stronger predictive power in women than in men, suggesting that more attention should be paid to postprandial hyperglycemia, particularly in women. (*J Clin Endocrinol Metab* **91: 813–819, 2006**)

PATIENTS AFFECTED BY type 2 diabetes show an increased cardiovascular morbidity and mortality (1, 2). Epidemiological studies demonstrate that blood glucose (BG) concentrations in the upper normal range are an independent risk factor for cardiovascular disease (3–8), as discussed in a meta-regression analysis (9), even with the limitations due to the inability to analyze the individual data and the inadequate adjustment for the known cardiovascular risk factors (9). A relationship between BG control and cardiovascular events has also been observed in type 2 diabetic patients (10–12).

The role of postprandial BG as an independent contributor to diabetes complications and the need to target it for prevention of cardiovascular events are a matter of intense debate. As exhaustively reviewed (13–16), studies carried out mainly in the general population show that postchallenge BG predicts the incidence of cardiovascular events and mortality more than fasting BG: however, results obtained measuring BG after an oral glucose tolerance test (*i.e.* postchallenge or postload BG) cannot be extrapolated to the postprandial (*i.e.* after a meal) condition. The extent at which postchallenge BG reflects BG after a mixed meal is not well understood (14); therefore, postprandial and postload glucose concentrations should be kept clearly distinct (17).

As far as we know, in only one study, the Diabetes Intervention Study (DIS), the role of postprandial BG in the prediction of cardiovascular events in type 2 diabetes has been addressed: BG after breakfast, but not fasting BG, has been found to predict myocardial infarction and mortality in newly diagnosed type 2 diabetic patients (11). In 2001, the American Diabetes Association stated that whether postprandial hyperglycemia is an independent risk factor for cardiovascular disease is still controversial and requires additional studies (18). Because the equivalence between postchallenge and postprandial BG has been criticized, it is of major interest to provide additional evidence on the predictive role of postprandial BG in the diabetic population.

In the general population, cardiovascular mortality rate is two to five times greater in men than in women (19, 20). In contrast, hyperglycemia seems to influence cardiovascular mortality more strongly in women than in men. Actually, many studies show that both diabetes (4, 20) and asymp-

First Published Online December 13, 2005

Abbreviations: AER, Albumin excretion rate; BG, blood glucose; BGAB, BG 2 h after breakfast; BGAL, BG 2 h after lunch; BGBD, BG before dinner; BMI, body mass index; CHD, coronary heart disease; DIS, Diabetes Intervention Study; FBG, fasting blood glucose; HDL, high-density lipoprotein; HR, hazard ratio; ICD9-CM, International Classification of Diseases 9–Clinical Modification.

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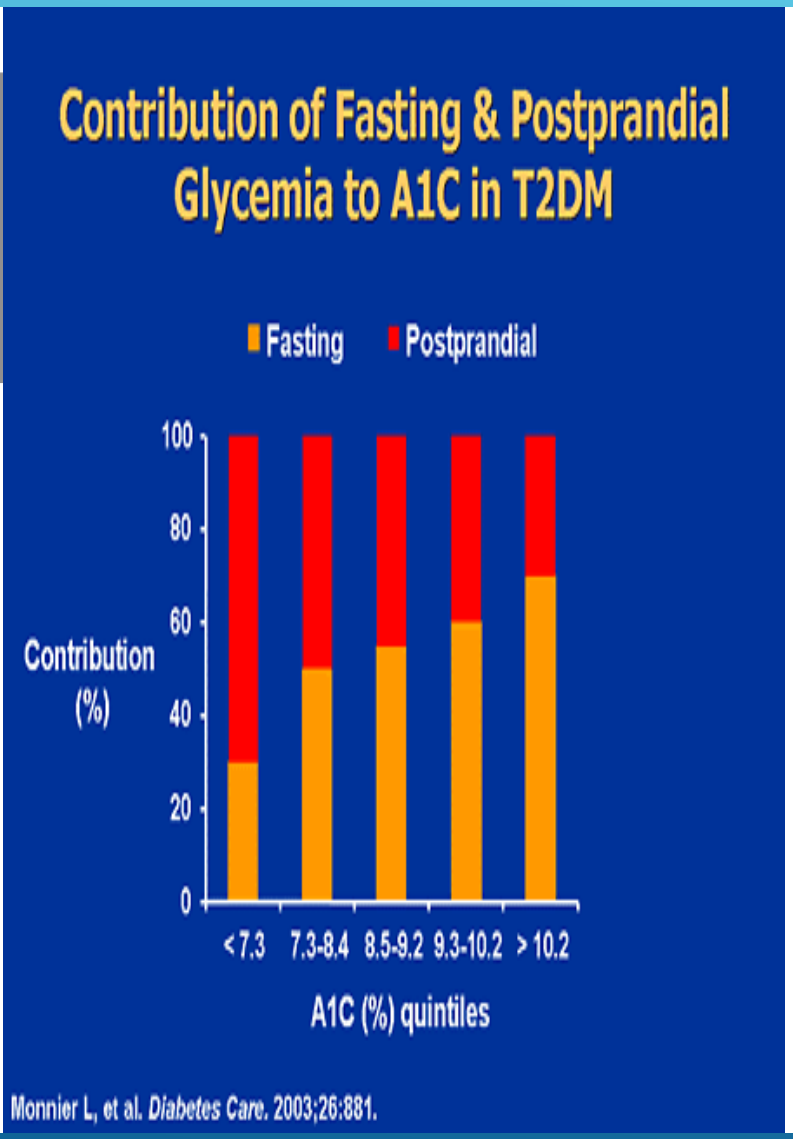


Postprandial Hyperglycemia and Glycemic Variability

Should we care?

EBERHARD STANDL, MD[1]
OLIVER SCHNELL, MD[1]
ANTONIO CERIELLO, MD[2]

The aim of this article is to evaluate the pros and cons of a specific impact of postprandial hyperglycemia and glycemic variability on the—mainly cardiovascular (CV)—complications of diabetes, above and beyond the average blood glucose (BG) as measured by HbA_{1c} or fasting plasma glucose (FPG). The strongest arguments in favor of this hypothesis come from impressive pathophysiological studies, also in the human situation. Measures of oxidative stress and endothelial dysfunction seem to be especially closely related to glucose peaks and even more so to fluctuating high and low glucose concentrations and can be restored to normal by preventing those glucose peaks or wide glucose excursions. The epidemiological evidence, which is more or less confined to postprandial hyperglycemia and postglucose load glycemia, is also rather compelling in favor of the hypothesis, although certainly not fully conclusive as there are also a number of conflicting results. The strongest cons are seen in the missing evidence as derived from randomized prospective intervention studies targeting postprandial hyperglycemia longer term, i.e., over several years, and seeking to reduce hard CV end points. In fact, several such intervention studies in men have recently failed to produce the intended beneficial outcome results. As this evidence by intervention is, however, key for the ultimate approval of a treatment concept in patients with diabetes, the current net balance of attained evidence is not in favor of the hypothesis here under debate, i.e., that we should care about postprandial hyperglycemia and glycemic variability. The absence of a uniformly accepted standard of how to estimate these parameters adds a further challenge to this whole debate.

Diabetes Care 34(Suppl. 2):S120–S127, 2011

Although undoubtedly diabetes, i.e., hyperglycemia, is associated with an increased risk of microvascular and macrovascular complications, how exactly the various parameters of hyperglycemia exert their influence on the vascular system is still under debate (1). Fasting plasma glucose (FPG), postprandial hyperglycemia, and glucose variability all contribute to the net balance of the long-term glycemic parameter HbA_{1c} (not to forget that hypoglycemia has recently re-emerged as an independent risk predictor of major cardiovascular (CV) and other negative events in its own right, but that is not the focus of this article). Does it not suffice to concentrate on HbA_{1c} values, because they have been shown by several meta-analyses in 2009 based on all available data from randomized intervention trials on blood glucose (BG)-lowering therapies to be clearly independent determinants of major CV events, especially myocardial infarction (2,3)? This article, therefore, aims to evaluate the pros and cons of a specific impact of postprandial hyperglycemia and glycemic variability on the vascular complications in diabetes, and whether they matter. Three areas of evidence mainly are to be considered: the epidemiology, the pathophysiology, and randomized prospective intervention trials. As a basis, methods of assessing postprandial hyperglycemia and glycemic variability are briefly discussed.

From the [1]Munich Diabetes Research Institute, Munich Helmholtz Centre, Munich, Germany; and the [2]Institut d'investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain.
Corresponding author: Eberhard Standl, eberhard.standl@lrz.uni-muenchen.de.
This publication is based on the presentations at the 3rd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, F. Hoffmann-La Roche, Janssen-Cilag, Johnson & Johnson, Novo Nordisk, Medtronic, and Pfizer.
DOI: 10.2337/dc11-s206

METHODS OF ASSESSMENT—

Table 1 gives an overview of the glucose-related measures used in studying the relationship with CV parameters, both short- and longer-term. So far, no uniformly accepted standard of measurement has emerged, which poses a challenge in its own when comparing or planning studies. The postprandial parameters are self-explanatory.

Numerous measures of glycemic variability have been proposed in the literature (4). Some of these tools are easy to use; others are very complex or difficult to apply in clinical practice, even when using new methods such as continuous glucose self-monitoring. Table 1 focuses on only a few of the most important methods.

Average glucose value and SD

The calculation of the glycemic average was thought to provide better insight into glycemic variability because several study groups could demonstrate that people with diabetes—and therefore a higher mean glycemic value—produced larger amounts of compounds related to oxidative stress (i.e., nitrotyrosine, 8-hydroxy-deoxyguanosine, or 8-iso-prostaglandin $F_{2\alpha}$) than did patients without diabetes (5,6):

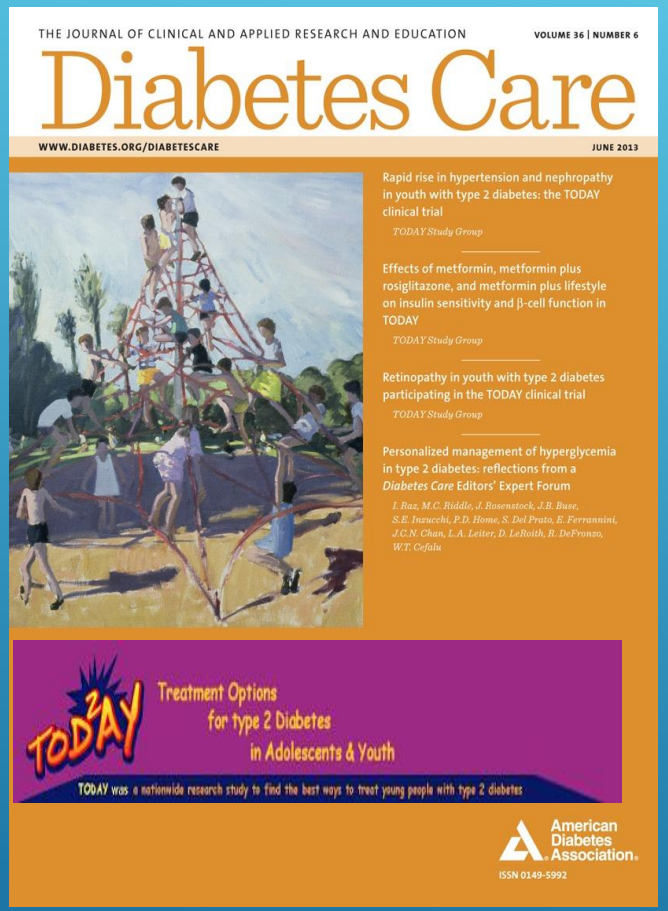
$$\frac{\sum_{i=1}^{k} GV_i}{k}$$

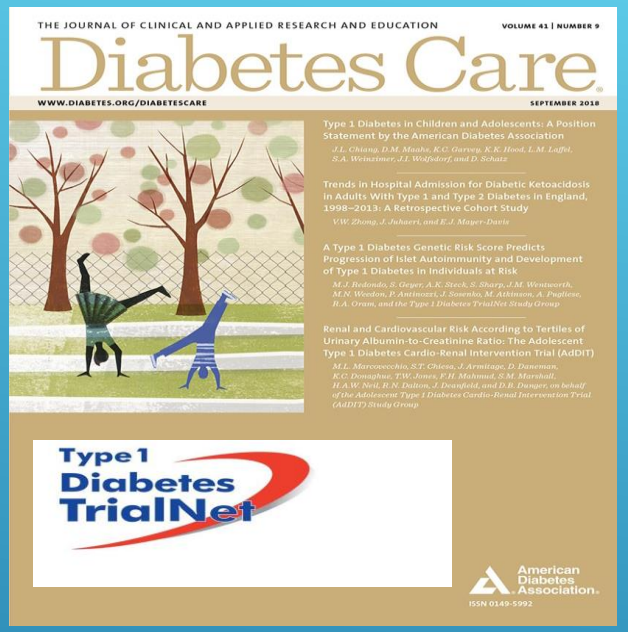
Table 1—*Measures of postprandial glucose and glycemic variability*

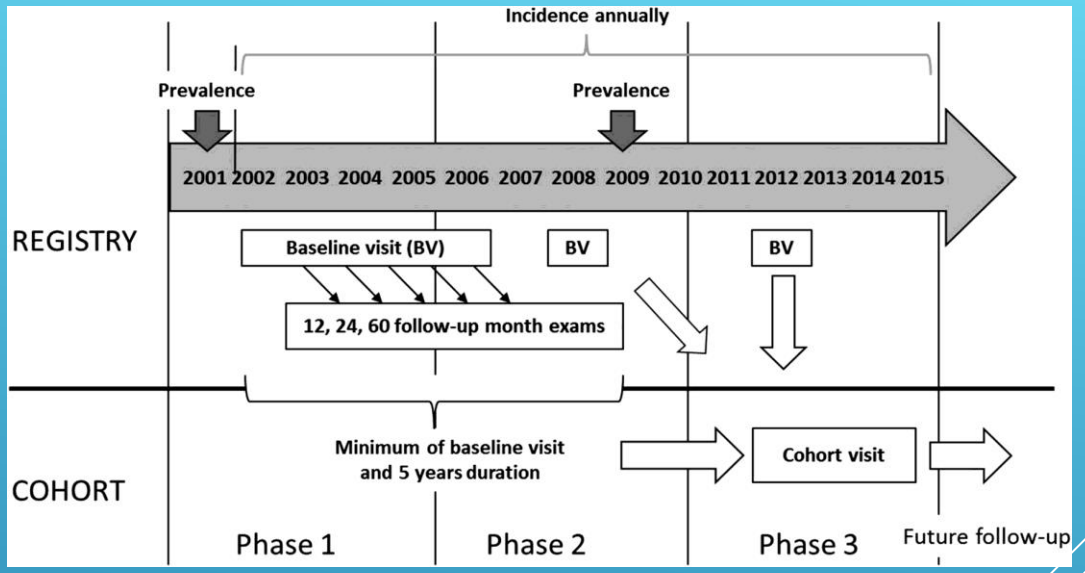
Postprandial hyperglycemia
2 h, 1 h, 90 min after meal
Meal, however, often undefined
In trials mainly 2 h after an oral glucose load (75 g)
Glycemic variability
Average glucose + SD
Hyperglycemic index (self-monitoring of BG)
MAGE (CGMS glucose excursions)
CONGA (CGMS intraday variability)
ADRR (log transformation)

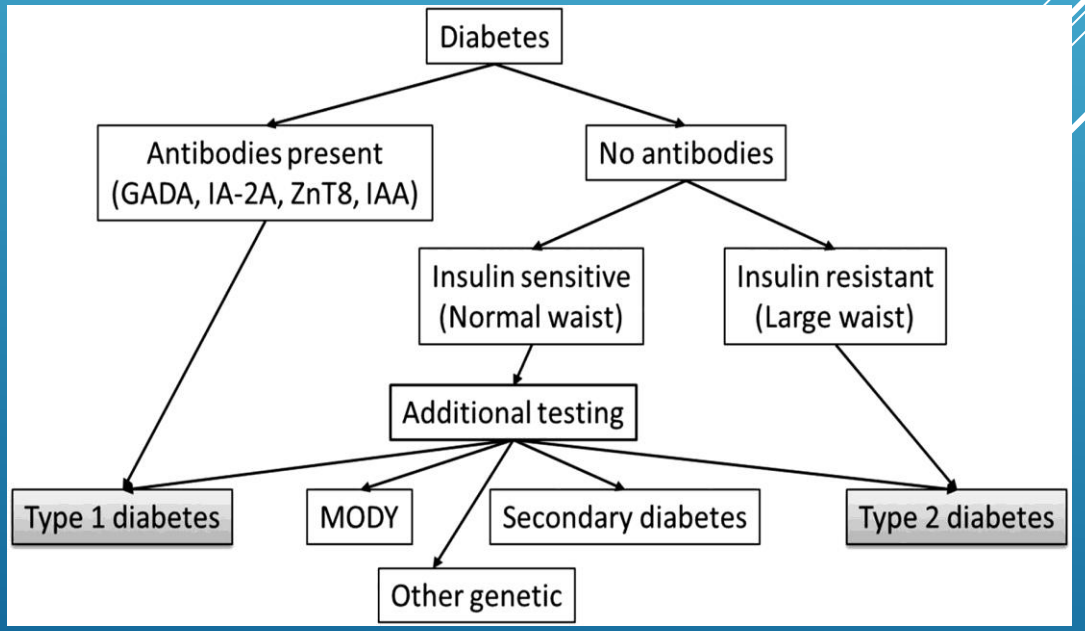
CGMS, continuous glucose monitoring system.

HOW ABOUT DIABETES IN CHILDREN AND ADOLESCENTS?

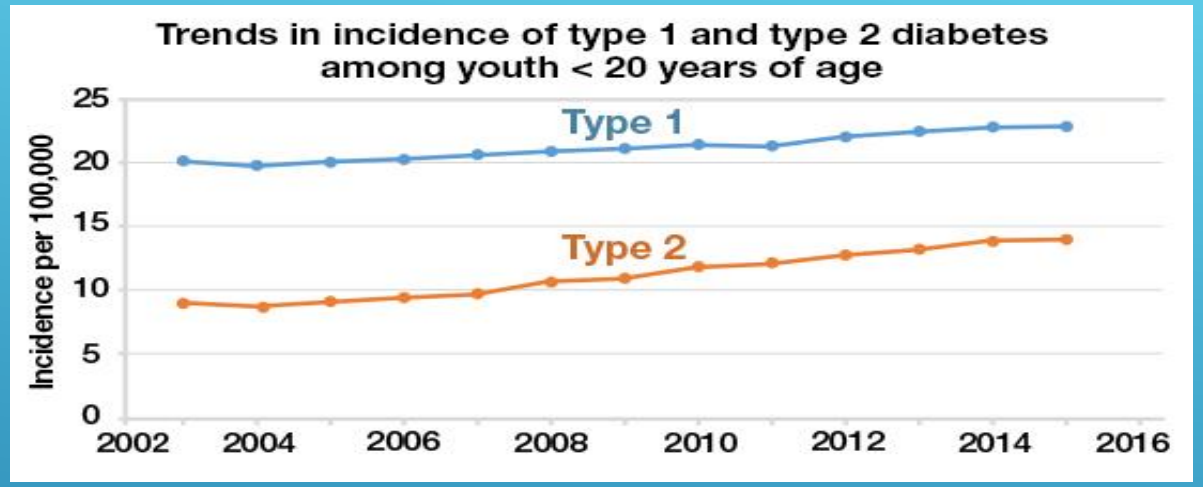


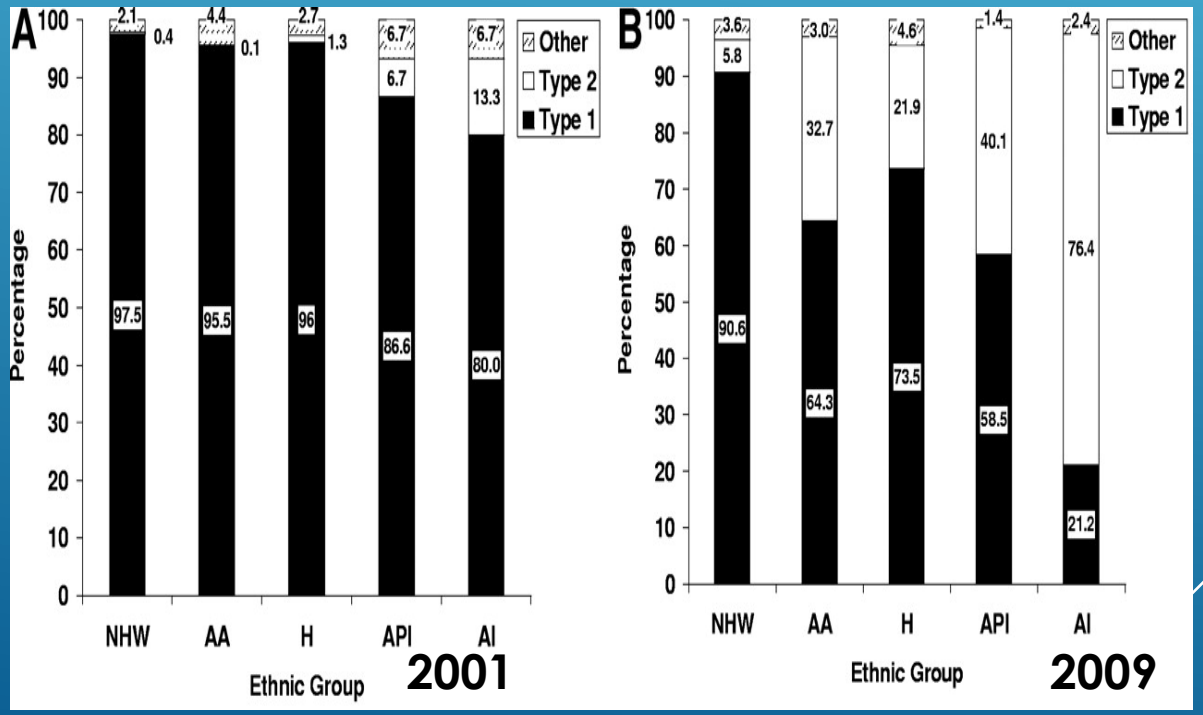


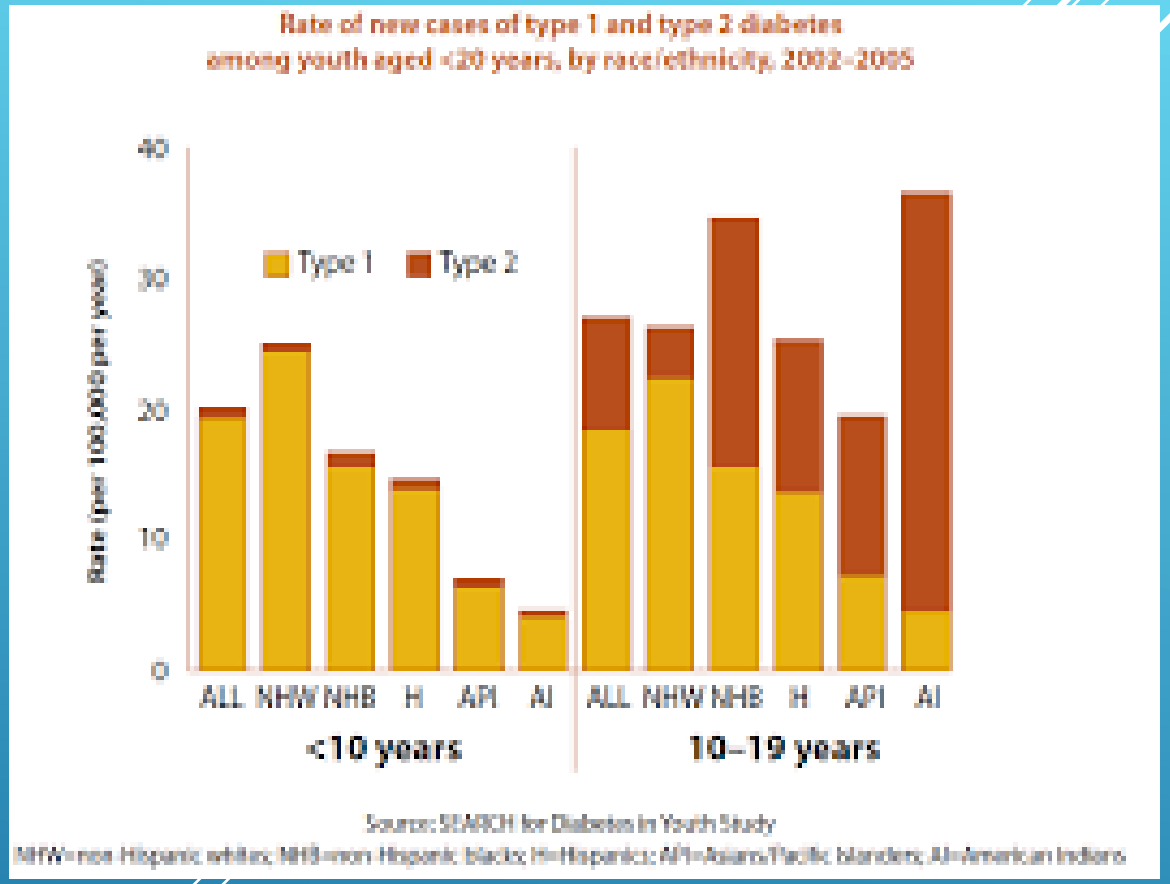




How about diabetes in Children and Adolescents?





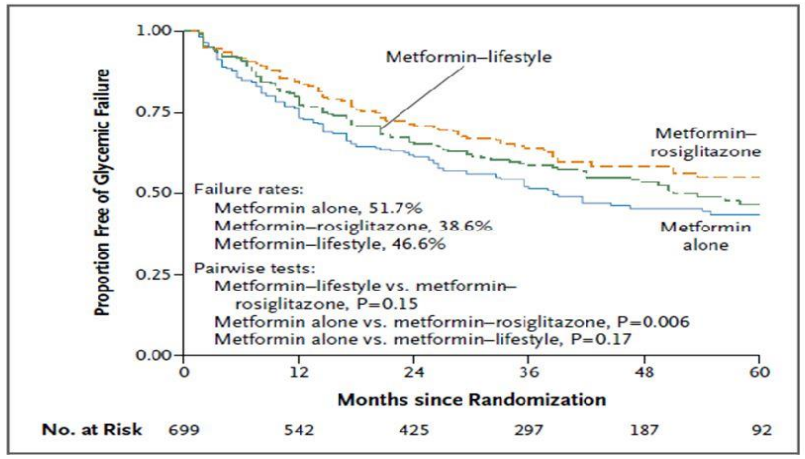


SEARCH for Diabetes in Youth study

- The prevalence of diabetes in children is increasing.
- The nature of diabetes in children is changing
- Type 2 diabetes with its “adult’ comorbidities is becoming more prevalent
- The nature of diabetes in children has major ethno-racial and age related determinants.

How about diabetes in Children and Adolescents?

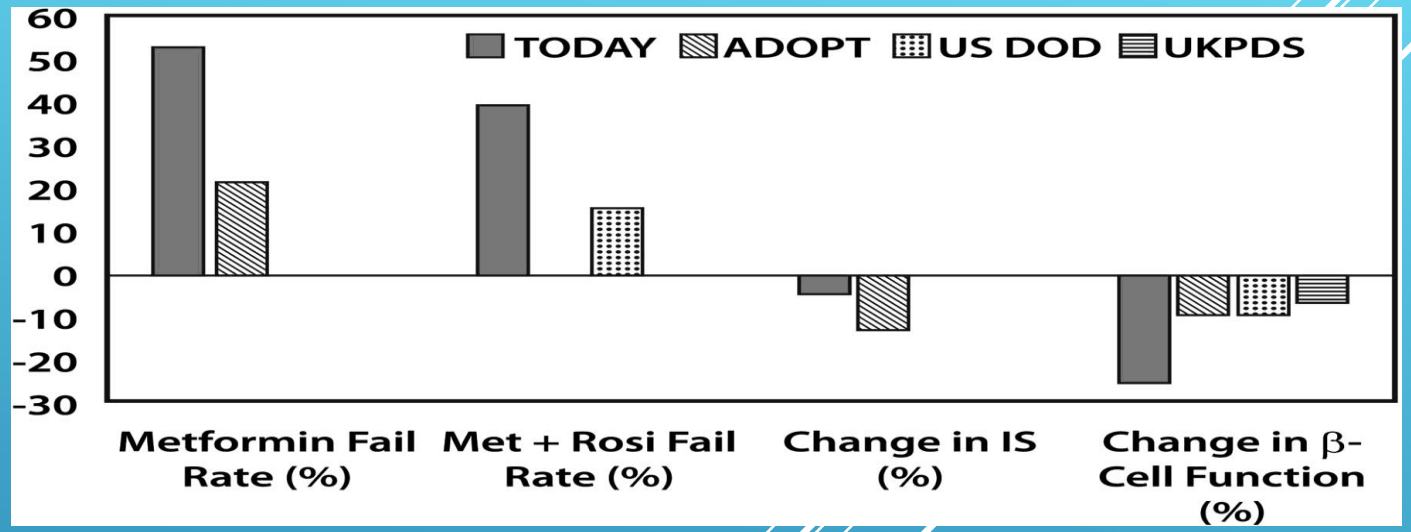
Treatment T2: The TODAY Trial Study Results



Supported, in part, by Mead Johnson Nutrition

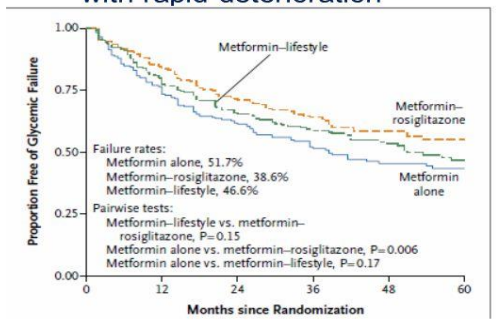
TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *New Eng J Med*. 2012:1–10

American Academy of Pediatrics



The Challenge of T2DM in Children

- Prevalence of prediabetes and diabetes has increased significantly, despite obesity stabilization (NHANES 1999-2008*)
- ½ of adolescents with T2DM fail metformin monotherapy, with rapid deterioration**



This implies a **more aggressive** disease and a tendency toward more severe insulin deficiency

*May et al. *Pediatrics* June 2012; 129(6): 1035-1041
**Today Study Group. *NEJM* June 14, 2012; 366 (24): 2247-2256

University of Michigan C.S. Mott Children's Hospital

Teen-LABS vs. TODAY: By the numbers

Mean HbA1c concentrations	↓ From 6.8 to 5.5 Teen-LABS Study	↑ From 6.4 to 7.8 TODAY Study
Mean body mass index	↓ 29% Teen-LABS Study	↑ 3.7% TODAY Study
Prevalence of high blood pressure	↓ From 45% to 20% Teen-LABS Study	↑ From 22% to 41% TODAY Study

- Type 2 diabetes in children is intricately tied to obesity
- The prevalence of both type 2 diabetes and obesity is increasing in children.
- Type 2 diabetes in children appears to be a more rapidly evolving disease with all typical " adult" comorbidities and complications
- Bariatric surgery appears to be even more effective among children with type 2 diabetes than in adults.
- Clinical trial evidence is accumulating suggesting utility for more strict glycemic targets in children with diabetes (both type 1 and 2).

HBA1C HAS IMPORTANT LIMITATIONS AND CAVEATS THAT ARE NOW BETTER UNDERSTOOD AND APPRECIATED.

HbA1c has its limits!

Falsely Increase A1C:

- Anemias w/ lower RBC turnover
- Uremia
- Chronic opiates, salicylate, EtOH
- Asplenia
- Severe hypertriglyceridemia

Falsely Decrease A1C:

- Anemia from acute/chronic blood loss
- Splenomegaly
- Pregnancy

Variable effects: Hemoglobin variants, CKD, liver disease, racial differences, genetic variants, etc.

Radin, J Gen Int Med, 2013; Bergenstal et al, Ann Int Med, 2017; Beck et al, Diabetes Care, 2017

HBA1c has important limitations and caveats that are now better understood and appreciated.

Published in final edited form as:
Diabetes Care. 2007 October ; 30(10): 2453–2457.

Differences in A1C by Race and Ethnicity Among Patients With Impaired Glucose Tolerance in the Diabetes Prevention Program

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Abstract

Objective—We sought to examine racial and ethnic differences in A1C in individuals with impaired glucose tolerance (IGT).

Research Design and Methods—We studied 3,819 individuals aged ≥25 years with IGT who were found to be eligible to participant in the Diabetes Prevention Program. A1C was compared among five racial and ethnic groups before and after adjustment for factors that differed among groups or might affect glycemia including age, sex, education, marital status, blood pressure, adiposity (BMI and waist circumference), hematocrit, fasting and post–glucose load glucose levels, glucose area under the curve (AUC), β-cell function, and insulin resistance.

Results—Mean ± SD A1C was 5.91 ± 0.50%. Among whites, A1C was 5.80 ± 0.44%, among Hispanics 5.89 ± 0.46%, among Asian 5.96 ± 0.45%, among American Indians 5.96 ± 0.46%, and among blacks 6.19 ± 0.59%. Age, sex, systolic blood pressure, diastolic blood pressure, BMI, fasting glucose, glucose AUC, corrected insulin response, and insulin resistance were each independent predictors of A1C. Adjusting for these and other factors, mean A1C levels were 5.78% for whites, 5.93% for Hispanics, 6.00% for Asians, 6.12% for American Indians, and 6.18% for blacks ($P < 0.001$).

Conclusions—A1C levels are higher among U.S. racial and ethnic minority groups with IGT after adjustment for factors likely to affect glycemia. Among patients with IGT, A1C may not be valid for assessing and comparing glycemic control across racial and ethnic groups or as an indicator of health care disparities.

Carbohydrates are covalently attached to the NH_2-terminal valine of the β-chain of hemoglobin by a slow nonenzymatic process. The most common modification, glucose attachment, can be measured as A1C. Since the early 1980s, A1C has been used as a clinical measure of average

Address correspondence and reprint requests to William H. Herman, MD, Diabetes Prevention Program Coordinating Center, Biostatistics Center, George Washington University, 6110 Executive Blvd., Suite 750, Rockville, MD 20852. E-mail: dppmail@biostat.bsc.gwu.edu.
*A full list of the members of the Diabetes Prevention Program Research Group can be found in *N Engl J Med* 346:393–403, 2002.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

2353-PUB

The Lies HbA1c Tells

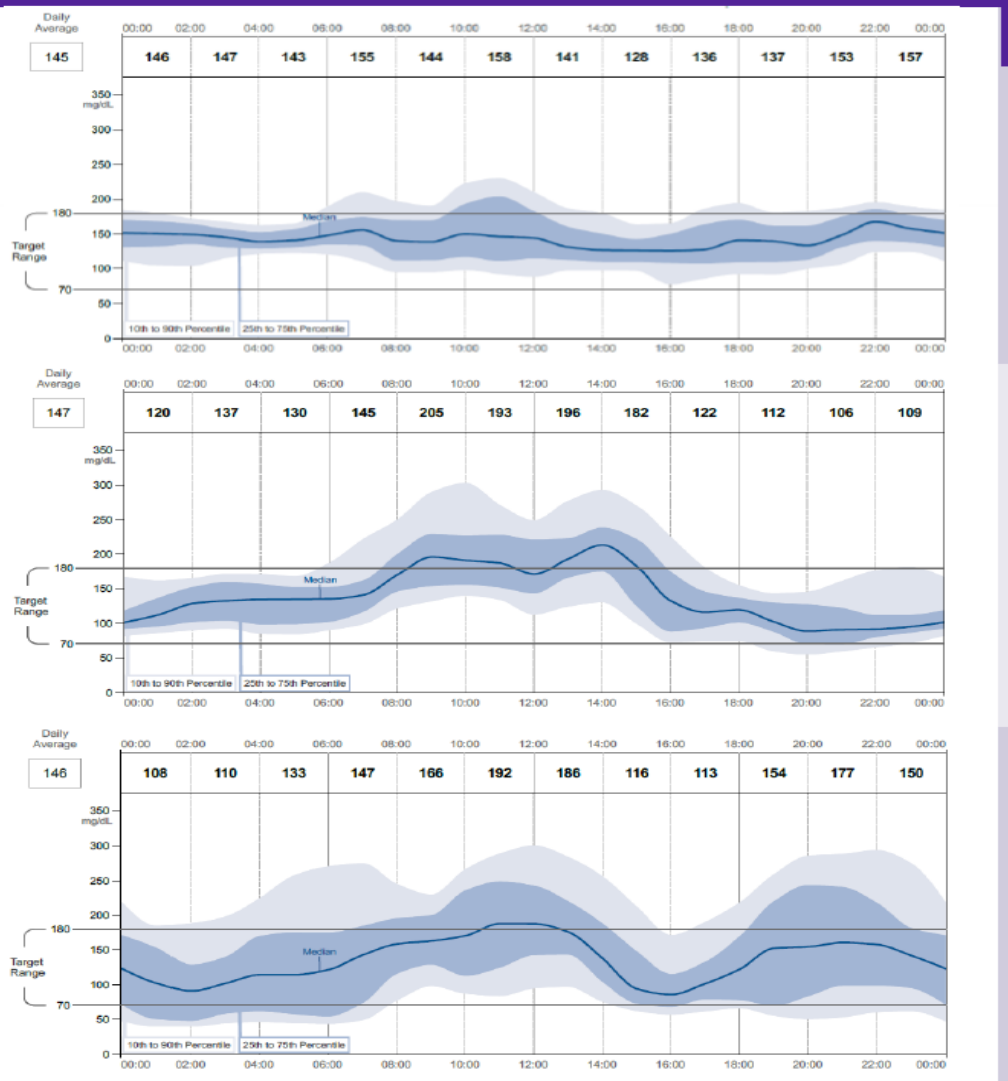
GABRIEL UWAIFO, JENEE NGUYEN, *New Orleans, LA, Slidell, LA*

HbA1c is used for diagnosis and monitoring of diabetes (DM) but there are limitations to its accuracy. We present three cases that highlight the need for caution in HbA1c use in clinical care. Case 1 is a 59 yr old African American man with > 12 yr history of type 2 DM and sickle cell disease. Past records showed normal HbA1c (4.5-5) and near normal glycoHemoglobin (5.4-7.4) despite mean blood glucose (BG) > 180mg/dl. At initial visit with us attempts to obtain HbA1c were impossible due to finding of a hemoglobin variant that influenced both ion exchange and boronate affinity HPLC. Instead, his glycemic profile is tracked using BG, Fructosamine and glycomark. Hemoglobin electrophoresis (HBE) showed HBSC disease. Case 2 is a 72 yr old Caucasian (C) lady referred because of discrepancies between HbA1c and BG. In the last year HbA1cs were 4.0-4.8 despite BG values in the 106-185mg/dl range. OGTT showed impaired fasting glucose. Prior HbA1cs were done using immunoassay. At our review repeat HbA1c was sent to Mayo labs. This showed an interfering substance affecting ion-exchange HPLC. Her sample was measured using boronate affinity HPLC and HbA1c was 6.0. HBE revealed HB J- Baltimore. Case 3 is a 46 yr old C lady with morbid obesity. Her HbA1cs were in the 5.6-5.9 range and she enrolled in a lifestyle modification plan with metformin 500mg BID. After ~ 1 yr she developed intermittent bilateral leg paraesthesiae due to small fiber peripheral sensory neuropathy. She also had sudden onset visual blurring. Ophthalmology review showed right retinal hemorrhage with partial retinal detachment and bilateral background retinopathy consistent with diabetic retinopathy. OGTT done after holding metformin showed DM. She was commenced on liraglutide and metformin dose increased to 1000mg BID. HBE revealed a variant of HB Barts. HbA1c should be interpreted with accompanying BG measurements. When a discrepancy is found other indices like fructosamine and glycomark can be useful. Repeat HbA1cs with other methods may help identify artefactually high or low HbA1cs and so guide appropriate clinical care.

ADA 2017 Annual scientific sessions

Variations in Glycosylation in an Ethnically Diverse Cohort
Year:
2010
Abstract Number:
1172-P
Variations in Glycosylation in an Ethnically Diverse Cohort Hyperglycemia is a major dete Hyperglycemia is a major determinant of microvascular disease in patients with diabetes (DM). The best clinical indices of glycemic burden are Amadori glycosylation products; HBA1c and fructoseamine are most commonly used clinically. While data suggests ethnic disparities in chronic DM complications the possible role of ethnic differences in tissue glycosylation has not been closely investigated. We performed a preliminary comparison of HBA1C and fructoseamine levels in an ethnically diverse cohort.[br]Seventy subjects with variable glycemia (8 with DM) were recruited and had demographics, anthropometrics, fasting blood glucose (FBG), insulin, HBA1C and fructoseamine obtained. There were 32 African American (AA) and 38 Caucasian (CC) subjects. After excluding subjects with DM, indices were compared.[br]AA subjects were slightly younger (45.5vs49.7yr P[lt]0.05) but had similar body mass indices (BMI), sex distribution, FBG, HBA1C, and HOMA B%. However, AA subjects had greater waist circumference (WC) (110vs98cm), fasting insulin (18.3vs15.7mu/ml) and insulin resistance by HOMA-IR (5.1vs4.14) and QUICKI (0.31vs0.34) all Ps[lt]0.05. Despite comparable HBA1C and FBGs, AA subjects had higher fructoseamine (231.6vs224.4umol/L, p[lt]0.05) and this disparity increased when non obese AA and CC were compared. While HBA1C positively correlated with BMI and WC, fructoseamine negatively correlated with both BMI and WC. The degree of correlation for fructoseamine was less in AA than CC but similar for HBAIC (Rs; 0.22 to 0.36 Ps [lt]0.05).[br]In our cohort of ethnically diverse subjects despite comparable glycemic burden significant ethnic differences in fructoseamine levels were noted. An inverse relationship between fructoseamine and adiposity was observed compared to that between adiposity and both FBG and HBAIC.[br]Glycemic burden is not the sole determinant of amadori glycosylation production. Ethnicity and adiposity may influence the degree of glycosylation measured by fructoseamine as compared to HBA1C. These findings may have implications for the use of fructoseamine in clinical care and may offer some insight into known differences in ethnic risk for DM related microvascular disease. Further relevant studies are needed in this area. GABRIEL I. UWAIFO, EUGEN MELCESCU, MARILYN B. BRAY, SHEILA S. BELK, CHRISTIAN A. KOCH 1172-P Jackson, MS Epidemiology
Author:
GABRIEL I. UWAIFO
Congress:
70th Scientific Sessions (2010)
Category:
Epidemiology

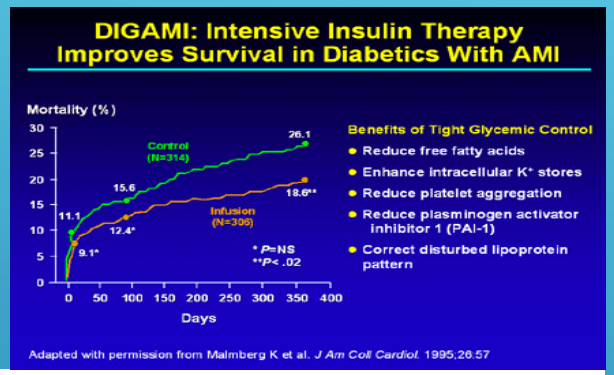
HBA1c has important limitations and caveats that are now better understood and appreciated

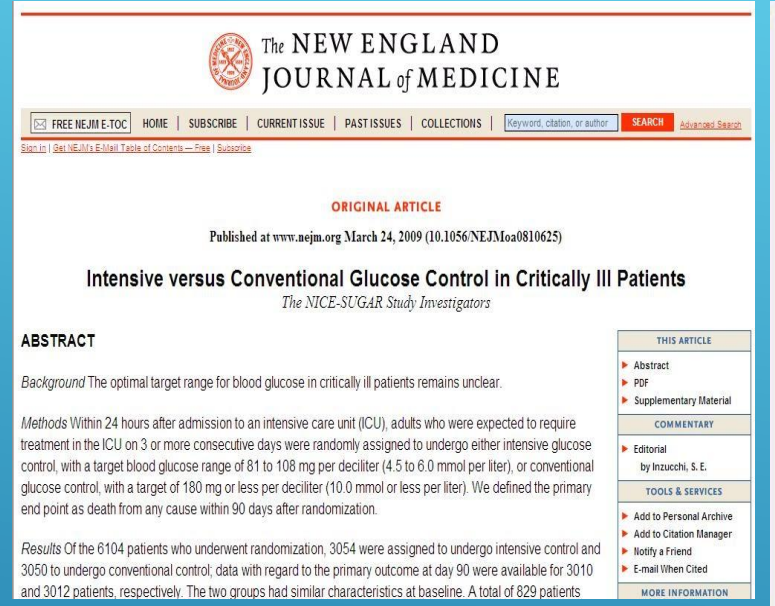


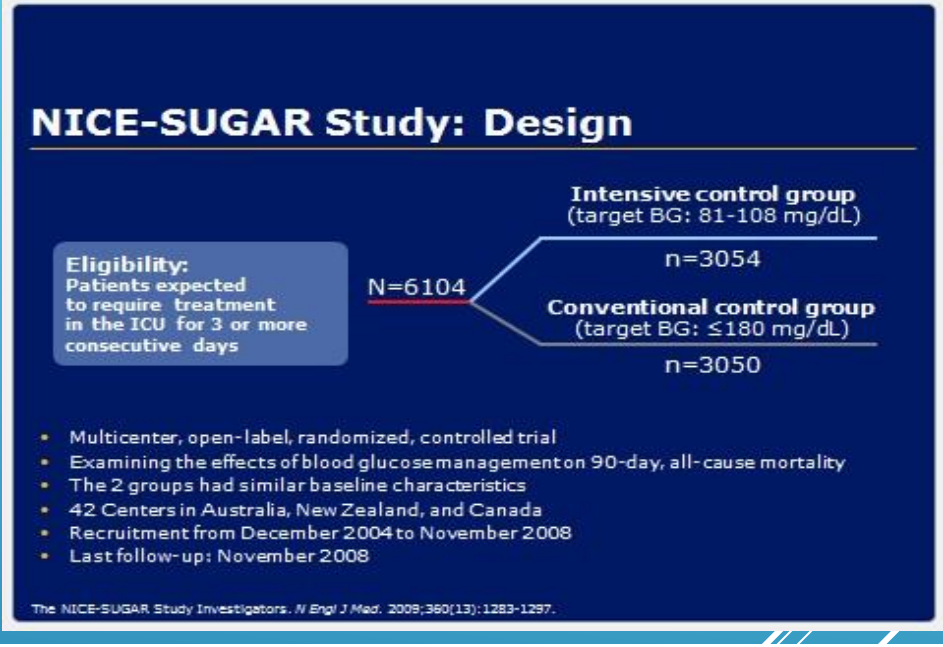
HbA_{1c} (%)	% Time Hypo (< 70 mg/dL)	Glu. Variability (CV %)
6.7	1	26
6.7	6	42
6.7	9	53

CV, coefficient of variation

HOW ABOUT DIABETES AND HYPERGLYCEMIA IN INPATIENT SETTINGS?







The New England Journal of Medicine

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VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

ABSTRACT

Background Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

Methods We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter).

Results At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent (P=0.04, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy; P=0.005). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.

Conclusions Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. (N Engl J Med 2001;345:1359-67.)

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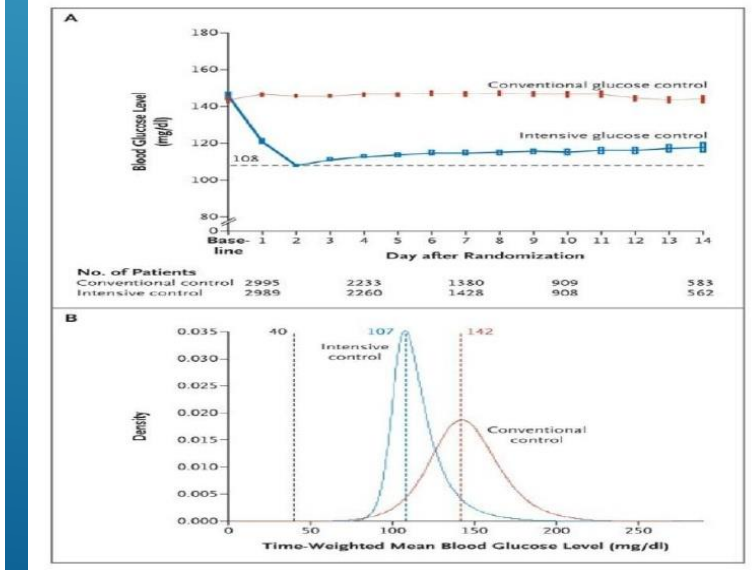
CRITICALLY ill patients who require intensive care for more than five days have a 20 percent risk of death and substantial morbidity.[1] Critical-illness polyneuropathy and skeletal-muscle wasting prolong the need for mechanical ventilation.[2-5] Moreover, increased susceptibility to severe infections and failure of vital organs amplify the risk of an adverse outcome.

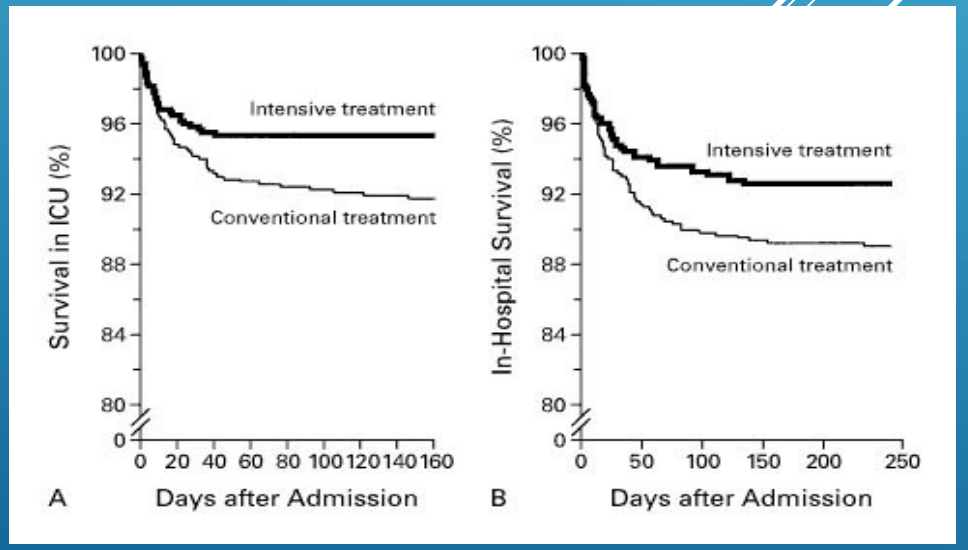
Hyperglycemia associated with insulin resistance[6-8] is common in critically ill patients, even those who have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to complications in such patients,[9-13] although data from controlled trials are lacking. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg per deciliter (11.9 mmol per liter) improves the long-term outcome.[14-16] In nondiabetic patients with protracted critical illnesses, high serum levels of insulin-like growth factor–binding protein 1, which reflect an impaired response of hepatocytes to insulin, increase the risk of death.[17,18]

We hypothesized that hyperglycemia or relative insulin deficiency (or both) during critical illness may directly or indirectly confer a predisposition to complications,[11,19,20] such as severe infections, polyneuropathy, multiple-organ failure, and death. We performed a prospective, randomized, controlled trial at one center to determine whether normalization of blood glucose levels with intensive insulin therapy reduces mortality and morbidity among critically ill patients.

From the Department of Intensive Care Medicine (G.V.B., P.W., F.W., C.V., M.S., D.V., P.F., P.L.), the Electromyography Laboratory, Department of Physical Medicine and Rehabilitation (F.B.), and the Laboratory for Experimental Medicine and Endocrinology (R.B.), Catholic University of Leuven, Leuven, Belgium. Address reprint requests to Dr. Van den Berghe at the Department of Intensive Care Medicine, University Hospital Gasthuisberg, University of Leuven, B-3000 Leuven, Belgium, or at greta.vandenberghe@med.kuleuven.ac.be.

N Engl J Med, Vol. 345, No. 19 · November 8, 2001 · www.nejm.org · 1359





HOW ABOUT DIABETES AND HYPERGLYCEMIA IN INPATIENT SETTINGS?

Intensive Glucose Management in RCT

Trial	N	Setting	Primary Outcome	ARR	RRR	Odds Ratio (95% CI)	P-value
Van den Berghe 2006	1200	MICU	Hospital mortality	2.7%	7.0%	0.94* (0.84-1.06)	N.S.
HI-5 2006	240	CCU AMI	6-mo mortality	-1.8%*	-30%*	NR	N.S.
Glucontrol 2007	1101	ICU	ICU mortality	-1.5%	-10%	1.10* (0.84-1.44)	N.S.
Ghandi 2007	399	OR	Composite	2%	4.3%	1.0* (0.8-1.2)	N.S.
VISEP 2008	537	ICU	28-d mortality	1.3%	5.0%	0.89* (0.58-1.38)	N.S.
De La Rosa 2008	504	SICU MICU	28-d mortality	-4.2% *	-13%*	NR	N.S.
NICE-SUGAR 2009	**6104**	**ICU**	**3-mo mortality**	**-2.6%**	**-10.6**	**1.14 (1.02-1.28)**	**< 0.05**

* not significant

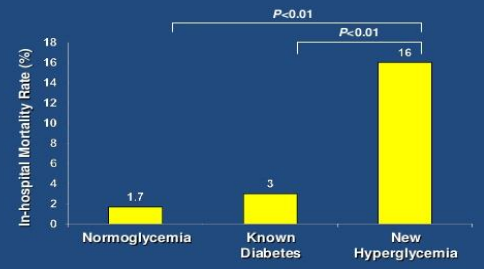
Benefits of Tight Glycemic Control: Observational Studies and Early Intervention Trials

Study	Setting	Population	Clinical Outcome
Furnary, 1999	ICU	DM undergoing open heart surgery	65% ↓ infection
Furnary, 2003	ICU	DM undergoing CABG	57% ↓ mortality
Krinsley, 2004	Medical/surgical ICU	Mixed, no Cardiac	29% ↓ mortality
Malmberg, 1995	CCU	Mixed	28% ↓ mortality After 1 year
Van den Berghe, 2001*	Surgical ICU	Mixed, with CABG	42% ↓ mortality
Lazar, 2004	OR and ICU	CABG and DM	60% ↓ A Fib post op survival 2 yr

*RCT, randomized clinical trial.

Kitabchi & Umpierrez. *Metabolism*. 2008;57:116-120.

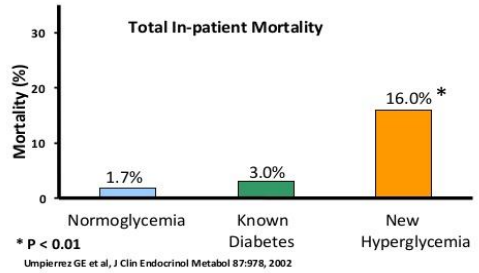
Hyperglycemia: An Independent Marker of ICU Mortality



Umpierrez GE., et al. *J Clin Endocrinol Metab*. 2002;87:978-982.

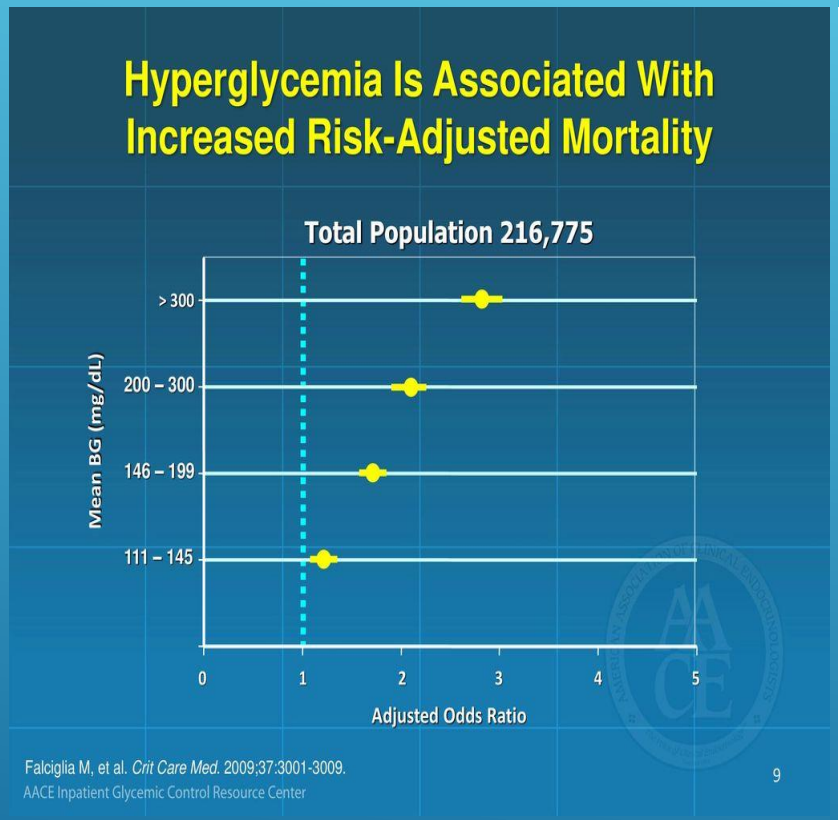
6

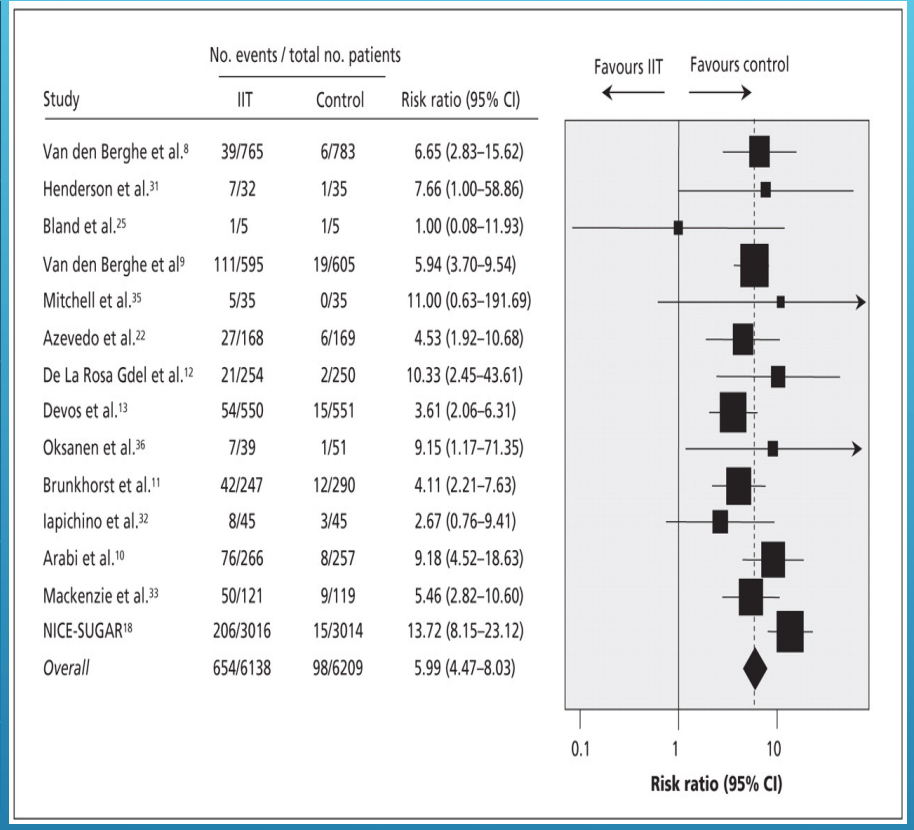
Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes



Umpierrez GE et al, J Clin Endocrinol Metabol 87:978, 2002

HOW ABOUT DIABETES AND HYPERGLYCEMIA IN INPATIENT SETTINGS?





Study	No. events / total no. patients: IIT	Control	Risk ratio (95% CI)
Van den Berghe et al.[8]	39/765	6/783	6.65 (2.83–15.62)
Henderson et al.[31]	7/32	1/35	7.66 (1.00–58.86)
Bland et al.[25]	1/5	1/5	1.00 (0.08–11.93)
Van den Berghe et al[9]	111/595	19/605	5.94 (3.70–9.54)
Mitchell et al.[35]	5/35	0/35	11.00 (0.63–191.69)
Azevedo et al.[22]	27/168	6/169	4.53 (1.92–10.68)
De La Rosa Gdel et al.[12]	21/254	2/250	10.33 (2.45–43.61)
Devos et al.[13]	54/550	15/551	3.61 (2.06–6.31)
Oksanen et al.[36]	7/39	1/51	9.15 (1.17–71.35)
Brunkhorst et al.[11]	42/247	12/290	4.11 (2.21–7.63)
Iapichino et al.[32]	8/45	3/45	2.67 (0.76–9.41)
Arabi et al.[10]	76/266	8/257	9.18 (4.52–18.63)
Mackenzie et al.[33]	50/121	9/119	5.46 (2.82–10.60)
NICE-SUGAR[18]	206/3016	15/3014	13.72 (8.15–23.12)
Overall	654/6138	98/6209	5.99 (4.47–8.03)

Table 2

ADA Recommendations for Target Blood Glucose Levels

Description	Target Blood Glucose Level
Critically ill surgical patients	As close to 110 mg/dL as possible; generally <140 mg/dL
Critically ill nonsurgical patients	<140 mg/dL
Noncritically ill patients	Optimal range not clearly defined; <126 mg/dL and random levels <180-200 mg/dL considered reasonable if they can be safely achieved

ADA: American Diabetes Association.
Source: Reference 2.

New AACE-ADA Consensus Statement on Inpatient Glycemic Control

ICU Setting	Non–ICU Setting
- Insulin infusion preferred - Starting threshold not higher than 180 mg/dl - Maintain BG 140-180 mg/dl (greater benefit likely at *lower end of this range*) - Lower targets (not evidence-based) may be appropriate in selected patients if already being successfully achieved - <110 NOT recommended (not safe)	- Most patients: • pre-meal BG <140 mg/dL • random BG <180 mg/dL -More stringent targets may be appropriate in stable patients - Less stringent targets may be appropriate in patients with severe comorbidities

Moghissi E et al. *Diabetes Care 2009, Endocrine Practice 2009*

- HBA1c not shown to be a robust target
- Outcomes seem independent of type of diabetes
- Outcomes seen independent of diabetes vs non diabetes cohorts
- Mortality and Morbidity indices appear to be glucocentric driven
- The role and place of CGMS based data is emerging but not yet fully established.

THERAPEUTIC AND DIAGNOSTIC TOOLS HAVE IMPROVED SUBSTANTIVELY SINCE THE AGE OF THE DCCT, UKPDS AND KUMMATO TRIALS; THE AGE OF THE CGMS

Mini Med Guardian

DEXCOM

FreeStyle Libre

Eversense Sensionics

Pros;

- Provides lots of data
- Data is virtually real-time
- Relatively easy to implant and use
- Added layer of safety
- An important piece in the grail diabetic goal of the "closed loop" device

Cons;

- Provides lots of data
- Does not actually measure blood glucose
- Not exactly real time data especially in patients with circulatory and vascular pathology
- Invasive
- Limited access and expensive

AGP Report

Metrics & Targets

AGP profile (14 days)

Daily views

GLUCOSE STATISTICS AND TARGETS

21 Nov 2018–3 Dec 2018	13 days
% Time CGM is Active	99.9%

Glucose Ranges	Targets [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose	**165 mg/dL**
Glucose Management Indicator (GMI)	**7.3%**
Glucose Variability	**49.4%**

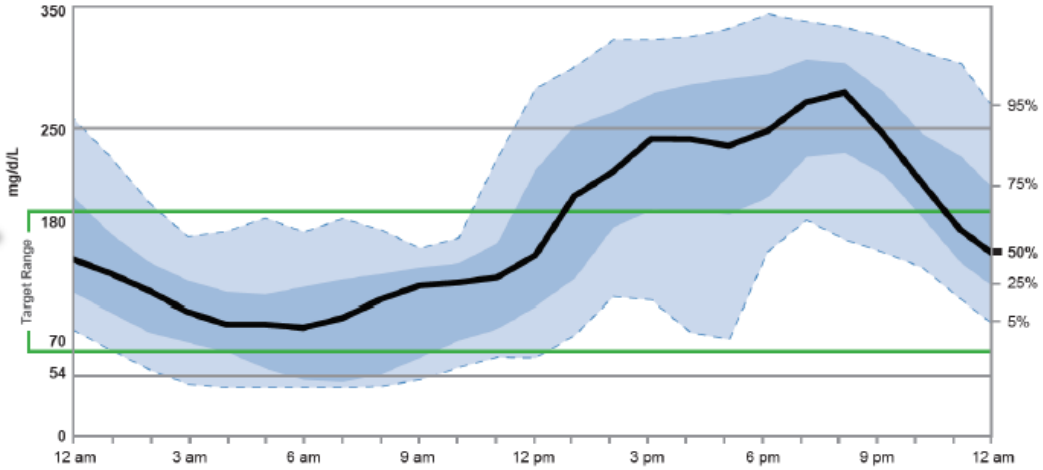
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

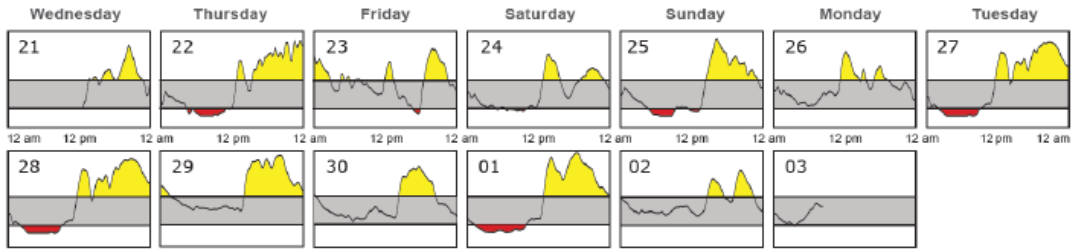
- **Very High** (>250 mg/dL) **19%** (4h 34min)
- **High** (181–250 mg/dL) **20%** (4h 48min)
- **Target Range** (70–180 mg/dL) **49%** (11h 46min)
- **Low** (54–69 mg/dL) **4%** (58min)
- **Very Low** (<54 mg/dL) **8%** (1h 55min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES



Each daily profile represents a midnight-to-midnight period.

Battelino T, Danne T, Bergenstal R. et al.
Diabetes Care 2019;42:1593–1603

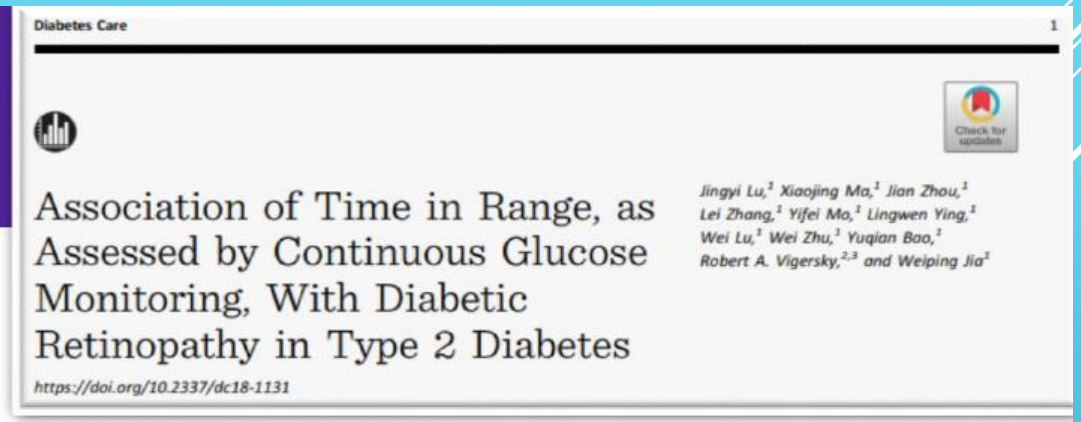
How do patients rank importance of time in range?

TABLE 1. Ranking of Factors That Have a "Big Impact" on Daily Life With Diabetes by Respondents' Diabetes Type and Therapy

Rank*	Diabetes/Therapy Type		
	T1	T2I	T2NI
1	Food choices (63%)	Food choices (67%)	Food choices (64%)
2	Time-in-range (57%)	Time-in-range (45%) A1C (44%)	Time-in-range (41%) A1C (41%)
3	Unexpected blood glucose numbers (42%)	Nondiabetes health issues (36%) Dosing insulin (34%)	Nondiabetes health issues (31%)
4	Dosing insulin (37%)	Unexpected blood glucose numbers (28%)	Unexpected blood glucose numbers (20%)
5	Hypoglycemia (30%) A1C (30%) Nondiabetes health issues (27%)	Symptoms of complications (24%)	Symptoms of complications (15%)

Runge A, et al. *Clinical Diabetes,* 2018. 36(2):112-119

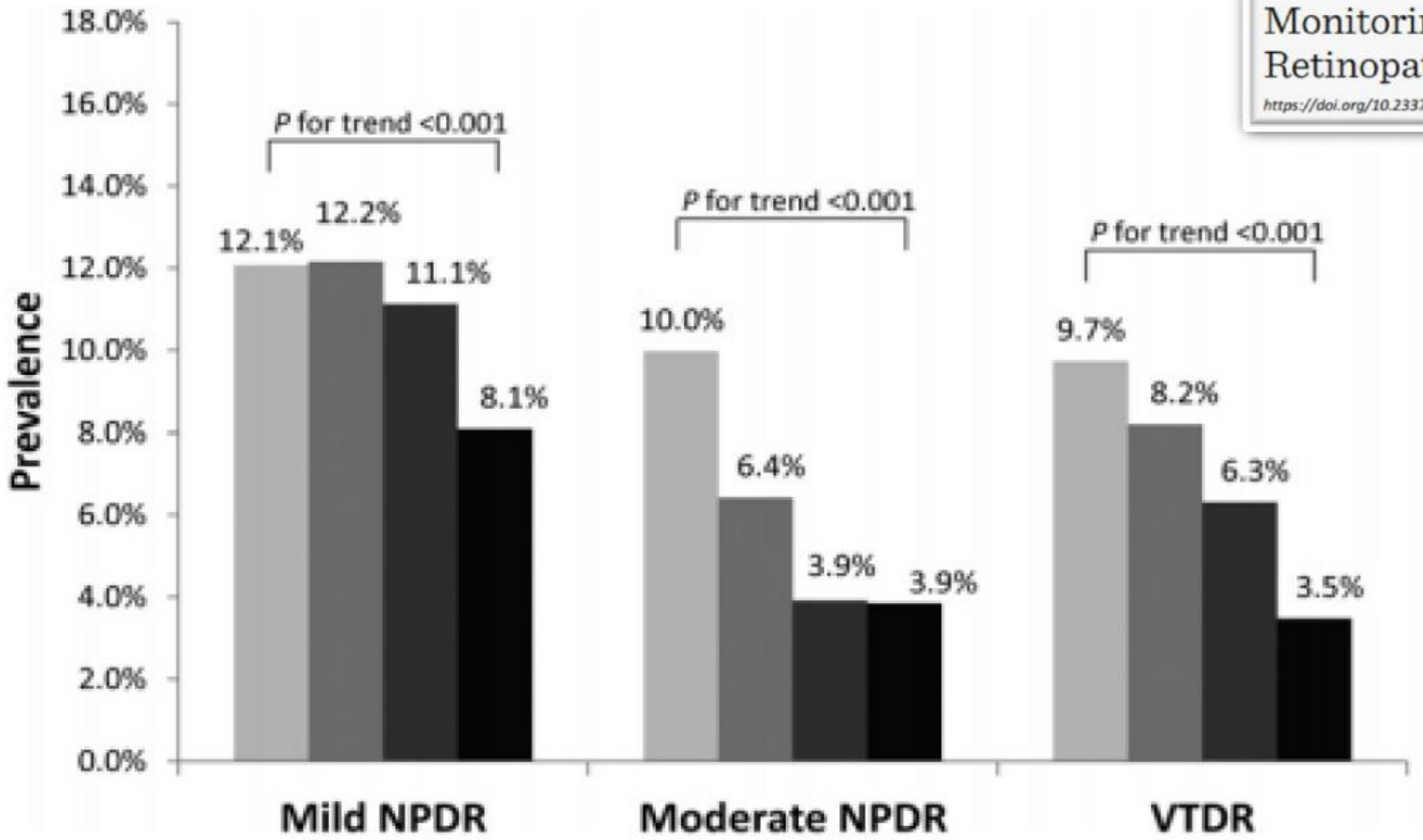
Time in Range and Outcomes?


Diabetes Care 1

Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes

Jingyi Lu,[1] Xiaojing Ma,[1] Jian Zhou,[1] Lei Zhang,[1] Yifei Mo,[1] Lingwen Ying,[1] Wei Lu,[1] Wei Zhu,[1] Yuqian Bao,[1] Robert A. Vigersky,[2,3] and Weiping Jia[1]

https://doi.org/10.2337/dc18-1131



Q1 (≤51%)
Q2 (51-71%)
Q3 (71-86%)
Q4 (>86%)

Quartiles of % Time in Range

Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

Lu et al, Diabetes Care, Sep 2018

Validation of time in range as an outcome measure for diabetes clinical trials

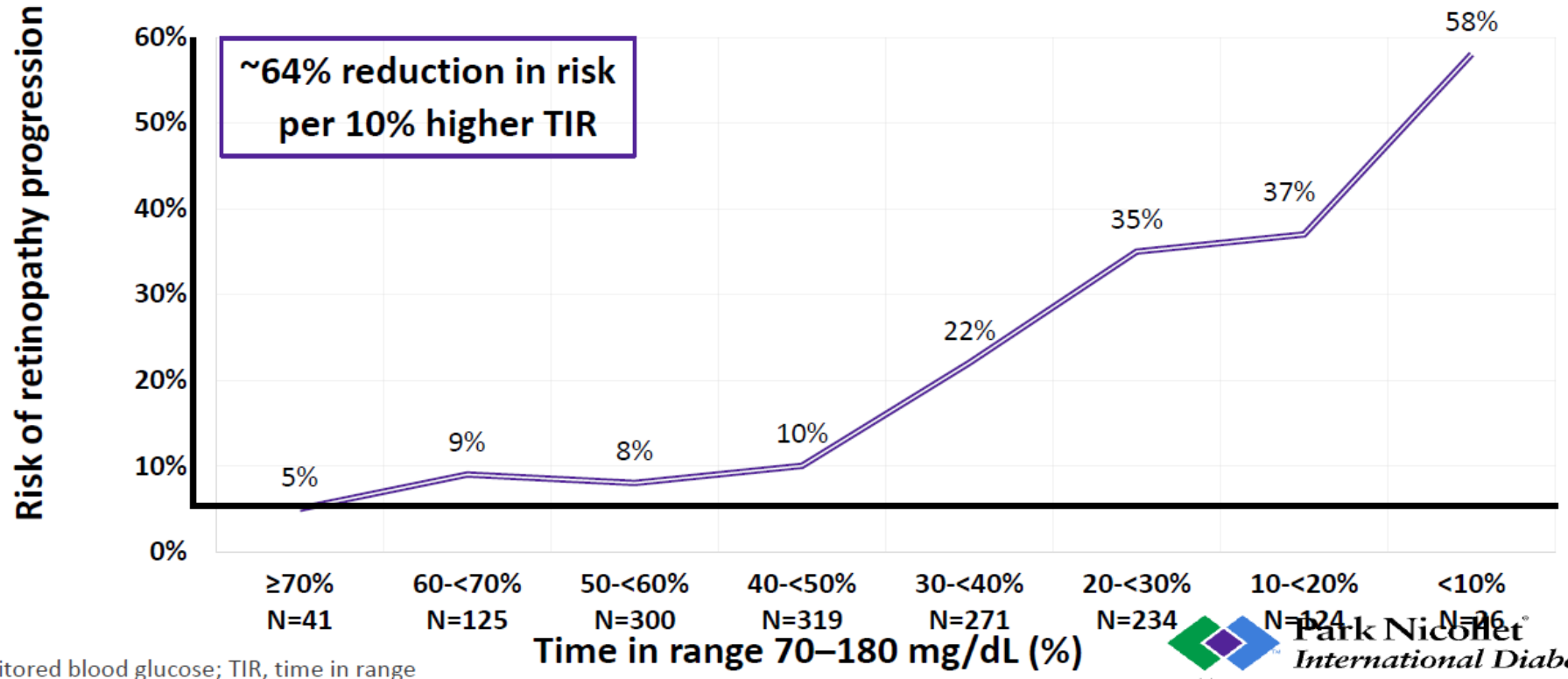
Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials

Roy W. Beck,[1] Richard M. Bergenstal,[2] Tonya D. Riddlesworth,[1] Craig Kollman,[1] Zhaomian Li,[1] Adam S. Brown,[3] and Kelly L. Close[4]

https://doi.org/10.2337/dc18-1444

Relationship between TIR (70–180) and HbA_{1c}

(TIR: 7-point SMBG profiles on 1,440 patients in DCCT)



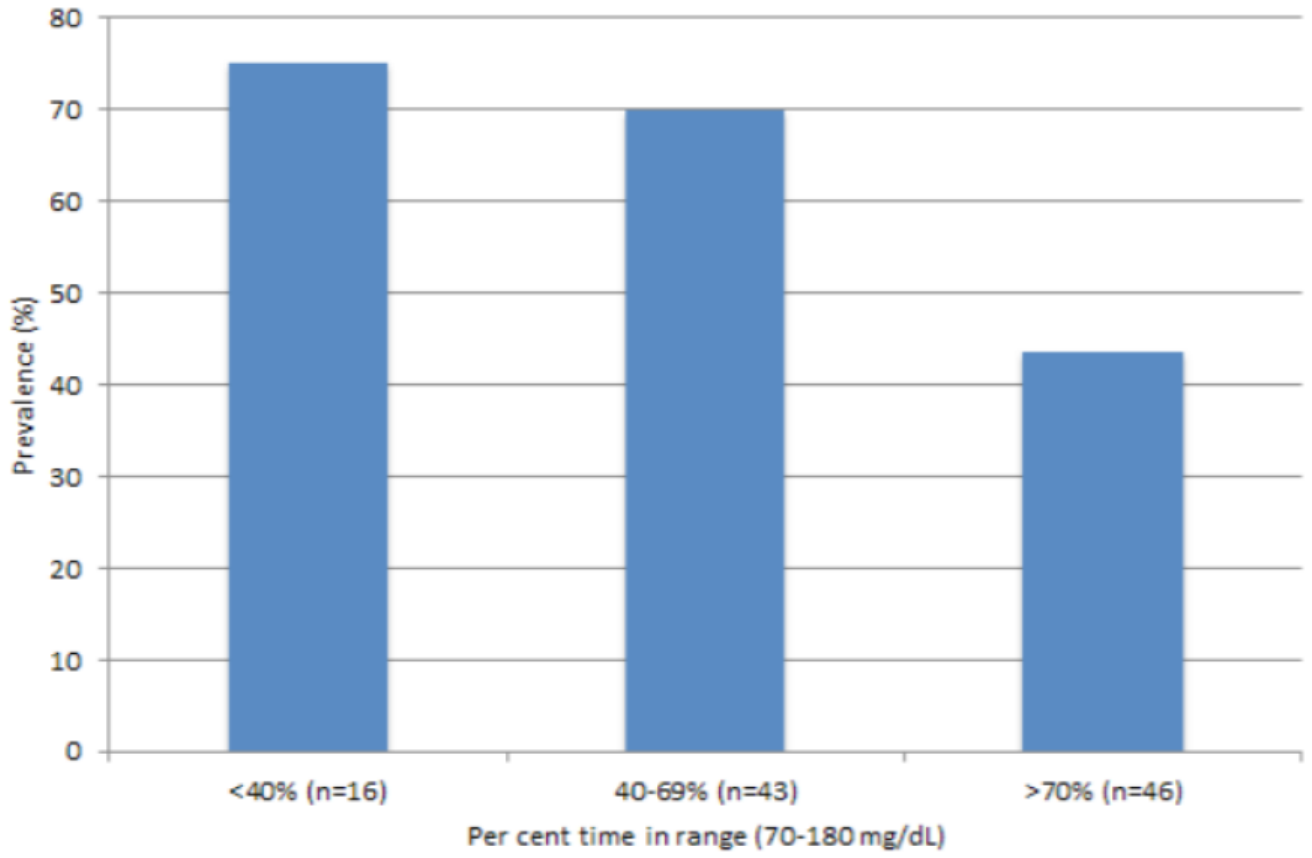
SMBG, self-monitored blood glucose; TIR, time in range

Beck R, Bergenstal R et al. Diabetes Care 2019;42:400–5

HealthPartners

Park Nicollet International Diabetes Center

TIR and neuropathy in type 2 diabetes



-For every 10% lower TIR there is a 25% increased risk of DPN

-Laboratory value HbA1c was not found to be associated with peripheral neuropathy

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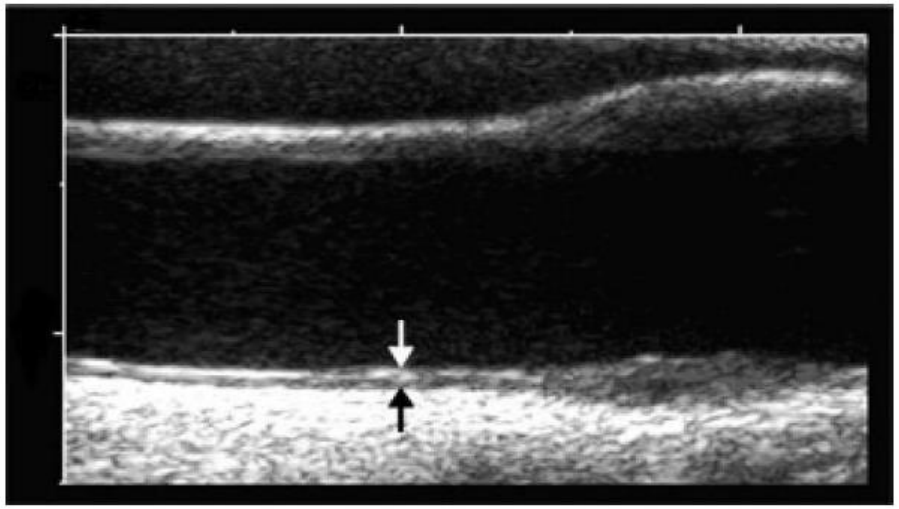
Mayeda et al, BMJ Open Diab, Jan 2020

Macrovascular disease: CIMT and Time in Range



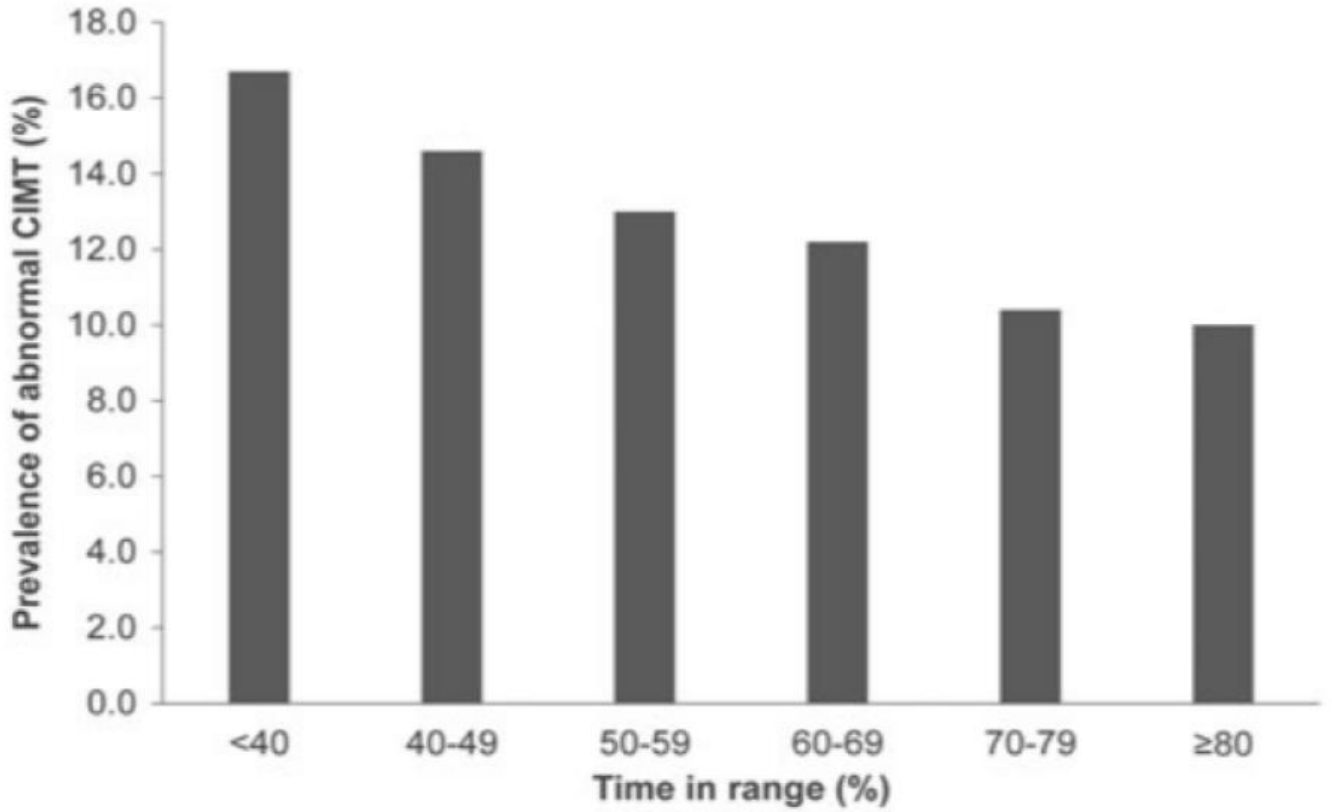
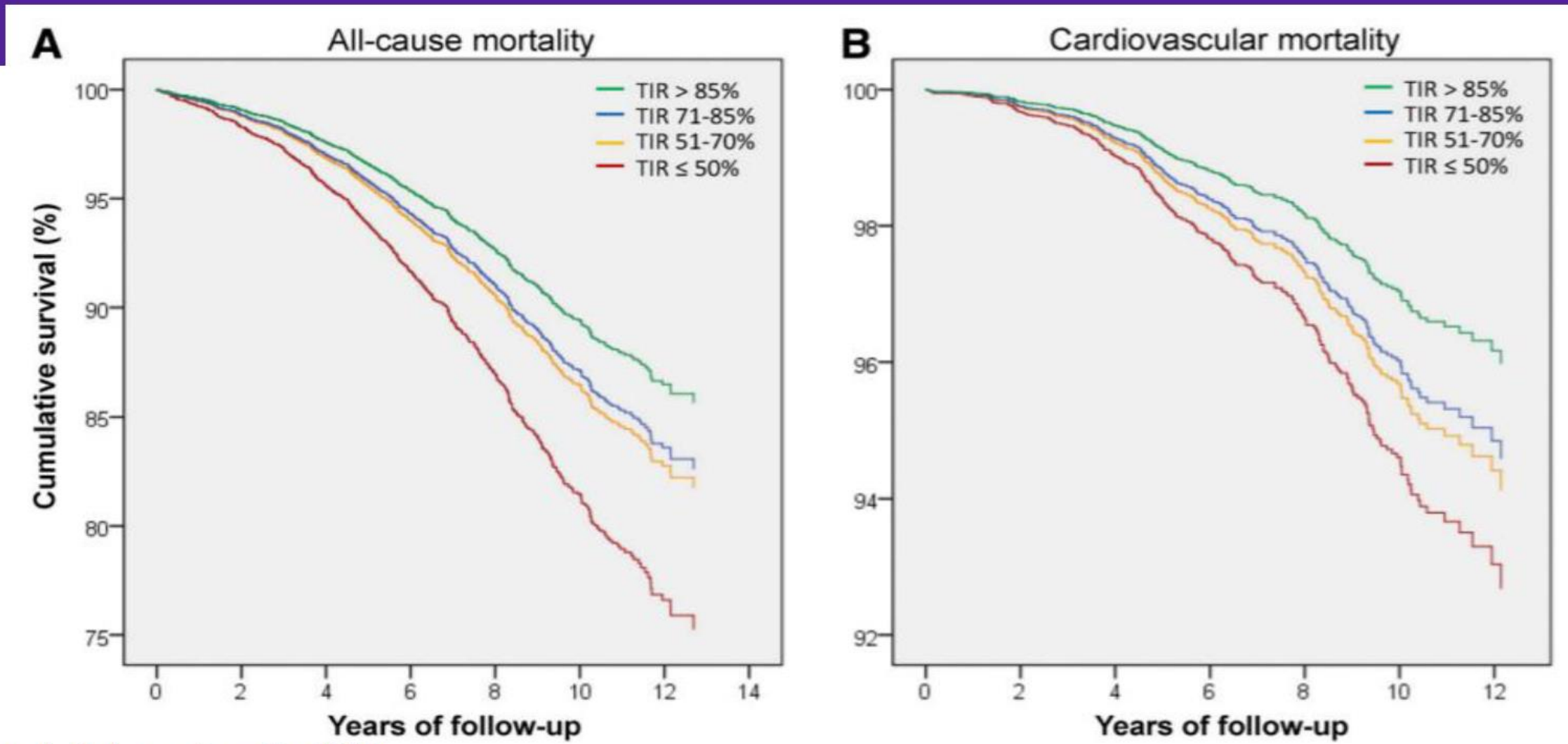


FIG. 1. Prevalence of abnormal CIMT according to TIR categories. CIMT, carotid intima-media thickness; TIR, time in range.

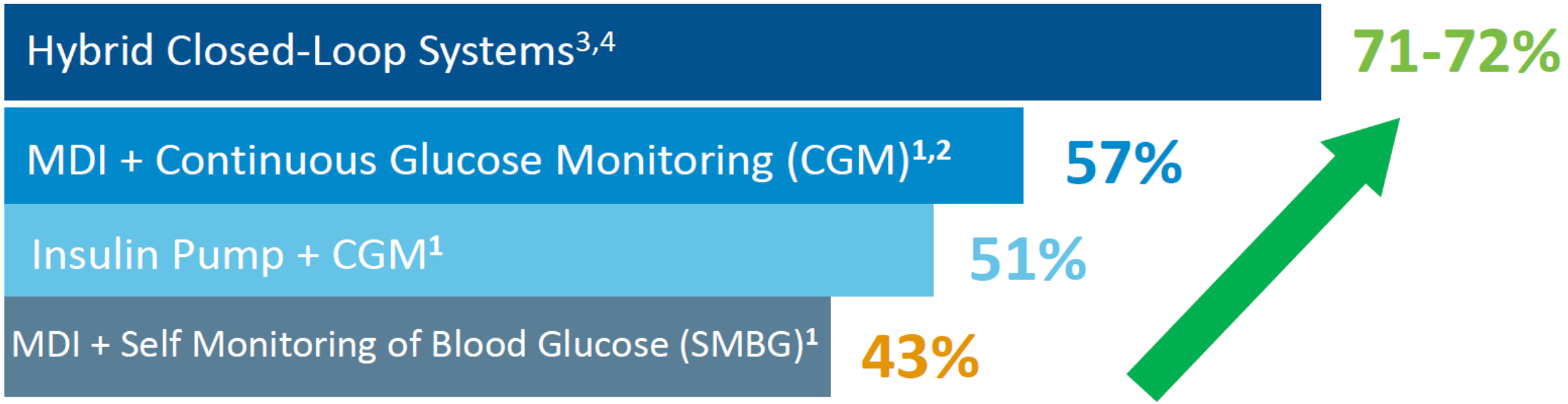
Lu et al, DTT, Oct 2019

All-cause & CV mortality correlates with TIR



Lu et al, Diabetes Care, Oct 2020

Time in Range Progression



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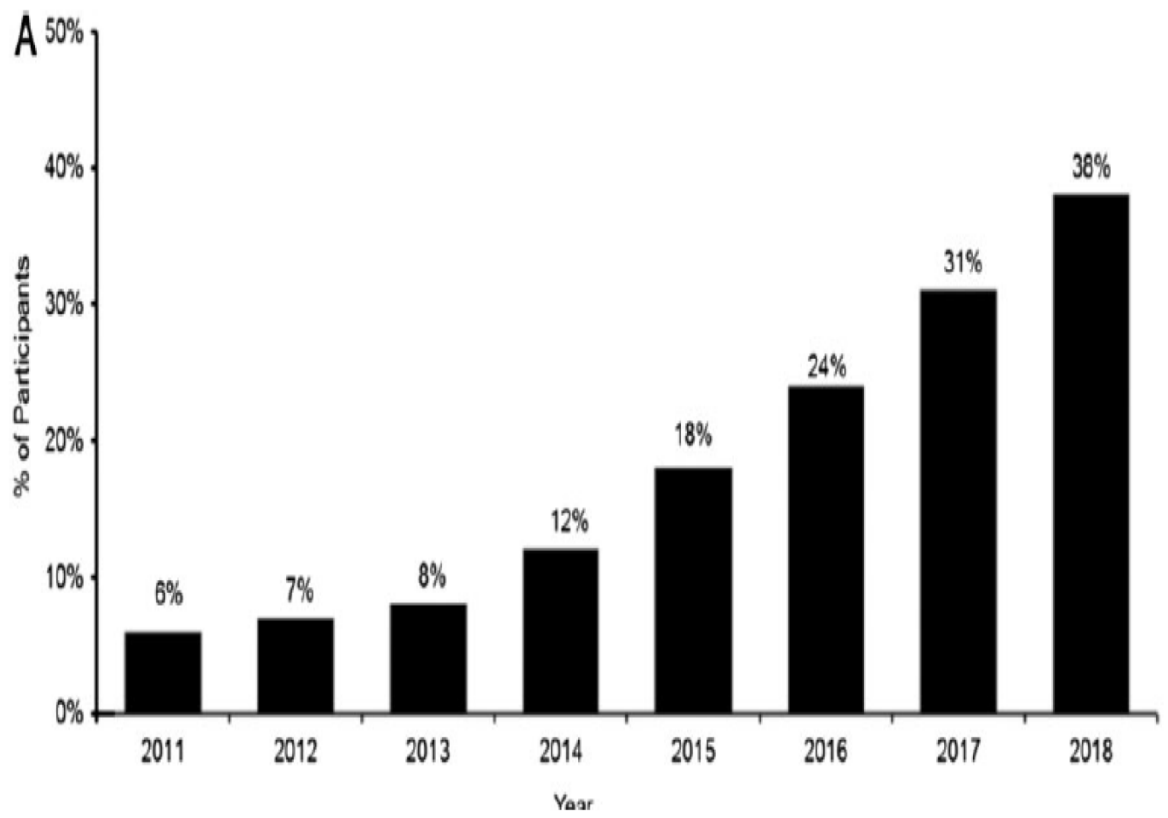
1. Beck R. *JAMA*. 2017;317(4): 371-378. *2.* Bergenstal R, et al. *N Engl J Med*. 2010; 363:311-20. 3.Bergenstal R, et al. *JAMA*. 2016;316(13):1407–1408. 4. Bergenstal et al, JAMA 2016. 5. Brown et al, NEJM 2019

What percent of T1D patients currently use CGM?



Foster N, Beck R, Miller K et al, *DTT*, Feb 2019

This is however not representative of most patients with type 1 diabetes nationwide and even less so for patients with type 2 diabetes.

CGMS use has been shown to closely track with access which is heavily dependent on insurance coverage, socio-economic status, geo location and to a less extent with age

Check for updates

Symposium/Special Issue

The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c

Journal of Diabetes Science and Technology
1–13

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A. Estimation of A1C for a given TIR Level of CGM metric

$TIR^{70\text{-}180}$	Estimate	95% CI for the predicted value[b]
$TIR^{70\text{-}180}$		
20%	9.4	(8.0, 10.7)
30%	8.9	(7.6, 10.2)
40%	8.4	(7.1, 9.7)
50%	7.9	(6.6, 9.2)
60%	7.4	(6.1, 8.8)
70%	7.0	(5.6, 8.3)
80%	6.5	(5.2, 7.8)
90%	6.0	(4.7, 7.3)

70% $TIR^{70\text{-}180}$ ≈ 7% A1c

50% $TIR^{70\text{-}180}$ ≈ 8% A1c

10% ΔTIR ≈ 0.5% ΔA1c

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DTT

ORIGINAL ARTICLE

The Relationship of Hemoglobin A1c to Time-in-Range in Patients with Diabetes

Robert A. Vigersky, MD and Chantal McMahon, PhD

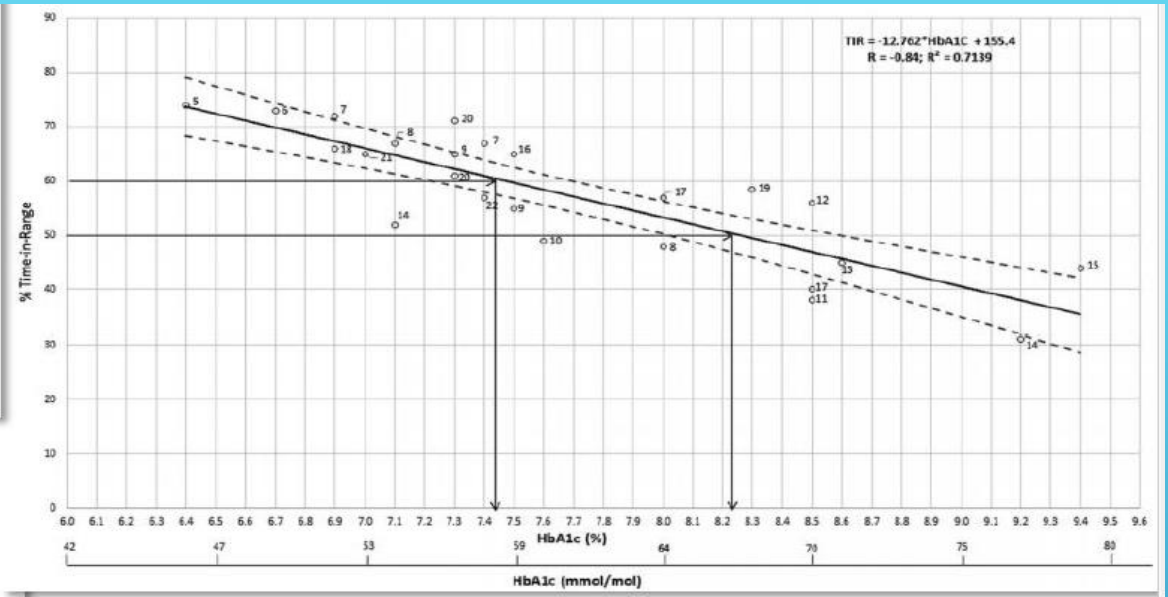

Table 2. Hemoglobin A1c in % and mmol/mol at Each Decile of Time-in-Range per Equation in the Figure

Time-in-range	*HbA1c (%)*	*HbA1c (mmol/mol)*
0%	12.1	109
10%	11.4	101
20%	10.6	92
30%	9.8	84
40%	9.0	75
50%	8.3	67
60%	7.5	59
70%	6.7	50
80%	5.9	42
90%	5.1	32
100%	4.3	23

70% TIR$^{70\text{-}180}$ ≈ 6.7% A1c

50% TIR$^{70\text{-}180}$ ≈ 8.3% A1c

10% ΔTIR ≈ 0.8% ΔA1c

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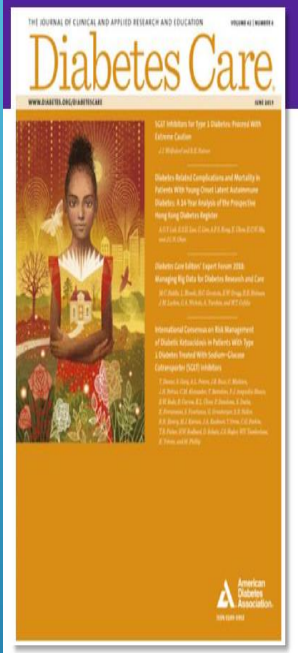
June 2019



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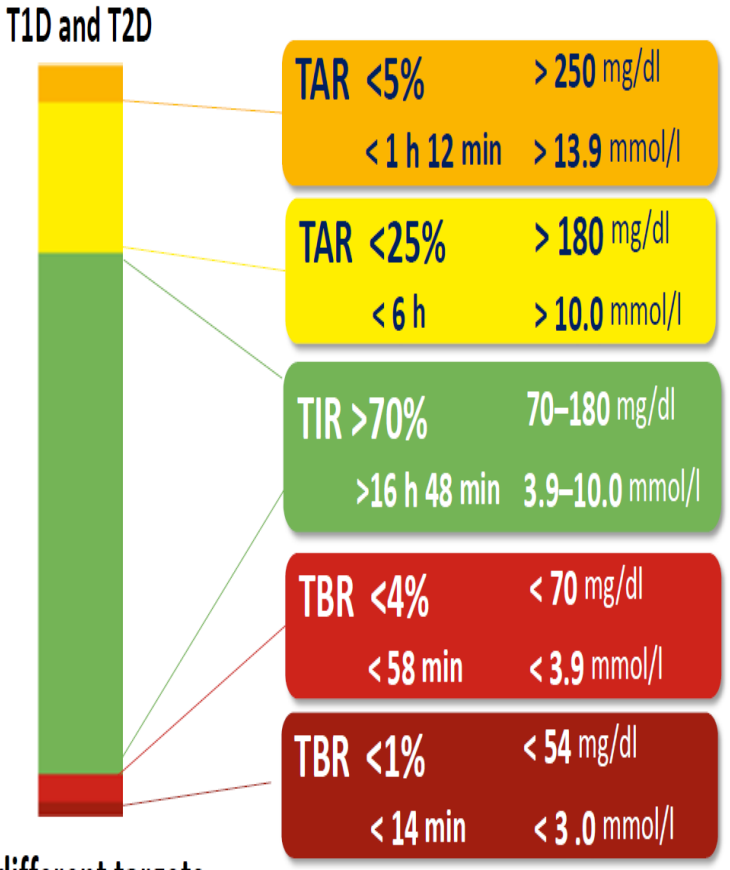
Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

https://doi.org/10.2337/dci19-0028

CGM TIR targets for most individuals with T1D and T2D



High risk individuals have different targets
(with complications or comorbidities or pregnancy)

Battelino T, Danne T, Bergenstal RM, et al. *Diabetes Care* 2019;42:1593–1603

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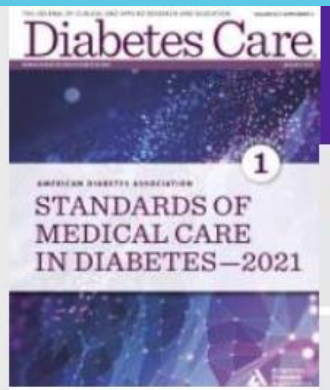

ADA 2021 Standards of Care (*Diabetes Care*, Jan 2021)

Table 6.2—Standardized CGM metrics for clinical care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target ≤36%*	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (26).

Future Directions

- More clinical outcomes data
- Regulators and insurers approval and coverage
- More advocacy: equal and improved access for all who would benefit
- More competition for less burden: smaller size, better apps, etc of devices worn on/in body

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FDA approval of diabetes drugs and therapeutic biologics utilizes HbA1c reduction as a surrogate endpoint

Type 1 diabetes

Diabetes Control and Complications Trial 1993

DCCT/EDIC 2000
Retinopathy, nephropathy

DCCT/EDIC 2005
MACE+

Type 2 diabetes

UKPDS 1998
Microvascular

"Reductions in HbA1c directly reflect improvements in glycemic control…and is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus"

DCCT Research Group. *N Engl J Med* 1993;329:977-986.
DCCT/EDIC Research Group. *N Engl J Med* 2000;342:381-389.
DCCT/EDIC Research Group. *N Engl J Med* 2005; 353:2643-2653
UKPDS. *Lancet* 1998;352:837-853 and 854-865.

Selected potential study endpoints in investigational device exemption and premarket applications for artificial pancreas device systems

- Number of hypoglycemic and hyperglycemic events
- Time spent in, average duration of, mean AUC for hypoglycemia and hyperglycemia
- HbA1c. Acceptable increases in % HbA1c may be offset by benefit in another endpoint (such as a reduction in hypoglycemic events)
- **Time in Range (TIR).** Important to also assess the effect of the device on clinical symptoms, glucose values above and below the desired ranges, and understand its relationship to other markers of glycemic control
- Safety: incidence of severe hypoglycemia, severe hyperglycemia, or DKA
- Other: **Glycemic variability (such as coefficient of variation and standard of deviation), Quality of Life**

FDA CDRH. The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems. Nov 2012

Cardiovascular effects of anti-diabetes drugs

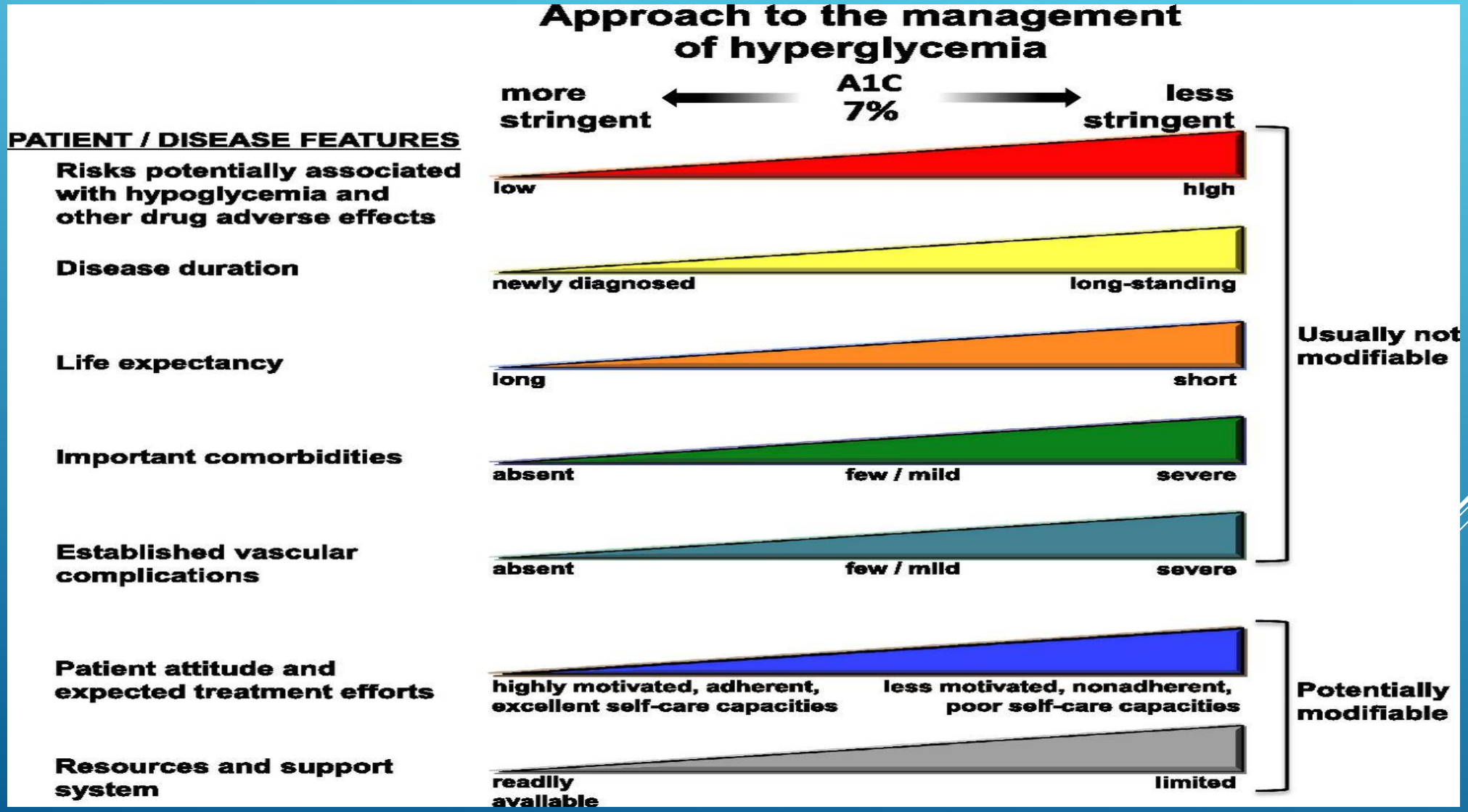
- "…reducing long-term cardiovascular complications in patients with diabetes should be an important goal of disease management. However, a premarketing recommendation to demonstrate macrovascular risk reduction in the absence of a signal for an adverse cardiovascular effect may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy." – Feb 2008
- "To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk." – Dec 2008
- "the Agency recommends a new approach in the evaluation of the safety profile of new drugs to improve glycemic control in patients with type 2 diabetes mellitus." – Mar 2020

FDA CDER. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Feb 2008
FDA CDER. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Dec 2008
FDA CDER. Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control. Mar 2020
Chong WH, et al. Assessing the Safety of Glucose-Lowering Drugs - A New Focus for the FDA. *NEJM* 2020;383(13):1199-1202.

Closing thoughts: Changing end points for FDA approval of diabetes drugs

- Reduction in HbA1c is currently the primary efficacy endpoint for approval of new anti-diabetes drugs
- Draft guidance from 2020 for type 2 diabetes drug approval focuses on development of a safety database but replaces the previous 2008 guidances for types 1 and 2 diabetes, and evaluation of CV safety
- The FDA drug approval process encourages development of novel endpoints
- There is precedent for patient-reported outcomes as clinical endpoints, and time-in-range as an endpoint for artificial pancreas devices
- FDA guidance is needed. With adequate evidence that TIR and PROs accurately predict clinical benefit, using these as endpoints would facilitate approval of anti-diabetes drugs with greater relevance to patients

A PARADIGM SHIFT IN APPROACH TO INDIVIDUAL PATIENT GOAL SETTING FOR ONGOING DIABETES CARE



CONCLUDING REMARKS

- While the long held glycemic target goal of HBA1c <7.0 for patients with diabetes has strong scientific basis it also has many important limitations and caveats.

- The heterogeneity of diabetes types, population demographics and associated comorbidities make it clear that HBA1c goals in patients with diabetes need to be nuanced and individualized. One size certainly does not fit all.

- For certain circumstances and types of diabetes HBA1c is clearly not the preferred nor ideal target measure and this needs to be appreciated.

- The growing availability of CGMS technology has opened new vistas of information regarding other important targets of diabetes control that are likely to grow in importance and prominence over time especially in the population of patients on insulin pumps and with closed loop systems.

Concluding Remarks

- The importance of diabetes as a cardio-metabolic syndrome rather than a simple glucocentric state has brought the importance of cardiovascular end points to the fore in setting desirable diabetes therapeutic goals and targets. The age of the CVOT is here to stay and will likely grow in importance and prominence with time.

- Patient related outcomes including indices that utilize quality of life measures, hypoglycemia prevalence, impact on weight, adverse events etc are likely to grow in prominence and importance with time.

- While defining treatment goals in diabetes care requires nuance and careful individual clinical decision making similar nuance is needed in the FDA approval targets for diabetes medications and devices as well as in the tracking and interpretation of so called "quality of care" measures applied to diabetes care.

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THANK YOU VERY MUCH FOR YOUR KIND ATTENTION

Questions???, Comments???