Endocrine and Metabolism PRN Focus Session—Rapid Clinical Pearls and a Clinical Debate in Endocrinology and Metabolism
Activity No. 0217-0000-11-081-L01-P (Knowledge-Based Activity)

Monday, October 17
3:45 p.m.–5:45 p.m.
Convention Center: Rooms 315 & 316

Moderator: Daniel M. Riche, Pharm.D., BCPS, CDE
Assistant Professor of Pharmacy Practice and Medicine, University of Mississippi School of Pharmacy, University of Mississippi Medical Center, Jackson, Mississippi

Agenda

3:45 p.m.	Emerging Therapies in Diabetes *Nicole R. Pinelli, Pharm.D.* Assistant Professor of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, Michigan
4:00 p.m.	GLP-1 Agents in Metabolic Syndrome/Obesity *Rick Hess, Pharm.D., CDE, BC-ADM* Assistant Professor, Department of Pharmacy Practice, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, Tennessee
4:15 p.m.	Metformin Use for Chronic Kidney Disease Patients *Marissa Escobar Quinones, Pharm.D.* Clinical Pharmacy Specialist, Parkland Southeast Dallas Health Center, Grand Prairie, Texas
4:30 p.m.	Glucose Variability Impact *Kim L. Kelly, Pharm.D., FCCP, BCPS* President, Kelly Diabetes Associates, LLC, Cupertino, California
4:45 p.m.	U-500: Appropriate Use and Common Pitfalls *Jessica Trompeter, Pharm.D.* Assistant Professor, Bernard J. Dunn School of Pharmacy, Winchester, Virginia

5:00 p.m.	ADA Algorithm Versus AACE Algorithm for Diabetes—A Debate *Craig D. Logemann, Pharm.D., BCPS, CDE* Clinic Pharmacist, Partners in Health Clinics, Des Moines, Iowa and *Tricia M. Russell, Pharm.D., BCPS, CDE* Assistant Professor, Department of Pharmacy Practice, Wilkes University, Nesbitt School of Pharmacy & Nursing, Wilkes Barre, Pennsylvania

Faculty Conflict of Interest Disclosures

Marissa Escobar Quinones: no conflicts to disclose
Rick Hess: no conflicts to disclose
Kim L. Kelly: member of advisory board for LifeScan
Craig D. Logemann: no conflicts to disclose
Nicole R. Pinelli: no conflicts to disclose
Tricia M. Russell: no conflicts to disclose
Jessica Trompeter: no conflicts to disclose

Learning Objectives

1. Explain at least 3 pharmacological mechanisms of emerging therapies for diabetes mellitus.
2. Summarize the preliminary clinical trial data examining the efficacy and safety of new medications for the management of diabetes mellitus.
3. Target individuals with diabetes mellitus who may benefit from emerging therapies.
4. Review the prevalence of metabolic syndrome/obesity.
5. Review current pharmacotherapy used in the treatment of metabolic syndrome/obesity.
6. Examine the clinical evidence for the utilization of GLP-1 agonists as pharmacotherapy options in the treatment of metabolic syndrome/obesity.
7. Review the history and contraindications of metformin in patients with chronic kidney disease.
8. Evaluate the current literature regarding the use of metformin in patients with chronic kidney disease.
9. Provide recommendations for the use of metformin in chronic kidney disease.
10. Write a brief description of the evidence that glycemic variability is an independent risk factor for cardiovascular disease.
11. Write a brief description of the mechanism by which glycemic variability can result in oxidative stress.
12. Discuss at least three variables which may affect the pathophysiology of oxidative stress.
13. Discuss the studies that do not support glycemic variability and pathology, including at least one methodologic flaw in each study.
14. Recognize the role of U-500 insulin in the treatment of severe insulin resistance.
15. Evaluate the safety and educational barriers associated with initiating U-500 insulin and discuss potential solutions.
16. Summarize a dosing scheme for initiation and titration of U-500 insulin.

17. Review the advantages of recommending an A1c goal of <7% for the management of type 2 diabetes according to the ADA treatment algorithm.
18. Identify any concerns with the AACE treatment algorithm glycemic goal of A1c of <6.5%.
19. Discuss the benefits of initiating metformin as a preferred treatment early in the management of type 2 diabetes.
20. Review the advantages of recommending an A1c goal of <6.5% for the management of type 2 diabetes according to the AACE treatment algorithm.
21. Identify any concerns with the ADA treatment algorithm glycemic goal of A1c of <7%.
22. Discuss the benefits of initiating other medications besides metformin as monotherapy options, such as thiazolidinediones, DPP-4 inhibitors, incretin mimetics or alpha-glucosidase inhibitors.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

Rapid Clinical Pearls…

Emerging Therapies in Diabetes

Nicole R. Pinelli, Pharm.D., M.S., CDE
Assistant Professor of Pharmacy Practice
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University
Detroit, Michigan

Disclosure

No relevant financial relationship with any commercial interests to disclose

Learning Objectives

At the end of this presentation, participants should be able to:

- Explain at least 3 pharmacological mechanisms of emerging therapies for diabetes mellitus
- Summarize the preliminary clinical trial data examining the efficacy and safety of new medications for the management of diabetes mellitus
- Target individuals with diabetes mellitus who may benefit from emerging therapies

Emerging Therapies in Diabetes

Today's Menu

Appetizer

"Triumvirate" to the "Ominous Octet" Sampler

Type 2 Courses

The Many Flavors of "GLP-1"

Recipe for Disaster with "SGLT2"?

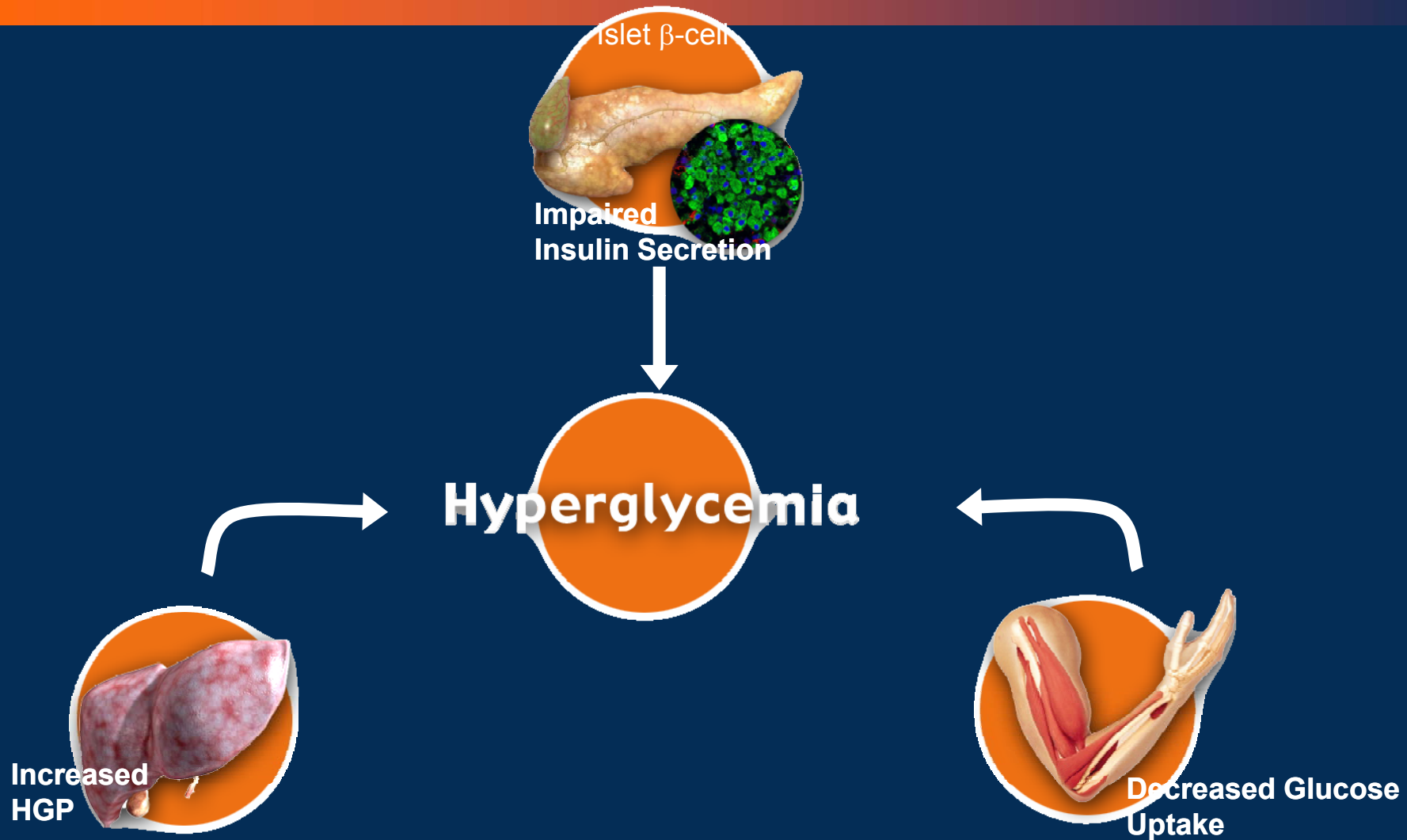
Something for Everyone

"Ultra-Long-Acting" … Better in the Fasting State?

Dessert

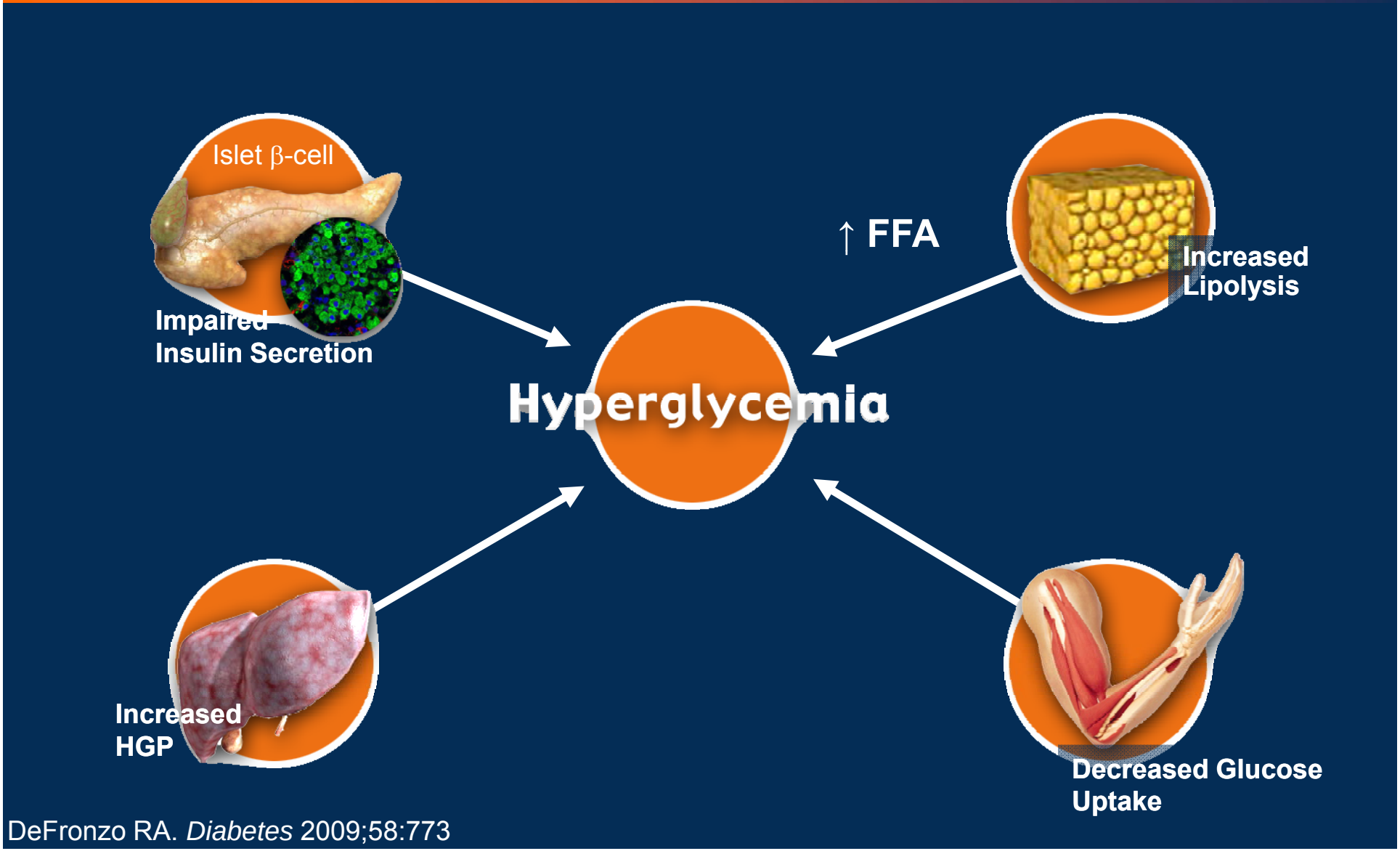
"Pipeline" Sweet Table

"Triumvirate" to the "Ominous Octet" Sampler



DeFronzo RA. *Diabetes* 2009;58:773

"Triumvirate" to the "Ominous Octet" Sampler



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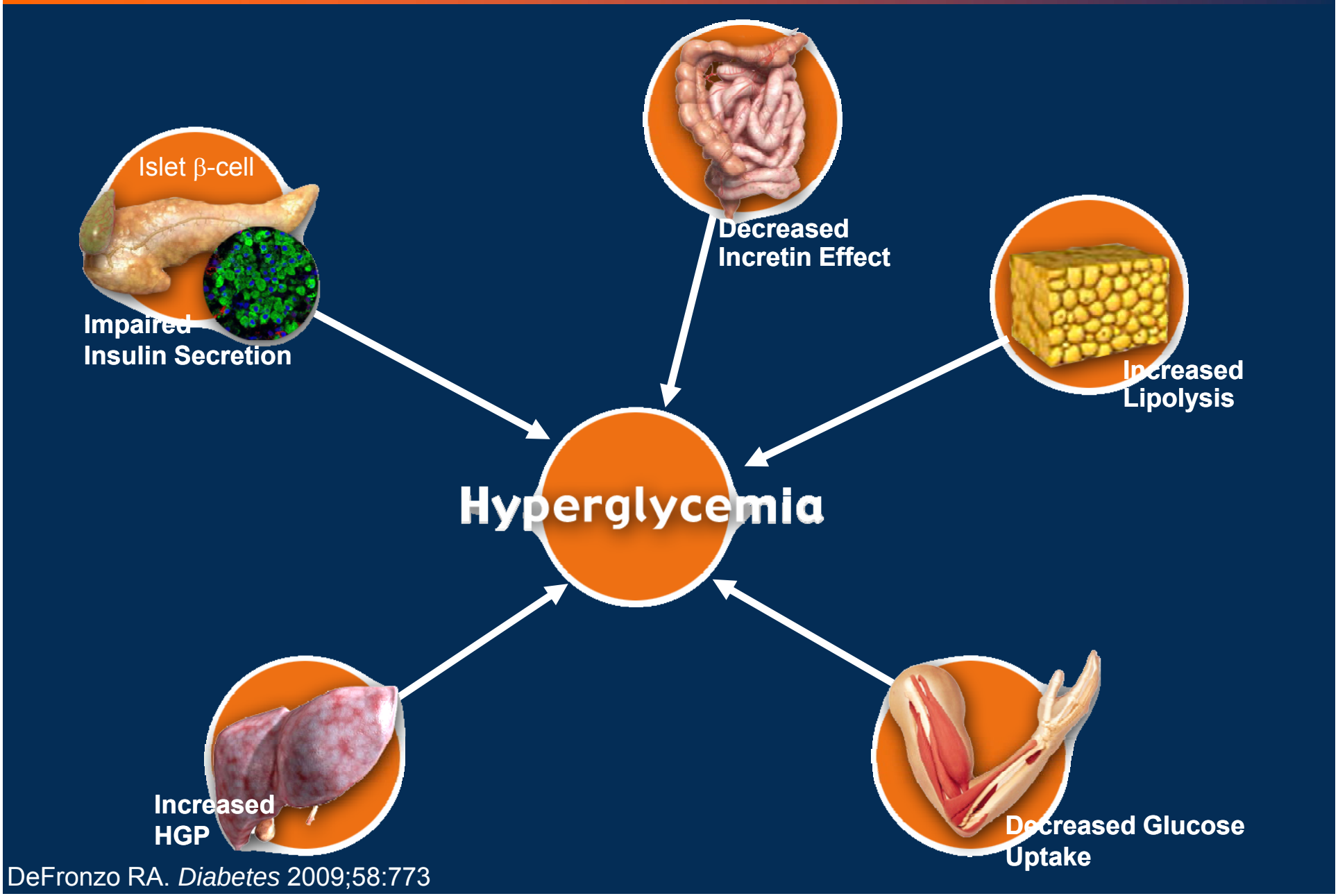

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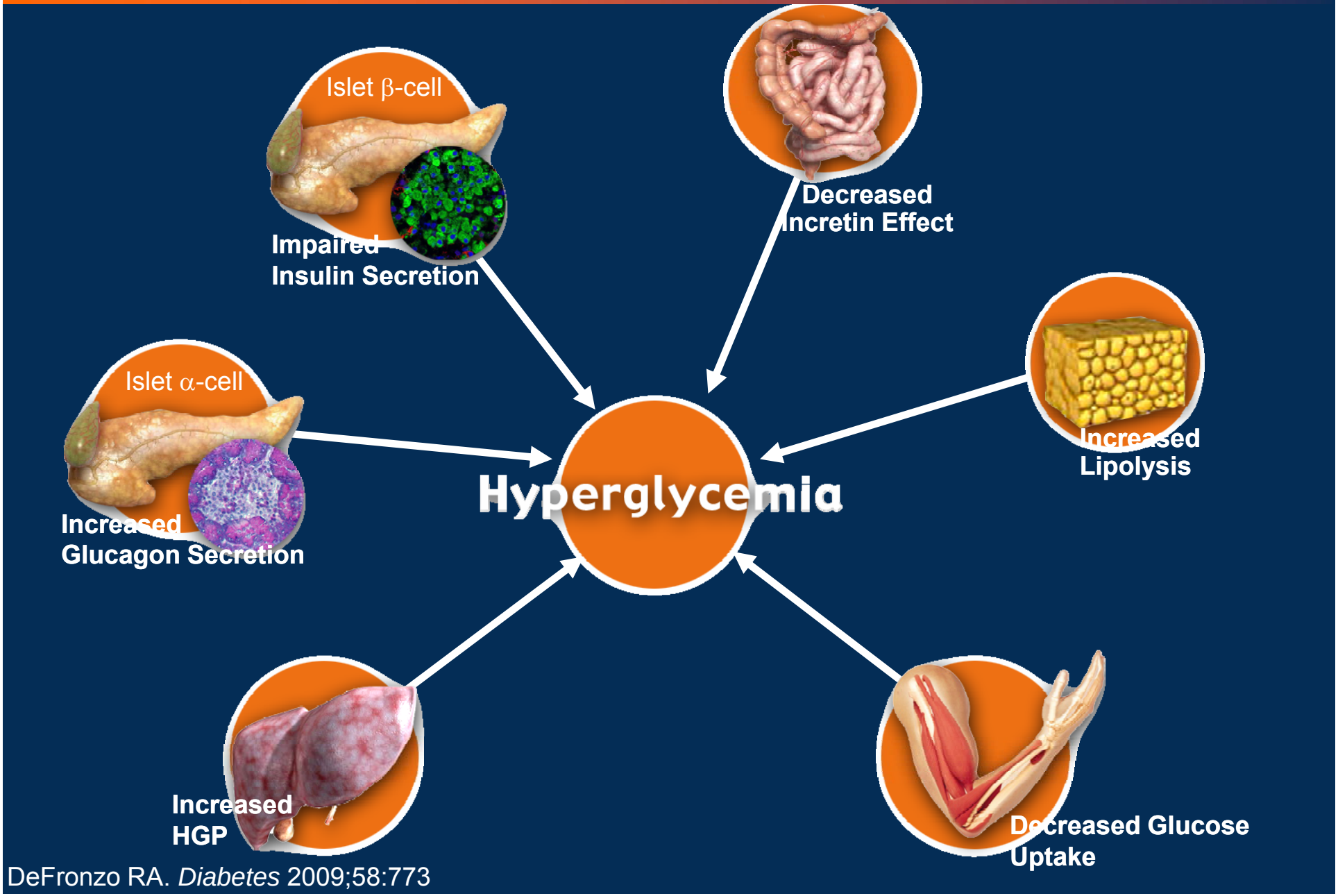

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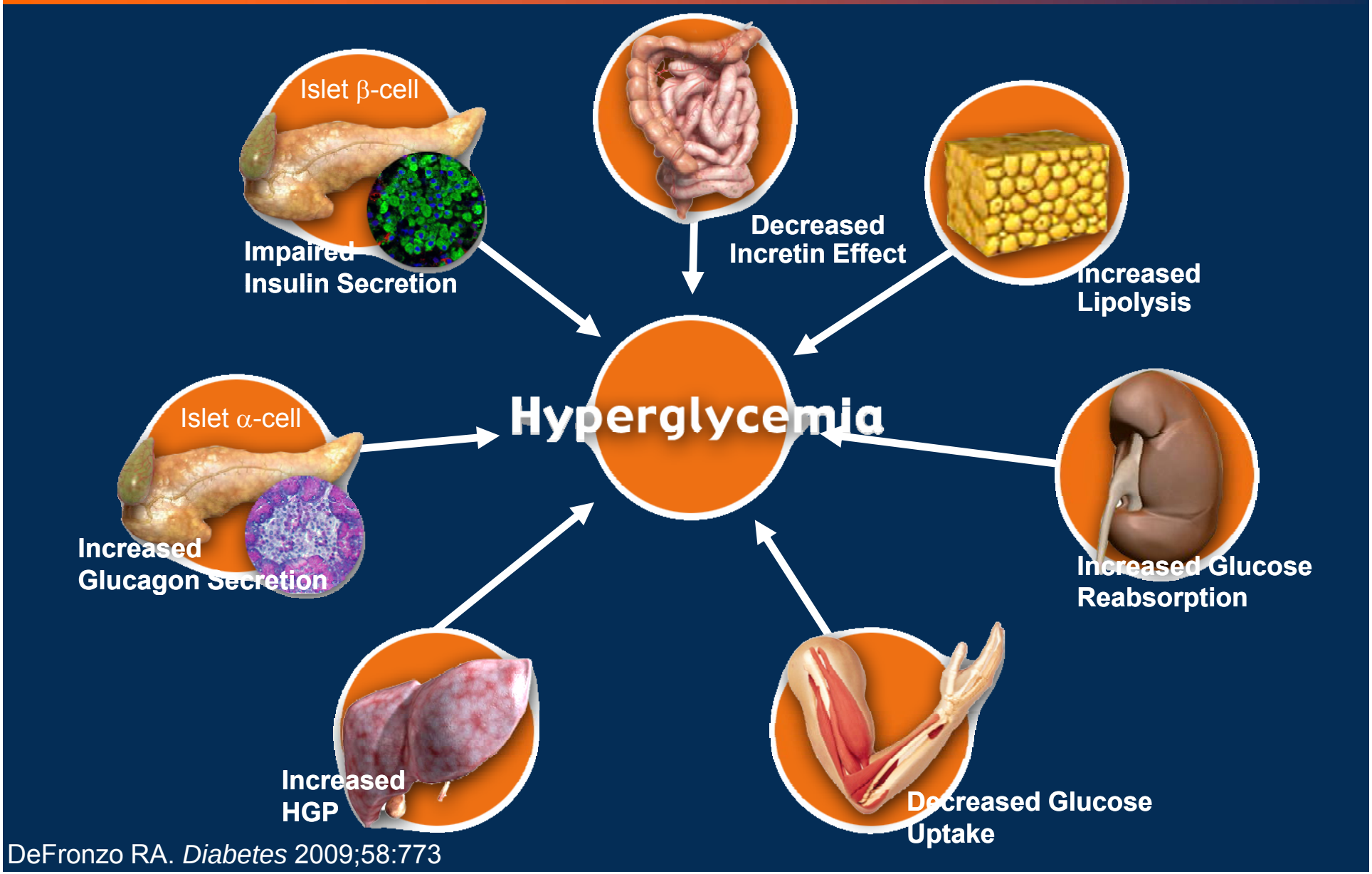

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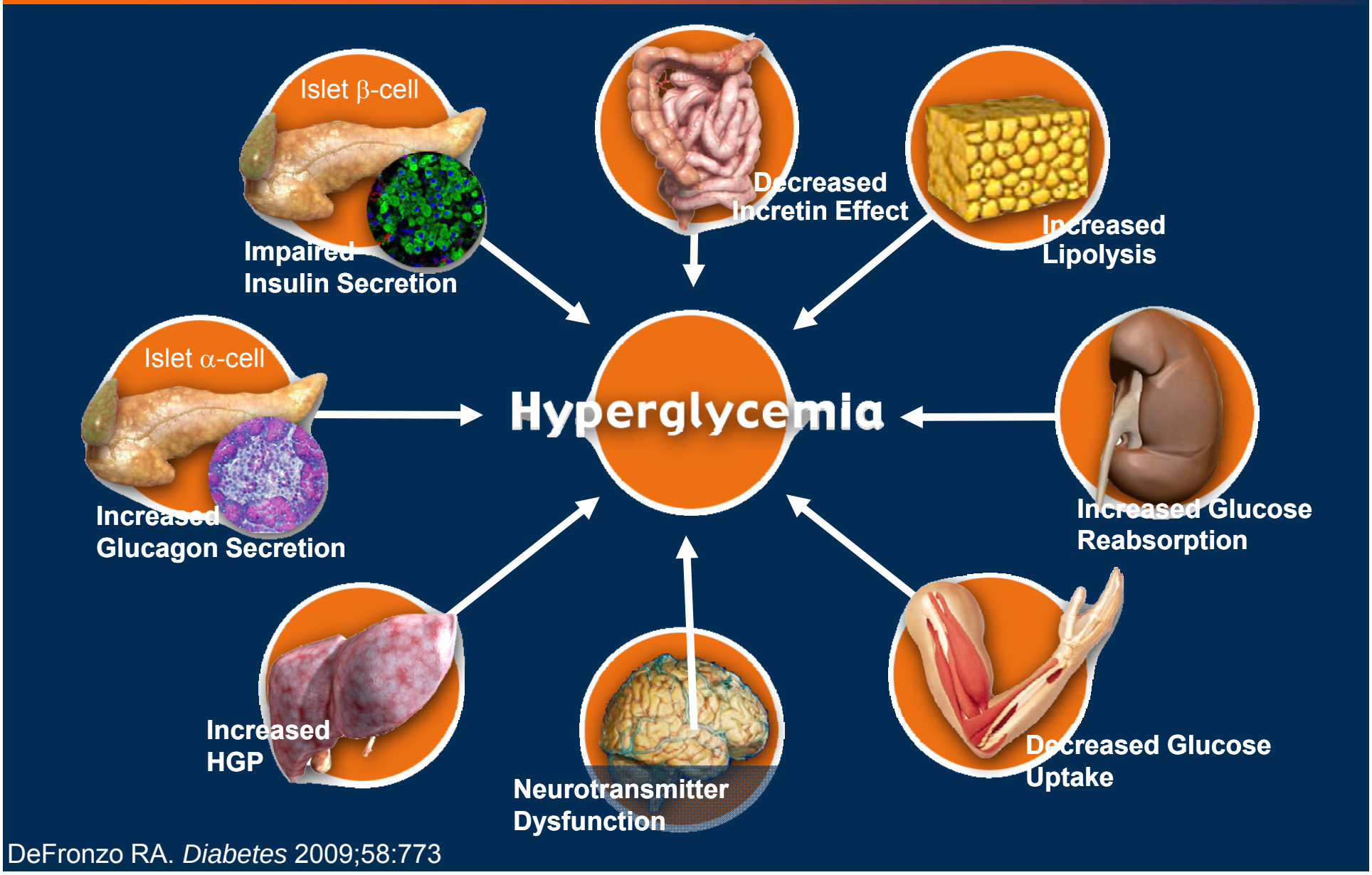
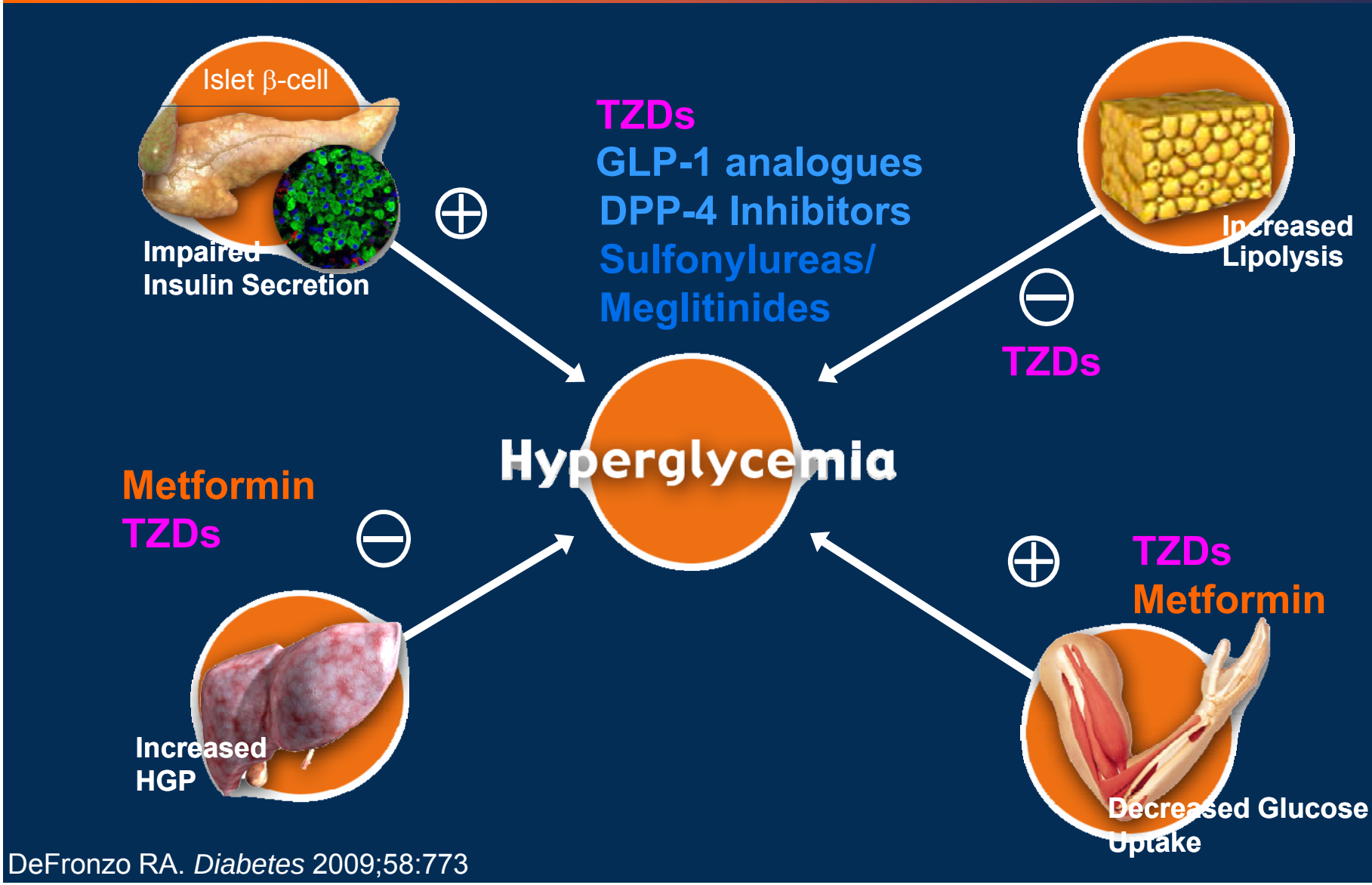


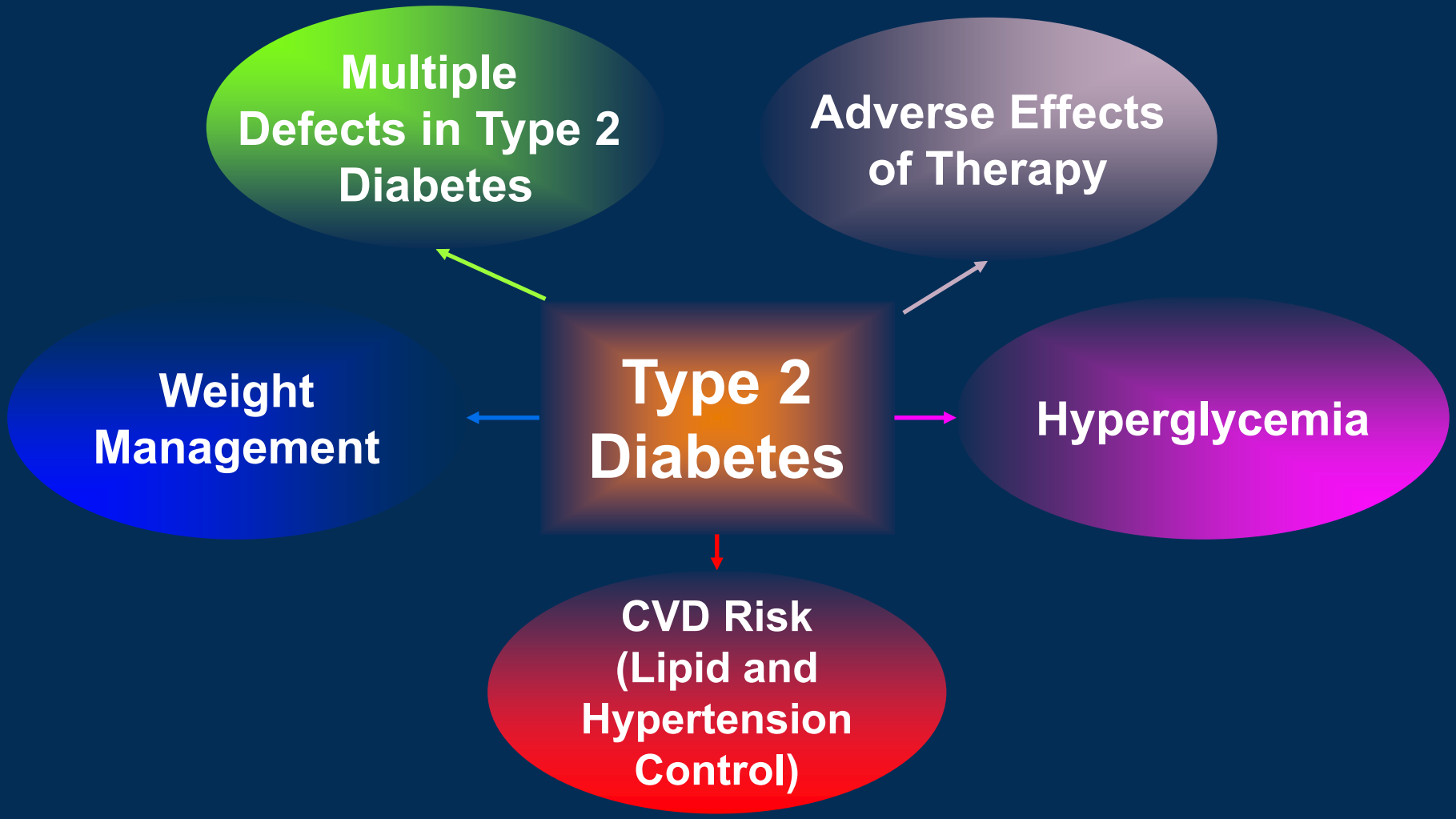
DeFronzo RA. *Diabetes* 2009;58:773

Current Treatment of Type 2 Diabetes



DeFronzo RA. *Diabetes* 2009;58:773

Unmet Needs in Type 2 Diabetes



Emerging Therapies in Diabetes

Today's Menu

Appetizer

"Triumvirate" to the "Ominous Octet" Sampler

Type 2 Courses

The Many Flavors of "GLP-1"

Recipe for Disaster with "SGLT2"?

Something for Everyone

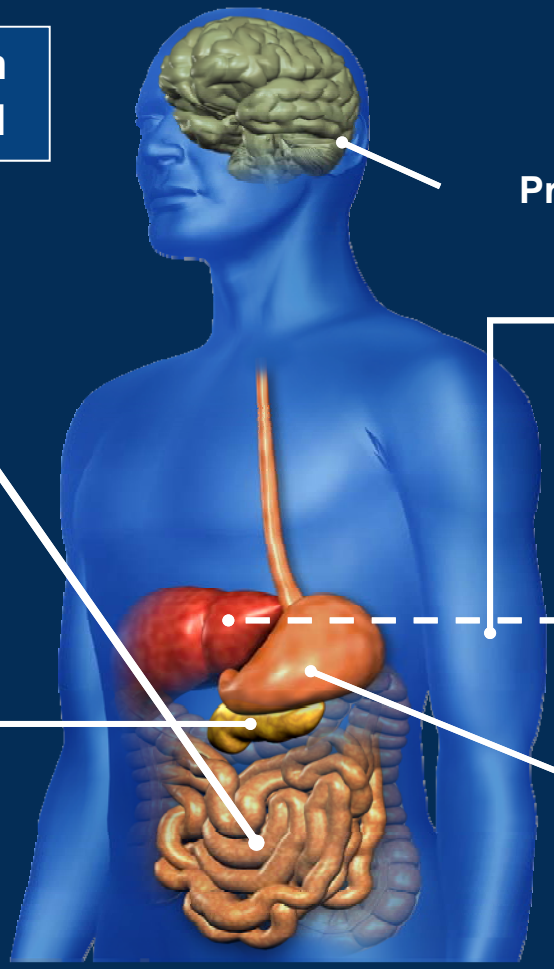
"Ultra-Long-Acting" … Better in the Fasting State?

Dessert

"Pipeline" Sweet Table

The Many Flavors of "GLP-1"

Incretins Modulate Numerous Functions in Humans



GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

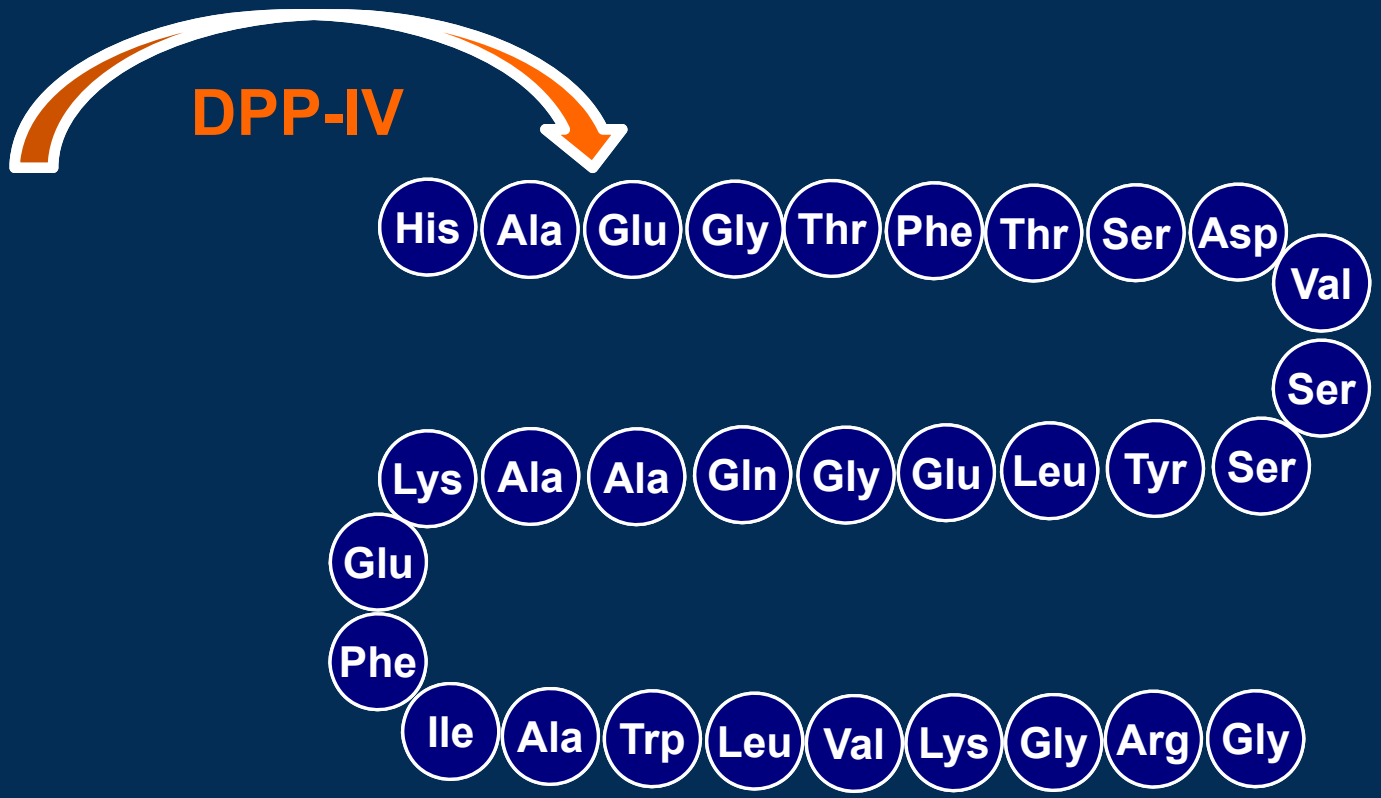
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

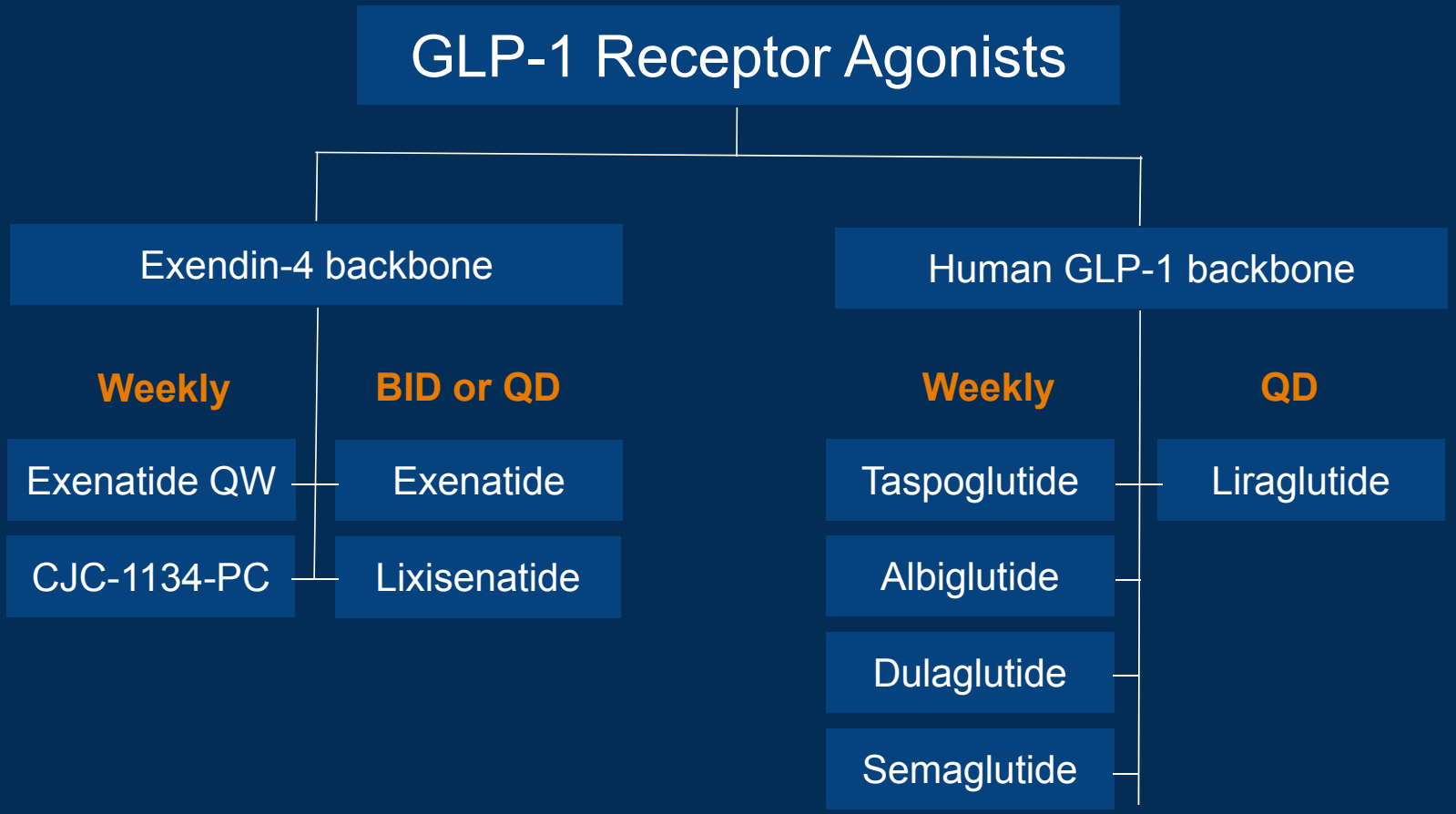
Flint A. et al. *J Clin Invest*. 1998;101:515-520; Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Nauck MA. et al. *Diabetologia*. 1996;39:1546-1553; Drucker DJ. *Diabetes*. 1998;47:159-169

The Many Flavors of "GLP-1"
Limitations of the Endogenous Incretin Hormone



Mentlein R. *Eur J Biochem*. 1993;214:829-836

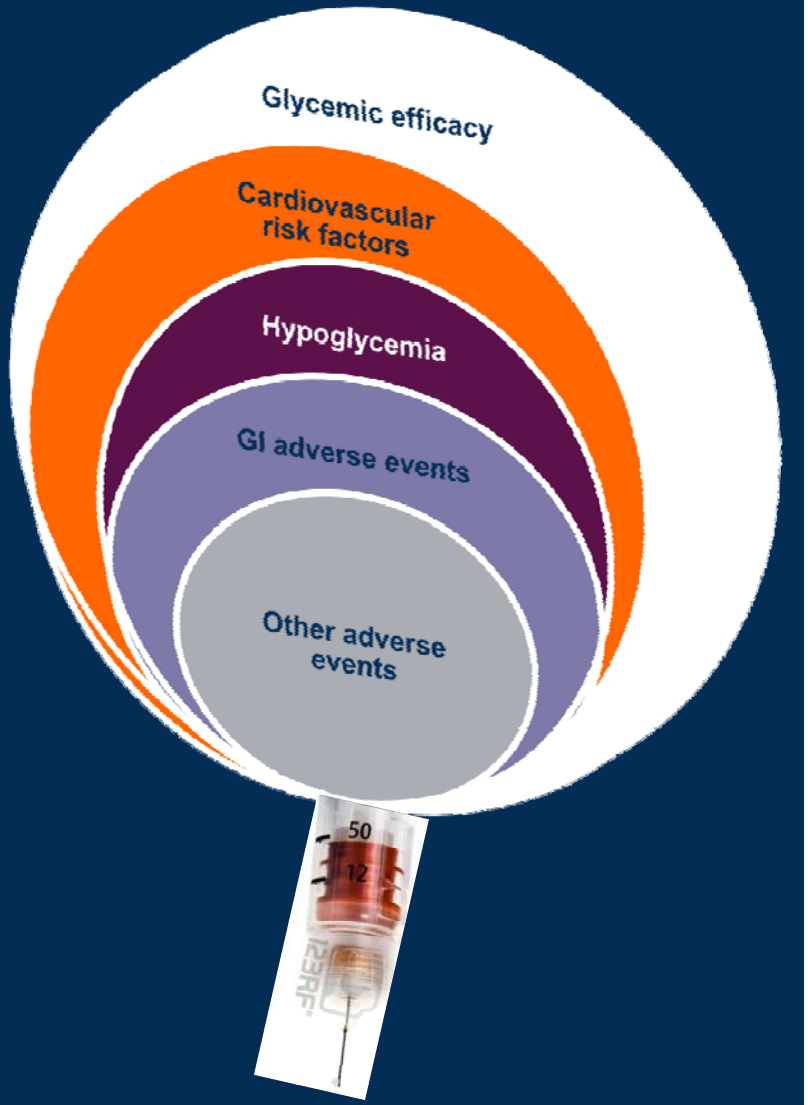
The Many Flavors of "GLP-1"
Long Acting GLP-1 Receptor Agonists



Madsbad S., et al. *Diabetes Obes Metab* 2011;13:394

The Many Flavors of “GLP-1”

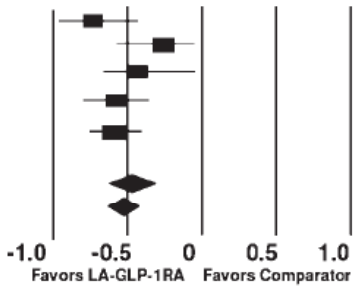
Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies



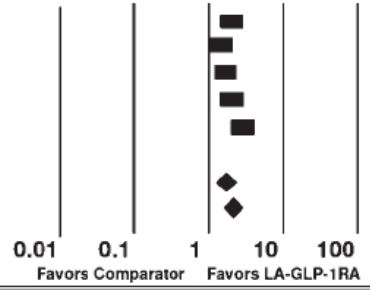
The Many Flavors of "GLP-1"

Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

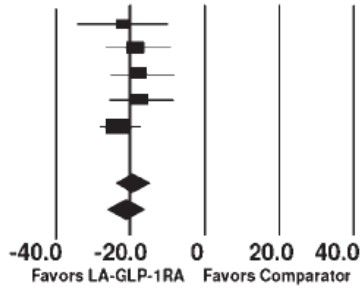
Study name	WMD	Lower limit	Upper limit
Blevins (2010)[26]	-0.70	-0.98	-0.42
Buse (2009)[27]	-0.33	-0.55	-0.11
Drucker (2008)[28]	-0.40	-0.68	-0.12
Bergenstal (2010)[30]	-0.60	-0.85	-0.35
Pratley (2010)[29]	-0.60	-0.78	-0.42
Vs. Exenatide BID	**-0.47**	**-0.69**	**-0.25**
Vs. Sitagliptin	**-0.60**	**-0.75**	**-0.45**

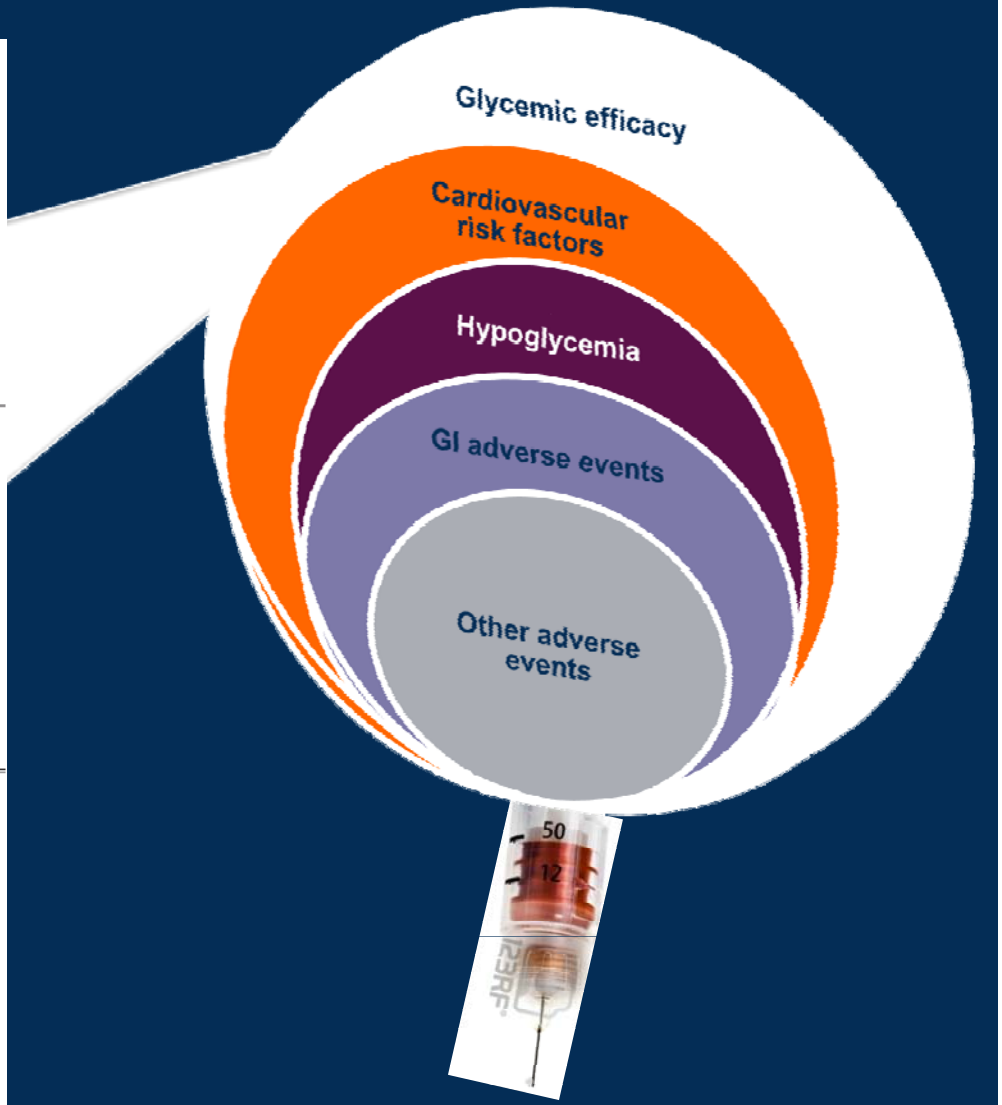


Study name	Odds ratio	Lower limit	Upper limit
Blevins (2010)[26]	3.31	1.97	5.58
Buse (2009)[27]	1.54	1.07	2.23
Drucker (2008)[28]	2.10	1.27	3.48
Bergenstal (2010)[30]	3.21	2.04	5.07
Pratley (2010)[29]	4.47	2.95	6.78
Vs. Exenatide BID	**2.14**	**1.38**	**3.34**
Vs. Sitagliptin	**3.84**	**2.78**	**5.31**



Study name	WMD	Lower limit	Upper limit
Blevins (2010)[26]	-23.00	-36.86	-9.14
Buse (2009)[27]	-18.18	-28.16	-8.20
Drucker (2008)[28]	-16.20	-26.18	-6.22
Bergenstal (2010)[30]	-16.20	-27.02	-5.38
Pratley (2010)[29]	-23.58	-31.09	-16.07
Vs. Exenatide BID	**-18.39**	**-24.67**	**-12.10**
Vs. Sitagliptin	**-20.96**	**-27.88**	**-14.04**





Pinelli NR et al. *Ann Pharmacother*. 2011;45:850

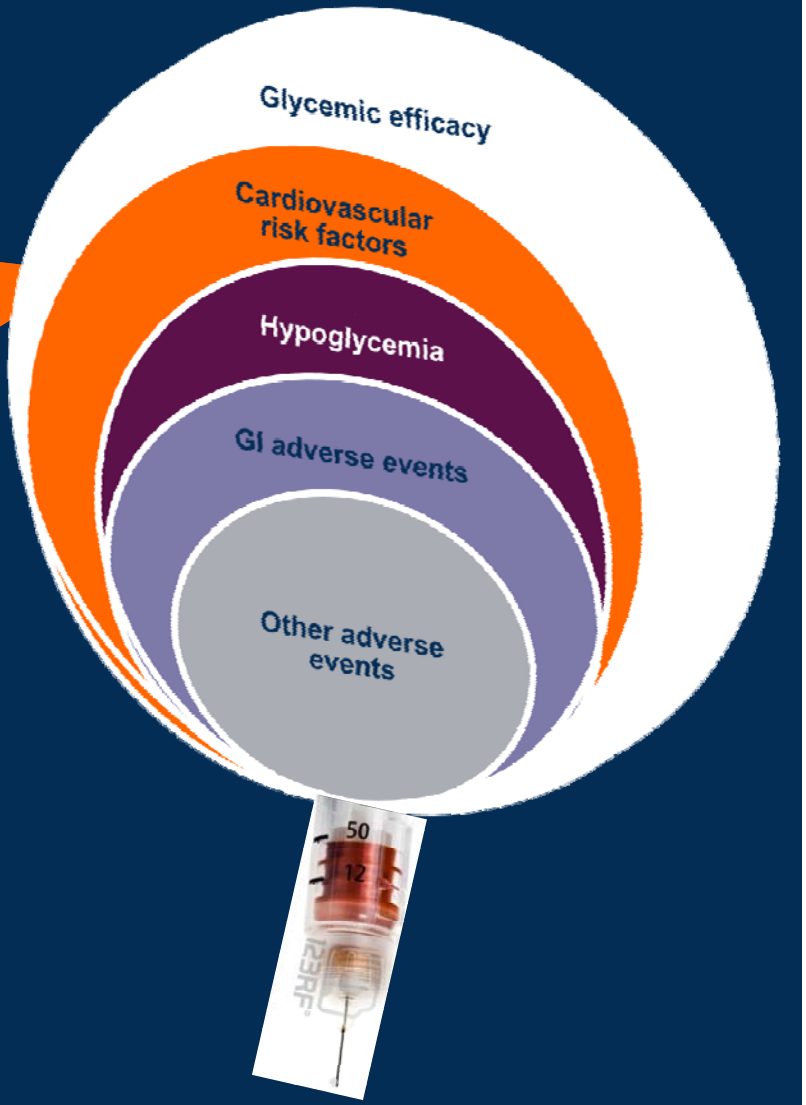
The Many Flavors of "GLP-1"

Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

Body Weight
Greater mean body weight reduction vs. sitagliptin (WMD -1.99 kg), but not vs. exenatide twice daily.

Blood Pressure
Although trial results are inconsistent, the blood pressure lowering (SBP and DBP) ability of long acting agents and other incretin-based therapies appears to be similar.

Lipids
Current evidence cannot confirm a difference in lipid lowering between incretin-based therapies.



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The Many Flavors of "GLP-1"

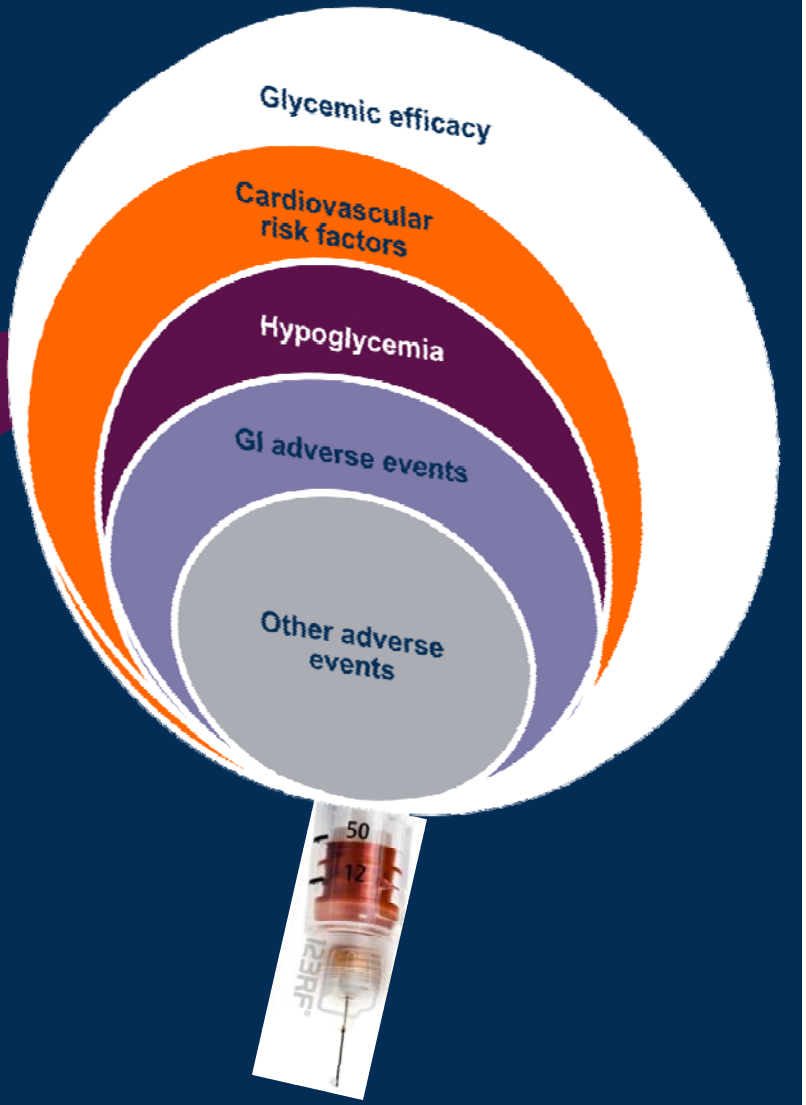
Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

Severe Hypoglycemia

- Did not occur in the majority of trials
- Two patients receiving exenatide BID and concomitant SU had an episode in one trial

Nonsevere Hypoglycemia

- Occurred infrequently and at similar rates in the majority of trials
- More frequently associated with SU



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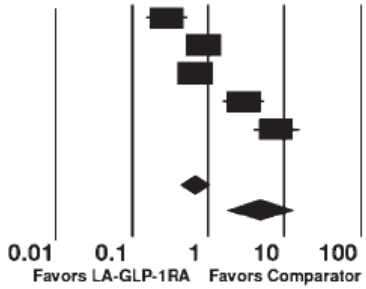
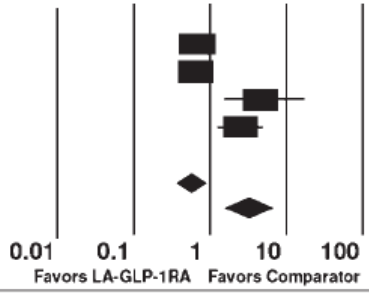
The Many Flavors of "GLP-1"

Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

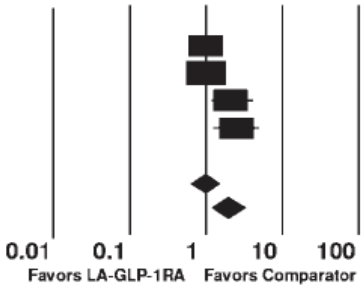
Study name	Odds ratio	Lower limit	Upper limit
Blevins (2010)[26]	0.29	0.15	0.55
Buse (2009)[27]	0.88	0.58	1.33
Drucker (2008)[28]	0.68	0.41	1.12
Bergenstal (2010)[30]	2.92	1.55	5.49
Pratley (2010)[29]	7.76	3.85	15.64
Vs. Exenatide BID	**0.58**	**0.32**	**1.06**
Vs. Sitagliptin	**4.70**	**1.81**	**12.24**

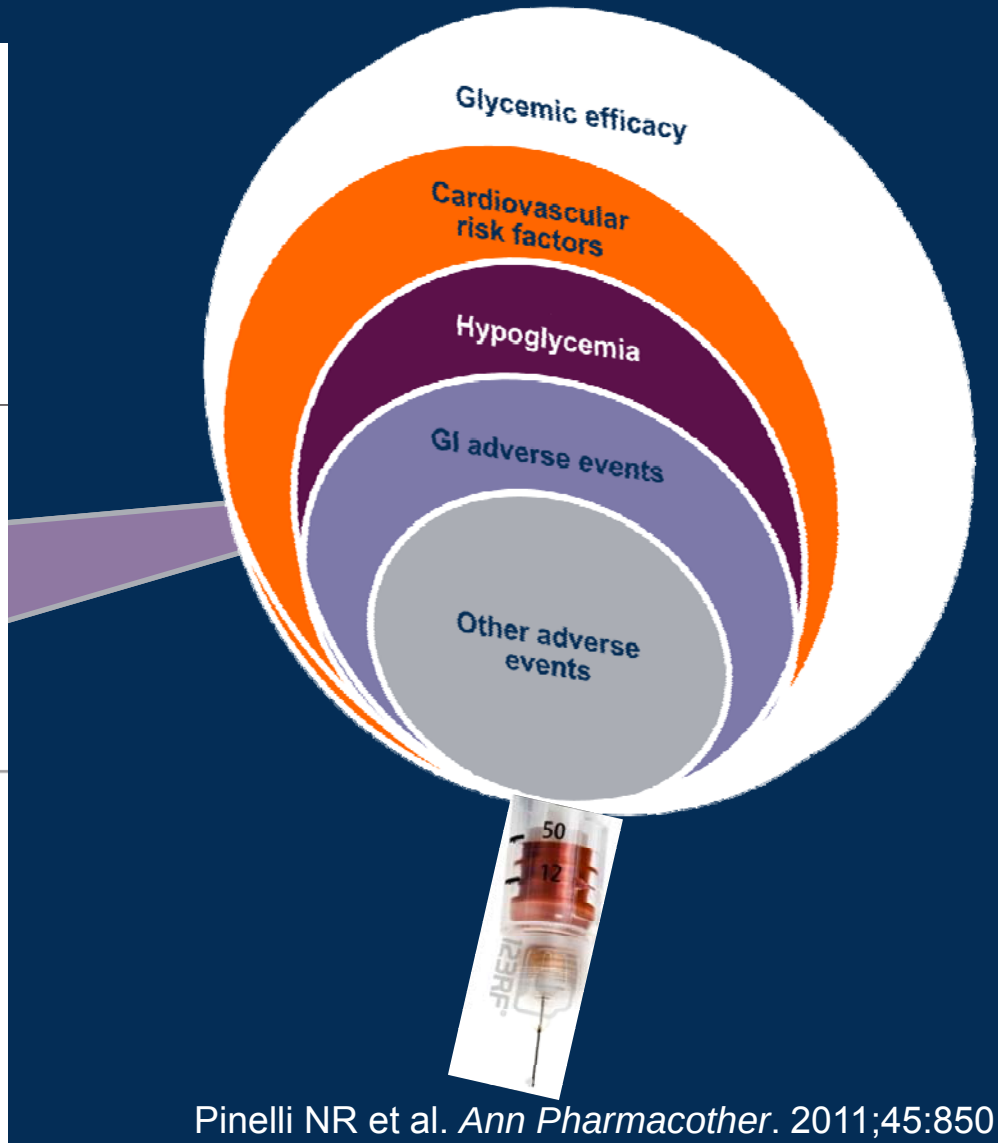


Study name	Odds ratio	Lower limit	Upper limit
Buse (2009)[27]	0.58	0.29	1.15
Drucker (2008)[28]	0.53	0.27	1.03
Bergenstal (2010)[30]	5.13	1.70	15.52
Pratley (2010)[29]	2.49	1.11	5.56
Vs. Exenatide BID	**0.55**	**0.34**	**0.89**
Vs. Sitagliptin	**3.22**	**1.63**	**6.36**



Study name	Odds ratio	Lower limit	Upper limit
Buse (2009)[27]	1.03	0.59	1.79
Drucker (2008)[28]	1.04	0.53	2.03
Bergenstal (2010)[30]	2.08	1.08	3.99
Pratley (2010)[29]	2.71	1.27	5.78
Vs. Exenatide BID	**1.03**	**0.67**	**1.58**
Vs. Sitagliptin	**2.32**	**1.42**	**3.81**





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The Many Flavors of "GLP-1"

Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

Antibodies

- Mean anti-exenatide antibody levels were higher with exenatide once weekly compared with twice daily

Injection site reactions

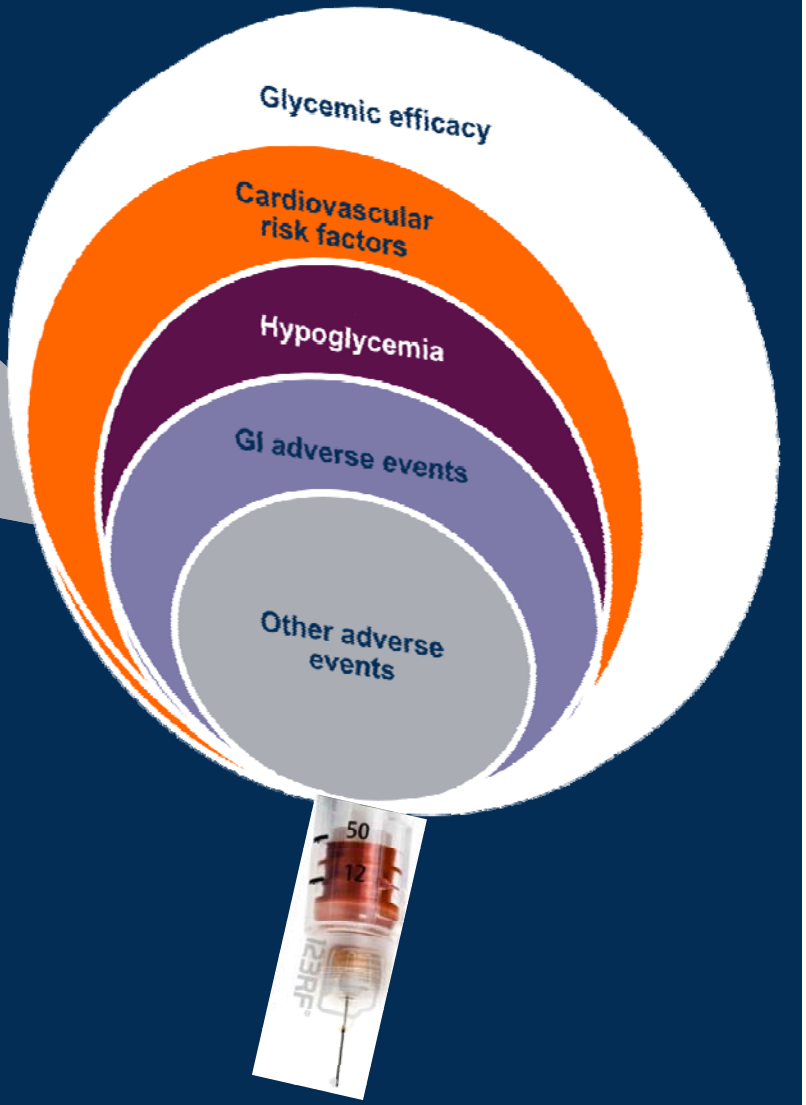
- More frequent injection site pruritis with exenatide once weekly in the majority of trials

Calcitonin levels

- No differences between therapies

Pancreatitis

- No acute pancreatitis reported
- One case reported after 88 days of therapy with long acting GLP-1RA



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The Many Flavors of "GLP-1"

Long Acting GLP-1 Receptor Agonists vs. Incretin-Based Therapies

DURATION 4:

- 26-week, randomized, double-blind, double-dummy superiority trial
- Exenatide once weekly (2 mg) vs. metformin (1000 mg/day), pioglitazone (30 mg/day), and sitagliptin (100 mg/day) as monotherapy in patients with T2DM
- Primary endpoint, reduction in A1c
  - 1.5% with both exenatide once weekly and metformin, 1.6% with pioglitazone, 1.2% with sitagliptin
- Safety
  - No major hypoglycemia
  - Expected AEs

DURATION 6:

- 26-week, randomized, open-label superiority study
- Exenatide once weekly (2 mg) vs. liraglutide (1.8 mg) added to oral agent(s) in T2DM
- Primary endpoint, reduction in A1c
  - 1.3% exenatide once weekly (n=461), 1.5% liraglutide (n=451)
- Safety
  - No major hypoglycemia reported
  - Less GI adverse events with exenatide once weekly

Presented at ADA, 71st Sessions; 2011; San Diego, CA (280-OR)

The Many Flavors of "GLP-1"
Comparison of DPP-IV Inhibitors

- *Diabetes Metab Res Rev* 2010;26:540-549
  - 18-week, randomized, double-blind, non-inferiority trial
  - Sitagliptin vs. Saxagliptin both added to metformin
  - Similar efficacy
  - Both well-tolerated

	Sitagliptin	Linagliptin	Alogliptin	Saxagliptin	Vildagliptin
Structure	Non-covalent	Non-covalent	Non-covalent	Covalent	Covalent
Dose	100 mg QD	5 mg QD	25 mg QD	5 mg QD	50 mg BID
Half-Life	12.4 hrs	12 hours	12.5-21.1 hrs	2.2-3.8 hrs	1.3-2.4 hrs
Elimination	Renal	Hepatic	Renal	Hepatic/Renal	Hepatic/Renal
Renal Adjustment	Yes	No	Yes	Yes	Yes
Potential for DDI	Low	Strong 3A4/PGP inducers	Low	Strong 3A4/5 inhibitors	Low

The Many Flavors of "GLP-1"
Summary

Characteristic	LA GLP-1RA	Exenatide BID	DPP-IV
A1c reduction	~1.5%	~1.0%	~0.5-0.8%
FPG reduction	Good	Modest	Modest
PPG reduction	Modest	Good	Good
Gastric emptying	Little or None	Yes	None
Body weight	Weight loss	Weight loss	Weight neutral
Effect CVD risk factors	Improve	Improve	Improve
Adverse effects	? Less Nausea	Nausea	Well-Tolerated
Injection site reactions	More	Less	NA
Pancreatitis	Rare	Rare	Rare
Hypoglycemia with SU	Yes	Yes	Yes
Dosage form	Injection	Injection	Oral
Administration	QD or Weekly	BID with Meals	QD

Emerging Therapies in Diabetes

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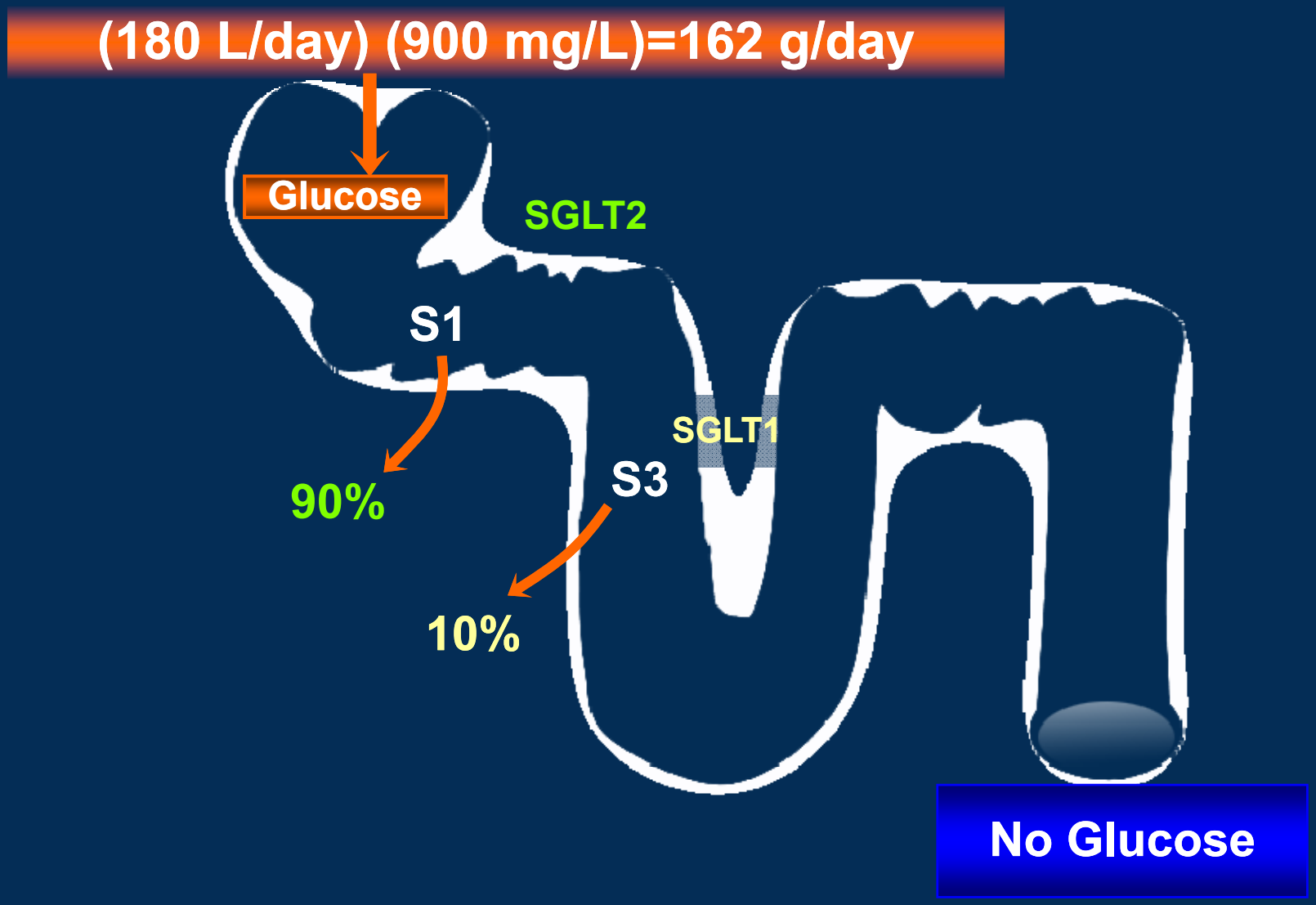
"Pipeline" Sweet Table

Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes will likely respond

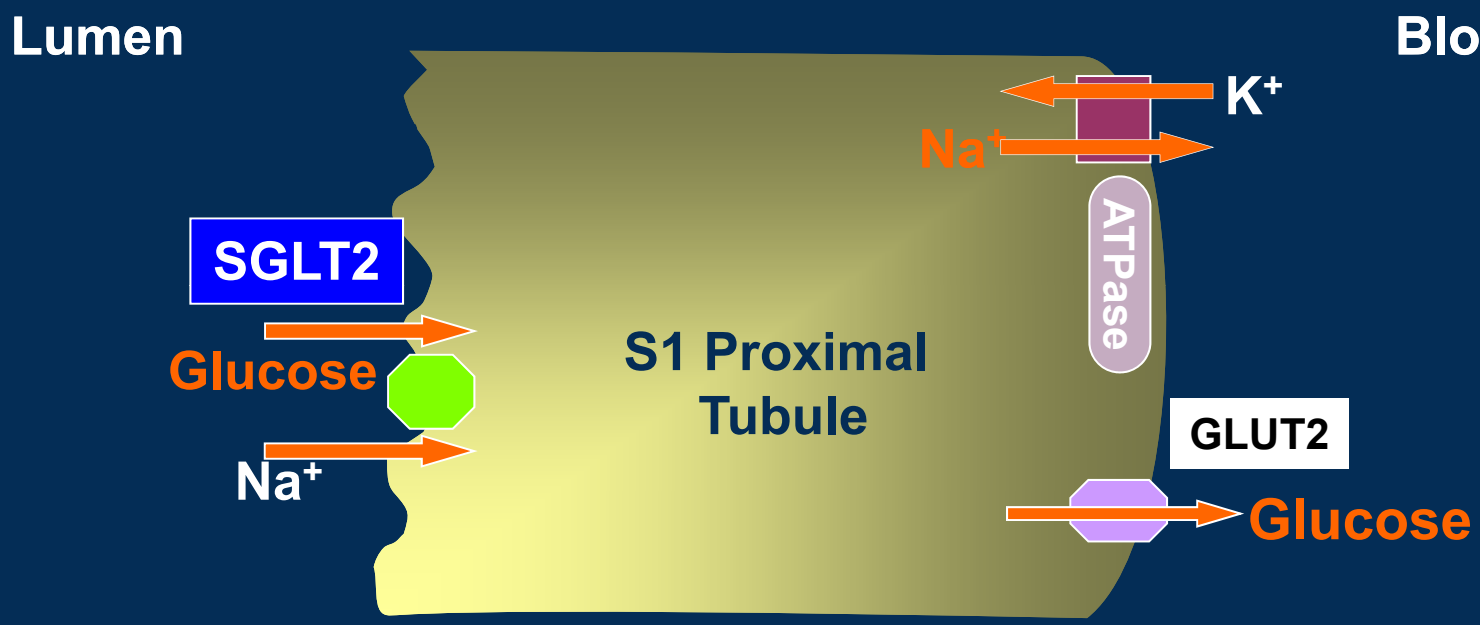
Renal Handling of Glucose



Sodium-Glucose Cotransporters

	SGLT1	SGLT2
Site	Intestine, kidney	Kidney
Sugar specificity	Glucose or galactose	Glucose
Glucose affinity	High K_m=0.4 mM	Low K_m=2 mM
Glucose transport capacity	Low	High
Role	Dietary absorption of glucose and galactose Renal glucose reabsorption	Renal glucose reabsorption

SGLT2 Mediates Glucose Reabsorption in the Kidney



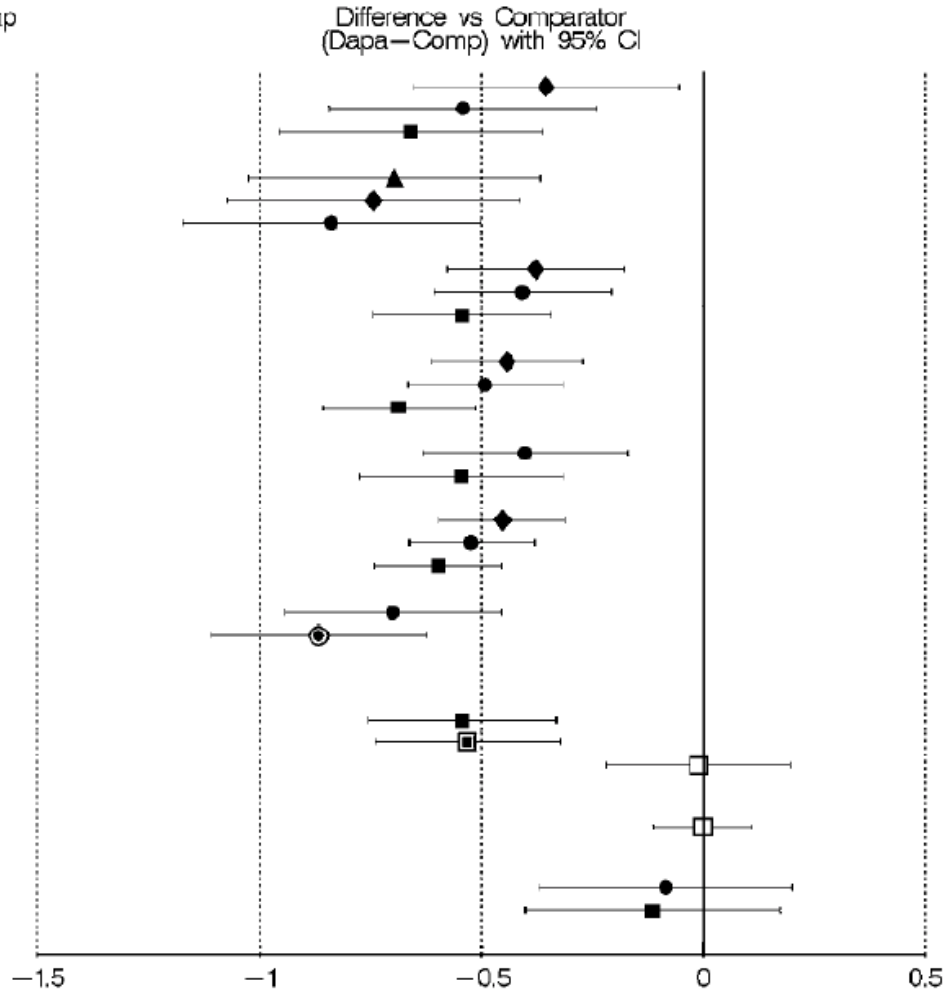
Major transporter of glucose in the kidney

- Low affinity, high capacity for glucose
- Nearly exclusively expressed in the kidney
- Responsible for ~90% of renal glucose reabsorption in the proximal tubule

Hediger MA, Rhoads DB. *Physiol. Rev*. 1994;74:993-1026.

Dapagliflozin: Clinical Efficacy

Study	Dapa vs Comparator	Dapa N	Comp N
MB102013 (Monotherapy)	2.5mg vs Pla	64	72
	5mg vs Pla	61	72
	10mg vs Pla	65	72
MB102032 (Monotherapy)	1mg vs Pla	72	68
	2.5mg vs Pla	72	68
	5mg vs Pla	66	68
MB102014 (Add–on to Met)	2.5mg vs Pla	135	134
	5mg vs Pla	133	134
	10mg vs Pla	132	134
D1690C00005 (Add–on to SU)	2.5mg vs Pla	154	143
	5mg vs Pla	142	143
	10mg vs Pla	150	143
MB102030 (Add–on to Pio)	5mg vs Pla	140	138
	10mg vs Pla	140	138
D1690C00006 (Add–on to Ins)	2.5mg vs Pla	198	188
	5mg vs Pla	210	188
	10mg vs Pla	192	188
MB102021 (Initial Combo)	5mg+Met vs Met	185	195
	5mg+Met vs 5mg	185	196
	5mg vs Met	196	195
MB102034 (Initial Combo)	10mg+Met vs Met	202	203
	10mg+Met vs 10mg	202	216
	10mg vs Met	216	203
D1690C00004 (SU Active Control)	10mg vs SU	400	401
MB102029 (Renal Impairment)	5mg vs Pla	83	82
	10mg vs Pla	82	82



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM264312.pdf

Dapagliflozin: Glucosuric & Metabolic Effects

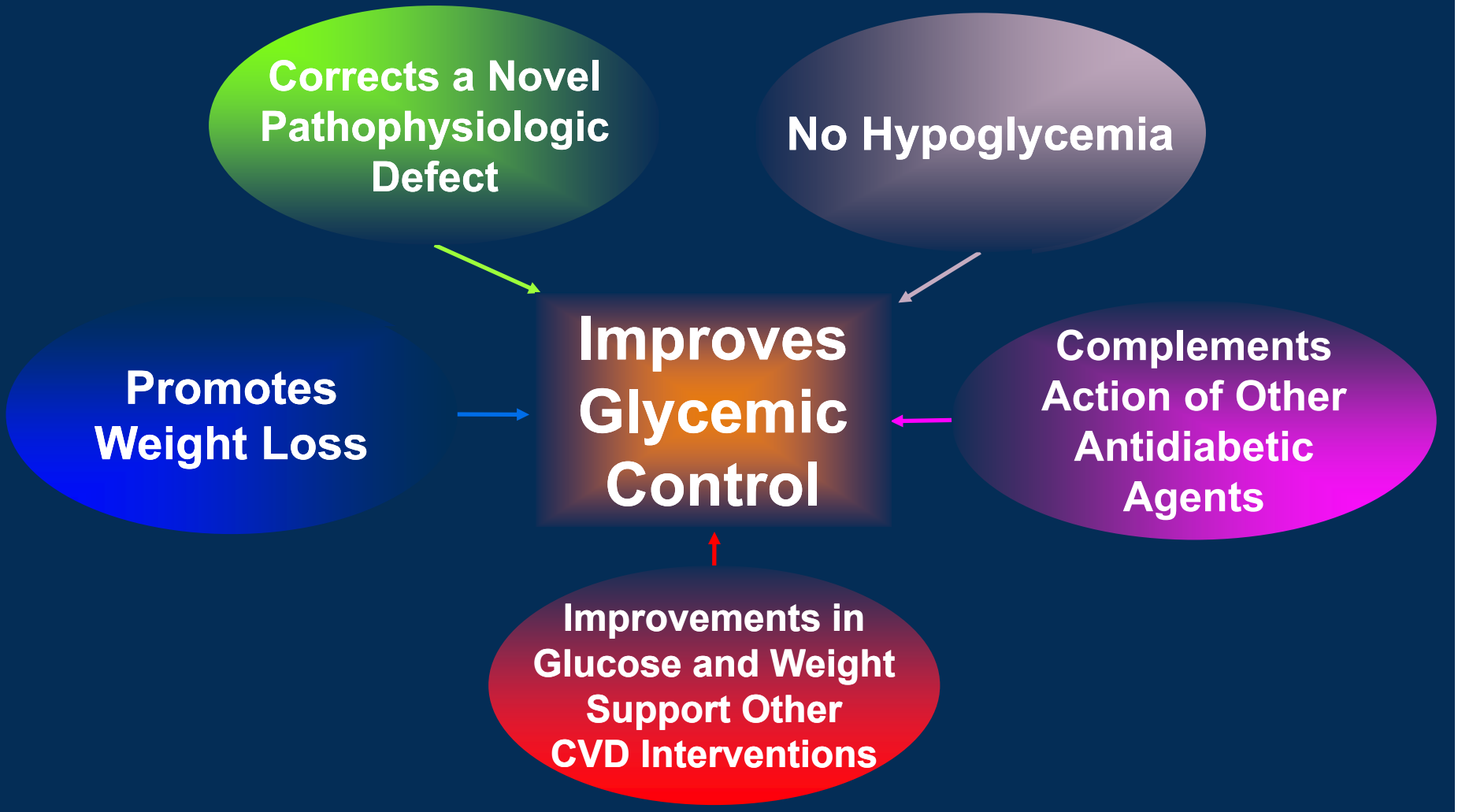
Glucosuria	↑ 52-85 g/day
FPG	↓ 16-30 mg/dL
PPG	↓ 23-29 mg/dL
Body weight	↓ 2.2-3.2 kg (↓ 2.5%-3.4%)
Urine volume	↑ 107-470 mL/day

List JF, et al. *Diabetes Care*. 2009;32:650-657.

A Recipe for Disaster with "SGLT2"?
Unanswered Questions About SGLT2 Inhibition

Durability	Data submitted to FDA to provide evidence of dapagliflozin durability is not convincing. Only 21-43% of individuals receiving dapagliflozin completed long-term extension studies because of the need for 'rescue' therapy or due to subject attrition.
Safety and Tolerability	Risk of genitourinary infections recognized in phase III trials Possible safety concerns include bladder and breast CA and hepatic injury Long-term CV safety needs to be established
Renal Impairment	SGLT2 inhibition does not appear to be effective in patients with renal impairment (<60 mL/min/1.73m^2)

Meeting Unmet Needs in Diabetes Care



Emerging Therapies in Diabetes

Today's Menu

Appetizer

"Triumvirate" to the "Ominous Octet" Sampler

Type 2 Courses

The Many Flavors of "GLP-1"

Recipe for Disaster with "SGLT2"?

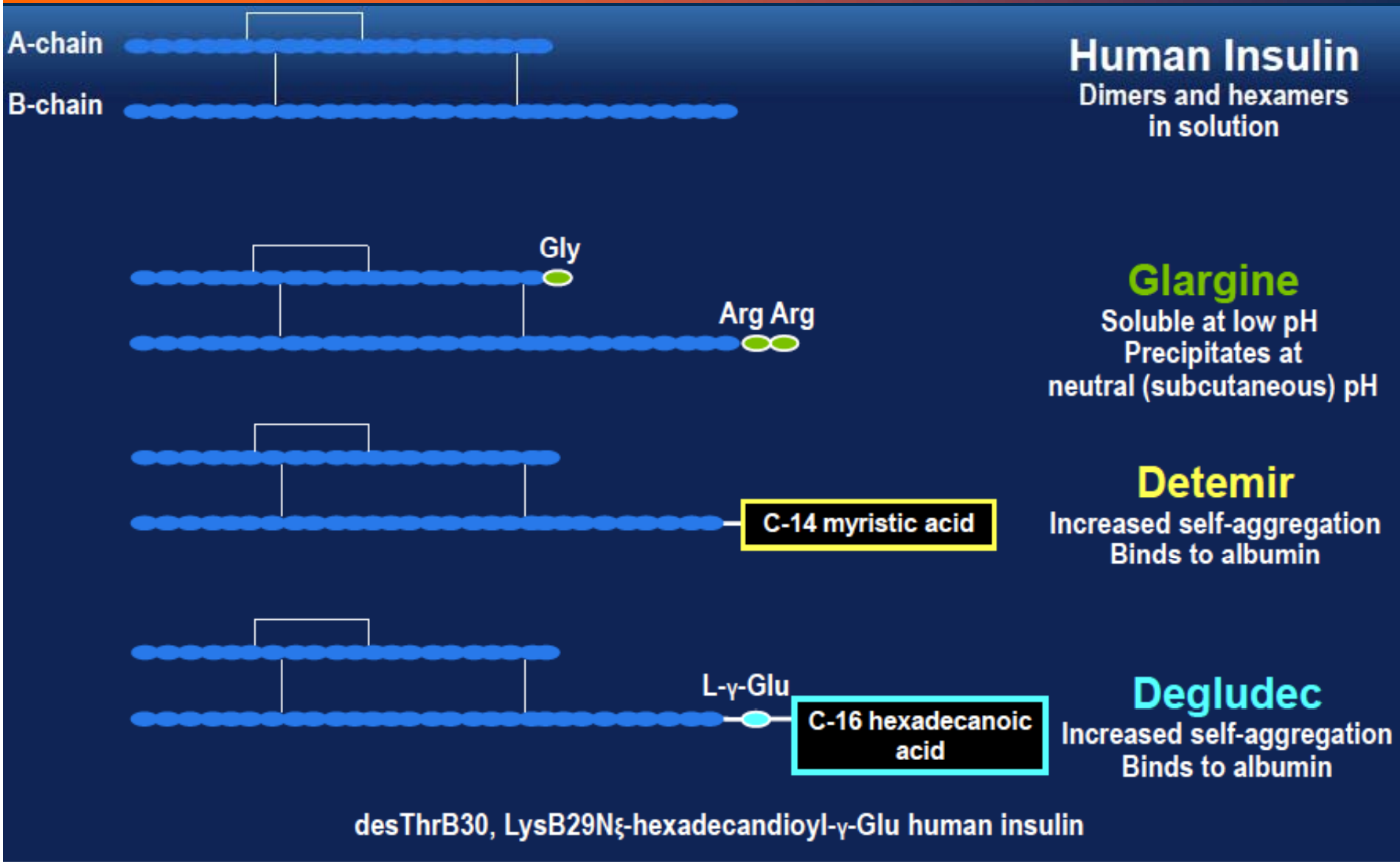
Something for Everyone

"Ultra-Long-Acting" … Better in the Fasting State?

Dessert

"Pipeline" Sweet Table

“Ultra-Long-Acting” … Better in the Fasting State?



"Ultra-Long-Acting" … Better in the Fasting State?
Evidence in T1DM

Author	Population	Intervention	Results
Birkeland KI et al. Diabetes Care 2011;34:661	T1DM •46 years •A1c 8.4% •FPG 178 mg/dL •BMI 26.9 kg/m^2	Basal insulin (qHS): •IDeg 600 µmol/L, n=59 •IDeg 900 µmol/L, n=60 •IGlargine, n=59	At 16 weeks, IDeg is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to IGlargine at similar doses with reduced rates (10-28% overall, 29-
2011; San Diego, CA (70-OR)	•A1c 7.7%	Bolus insulin (qAC): Aspart	IGlargine at similar doses with reduced rates (25%) of confirmed nocturnal hypoglycemia (<56 mg/dL).
Hirsch IB et al. Presented at ADA, 71st Sessions; 2011; San Diego, CA (1064-P)	T1DM •n=548 •41 years •A1c 8.3% •FPG 189 mg/dL	Intervention: •IDeg70%/Aspart30% QD •Aspart with other meals Control: •IDetemir per labeling •Aspart with all meals	At 26 weeks, IDeg70/30 is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to IDetemir with reduced rates (37%) of confirmed nocturnal hypoglycemia (<56 mg/dL), increased weight (1.04 kg) and less injections.

Degludec appears to be as clinically effective as glargine and detemir as a basal insulin option for patients with T1DM and is associated with less confirmed nocturnal hypoglycemia!

Author	Population	Intervention	Results
Zinman B et al. Lancet 2011 2011;377:924	T2DM •54 years •A1c 8.7% •FPG 184 mg/dL •BMI 30 kg/m^2	Basal insulin (+Metformin): •IDeg 3 times/wk, n=62 •IDeg 600 µmol/L QD, n=60 •IDeg 900 µmol/L QD, n=61 •IGlargine QD, n=62	At 16 weeks, IDeg is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to IGlargine. Similar rates of confirmed overall and nocturnal hypoglycemia.
Garber AJ et al. Presented at ADA, 71st Sessions; 2011; San Diego, CA (74-OR)	T2DM •n=992 •59 years •A1c 8.3% •FPG 166 mg/dL	Basal insulin (Daily): •IDeg •IGlargine Bolus insulin (qAC): •Aspart	At 1 year, IDeg is safe and well tolerated and provides comparable glycemic control (A1c & FPG) to IGlargine at similar doses with reduced rates of confirmed overall
Heis Dial 201	•BMI 30 kg/m^2		nd & s of dL). IDeg55/45 had more confirmed overall and nocturnal hypoglycemia.
Vaag A et al. Presented at ADA, 71st Sessions; 2011; San Diego, CA (1141-P)	T2DM •n=182 •60 years •A1c 8.5% •FPG 209 mg/dL	Intervention (+Metformin): •IDeg70%/Aspart30% BID •IDeg55%/Aspart45% BID •BIAsp 30 BID	At 16 weeks, IDeg70/30 is safe and well tolerated, provides comparable glycemic control to BIAsp30. IDeg70/30 was associated with a significantly lower FPG and lower rate of confirmed overall (58%) and nocturnal hypoglycemia (<56 mg/dL) than BIAsp 30.

In T2DM, Degludec appears to be as clinically effective as glargine (added to OADs or as basal-bolus therapy) and BIAsp30. A reduction in confirmed nocturnal hypoglycemia was seen in most, but not all trials.

"Ultra-Long-Acting" … Better in the Fasting State?
Comparison of Basal Insulin Analogs

	Detemir	Glargine	Degludec
Long-duration	18-24 hr	24+ hr	48+ hr
	QD or BID	QD	QD or 3x/wk
Low variability			
Flat action curve	No	Nearly	Yes
Day-to-day consistency	Good	Fair	?
Between-patient consistency	Fair	Good	?
Clinical effectiveness			
A1c reduction	Good	Good	Good
Limited hypoglycemia	Good	Good	Better?

Emerging Therapies in Diabetes

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Type 2 Courses

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Recipe for Disaster with "SGLT2"?

Something for Everyone

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Dessert

"Pipeline" Sweet Table

“Pipeline” Sweet Table

- GLP-1 receptor agonists
  - Oral
  - Trans-dermal
  - Inhalation
  - Monthly injectable systems
  - Combination with glucagon receptor antagonist
- New insulin developments
  - Ultra-fast-insulin (linjeta, formerly known as VIAject)
  - Insupatch warming device
  - Co-formulation with hyaluronidase
  - Route manipulation (inhalation, nasal, oral/buccal/sublingual)
- Glucagon receptor antagonists (2 compounds currently in development)
- Glucokinase activators (3 compounds currently in development)
- GPR119 agonists (3 compounds currently in development)
- GPR40 agonists (2 compounds currently in development)

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American College of Clinical Pharmacy

GLP-1 Agents in Obesity/Metabolic Syndrome

Rick Hess, Pharm.D., CDE, BC-ADM

October 17th 2011

Conflicts of Interest

American College of Clinical Pharmacy

I have no conflicts of interest to disclose

Objectives

American College of Clinical Pharmacy

- Review the prevalence of obesity/metabolic syndrome
- Summarize current pharmacotherapy used in the treatment of obesity
- Examine the clinical evidence for the utilization of GLP-1 agonists as pharmacotherapy options in the treatment of obesity/metabolic syndrome

Prevalence

Obesity

- Definition
  - BMI ≥ 30kg/m^2
- Prevalence (2007 – 2008)
  - Adults
    - 32.2% men
    - 35.5% women

Metabolic Syndrome

- Definition
  - At least 3 out of 5 risk factors present
    - Waist circumference
    - HTN
    - Hypertriglyceridemia
    - Low HDL
    - Fasting hyperglycemia
- Prevalence (2003 – 2006)
  - Adults
    - 35.1% men
    - 32.6% women

JAMA 2010;303(3):235-241
Natl Health Stat Report. 2009; (13): 1–7

Criteria for Clinical Diagnosis of the Metabolic Syndrome

American College of Clinical Pharmacy

Measure	Categorical cut points
Elevated waist circumference	> 40 inches (102 cm) for males > 35 inches (88 cm) for females
Elevated triglycerides (Rx for elevated triglycerides is an alternate indicator)	≥150 mg/dL
Reduced HDL cholesterol (Rx for reduced HDL cholesterol is an alternate indicator)	<40 mg/dL for males and <50 mg/dL for females
Elevated blood pressure (Rx for elevated blood pressure is an alternate indicator)	Systolic ≥130 mm Hg and/or Diastolic ≥85 mm Hg
Elevated fasting glucose (Rx for elevated glucose is an alternate indicator)	≥100 mg/dL

Circulation 2009; 120:1640-1645.

Treatment Overview

American College of Clinical Pharmacy

Obesity

- Lifestyle changes
- Pharmacotherapy
  - BMI > 30 kg/m2
  - BMI of 27 – 30 kg/m2 with comorbid conditions

Metabolic Syndrome

- Lifestyle changes
- Treat individual risk factors

Pharmacol Rev. 2007;59(2):151 – 184
BMJ 2007;335(7631):1194 – 9

FDA Approved Anti-Obesity Pharmacotherapy Options

American College of Clinical Pharmacy

Medication Mechanism of Action	Daily dose (mg)	Average Baseline Characteristics	Mean Weight Loss	Duration (months)	Clinical notes
Orlistat *Lipase inhibitor*	180 – 360	Age 48 69% women BMI 36.7 kg/m^2	2.89kg	12	Dose dependent response ADRs: GI effects Malabsorption of fat-soluble vitamins Improves lipid and glucose control Adolescent indication (12 – 16 years old)
Phentermine *Sympathomimetic*	15 – 37.5	Age NA 78% women BMI NA	3.60kg	0.5 – 6	Most commonly prescribed ADRs: Insomnia, HTN, palpitations, arrhythmias Schedule IV Avoid in pts w/ HTN, CVD
Diethylpropion *Sympathomimetic*	75	Age NA 80% women BMI NA	3.00kg	1.5 – 12	ADRs: Insomnia, HTN, palpitations, arrhythmias Schedule IV Avoid in pts w/ HTN, CVD

Ann Intern Med. 2005;142:525 – 531
Ann Intern Med. 2005;142:532 – 546

"Off-Label" Anti-Obesity Pharmacotherapy Options

American College of Clinical Pharmacy

Medication Mechanism of Action	**Daily dose (mg)**	**Average Baseline Characteristics**	**Mean Weight Loss**	**Duration (months)**	**Clinical notes**
Buproprion *NE & DA reuptake inhibitor*	300 – 400	Age 43 81% women Weight 94.3kg	2.77kg	6 – 12	ADRs: Dry mouth, insomnia Indicated for depression & smoking cessation
Fluoxetine *SSRI*	60	Age 48 69% women BMI 35.5 kg/m^2	4.74kg	6	Indicated for depression Questionable long-term effectiveness Higher doses used than in the treatment of depression
Topiramate *Unknown; GABA modulator?*	96 – 192	Age 47 68% women Weight 102kg	6.5%	6	Indicated for seizures; migraine prophylaxis ADRs: Somnolence, difficulty concentrating, parathesias
Zonisamide *Unknown; Serotonergic & dopaminergic activity*	400 – 600	Age 37 92% women BMI 36 kg/m^2	6%	4	Indicated for seizures ADRs: dizziness, somnolence, cognitive impairment Better tolerated vs. topiramate

Ann Intern Med. 2005;142:525 – 531
Ann Intern Med. 2005;142:532 – 546
Pharmacol Rev. 2007;59(2):151 – 184

Obesity

American College of Clinical Pharmacy

- Options
  - Limited
    - Safety issues
      - Sibutramine withdrawn Oct. 2010
    - Recent investigational agents
      - Phentermine/topiramate rejected Oct. 2010
      - Locaserin rejected Oct. 2010
      - Naltrexone/bupropion rejected Feb. 2011

Weight Change in Patients With Diabetes Using GLP – 1 Agonists

American College of Clinical Pharmacy

Trial	GLP – 1 Agonist	Background Therapy	Mean Weight Change from baseline (kg)
AMIGO 1	Exenatide 10mcg BID	Metformin	**- 2.8**
AMIGO 2	Exenatide 10mcg BID	Sulfonylurea	**- 1.6**
AMIGO 3	Exenatide 10mcg BID	Sulfonylurea + Metformin	**- 1.6**
LEAD – 1	Liraglutide 1.8mg/day	Sulfonylurea	**- 0.2**
LEAD – 2	Liraglutide 1.8mg/day	Metformin	**- 2.8**
LEAD – 3	Liraglutide 1.8mg/day	None	**- 2.5**
LEAD – 4	Liraglutide 1.8mg/day	Metformin + Rosiglitazone	**- 2.0**
LEAD – 5	Liraglutide 1.8mg/day	Sulfonylurea + Metformin	**- 1.8**
LEAD – 6	Liraglutide 1.8mg/day Exenatide 10mcg BID	Sulfonylurea + Metformin	**- 3.2** **- 2.9**

Diabetes Care. 2005;28:1092. *Diabetes Care*. 2004;27:2628. *Diabetes Care*. 2005;28:1083 *Diabet Med*. 2009;26(3):268-278. *Diabetes Care*. 2009;32(1):84-90 *Lancet*. 2009;373(9662):473-481. *Diabetes Care*. 2009;32(7):1224-1230. *Diabetologia*. 2009;52(10):2046-2055. *Lancet* 2009;374(9638):39 – 47

GLP – 1 Agonist Therapy in Obesity

American College of Clinical Pharmacy

Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Prediabetes

Rosenstock J, Klaff LJ, Schwartz S, et al.

Diabetes Care 2010;33:1173 - 1175

Rosenstock J, et al.

- Design
  - 24 week RCT
    - Obese (BMI > 30 kg/m2) subjects
  - Exclusion
    - Diagnosis of T2DM
    - Previous use of glucose-lowering agents > 3 months or
    - Unstable body weight
  - Stratified into subgroups based on OGTT results

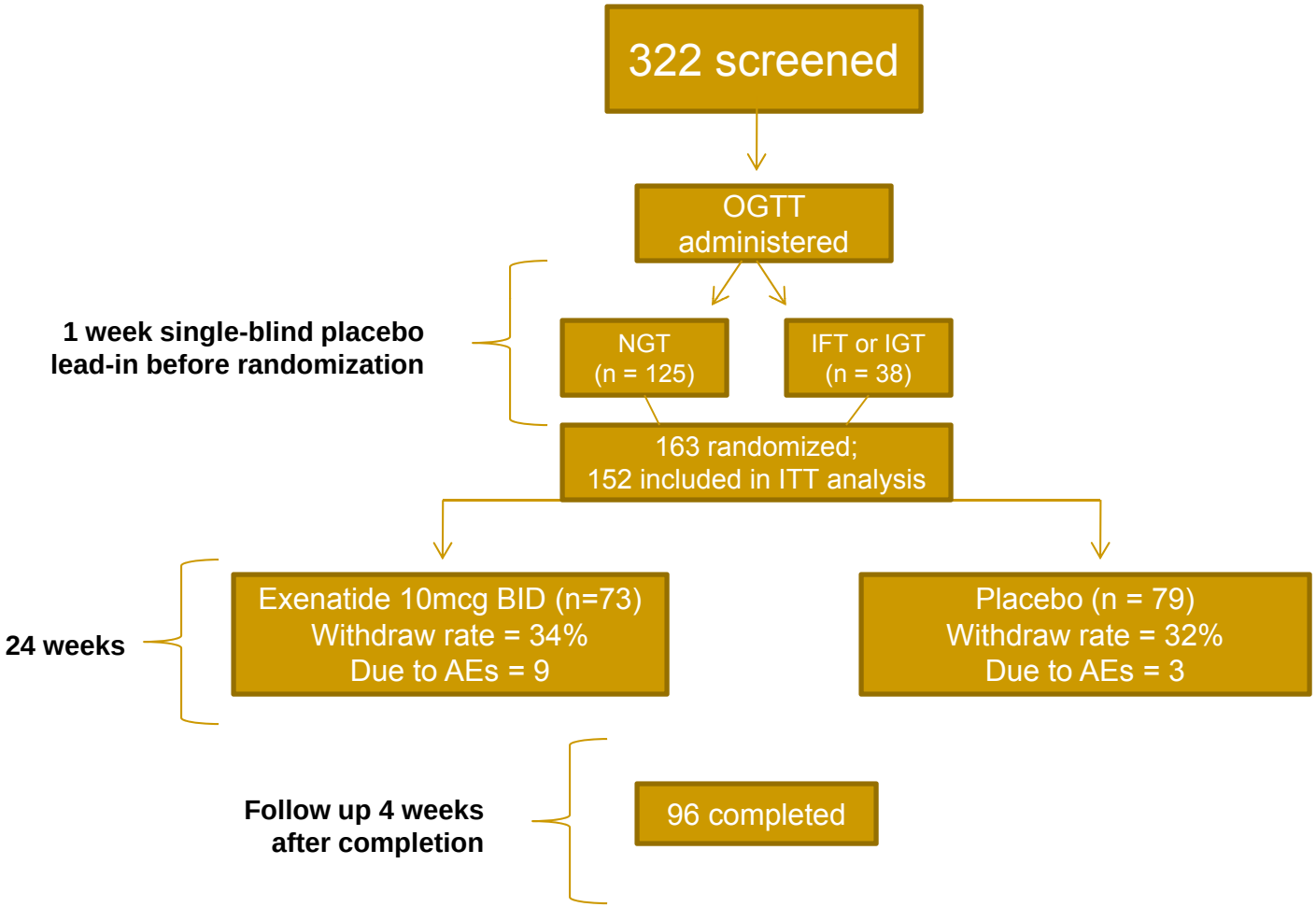
Diabetes Care 2010;33:1173-1175

Rosenstock J, et al.

- Design (continued)
  - 1 week single-blind placebo lead in period
  - Randomization
    - Exenatide 5mcg SQ BID x 4 weeks dose initiation period followed by 10mcg SQ BID x 20 weeks or Placebo
  - All participants received structured program of diet and physical activity x 24 weeks
  - Follow-up visit 4 weeks following completion
- Primary end-point
  - Change in body weight

Diabetes Care 2010;33:1173-1175

Rosenstock J, et al.



Diabetes Care 2010;33:1173-1175

Rosenstock J, et al.

American College of Clinical Pharmacy

- Results at week 24
  - Baseline characteristics comparable

	Exenatide (n = 73)	Placebo (n = 79)	P Value
Baseline Body Weight (kg)	109.5 ± 2.7	107.6 ± 2.6	NS
Weight loss (kg) @ week 24	5.1 ± 0.5	1.6 ± 0.5	< 0.001
Placebo subtracted difference in weight reduction (%)	- 3.3		
Participants experiencing > 5% weight reduction (%)	32	17	0.039
Daily caloric reduction	- 449 ± 64	- 387 ± 63	
Converted to NGT (%)	77	56	

Diabetes Care 2010;33:1173-1175

Rosenstock J, et al.

- Safety
  - No deaths, serious AEs or hypoglycemia reported

	Exenatide (n = 73)	Placebo (n = 79)
Nausea (%)	25	4
Diarrhea (%)	14	3

Diabetes Care 2010;33:1173-1175

Rosenstock J, et al.

American College of Clinical Pharmacy

- Conclusion
  - Exenatide plus lifestyle changes in obese patients without diabetes was associated with significantly greater reduction in body weight vs. lifestyle changes alone ($P < 0.001$)
  - Normalization of glucose tolerance and reduced caloric intake favored exenatide therapy

Diabetes Care 2010;33:1173-1175

GLP – 1 Agonist Therapy in Obesity

American College of Clinical Pharmacy

Effects of Liraglutide in the Treatment of Obesity: A Randomized, Double-Blind, Placebo-Controlled Study

Astrup A, Rössner S, Van Gaal L, et al.

Lancet 2009;374:1606 – 16

Astrup A, et al.

- Design
  - 20 week multicenter RCT with open label orlistat comparator
  - Obese adults (BMI 30 – 40 kg/m^2)
    - Stable body weight (<5% change during previous 3 months)
    - Fasting glucose < 126mg/dl
  - Exclusion
    - Diagnosis of T1DM or T2DM
    - Use of approved weight-lowering pharmacotherapy within previous 3 months
    - Previous bariatric surgery

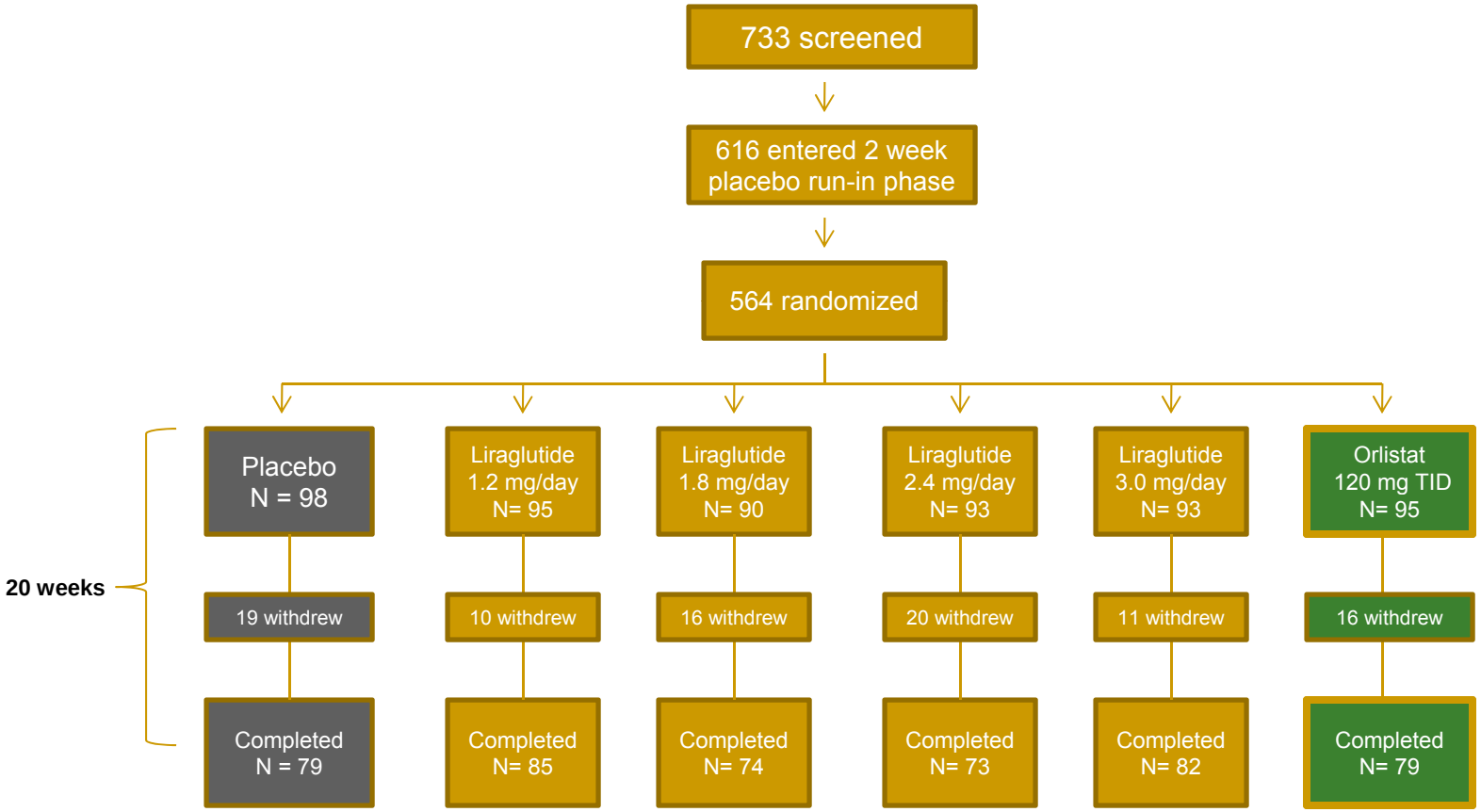
Lancet 2009;374:1606 – 16

Astrup A, et al.

- Design (continued)
  - 2 week single-blind placebo
  - 4 week dose titration period
  - 16 week constant dose period
  - All participates received counseling on low-fat diet and increase physical activity via pedometers
- Primary end point
  - Change in body weight
  - Proportion of people losing > 5% or >10% of baseline weight

Lancet 2009;374:1606 – 16

Astrup A, et al.



Lancet 2009;374:1606 – 16

Astrup A, et al.

American College of Clinical Pharmacy

- Results of primary end points at week 20
  - Baseline characteristics comparable across all groups

	Placebo	Liraglutide Dose/Day 1.2mg	1.8mg	2.4mg	3.0mg	Orlistat
Mean weight loss (kg)	- 2.8	- 4.8	- 5.5	- 6.3	- 7.2	- 4.1
Mean difference (kg) vs. placebo		- 2.1 (*P* = 0.003)	- 2.8 (*P* < 0.0001)	- 3.5 (*P* < 0.0001)	-4.4 (*P* < 0.0001)	
Mean difference (kg) vs. orlistat		- 0.7	- 1.4	-2.1 (*P* = 0.003)	-3.0 (*P* < 0.0001)	
% participants who lost > 5% of baseline weight	29.6	52.1 (*P* = 0.002 vs. placebo)	53.3 (*P* = 0.002 vs. placebo)	60.8 (*P* < 0.0001 vs. placebo)	76.1 (*P* < 0.0001 vs. placebo or orlistat)	44.2
% participants who lost > 10% of baseline weight	2.0	7.4	18.9	22.8	28.3	9.5

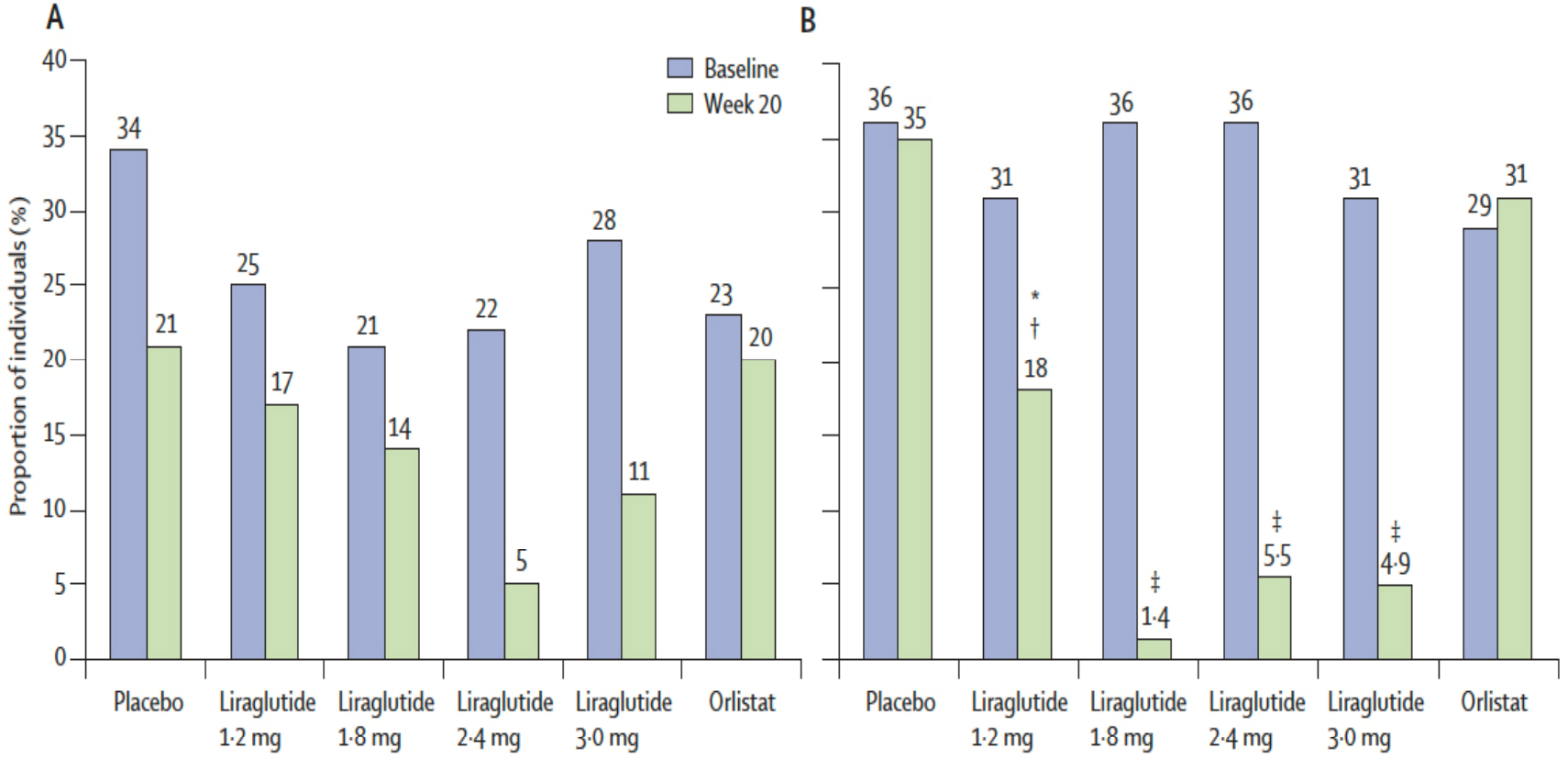
Lancet 2009;374:1606 – 16

Astrup A, et al.

American College of Clinical Pharmacy

Metabolic Syndrome

Prediabetes



Lancet 2009;374:1606 – 16

Astrup A, et al.

American College of Clinical Pharmacy

- Safety at week 20
  - No significant effects on serum calcitonin concentrations
  - No events of acute pancreatitis reported

	Placebo	Liraglutide Dose/Day 1.2mg	1.8mg	2.4mg	3.0mg	Orlistat
Overall withdraw rates (%)	19	11	18	22	12	17
Withdraw due to AEs (%)	3.1	4.2	5.6	9.7	5.4	3.2
Gastrointestinal						
Constipation (%)	12.2	14.7	11.1	17.2	14.0	6.3
Diarrhea (%)	7.1	8.4	10.0	12.9	12.9	25.3
Nausea (%)	5.1	24.2	31.1	36.6	47.3	4.2
Vomiting (%)	2.0	4.2	8.9	14.0	11.8	2.1

Lancet 2009;374:1606-16

Astrup A, et al.

- Conclusion
  - Liraglutide therapy along with a caloric-restricted, low-fat diet and exercise program leads to clinically relevant and dose-dependent weight loss
    - Significantly greater (at all doses) vs. placebo
    - Significantly greater at daily dose of 2.4mg and 3.0mg vs. orlistat
  - More than 50% of participants treated with liraglutide achieved 5 – 10% weight reduction
  - Positive effects on other cardiovascular disease risk factors

Lancet 2009;374:1606-16

Should GLP-1 Agonists Be Used to Treat Obesity?

American College of Clinical Pharmacy

- Pros
  - GLP – 1 agonists appear effective for weight loss in obese patients without diabetes
  - Positive effects on
    - Cardiovascular disease risk factors
    - Prediabetes/metabolic syndrome
- Cons
  - Gastrointestinal effects & safety concerns
  - Costs
  - Injectable dosage form
  - Long-term risk/benefit unknown

- Questions?

The use of metformin in diabetic patients with chronic kidney disease.

Marissa Quinones, Pharm.D.
Clinical Pharmacy Specialist
Parkland Health and Hospital
Southeast Dallas Health Center

Objectives

- Review the history and contraindications of metformin in patients with chronic kidney disease.
- Evaluate the current literature regarding the use of metformin in patients with chronic kidney disease.
- Provide recommendations for the use of metformin in chronic kidney disease.

History of Metformin

- In the 1970's, phenformin removed due to cases of lactic acidosis
- Metformin released for use in the U.S. in 1995
- Metformin – used widely as a 1st line agent in treatment of Type 2 diabetes

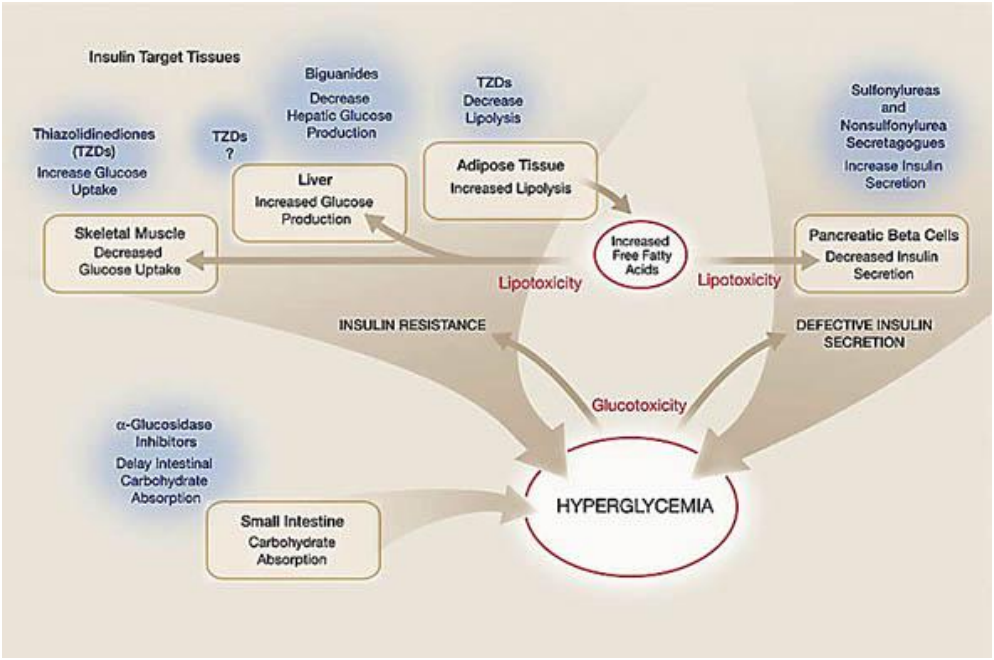


Figure. Pharmacological Approaches to the Major Metabolic Defects of Type 2 Diabetes Mellitus.

JAMA 2002;287:360-372.

Advantages and Disadvantages of Metformin

- Advantages
  - Great & Old Drug
  - No hypoglycemia
  - Weight loss
  - Reduces mortality and morbidity in Type 2
  - Decreases microvascular and macrovascular risk
  - Other benefits
  - A1c lowering 1.5-2%
  - Used in PCOS/Prevention of DM
- Disadvantages
  - Adverse events
    - GI upset (N/V/D)
  - Elimination unchanged in the kidney
  - Contraindications
    - SCr ≥ 1.4 mg/dL (females); ≥ 1.5 mg/dL (males)
  - Cases of lactic acidosis (rare)
    - Risk is minimal

JAMA 2002;287:360-372.
Cochrane Database Syst Rev. 2010 Jan 20;(1):CD002967.

Metformin and Renal Impairment

Subjects (n)	Cmax*	Tmax€	Renal Clearance (ml/min)
Adults with Type 2 DM			
850mg single dose (23)	1.48 (± 0.5)	3.32 (± 1.08)	491 (± 138)
850mg TID for 19 doses (9)	1.90 (± 0.62)	2.01 (± 1.22)	550 (± 160)
Adults with Renal impairment			
Mild (CrCl¥ 61-90 ml/min) (5)	1.86 (± 0.52)	3.20 (± 0.45)	384 (± 122)
Moderate (CrCl 31-60 ml/min) (4)	4.12 (± 1.83)	3.75 (± 0.50)	108 (± 57)
Severe (CrCl 10-30 ml/min) (6)	3.93 (± 0.92)	4.01 (± 1.10)	130 (± 90)

*peak plasma concentration, € time to peak concentration, ¥ CrCl = creatinine clearance normalized to body surface area of 1.73 m^2

Table taken from: Glucophage®package insert.

Metformin and Kidney Disease

The Problem

decreased renal impairment / CrCl decreases =

= decreased renal clearance

= metformin accumulation

= concerns for lactic acidosis

What do we do?

What do the guidelines say?

Guideline	Recommendation
Glucophage® Package Insert	Renal disease or renal dysfunction - SCr ≥ 1.4 (females); ≥ 1.5 (males) – or abnormal CrCl. Need to monitor closely in those with renal disease and elderly -No real guide regarding CrCl cut off
FDA	Stop if serum creatinine 1.4 mg/dL in women and 1.5 mg/dL in men or decreased clearance in people over age 80
KDOQI Guidelines	Serum creatinine of 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women "…it is cleared by the kidney and may build up with even modest impairment of kidney function, putting patients at risk of lactic acidosis"

Review by Herrington and Levy 2008 "Metformin: effective and safe in renal disease?"

Guideline/Paper	Recommendation
British National Formulary (BNF)	Warning not to use metformin in mild renal impairment (GFR 20-50ml/min)
Jones, et. al.	SCr absolute cut off point of 1.7mg/dL; use caution in elderly
Canadian Pharmacists Association	SCr ≥ 1.5 in males and ≥ 1.4 females; caution in advanced age (>80) unless CrCl not reduced
McCormack, et. al.	Acknowledged problem with use of SCr alone; use CrCl based on PK principles reduce the max dose of metformin by 50% when CrCl decreases < 60ml/min
Nisbet, et.al.	Use Cockcroft Gault; absolute cut off GFR of 30ml/min (discontinue metformin); GFR 30-50ml/min extreme caution

Int Urol Nephrol 2008;40:411-417.

Herrington and Levy 2008

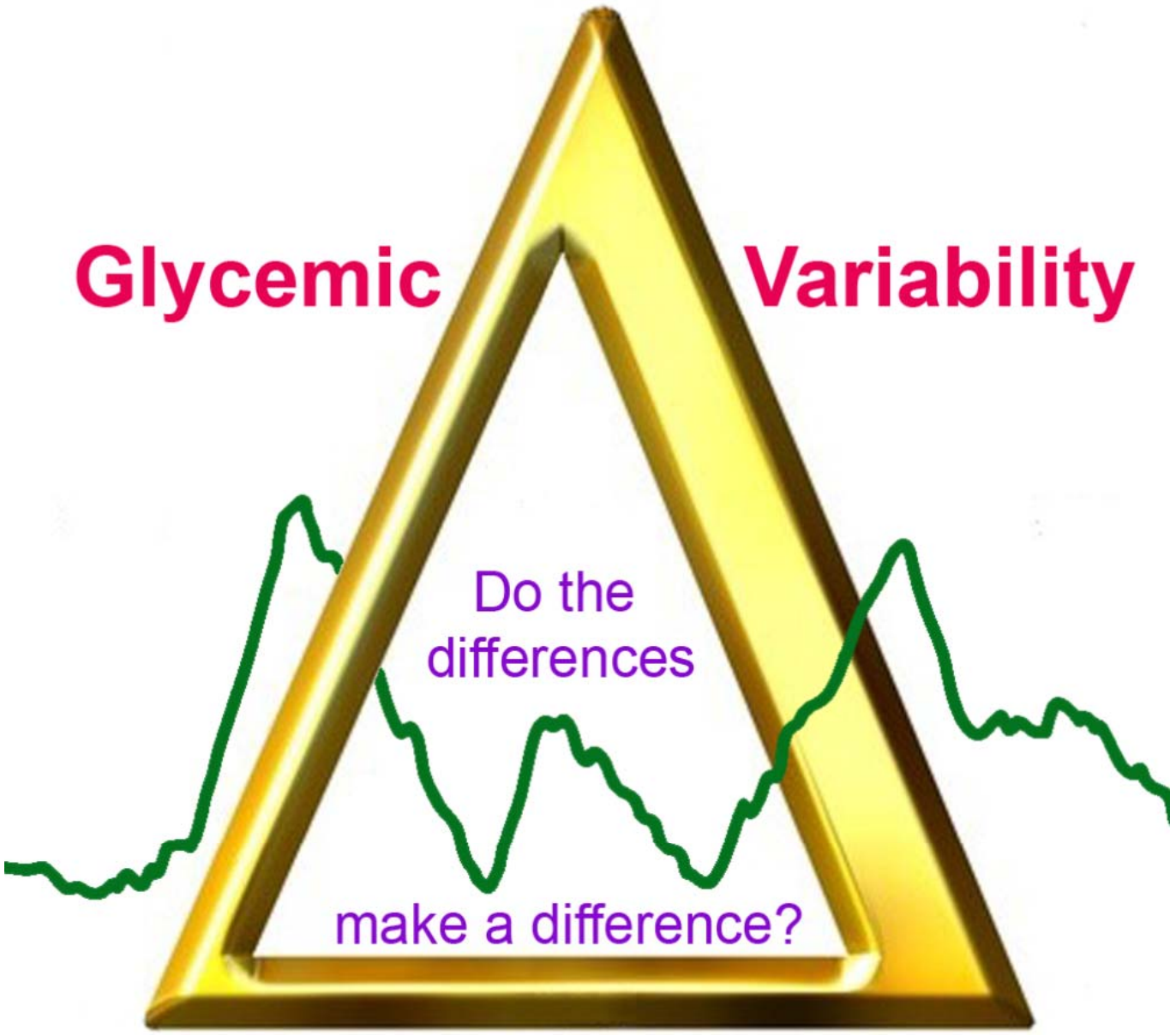
- Recommend
  - **Stage 1 – 2 (GFR 60 – 90 ml/min):** continue but may reduce starting dose of metformin by 50%
  - **Stage 3 (GFR 30 – 60 ml/min):** then further reduce metformin dose by another 50%
  - **Stage 5 (GFR < 30 ml/min):** do not use
- Once pt reaches Stage 3 we must consider the risk versus the benefit
- AND NEED TO CAREFULLY MONTIOR

Int Urol Nephrol 2008;40:411-417.

Conclusion

- The data is lacking
- Lack of studies of using metformin with renal impairment
- No good evidence base
- Use of SCr versus CrCL?
  - Cockcroft Gault versus MDRD
- Must consider risk versus benefit

Int Urol Nephrol 2008;40:411-417.



Kim L. Kelly, PharmD, BCPS, FCCP

Disclosures:

- Education Program consultant; LifeScan, Animas and J&J Diabetes Institute
- Stockholder; Johnson & Johnson

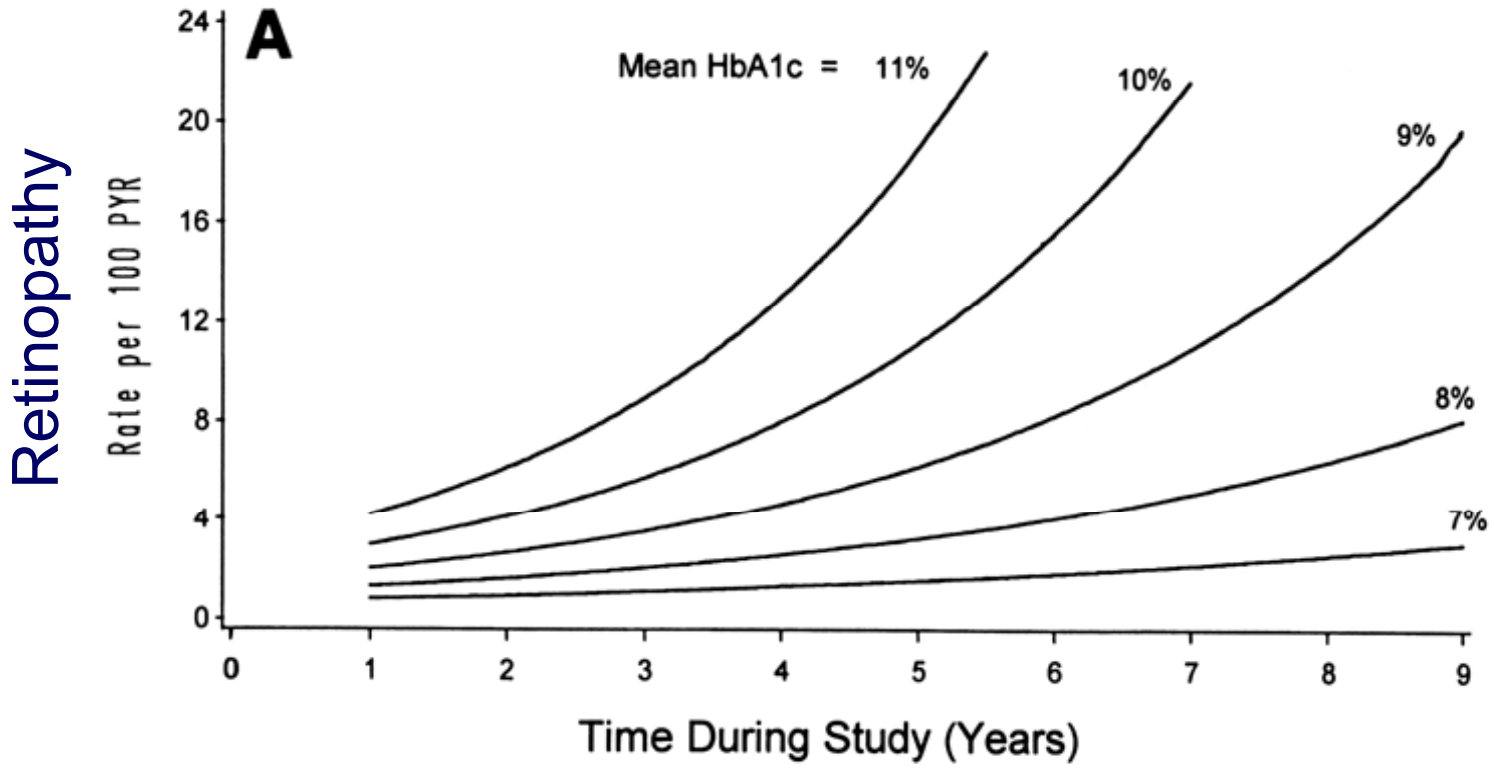
Objectives

At the conclusion of this presentation, the participant will be able to:

- **write a brief description of the evidence that glycemic variability is an independent risk factor for cardiovascular disease**
- **write a brief description of the mechanism by which glycemic variability can result in oxidative stress**
- **discuss at least three variables which may affect the pathophysiology of oxidative stress**
- **discuss the studies that do not support glycemic variability and pathology including at least one methodologic flaw in each study.**

Relationship Between Increasing A1C and Retinopathy

… it all started with an article in *Diabetes* in 1995



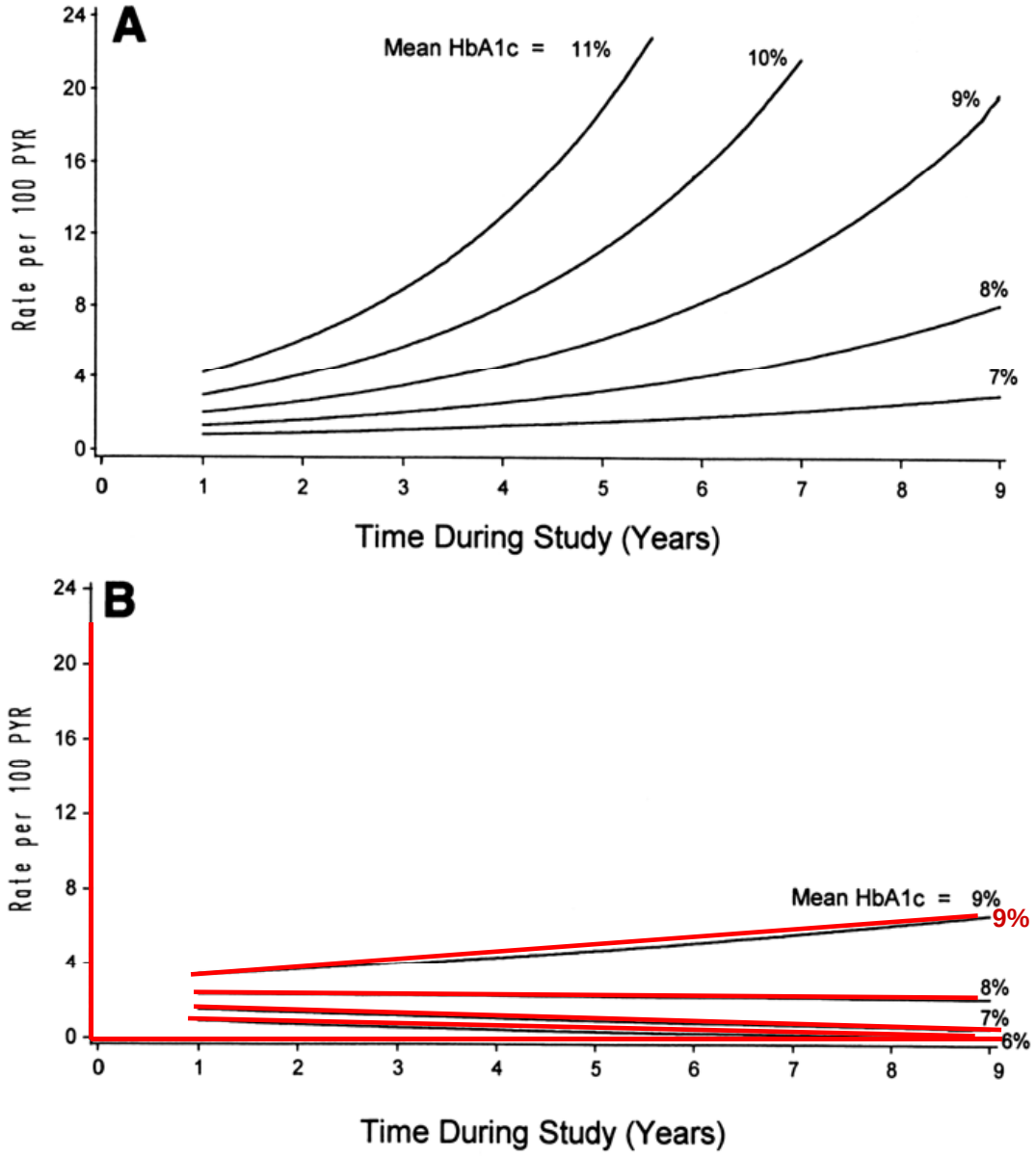
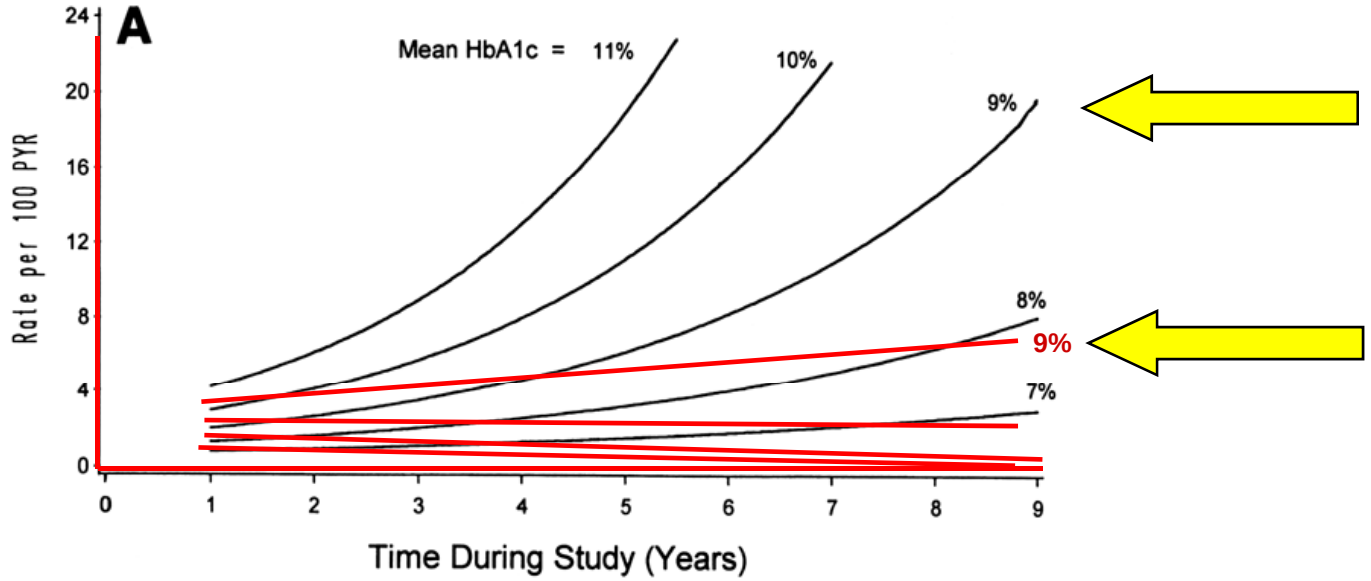


FIG. 6. Absolute risk of sustained retinopathy progression as a function of the updated mean HbA_{1c} (percentage) during the study and the time of follow-up during the study (years), estimated from absolute risk (Poisson) regression models (Table 8). *A*: Conventional treatment group. *B*: Intensive treatment group.



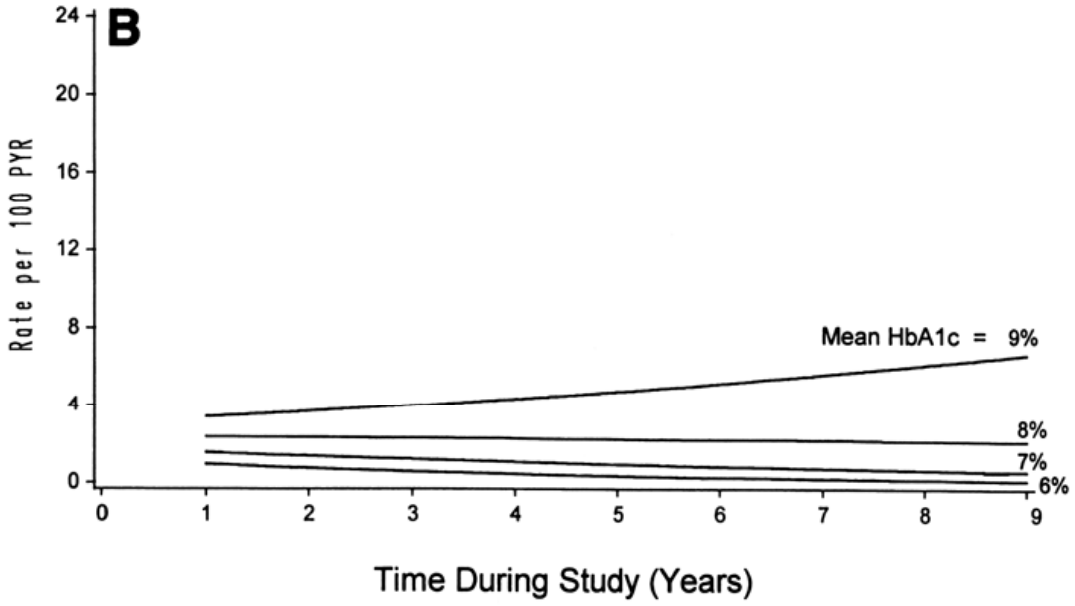


FIG. 6. Absolute risk of sustained retinopathy progression as a function of the updated mean HbA_{1c} (percentage) during the study and the time of follow-up during the study (years), estimated from absolute risk (Poisson) regression models (Table 8). *A*: Conventional treatment group. *B*: Intensive treatment group.

What's the difference?

Numerous Studies on PPG/PCG and CV Risk

Table 2—*Epidemiological studies on the effect of postprandial hyperglycemia on CV risk*

Study	Reference	Year of publication	Setting	Duration of follow-up	Risk measure
Cardiovascular Health Study	Smith et al.[16]	2002	4,014 American men and women from four U.S. communities, ≥65 years of age	8.5 years	HR for CV event = 1.29 for 2-h PG >8.5 mmol/L
Chicago Peoples Gas Company Study	Vaccaro et al.[17]	1992	873 American men, 34–65 years of age	19 years	CVD/CHD mortality; OR = 2.3–2.7 for 2-h PG >11.2 mmol/L vs. normoglycemic patients
Chicago Heart Association Detection Project in Industry Study	Lowe et al.[18]; Orencia et al.[19]	1997	12,220 white and black American men, 35–64 years of age	22 years	CVD mortality: RR = 1.18 for 2-h PG >8.9 mmol/L vs. normoglycemic patients
DECODA	Nakagami[20]	2004	6,817 subjects of Japanese and Asian Indian origin; 30–89 years of age	5 years (median)	RR all-cause mortality for 2-h PG >11.1 mmol/L = 2.80; RR of CVD mortality for 2-h PG >11.1 mmol/L = 3.42
DECODE	Decode Study Group[12]	2001	22,514 men and women in several European countries, 30–89 years of age	8.8 years (median)	HR for all-cause mortality = 1.73 for 2-h PG >11.2 mmol/L; HR for CVD mortality = 1.40; HR for CHD mortality = 1.56; HR for stroke mortality = 1.29
Framingham Offspring Study	Meigs et al.[21]	2002	3,370 American men and women, 26–82 years of age	4 years	RR for CVD in patients with 2-h PG >11.1 mmol/L = 1.42 per 2.1 mmol/L increase
Funagata Diabetes Study	Tominaga et al.[13]	1999	2,534 men and women from Funagata, Japan	6 years	OR for CVD mortality in patients with diabetes vs. normoglycemic subjects = 3.54
Honolulu Heart Program	Rodriguez et al.[22]	1999	8,006 Japanese-American men from Oahu, Hawaii, 45–68 years of age	23 years	RR for CHD mortality in patients with 1-h PG >12.5 mmol/L vs. normoglycemic subjects = 3.49
Hoorn Study	de Vegt et al.[23]	1999	2,363 Dutch men and woman in Hoorn, the Netherlands, 50–75 years of age	8 years	RR for CVD mortality in patients with 2-h PG >11.1 mmol/L = 3.31 vs. normoglycemic subjects
Mauritius-Fiji-Nauru Study	Shaw et al.[24]	1999	9,179 men and women from Mauritius, Fiji, and Nauru, >20 years of age	5–12 years	HR for CVD mortality in patients with 2-h PG >11.1 mmol/L vs. normoglycemic subjects = 2.3 in men, 2.6 in women
Paris Prospective and Helsinki Policemen Studies	Balkau et al.[25]	1998	7,260 subjects: 6,629 men from the Paris Prospective Study (mean age 48.5 years) and 631 subjects of the Helsinki Policemen Study	20 years	HR for CVD and CHD mortality in patients in the upper 20% (2.5%) of the 2-h PG distribution vs. those in the lower 80% of these distributions = 1.8 (2.7)

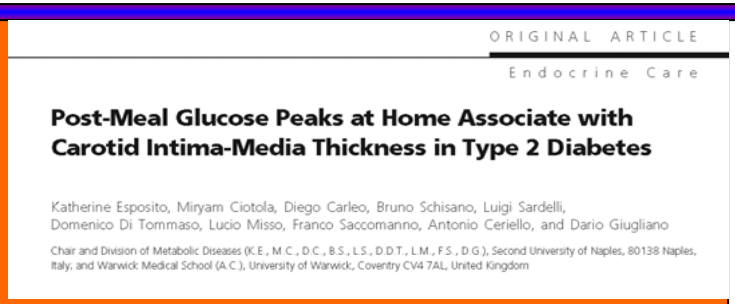
Table 2—*Continued*

Study	Reference	Year of publication	Setting	Duration of follow-up	Risk measure
	Qiao et al.[26]	2002	6,766 subjects from five Finnish cohorts	7–10 years	HR for 1 SD increase in 2-h PG = 1.22 for CVD mortality
Rancho Bernardo Study	Barrett-Connor and Ferrara[27]	1998	1,858 Caucasian adults of European ancestry in California, 50–85 years of age	7 years	HR for CVD and CHD mortality in patients with 2-h PG >11.1 mmol/L = 2.6 (CVD) and 2.9 (CHD) vs. normoglycemic control subjects
San Luigi Gonzaga Study	Cavalot et al.[28]	2006	529 men and women in a suburban area of Turin, Italy, mean age 60.4 years for men and 63.3 years for women	5 years	HR for CV event in patients with PPG in the third vs. first and second tertile = 5.54 for women and 2.12 for men
	Saydah et al.[29]	2001	3,092 American adults from the NHANES II cohort, 30–74 years of age	16 years	Relative hazard for CVD mortality in patients with 2-h PG >11.1 mmol/L = 2.3 vs. normoglycemic subjects
Whitehall Study	Brunner et al.[30]	2006	17,869 male civil servants in the U.K., 40–64 years of age	33 years	HR in patients with 2-h PG >11.1 mml/L for CVD mortality = 3.2, CHD mortality = 3.7, and stroke mortality = 1.16 vs. normoglycemic control subjects

CHD, coronary heart disease; CVD, CV disease; HR, hazard ratio; NHANES II, Second National Health and Nutrition Examination Survey; OR, odds ratio; PG, plasma glucose; RR, relative risk.

Standl E, Schnell O, Ceriello A. Diabetes Care 2011;34 (Suppl 2):S120

Other observations…



ORIGINAL ARTICLE

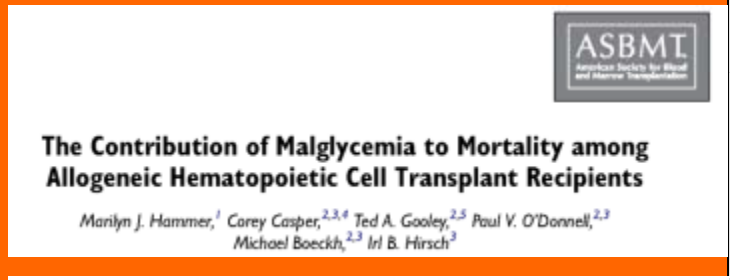
Endocrine Care

Post-Meal Glucose Peaks at Home Associate with Carotid Intima-Media Thickness in Type 2 Diabetes

Katherine Esposito, Miryam Ciotola, Diego Carleo, Bruno Schisano, Luigi Sardelli, Domenico Di Tommaso, Lucio Misso, Franco Saccomanno, Antonio Ceriello, and Dario Giugliano

Chair and Division of Metabolic Diseases (K.E., M.C., D.C., B.S., L.S., D.D.T., L.M., F.S., D.G.), Second University of Naples, 80138 Naples, Italy; and Warwick Medical School (A.C.), University of Warwick, Coventry CV4 7AL, United Kingdom

Esposito K, et al
J Clin Endocrinol Metab 2008;93:1345
Incremental glucose peaks are frequent…, occur for most(95%) within 1 h after meal, timing of IGPs is not influenced by treatment (diet or drugs), and IGPs correlate with CIMT

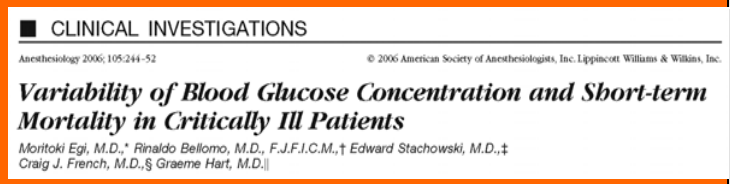


ASBMT

The Contribution of Malglycemia to Mortality among Allogeneic Hematopoietic Cell Transplant Recipients

Marilyn J. Hammer,[1] Corey Casper,[2,3,4] Ted A. Gooley,[2,5] Paul V. O'Donnell,[2,3] Michael Boeckh,[2,3] Irl B. Hirsch[3]

Hammer MJ, et al
Biol Blood Marrow Transplant 2009;15:344
The upper quartile of glucose variability was associated with a 14.57-fold increase in risk of non-relapse mortality by day 200 relative to the first quartile



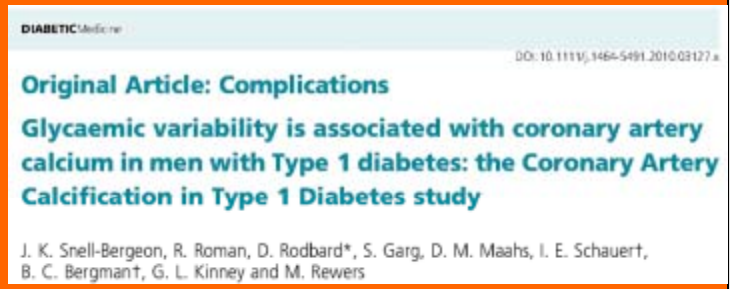
CLINICAL INVESTIGATIONS

Anesthesiology 2006; 105:244–52 © 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

Moritoki Egi, M.D., Rinaldo Bellomo, M.D., F.J.F.I.C.M.,† Edward Stachowski, M.D.,‡ Craig J. French, M.D.,§ Graeme Hart, M.D.‖*

Egi M, et al
Anesthesiology 2006;105:244
The SD of glucose concentration is a significant independent predictor of ICU and hospital mortality



DIABETIC Medicine

DOI: 10.1111/j.1464-5491.2010.03127.x

Original Article: Complications

Glycaemic variability is associated with coronary artery calcium in men with Type 1 diabetes: the Coronary Artery Calcification in Type 1 Diabetes study

J. K. Snell-Bergeon, R. Roman, D. Rodbard*, S. Garg, D. M. Maahs, I. E. Schauert, B. C. Bergmant, G. L. Kinney and M. Rewers

Snell-Bergeon JK, et al
Diabetic Medicine 2010;27:1436
Subclinical atherosclerosis is associated with glucose levels and variability in men with Type 1 diabetes. The relationship of coronary artery calcium and glucose variability in Type 1 diabetes, and potential gender differences in this association, deserve further study

Glycemic variability in NGT, IGR and T2DM

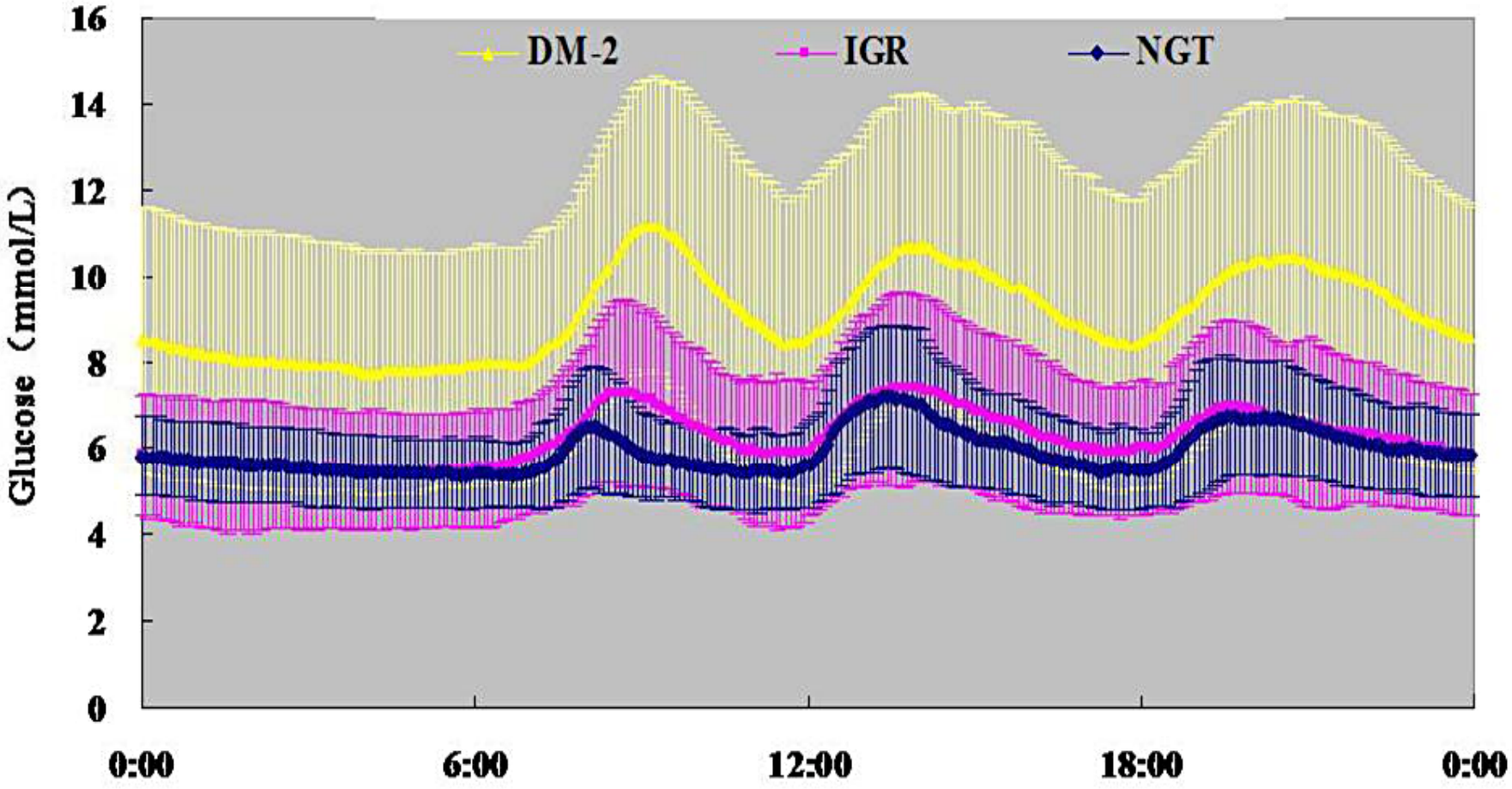
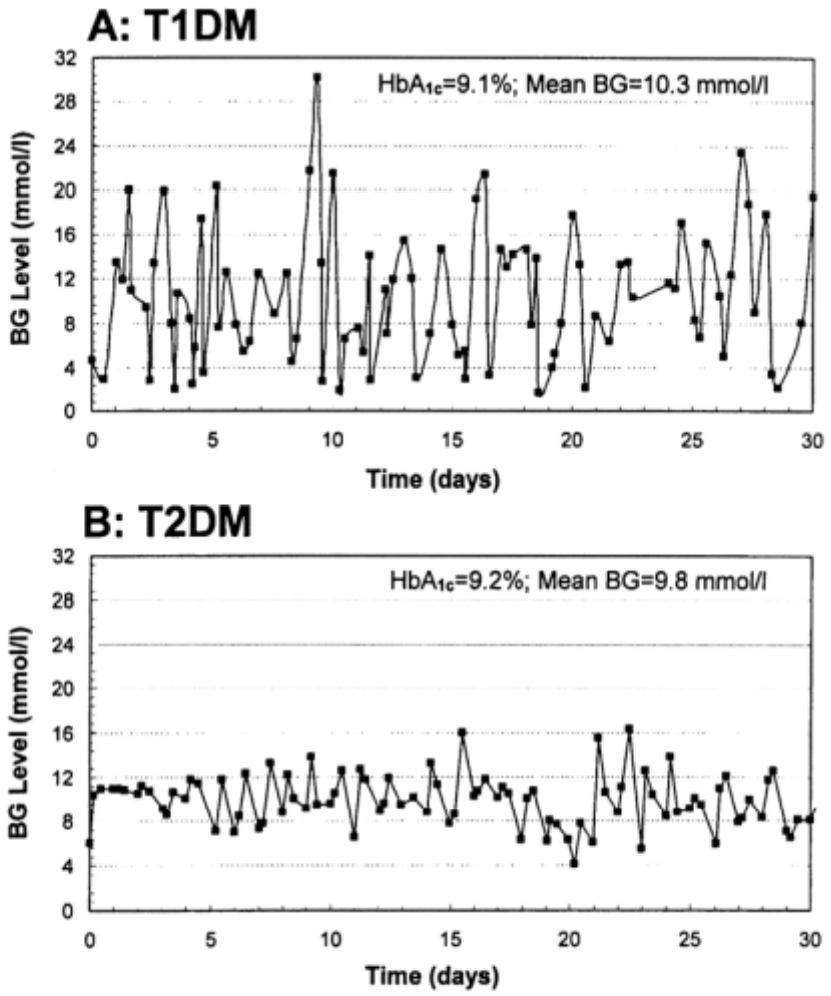


Figure 1. 24h sensor glucose profiles of the studied groups. The data represent means±SD.

Wang C, et al. Clinical Endocrinology [Epub ahead of print; Aug 13, 2011]

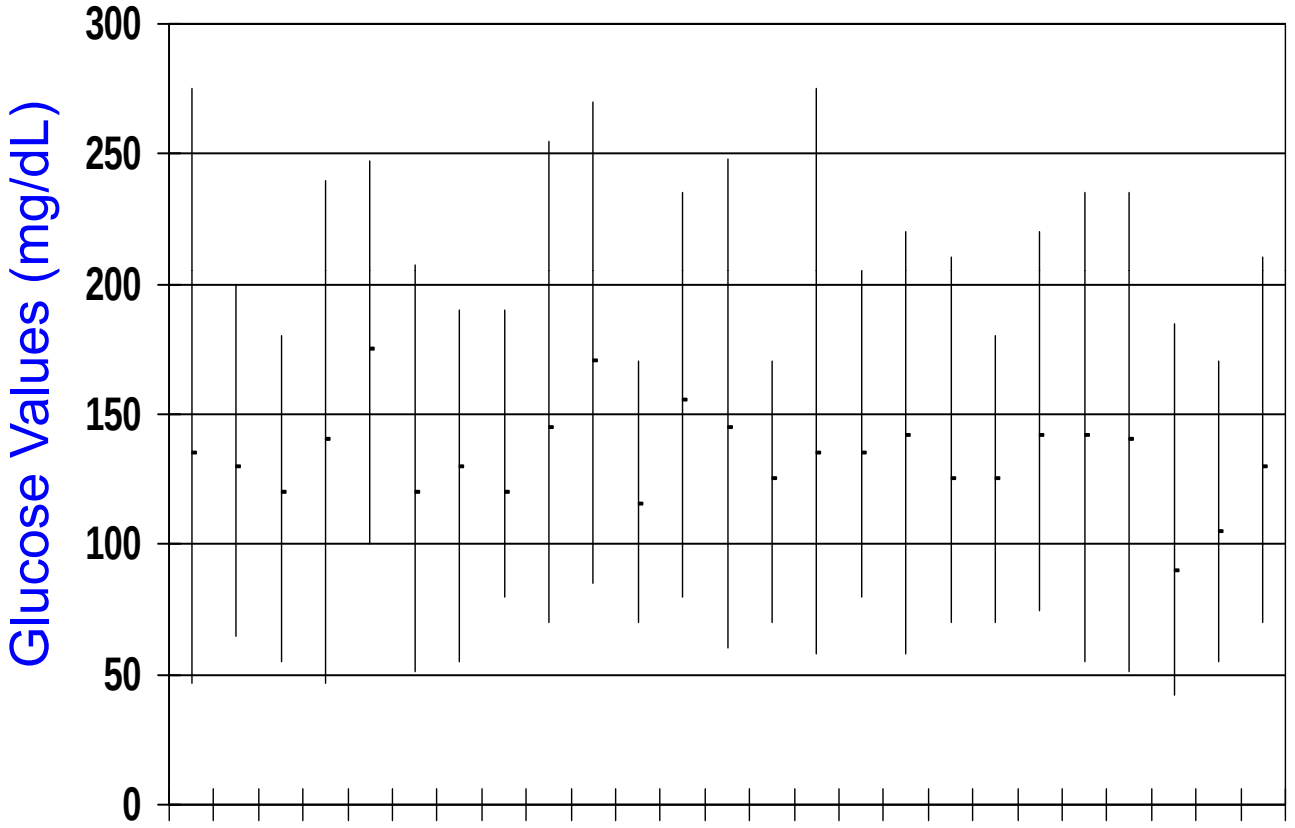
Variability of Blood Glucose Results in Type 1 and Type 2 Diabetes

- **N=277 T1DM, and 323 T2DM**
- **Avg of 230 SMBG and 3 A1c readings over 3 months**
- **Calculated indices of of hypo- and hyperglycemic episodes**



Kovatchev BP, Cox DJ, Gonder-Frederick L.
Diab Technol & Therapeutics 2002;4:295-303

Glucose excursions in ‘stable’ patients with type 2 diabetes on oral agents



Glucose Values (mean, 5th to 95th percentile) for each patient during the study

Glucose excursions during CGMS profiles showed significant variation in nearly every patient despite their being ‘controlled’ and ‘stable’ by current definitions

Hay LC, et al. *Diab Techol Ther* 2003; 5:19-26

“So many measures, I just can’t count them all…”

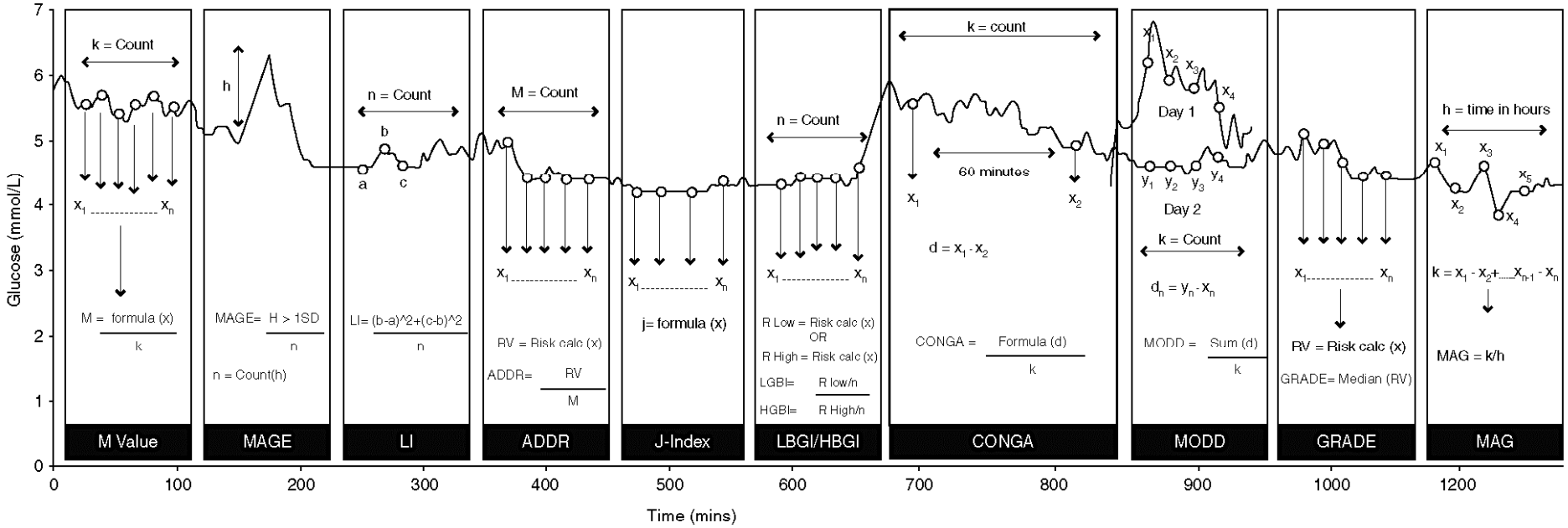
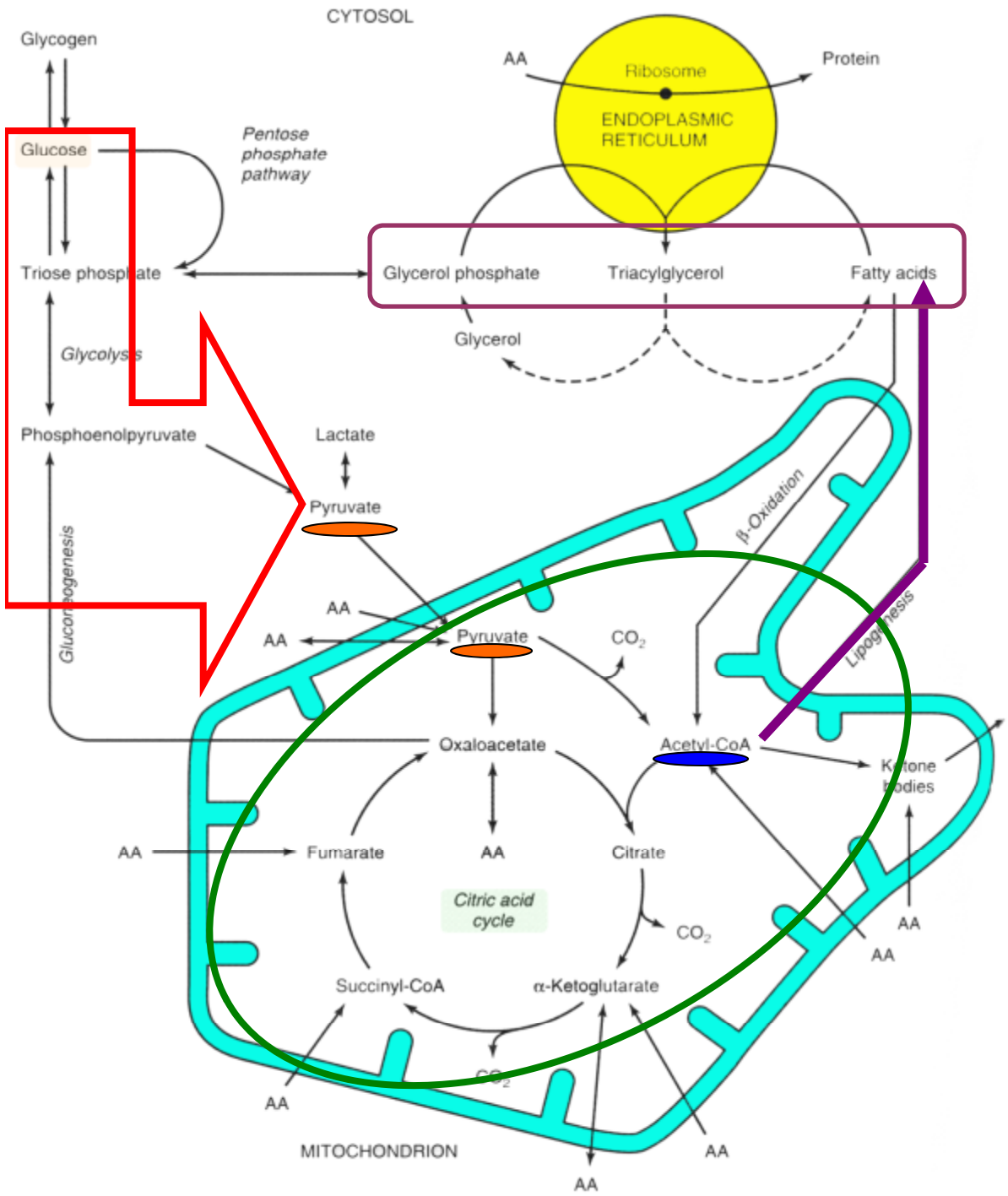


FIG. 1. Graphical illustration of how each of the 10 methods of glycemic variability assessment are calculated from a continuous glucose monitoring trace: average daily risk ratio (ADRR), continuous overlapping net glycemic action (CONGA), Glycemic Risk Assessment in Diabetes Equation (GRADE), High Blood Glucose Index (HBGI), Low Blood Glucose Index (LBGI), J-Index, Lability Index (LI), mean absolute glucose (MAG), mean amplitude of glucose excursions (MAGE), and mean of daily differences (MODD). In practice each method would independently assess the entire trace.

Hill NR, et al Diabetes Technology & Therapeutics 2011;13:921

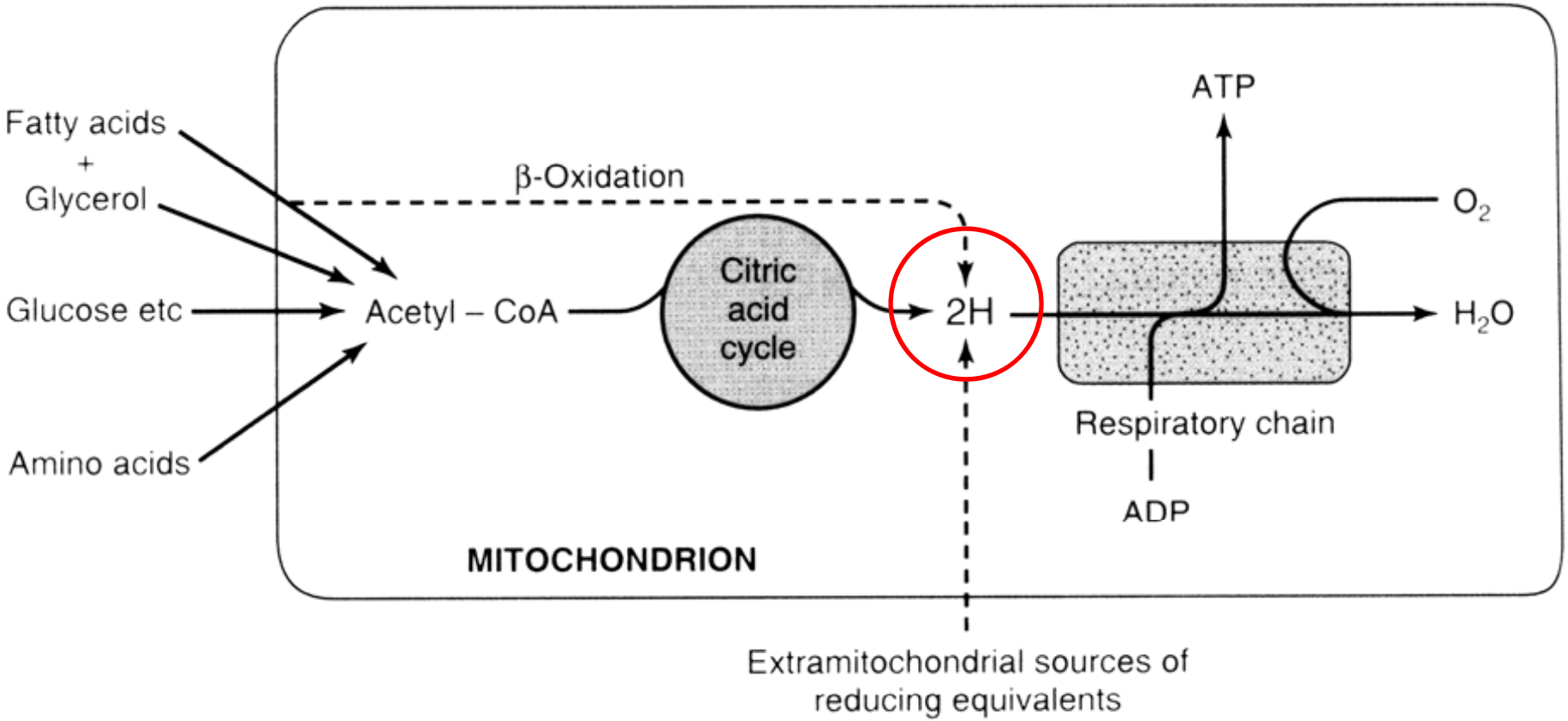
So how might variability affect processes we know are involved in complications?

Glucose Metabolism

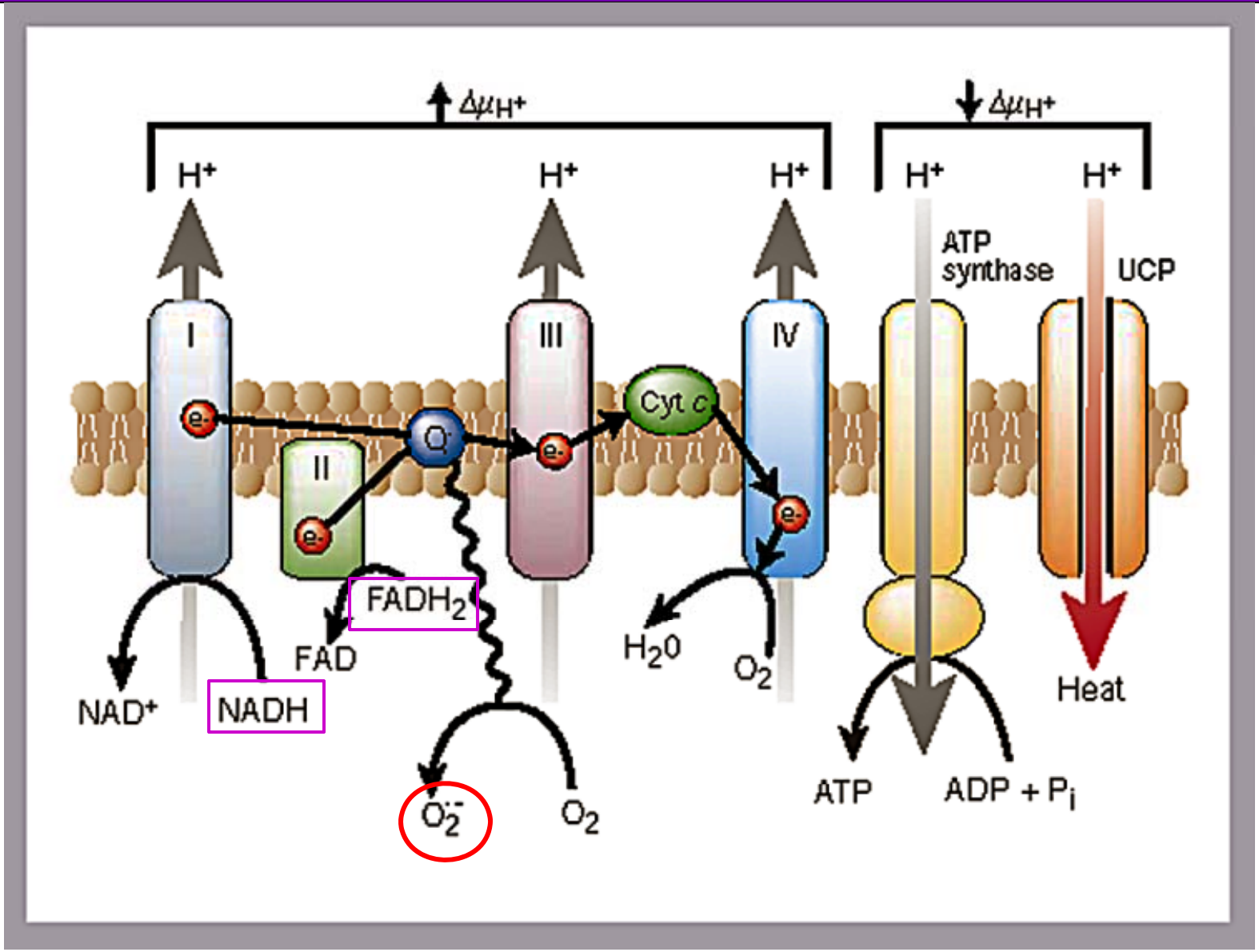


- **Glycolysis (Embden Meyerhoff)**
  - Takes the 6 carbon sugar and breaks it into three carbon chunks
- **Krebs (Citric Acid) Cycle**
  - Takes 3 carbon chunks breaks them down for energy, storing excess as fatty acids through lipogenesis

The Point of all this… Making H's



Making ATP


ΔμH+
H+
H+
H+
ΔμH+
H+
H+
ATP synthase
UCP
I
II
III
IV
Cyt c
Q
e-
FADH2
FAD
NAD+
NADH
H20
O2
Heat
O2-
O2
ATP
ADP + Pi

Superoxides occur in other ways…

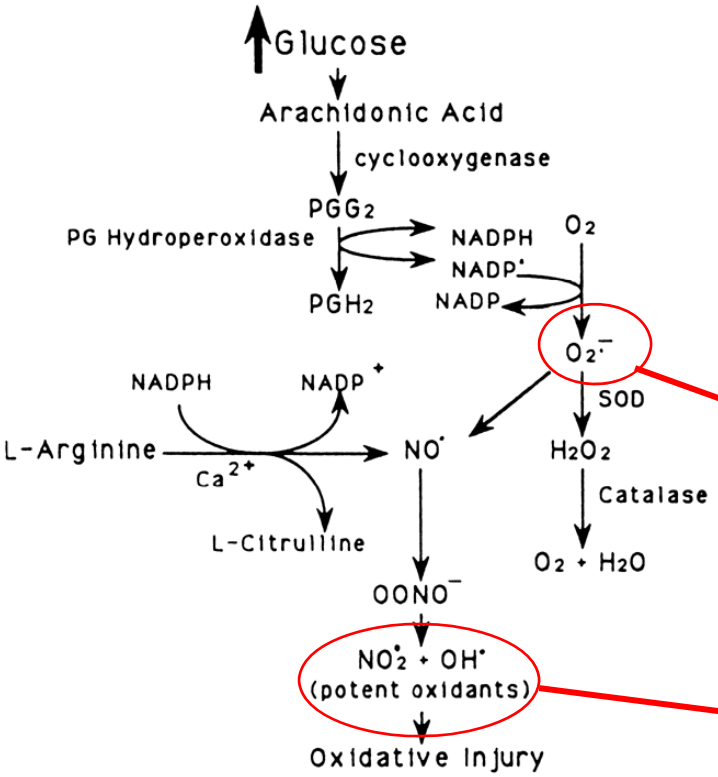
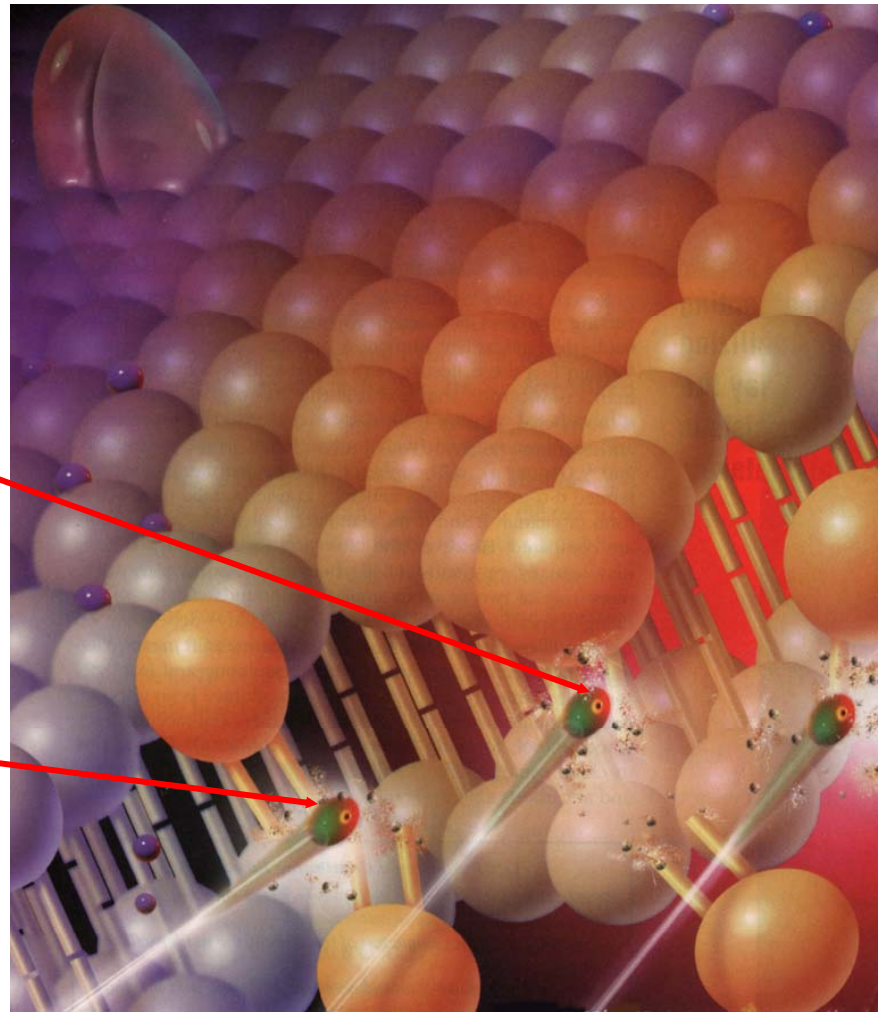
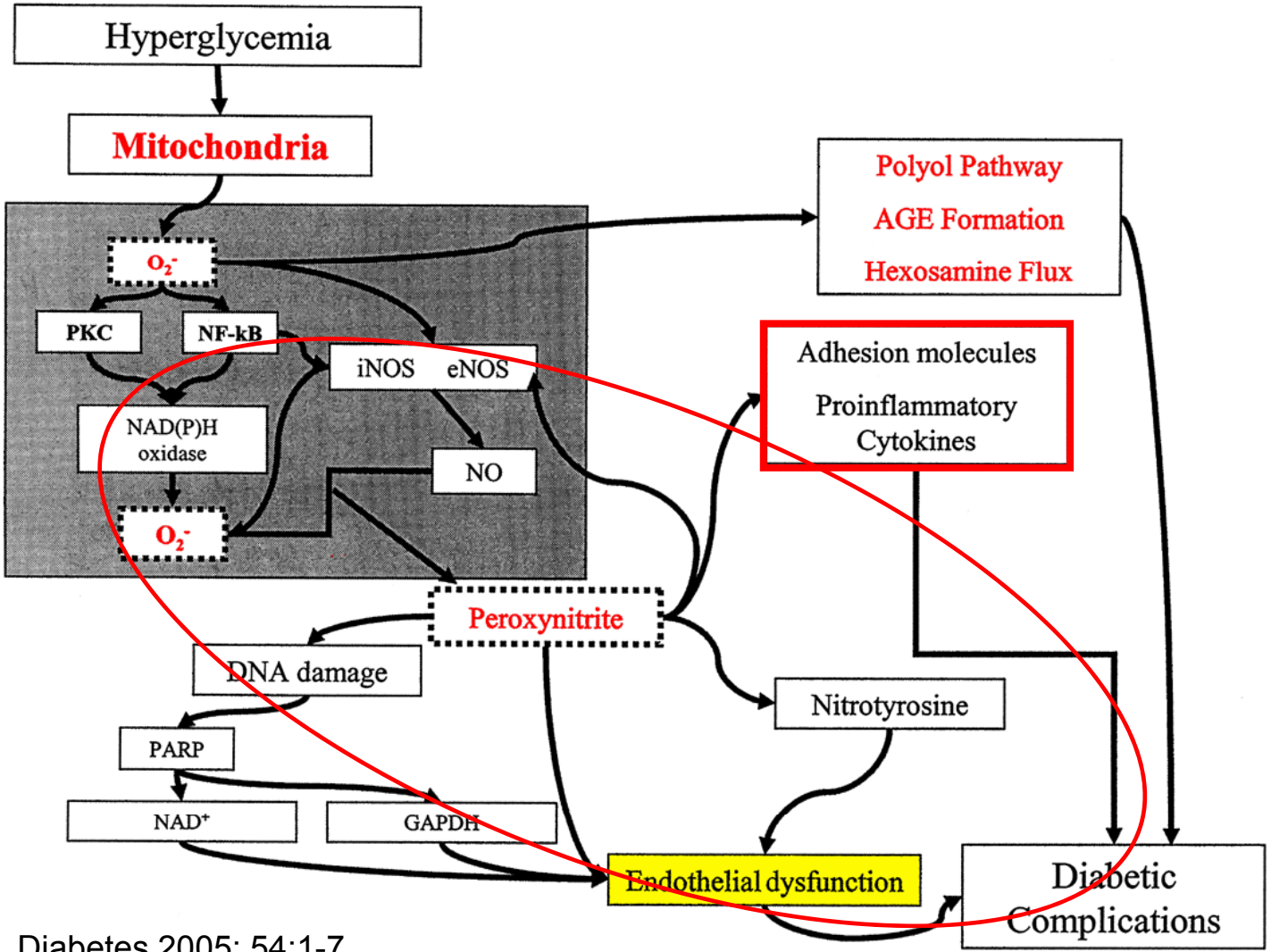


Fig. 5. Proposed interaction of arachidonic acid metabolism, free radical and NO in endothelium: cyclooxygenase pathway generates superoxide anion ($O_2^{\bullet -}$) by interaction of NADPH with an intermediate radical form of the enzyme associated with the conversion of prostaglandin (PG) G_2 to PGH_2. NADP. interact with oxygen (O_2) to produce $O_2^{\bullet -}$. NO is formed from L-arginine by a Ca^{2+}/calmodulin and NADPH dependent cofactors. NO interacts with $O_2^{\bullet -}$ to form peroxynitrite ($ONOO^-$) which then form hydroxyl radical ($^{\bullet}OH$) and nitrogen dioxide (NO_2). (H_2O_2 = hydrogen peroxide; SOD = superoxide dismutase).

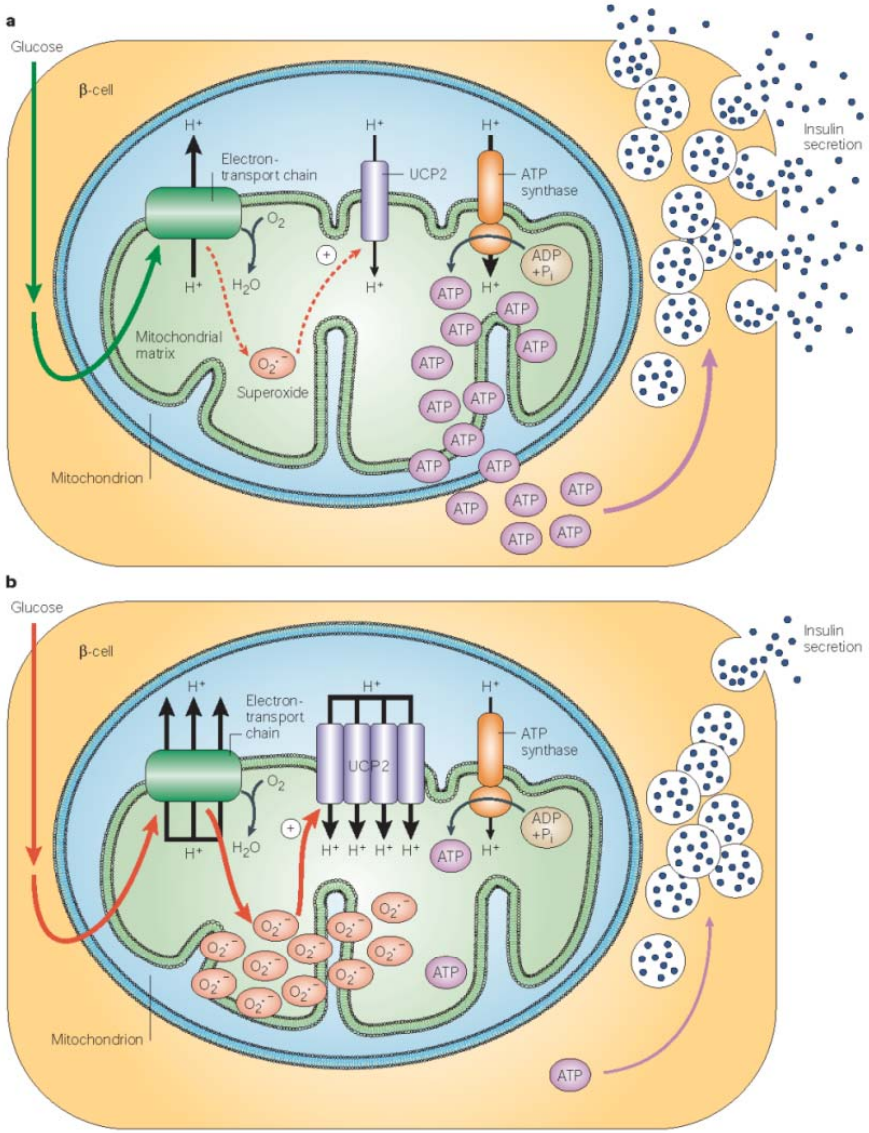


The excess $O_2^{\cdot}$ combines with NO resulting in production of other oxidative intermediates



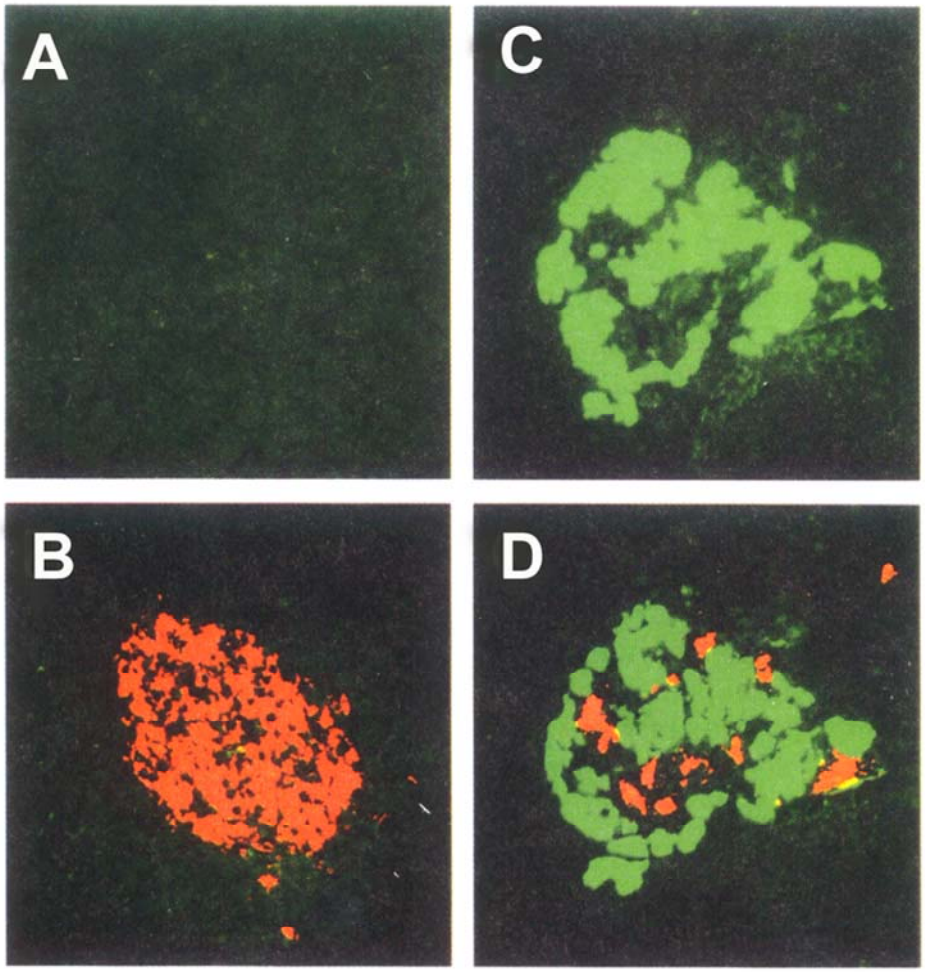
Ceriello A. Diabetes 2005; 54:1-7

Superoxides and Insulin Release



- Insulin release requires energy in the form of ATP
- ATP comes from glucose metabolism.
- Increased superoxide from excess glucose results in less energy (ATP) from glucose and decreases insulin release

Nature Rev Mol Cell Biol 2005;6:249



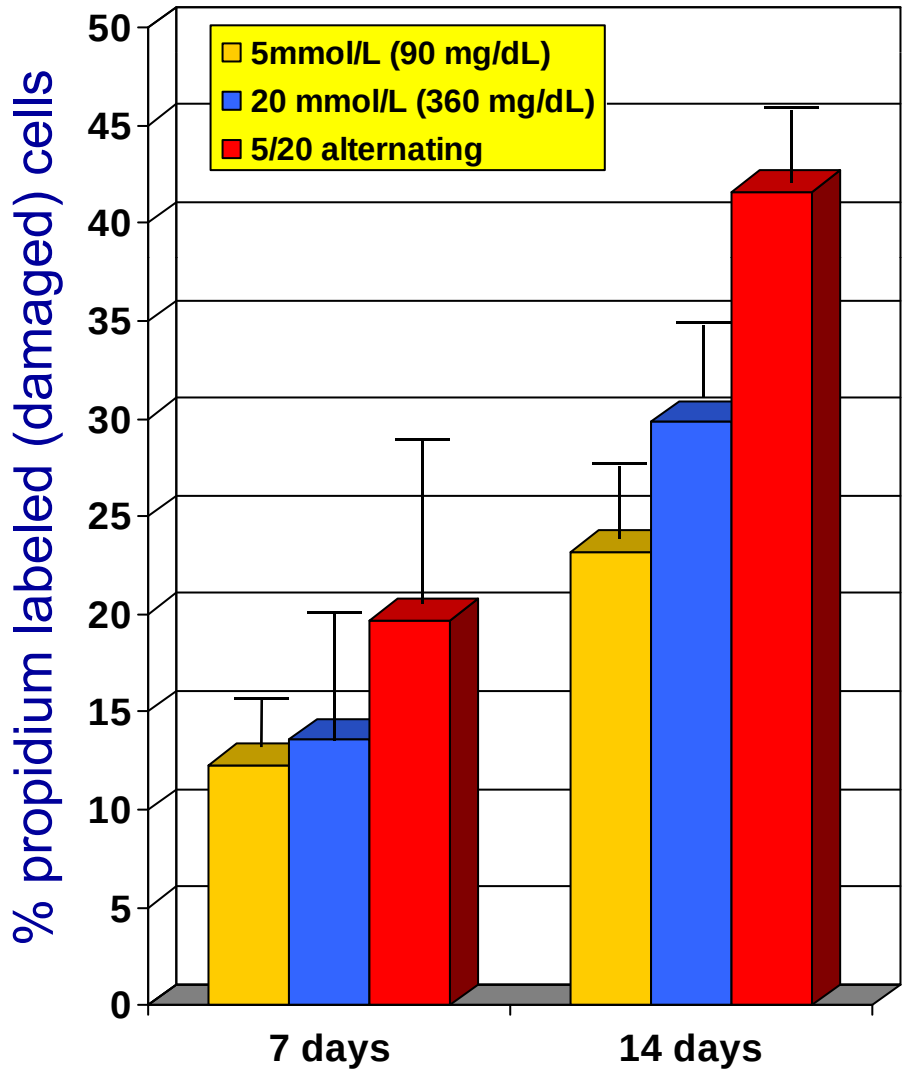
A - normal pancreas stained for amyloid
B - normal pancreas stained for insulin
C - type 2 diabetes pancreas stained for amyloid
D - type 2 diabetes pancreas stained for both amyloid and insulin

The pancreas is a target of glucotoxicity

Damage to the pancreas from "glucotoxicity" results in deposition of amyloid replacing viable insulin producing cells with amyloid deposits. This is the basis of the progressive nature of type 2 diabetes.

Kahn SE, et al Diabetes 1999;48:241

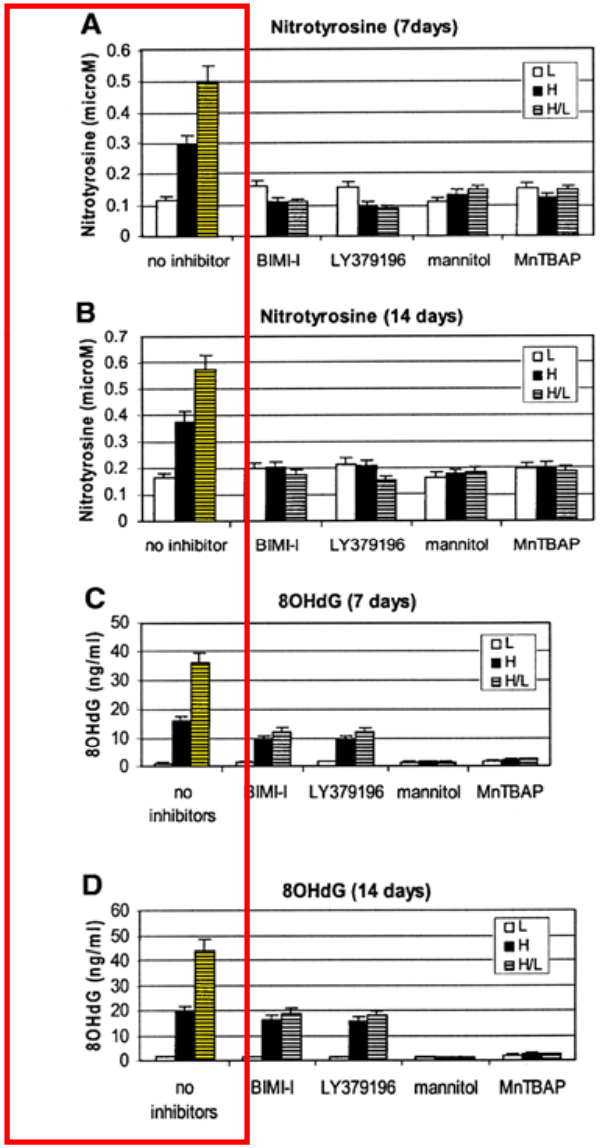
Glucose fluctuations and cell damage in experimental cell cultures



- Human umbilical vein endothelial cells were incubated in 5 mmol or 20 mmol or alternating 5 and 20 mmol/L solutions of glucose and then tested for markers of cell damage
- At 7 days and 14 days, there were significantly more damaged cells with the higher glucose concentration and even more damaged cells when the glucose was alternated between 5 and 20 mmol/L each day.

Quagliaro L, et al. Diabetes 2003; 52:2795-2804

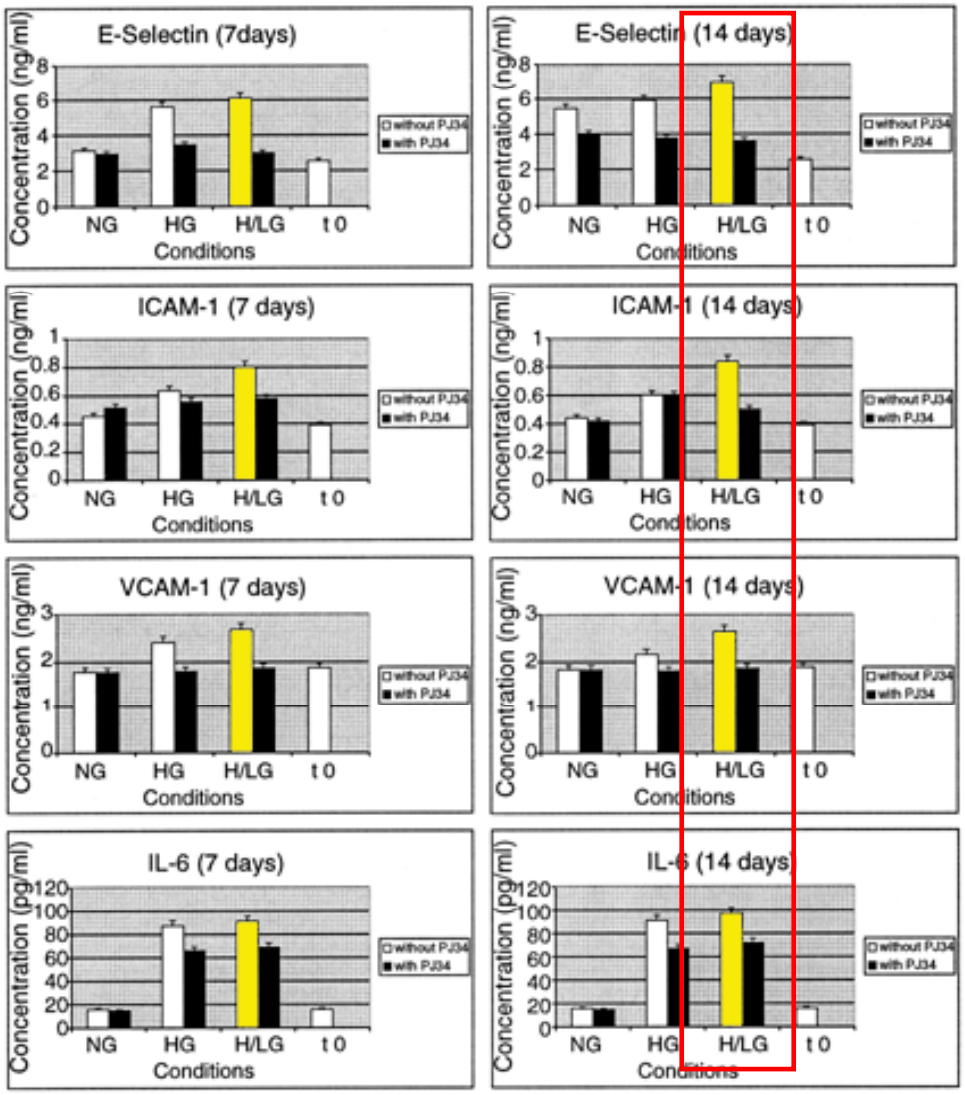
Variability in glucose is associated with oxidative stress…



- Nitrotyrosine (NT) and 8-OH deoxyguanosine (8OHDG) are markers of oxidative stress
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days.
- NT and 8OHDG levels are higher when glucose fluctuates between 5mmol/L and 20mmol/L than when held at 20mmol/L at 7 and 14 days

Quagliaro L, et al. *Diabetes* 2003; 52:2795-2804

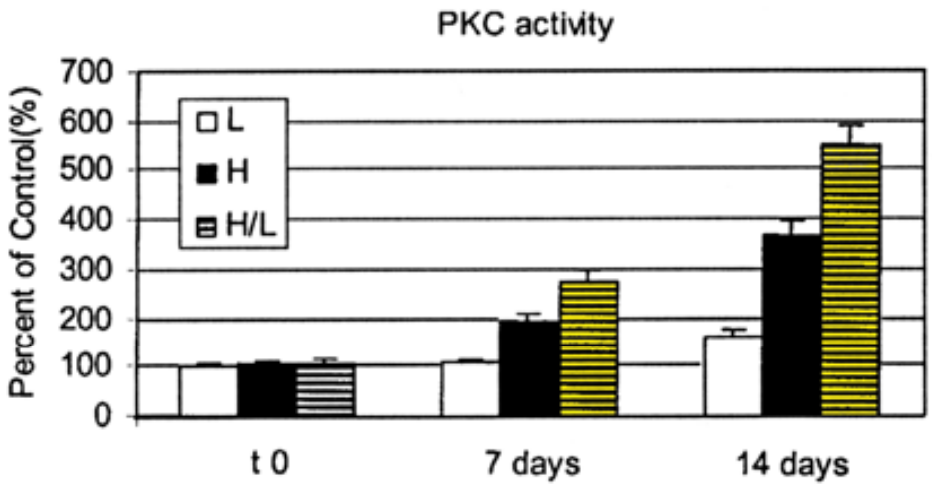
…and with increased cytokines and adhesion molecules



- Cytokines are a group of proteins that regulate the immune system, many are pro-inflammatory
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days
- All the cytokines measured were higher when the glucose was varied between 5mmol and 20mmol than when the solution was held at a constant 20 mmol

Piconi L. et al, *J Thrombosis and Haemostasis* 2004;2:1453

…and with increased levels of Protein Kinase-C

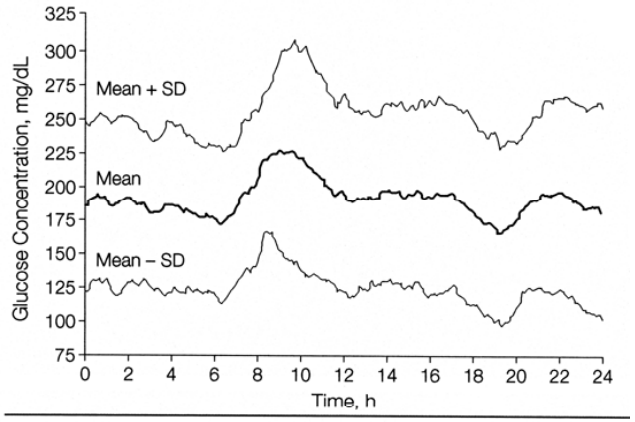


- Protein Kinase C (PKC) is a molecule that appears to be central to activation of a number of processes of cell damage
- Human umbilical vein endothelial cells were bathed in 5mmol and 20mmol and alternating 5mmol/20mmol glucose solutions for 14 days.
- PKC levels were increased more when glucose was varied from 5mmol to 20mmol than when held at 20mmol

Quagliaro L, et al. *Diabetes* 2003; 52:2795-2804

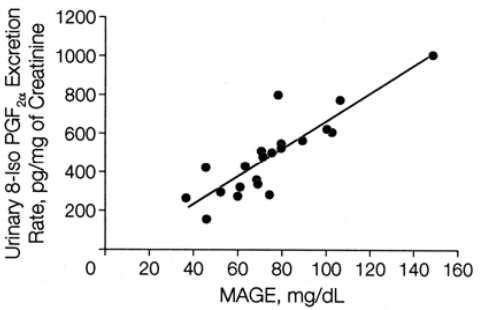
This increased oxidative stress has now been demonstrated in people with diabetes

Figure 1. 24-Hour Recordings From the Continuous Glucose Monitoring System in 21 Patients



To convert glucose to mmol/L, multiply values by 0.0555.

Figure 2. Linear Correlation Between 24-Hour Urinary Excretion Rates of 8-Iso Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and Mean Amplitude of Glycemic Excursions (MAGE)



r=0.86; P<.001.

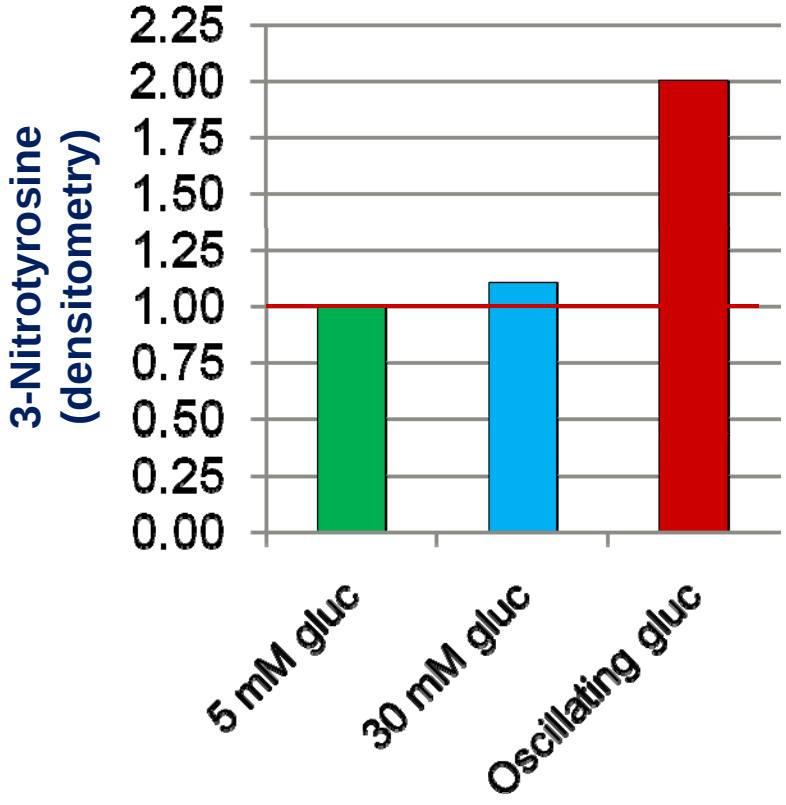
- Twenty one patients were studied with urinary excretion rates of 8-iso-prostaglandin $F_{2\alpha}$ (a marker of oxidative stress)
- Glucose fluctuations were monitored with CGMS, and calculations of Mean Amplitude of Glycemic Excursions (MAGE)
- "Glucose fluctuations during postprandial periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia"

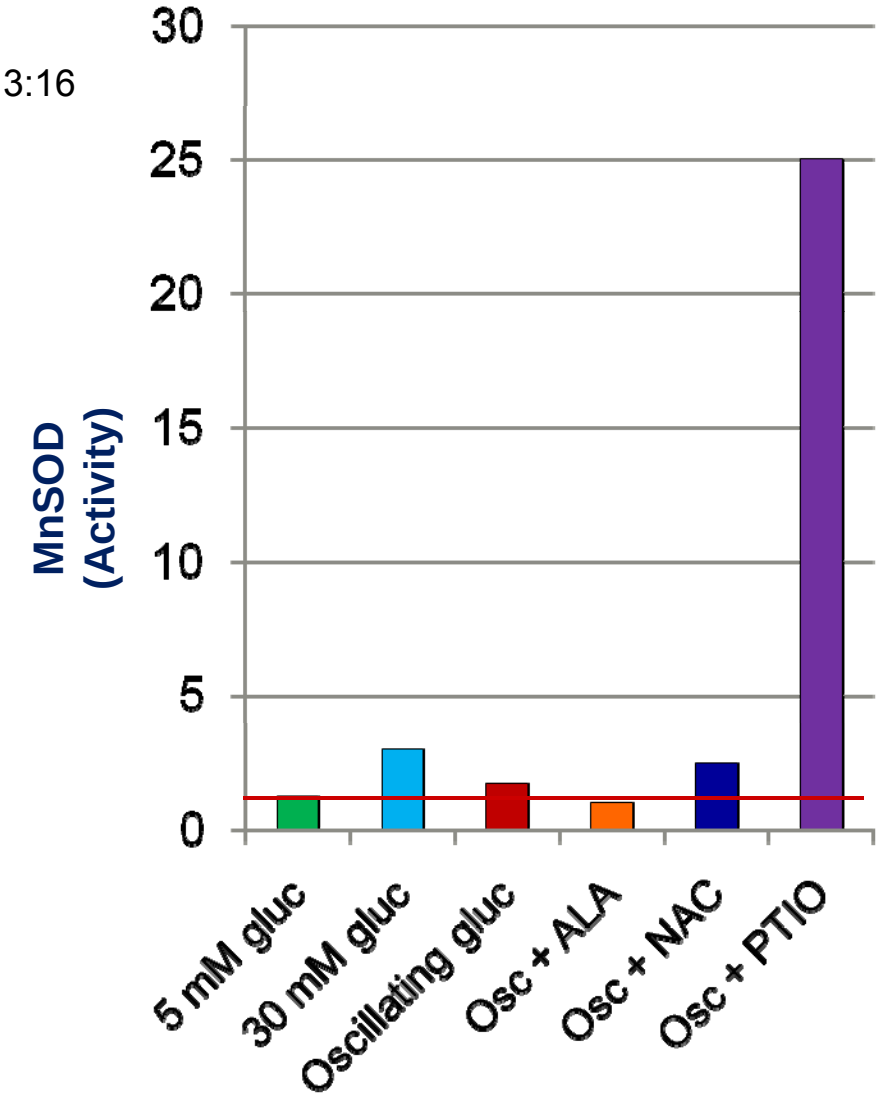
Monnier, et al JAMA 2006;295:1681

All this from transient glucose spikes after meals?

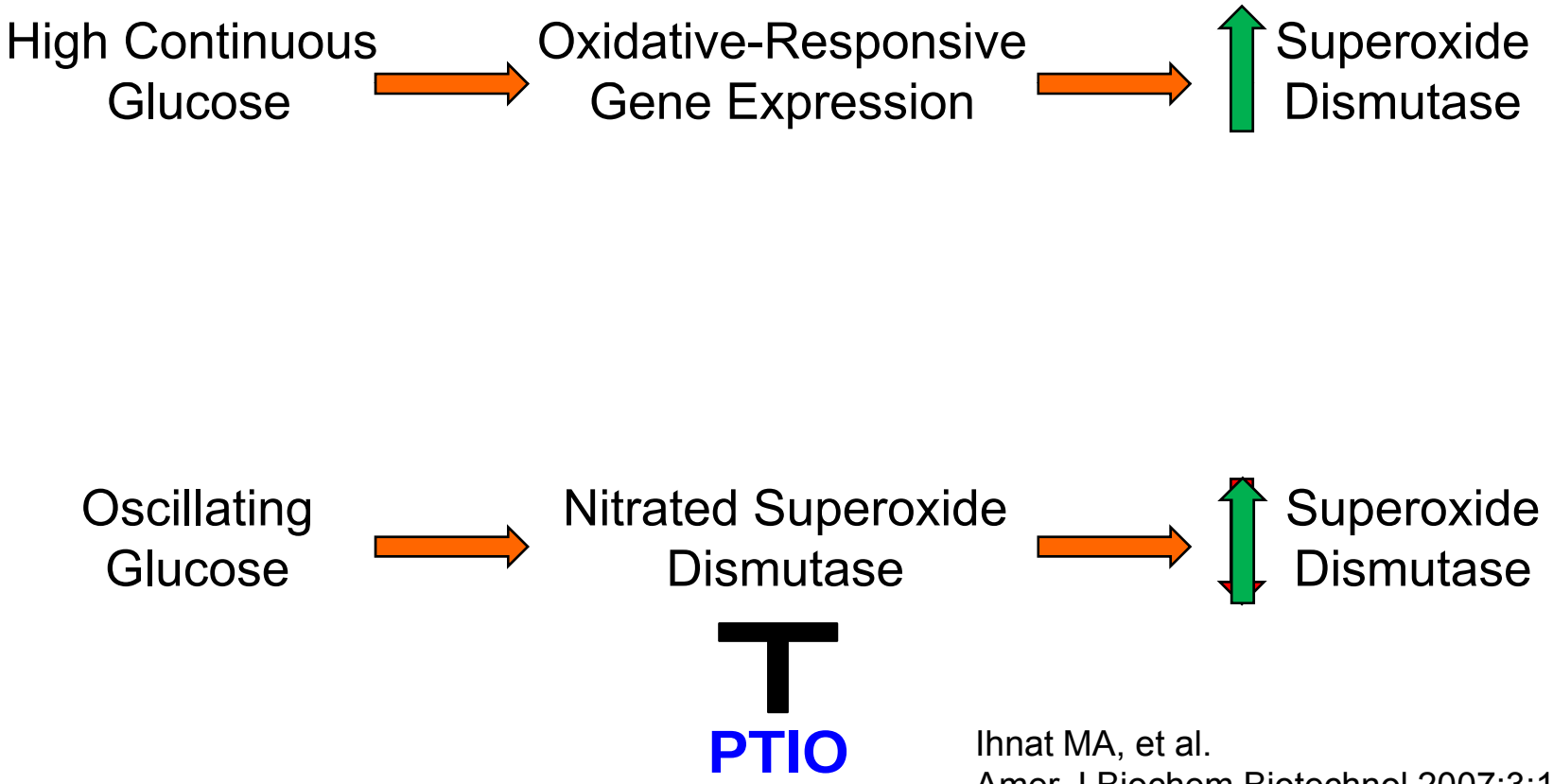
Nitrosative stress, oxidative stress and superoxide dismutase

Ihnat MA, et al. Amer J Biochem Biotechnol 2007;3:16





Differential effects of components of oxidative stress

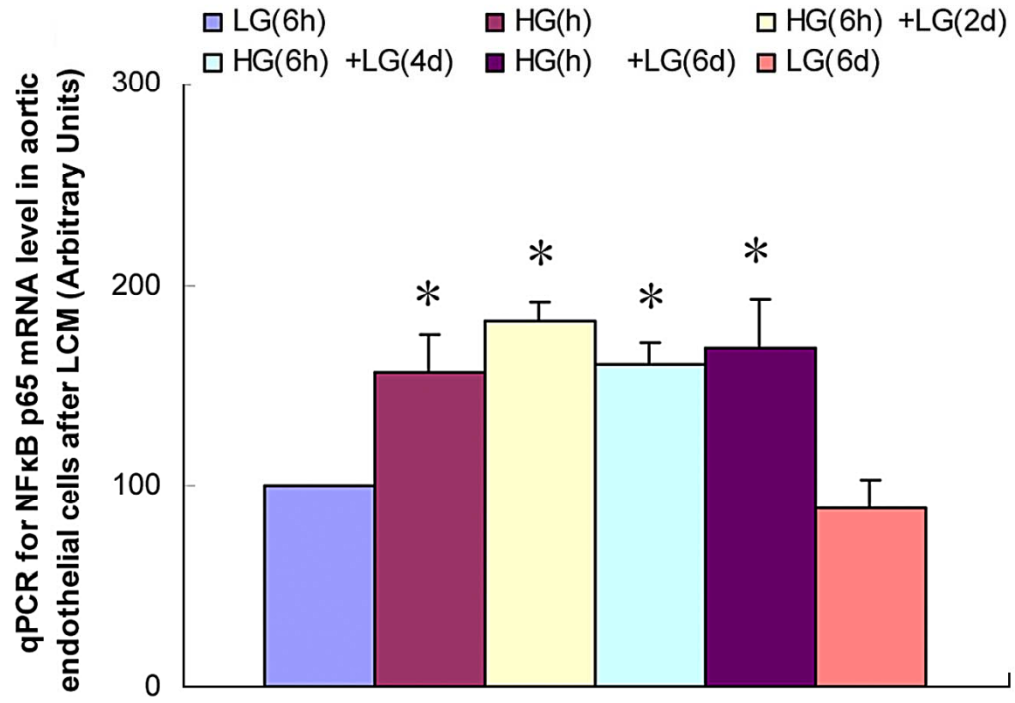


Ihnat MA, et al.
Amer J Biochem Biotechnol 2007;3:16

When is a spike not a spike?

Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia

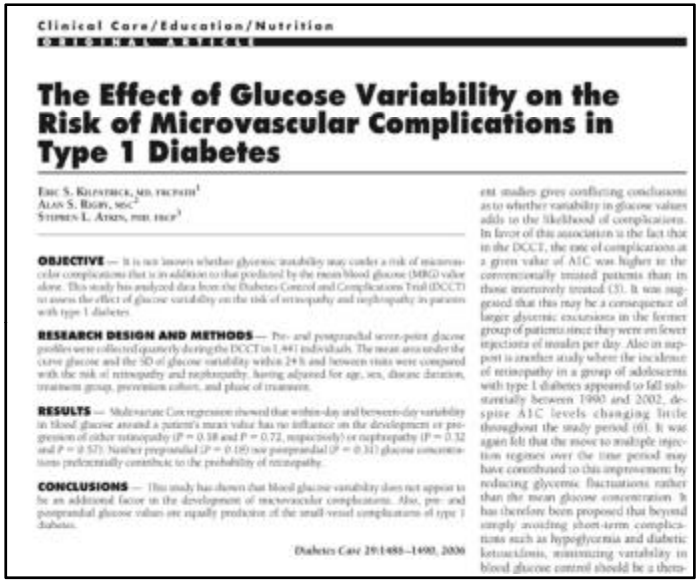
Assam El-Osta,[1] Daniella Brasacchio,[1] Dachun Yao,[3] Alessandro Pocai,[4] Peter L. Jones,[5] Robert G. Roeder,[6] Mark E. Cooper,[2,3] and Michael Brownlee[3]



"In summary, the observations reported here show that transient hyperglycemia causes persistent atherogenic effects during subsequent normoglycemia by inducing ***long-lasting changes*** in chromatin remodeling, recruitment of the histone methyltransferase Set7, and increased H3K4 monomethylation in the proximal NF-κB promoter, leading to increased expression of p65, MCP-1, and VCAM-1."

El-Osta A, et al.
J Experimental Med 2008;205:2409

Is there controversy about the importance of glycemic variability?



Clinical Care/Education/Nutrition

The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Eric S. Kilpatrick, MD, FRCPath[1]
Alan S. Rigby, MSc[2]
Stephen L. Atkin, PhD, FBPsS[3]

OBJECTIVE — It is not known whether glycemic instability may confer a risk of microvascular complications that is in addition to that predicted by the mean blood glucose (MBG) value alone. This study has analyzed data from the Diabetes Control and Complications Trial (DCCT) to assess the effect of glucose variability on the risk of retinopathy and nephropathy in patients with type 1 diabetes.

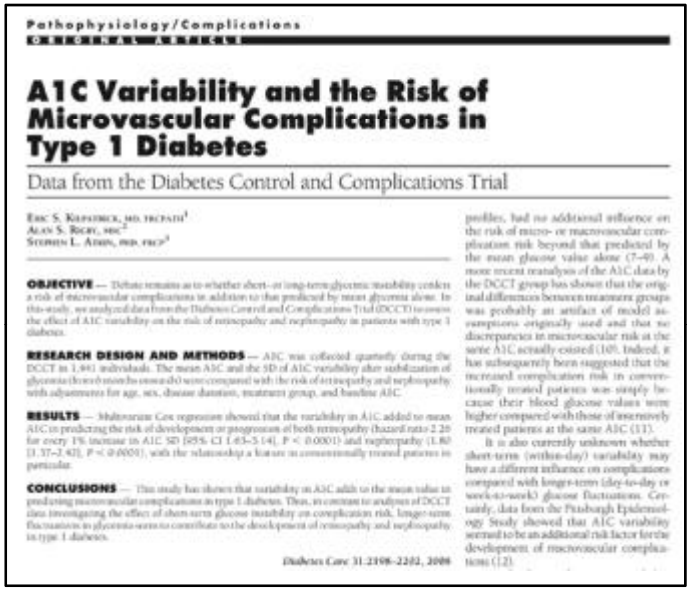
RESEARCH DESIGN AND METHODS — Pre- and postprandial seven-point glucose profiles were collected quarterly during the DCCT in 1,441 individuals. The mean area under the curve glucose and the SD of glucose variability within 24 h and between visits were compared with the risk of retinopathy and nephropathy, having adjusted for age, sex, disease duration, treatment group, prevention cohort, and phase of treatment.

RESULTS — Multivariate Cox regression showed that within-day and between-day variability in blood glucose around a patient's mean value has no influence on the development or progression of either retinopathy ($P = 0.38$ and $P = 0.72$, respectively) or nephropathy ($P = 0.32$ and $P = 0.57$). Neither preprandial ($P = 0.16$) nor postprandial ($P = 0.31$) glucose concentrations preferentially contribute to the probability of retinopathy.

CONCLUSIONS — This study has shown that blood glucose variability does not appear to be an additional factor in the development of microvascular complications. Also, pre- and postprandial glucose values are equally predictive of the small-vessel complications of type 1 diabetes.

Diabetes Care 29:1488–1490, 2006

ent studies gives conflicting conclusions as to whether variability in glucose values adds to the likelihood of complications. In favor of this association is the fact that in the DCCT, the rate of complications at a given value of A1C was higher in the conventionally treated patients than in those intensively treated (3). It was suggested that this may be a consequence of larger glycemic excursions in the former group of patients since they were on fewer injections of insulin per day. Also in support is another study where the incidence of retinopathy in a group of adolescents with type 1 diabetes appeared to fall substantially between 1990 and 2002, despite A1C levels changing little throughout the study period (6). It was again felt that the move to multiple injection regimes over the time period may have contributed to this improvement by reducing glycemic fluctuations rather than the mean glucose concentration. It has therefore been proposed that beyond simply avoiding short-term complications such as hypoglycemia and diabetic ketoacidosis, minimizing variability in blood glucose control should be a thera-



Pathophysiology/Complications

A1C Variability and the Risk of Microvascular Complications in Type 1 Diabetes

Data from the Diabetes Control and Complications Trial

Eric S. Kilpatrick, MD, FRCPath[1]
Alan S. Rigby, MSc[2]
Stephen L. Atkin, PhD, FBPsS[3]

OBJECTIVE — Debate remains as to whether short- or long-term glycemic instability confers a risk of microvascular complications in addition to that predicted by mean glycemia alone. In this study, we analyzed data from the Diabetes Control and Complications Trial (DCCT) to assess the effect of A1C variability on the risk of retinopathy and nephropathy in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A1C was collected quarterly during the DCCT in 1,441 individuals. The mean A1C and the SD of A1C variability after stabilization of glycemia (when values had stabilized) were compared with the risk of retinopathy and nephropathy, with adjustments for age, sex, disease duration, treatment group, and baseline A1C.

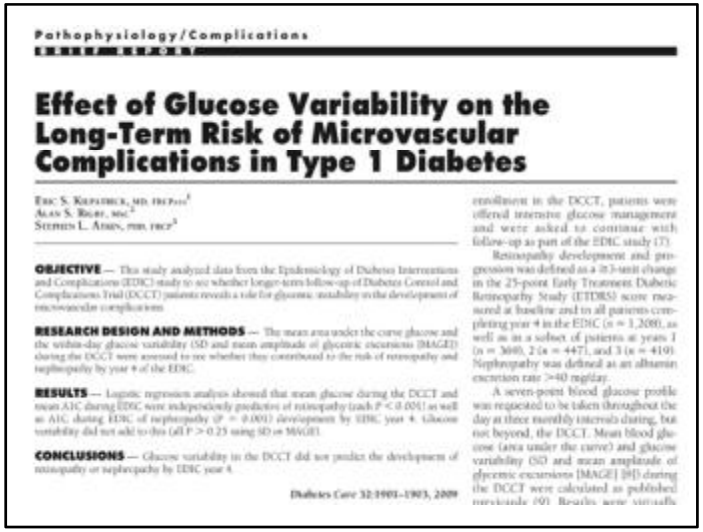
RESULTS — Multivariate Cox regression showed that the variability in A1C added to mean A1C in predicting the risk of development or progression of both retinopathy (hazard ratio 2.20 for every 1% increase in A1C SD [95% CI 1.63–3.14], $P < 0.0001$) and nephropathy (1.80 [1.37–2.42], $P < 0.0001$), with the relationship a feature in conventionally treated patients in particular.

CONCLUSIONS — This study has shown that variability in A1C adds to the mean value in predicting microvascular complications in type 1 diabetes. Thus, in contrast to analyses of DCCT data investigating the effect of short-term glucose instability on complication risk, longer-term fluctuations in glycemia seem to contribute to the development of retinopathy and nephropathy in type 1 diabetes.

Diabetes Care 31:2198–2202, 2008

profiles, had no additional influence on the risk of micro- or macrovascular complication risk beyond that predicted by the mean glucose value alone (7–9). A more recent reanalysis of the A1C data by the DCCT group has shown that the original differences between treatment groups was probably an artifact of model assumptions originally used and that no discrepancies in microvascular risk at the same A1C actually existed (10). Indeed, it has subsequently been suggested that the increased complication risk in conventionally treated patients was simply because their blood glucose values were higher compared with those of intensively treated patients at the same A1C (11).

It is also currently unknown whether short-term (within-day) variability may have a different influence on complications compared with longer-term (day-to-day or week-to-week) glucose fluctuations. Certainly, data from the Pittsburgh Epidemiology Study showed that A1C variability seemed to be an additional risk factor for the development of microvascular complications (12).



Pathophysiology/Complications

Effect of Glucose Variability on the Long-Term Risk of Microvascular Complications in Type 1 Diabetes

Eric S. Kilpatrick, MD, FRCPath[1]
Alan S. Rigby, MSc[2]
Stephen L. Atkin, PhD, FBPsS[3]

OBJECTIVE — This study analyzed data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study to see whether longer-term follow-up of Diabetes Control and Complications Trial (DCCT) patients reveals a role for glycemic instability in the development of microvascular complications.

RESEARCH DESIGN AND METHODS — The mean area under the curve glucose and the within-day glucose variability (SD and mean amplitude of glycemic excursions [MAGE]) during the DCCT were assessed to see whether they contributed to the risk of retinopathy and nephropathy by year 4 of the EDIC.

RESULTS — Logistic regression analysis showed that mean glucose during the DCCT and mean A1C during EDIC were independently predictive of retinopathy (each $P < 0.001$) as well as A1C during EDIC of nephropathy ($P = 0.001$) development by EDIC year 4. Glucose variability did not add to this (all $P > 0.25$ using SD or MAGE).

CONCLUSIONS — Glucose variability in the DCCT did not predict the development of retinopathy or nephropathy by EDIC year 4.

Diabetes Care 32:1901–1903, 2009

enrollment in the DCCT, patients were offered intensive glucose management and were asked to continue with follow-up as part of the EDIC study (7).

Retinopathy development and progression was defined as a ≥3-unit change in the 25-point Early Treatment Diabetic Retinopathy Study (ETDRS) score measured at baseline and to all patients completing year 4 in the EDIC ($n = 1,208$), as well as in a subset of patients at years 1 ($n = 360$), 2 ($n = 447$), and 3 ($n = 419$). Nephropathy was defined as an albumin excretion rate >40 mg/day.

A seven-point blood glucose profile was requested to be taken throughout the day at three monthly intervals during, but not beyond, the DCCT. Mean blood glucose (area under the curve) and glucose variability (SD and mean amplitude of glycemic excursions [MAGE] [8]) during the DCCT were calculated as published previously (9). Results were virtually

- Kilpatrick and others used DCCT 7-point profiles to assess glycemic variability.
- With that data, they have been unable to connect glycemic variability with outcomes
- They HAVE connected <u>A1C</u> variability with complications
- Other authors have connected glucose variability with A1C variability
- SOOoooo…what about the DCCT dataset?

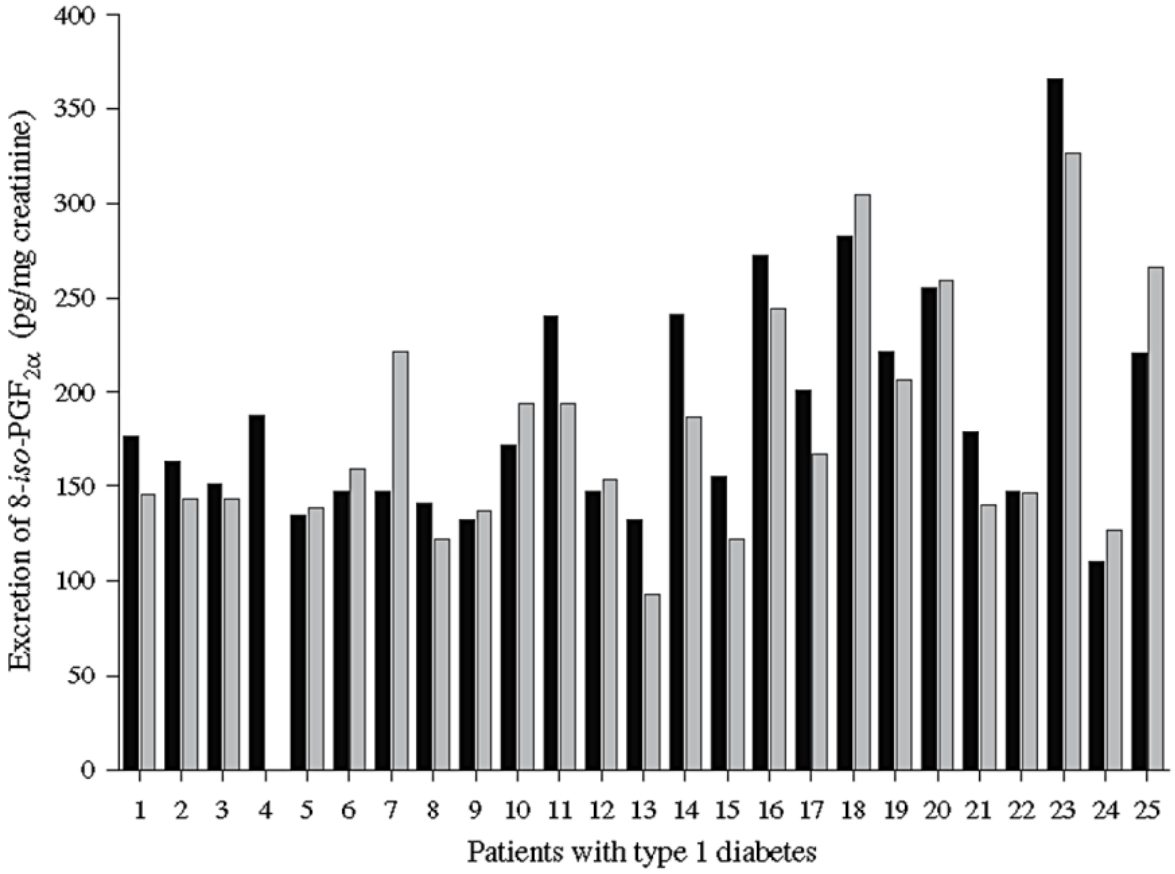
Variability and oxidative stress in T1DM

Diabetologia (2008) 51:183–190
DOI 10.1007/s00125-007-0842-6

ARTICLE

Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes

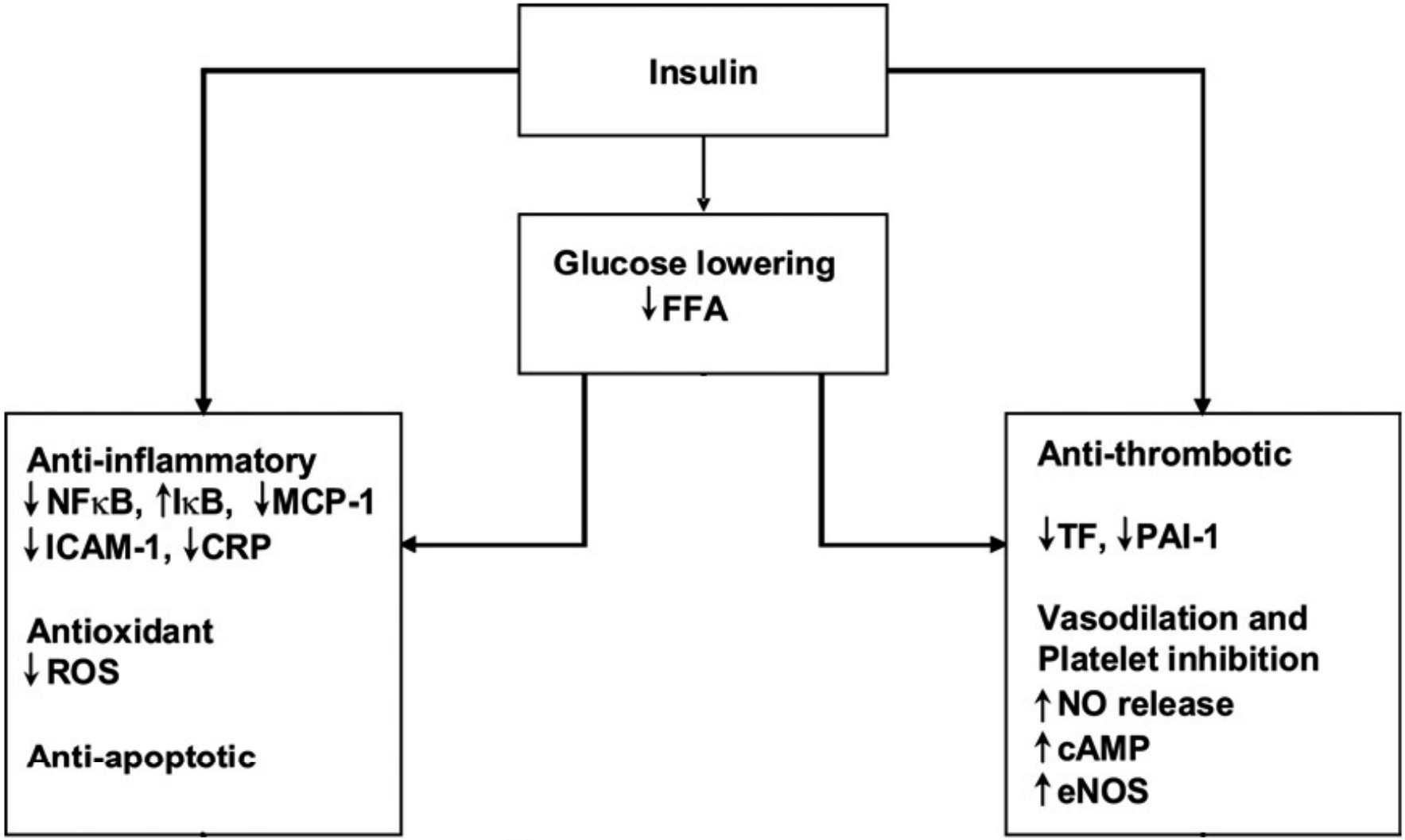
I. M. E. Wentholt · W. Kulik · R. P. J. Michels · J. B. L Hoekstra · J. H. DeVries



- Patients with type 1 diabetes have higher levels of urinary 15(S)-8-iso-PGF2α than healthy controls, suggesting that in addition to glucose variability, other factors favouring oxidative stress may exist
- There is no relationship between glucose variability and urinary 15(S)-8-iso-PGF2α.

Wentholt IME, et al. Diabetologia 2008;51:183

…but insulin is anti-inflammatory



Adapted from: Dandona P, et al Journal of the American College of Cardiology 2009;53:S14

What affects oxidative stress from glycemic variability?

Journal of Diabetes Science and Technology
Volume 5, Issue 1, January 2011

ORIGINAL ARTICLES

No Relevant Relationship between Glucose Variability and Oxidative Stress in Well-Regulated Type 2 Diabetes Patients

Sarah E. Siegelaar, M.D.,[1] Temo Barwari, B.Sc.,[1] Wim Kulik, Ph.D.,[2] Joost B. Hoekstra, M.D., Ph.D.,[1] and J. Hans DeVries, M.D., Ph.D.[1]

"We did not find a relevant relationship between glucose variability and 15(*S*)-8-iso-PGF2α excretions in T2DM patients well-regulated with oral medication that would support an interaction between hyperglycemia and glucose variability with respect to the formation of reactive oxygen species."

Table 1.
Baseline Characteristics

Characteristics[a]	Patients (n = 24)
Age (year)	58.9 (36–76)
Men/women (n)	16/8
Diabetes duration (year)	7.2 (4.2)
Diabetes treatment [n (%)]	
Metformin	23 (96)
Sulfonylurea	15 (63)
Rosiglitazone	2 (8)
Other treatments [n (%)]	
ACE inhibitor	9 (38)
Statin	19 (79)
Aspirin	7 (29)
Cigarette smoking [n (%)]	2 (8)
BMI, kg/m^2	30.5 (5.5)
Systolic blood pressure (mm Hg)	135 (17)
Diastolic blood pressure (mm Hg)	82 (10)
Plasma creatinine (μmol/liter)	76.3 (13.1)
Total cholesterol (mmol/liter)	4.18 (0.80)
HDL cholesterol (mmol/liter)	1.10 (0.20)
LDL cholesterol (mmol/liter)	2.31 (0.71)
Triglycerides (mmol/liter)	1.71 (0.72)
HbA1c (%)	6.9 (0.7)
FPG (mg/dl)	144 (32)
Mean sensor glucose (mg/dl)	146 (27)
AUCpp[b] (mg/dl/h)	129 (54)
Markers of glucose variability [median (IQR)]	
SD (mg/dl)	31 (23–40)
MAGE (mg/dl)	85 (56–106)
Urinary 15(*S*)-8-iso-PGF$_{2\alpha}$, pg/mg creatinine [median (IQR)]	176.1 (113.6–235.8)

[a] Data are means (SD) or means (range), unless stated otherwise in parentheses. To convert mean glucose, AUCpp, MAGE, and SD from mg/dl to mmol/liter, multiply by 0.0555.
[b] AUCpp is the 4-hour postprandial incremental area under the curve.

Are superoxides the only problem?

Relationship between glucose variability and hypoglycemia

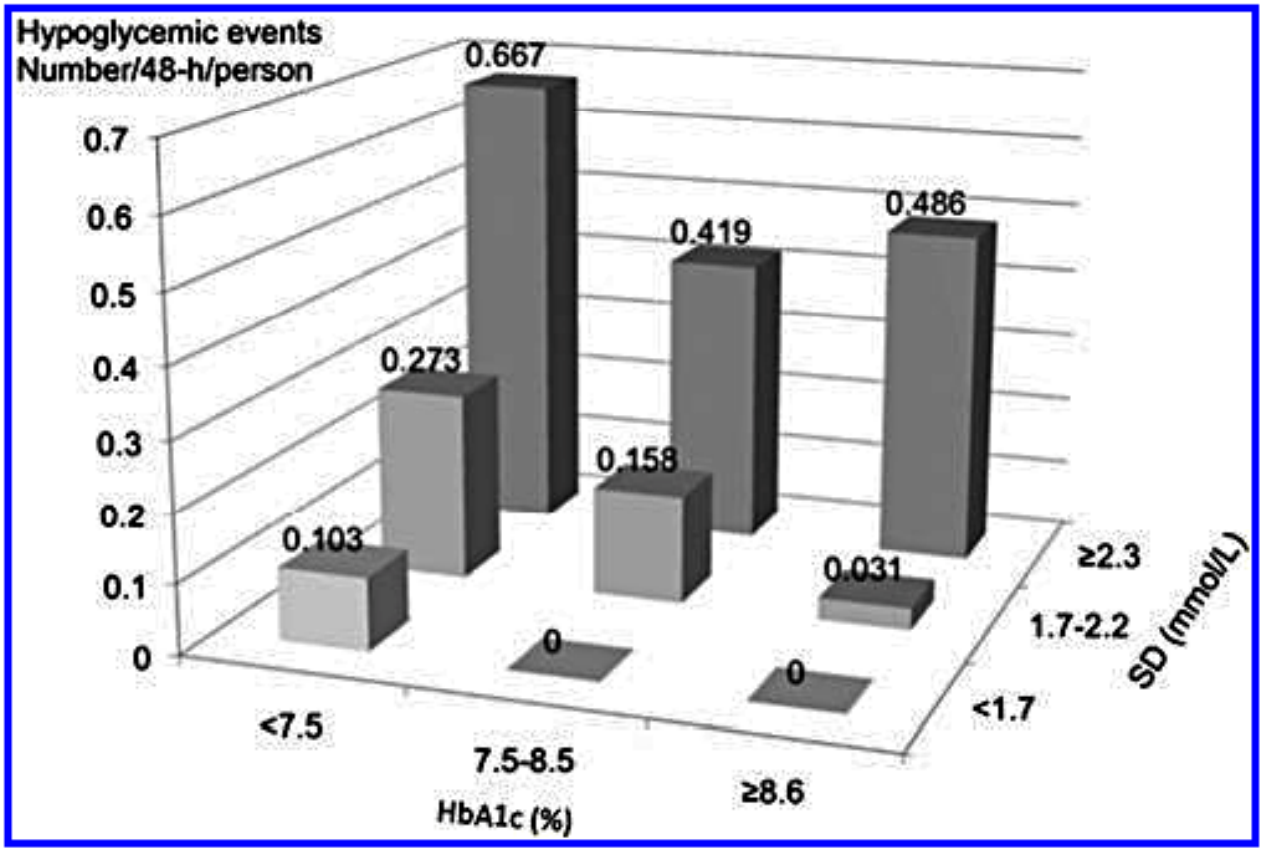


FIG. 2. Number of hypoglycemic events as a function of tertiles of hemoglobin A1c (HbA1c) and tertiles of glycemic variability (SD around the mean glucose concentration).

Monnier L, et al Diabetes Technology & Therapeutics 2011;13:813

Take Home Messages

- Chronic elevations of glucose produce toxicity to major end organs; oxidative stress and superoxides are major components of glucotoxicity
- Glucose excursions may be significant in glucose toxicity as their effects last longer than the excursion
- Lowering variability should be a therapeutic goal
- What we still don't know:
  - Is it the degree or the frequency of elevations that makes a difference?
  - What is the best variability index?
  - How much weight should variability be given vs. A1C (or in combination)?
  - If we are trying to control variability, what does success look like?

U-500: Appropriate Use and Common Pitfalls

Jessica Tompeter, Pharm.D.

Conflicts of Interest

American College of Clinical Pharmacy

No conflict of interest to declare

Objectives

American College of Clinical Pharmacy

- Recognize the role of U-500 insulin in the treatment of severe insulin resistance.
- Summarize a dosing scheme for initiation and titration of U-500 insulin.
- Evaluate the safety and educational barriers associated with initiating U-500 insulin and discuss potential solutions.

U-500 insulin

American College of Clinical Pharmacy

- "Concentrated"

PK profile	Nonobese subjects[1] (n=3)	Obese subjects[2] (n=2)
Onset of action	30 minutes	45 minutes
Peak PD action	3.5-4.5 hours	7-8.5 hours
Duration of action	6-10+ hours	11.5 hours

Use of U-500 insulin

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- Reserved for[3]:
  - Insulin receptor defects
  - Insulin receptor autoantibodies
  - Endocrine disorders associated with insulin resistance
  - Severe insulin resistance
    - >200 units of insulin daily

Efficacy of U-500 insulin[3-6]

American College of Clinical Pharmacy

- Based on case series
- A1C reduction ~1.6%
  - Some case reports reduction >2%

- Benefits:
  - Decreased volume
  - Cost effective

Safety Issues and Solutions[3-8]

American College of Clinical Pharmacy

Dosing	Administration	Dispensing	Hypoglycemia	Transitions of Care
Clear prescribing	Tuberculin syringes	Storage	Education	U-500 Specific Protocol
Education	Clear instructions	Clarification of orders	Blood Glucose Monitoring	

Dosing: Initiation U-500 insulin[3]

American College of Clinical Pharmacy

Total Daily Dose 150-300 units

- Before breakfast and dinner 50/50 or 60/40
- Before meals 33/33/33

Total Daily Dose 300-600 units

- Before meals 33/33/33
- Before meals and bedtime 30/30/30/10

Total Daily Dose > 600 units

- Four times daily 30/30/30/10

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1. Khan M, Lee YY. The pharmacokinetic and pharmacodynamic properties of regular U-500 insulin in healthy subjects. Diabetes. 2007; 56 (suppl):1294-P Abstract.
2. Khan MI, Sarabu B. The pharmacokinetic and pharmacodynamic properties of regular U-500 insulin in healthy obese subjects. Diabetes. 2009; 58(suppl):2333-PO. Abstract
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6. Neal JM. Analysis of effectiveness of human U-500 insulin in patients unresponsive to conventional insulin therapy. Endocr Pract. 2005;11:305-7.
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8. Samaan KH, Dahlke M, Stover J. Addressing safety concerns about U-500 insulin in a hospital setting. Am J Health-Syst Pharm. 2011; 68:63-8.

CLINICAL DEBATE:
ADA ALGORITHM VERSUS AACE ALGORITHM FOR TYPE 2 DIABETES MELLITUS

TRICIA M. RUSSELL, PHARM.D., BCPS, CDE
CRAIG LOGEMANN, PHARM.D., BCPS, CDE

MONDAY, OCTOBER 17, 2011
CONVENTION CENTER, ROOMS 315 & 316

ADA Pro

Tricia M. Russell, PharmD, BCPS, CDE
Assistant Professor, Department of Pharmacy Practice
Ambulatory Care
Wilkes University, Nesbitt College of Pharmacy & Nursing
Wilkes-Barre, Pennsylvania

Conflict of Interest Disclosure

American College of Clinical Pharmacy

- Dr. Russell has no conflicts of interest to disclose.

Objectives

American College of Clinical Pharmacy

- Review the advantages of recommending an A1c goal of <7% for the management of type 2 diabetes according to the ADA treatment algorithm.
- Identify any concerns with the AACE treatment algorithm glycemic goal of A1c of ≤6.5%.
- Discuss the benefits of initiating metformin as a preferred treatment early in the management of type 2 diabetes.

Background

- American Diabetes Association (ADA) Diabetes Guidelines
  - Clinical Practice Recommendations – Jan 2011 (annually)
  - Consensus Algorithm on Medical Management of Type 2 DM: (ADA/European Association for the Study of Diabetes [EASD]) – Jan 2009
    - 7 authors (clinicians and clinical investigators)

American Diabetes Association: Standards of medical care. *Diabetes Care.* 2011;34(1):S11-61.; American Diabetes Association and the European Association for the Study of Diabetes. Consensus algorithm on medical management of type 2 diabetes. *Diabetes Care.* 2009;32:193-203.

Treatment Goals

	ADA	AACE
A1c (%)	<7	≤6.5
Fasting plasma glucose (mg/dL)	70-130	<110
Postprandial plasma glucose* (PPG in mg/dL)	<180	<140
LDL cholesterol (mg/dL)	<100 (<70 if CHD)	≤70 highest risk#; <100 high risk#
HDL cholesterol (mg/dL)	>40 for men >50 for women	>40 for men >50 for women
Triglycerides (mg/dL)	<150	<150

*PPG glucose measurements should be made 1-2 h after beginning meal.
#Highest risk = DM plus CVD and high risk = DM without CVD.

ADA: Standards of medical care. *Diabetes Care.* 2011;34(1):S11-61.; American Association of Clinical Endocrinologists medical guidelines for DM. *Endocr Pract* 2011;17(2);287-302.

ADA: Current Glycemic Recommendations

American College of Clinical Pharmacy

Table 10—*Summary of glycemic recommendations for many nonpregnant adults with diabetes*

A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dl* (3.9–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl* (<10.0 mmol/l)
• Goals should be individualized based on*:	
• duration of diabetes	
• age/life expectancy	
• comorbid conditions	
• known CVD or advanced microvascular complications	
• hypoglycemia unawareness	
• individual patient considerations	
• More or less stringent glycemic goals may be appropriate for individual patients.	
• Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals.	

ADA: Standards of medical care. *Diabetes Care.* 2011;34(1):S11-61.

AACE/ACE Current Glycemic Recommendations

- A1c ≤6.5% is treatment goal

  - Individualize on basis of age, comorbidities, duration of diabetes; in general ≤6.5 for most; closer to normal for healthy; less stringent for "less healthy"

American Association of Clinical Endocrinologists Medical guidelines for DM. *Endocr Pract* 2011;17(2);287-302.

Glycemic Control: Reviewing Known Evidence

American College of Clinical Pharmacy

DCCT
(Type 1 DM)

Kumamoto Study
(Type 2 DM)

UK Prospective Diabetes Study (UKPDS)
(Type 2 DM)

"Improved glycemic control…decreases microvascular complications."

ADA : Standards of medical Standards of care. *Diabetes Care.* 2011;34(1):S11-61.

ADA DM Treatment Algorithm

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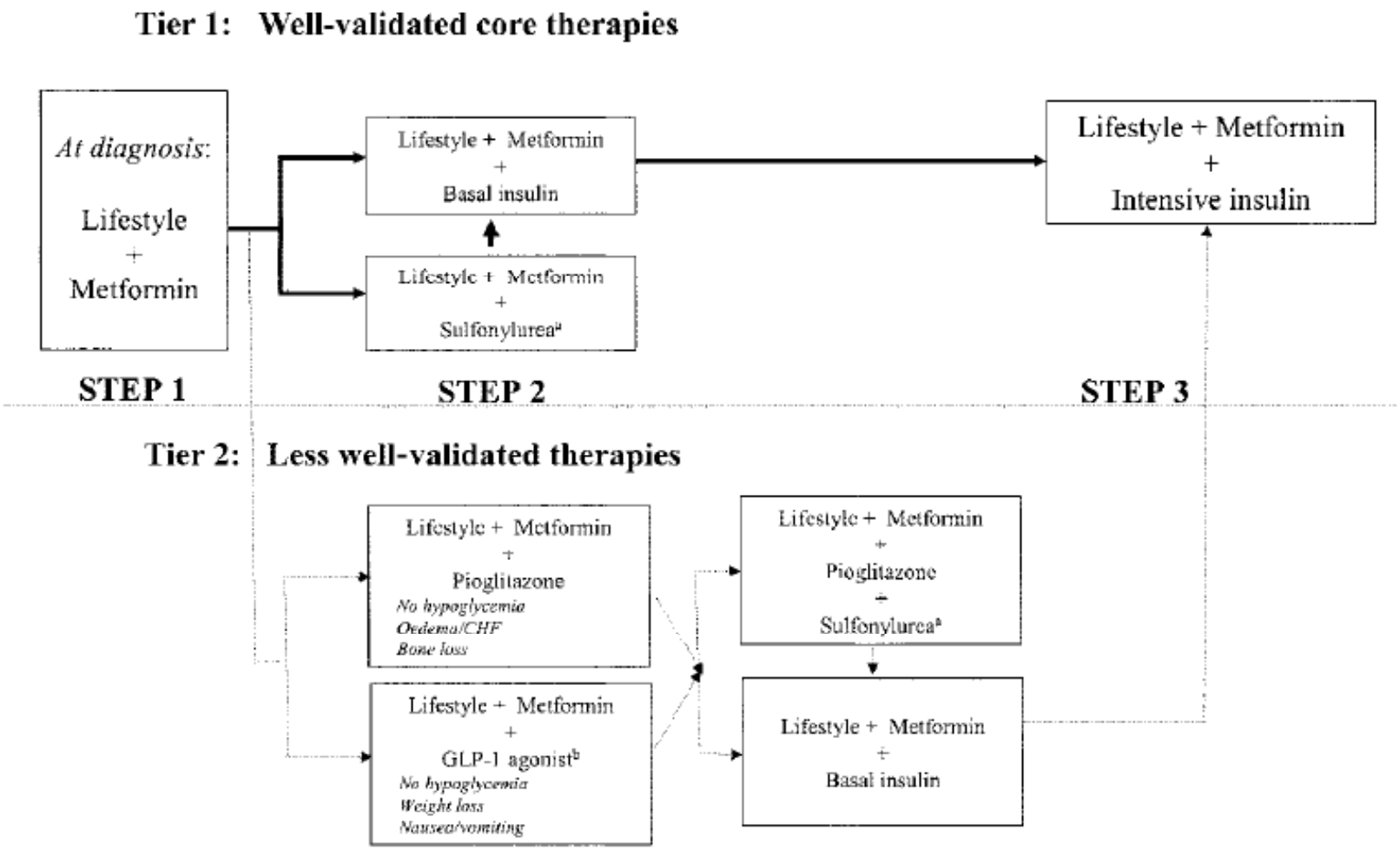


ADA and the EASD. Consensus algorithm on medical management of type 2 diabetes. *Diabetes Care*. 2009;32:193-203.

Intensive Glucose Lowering-Cardiovascular Outcomes ACCORD: Long-Term Follow-up

- Randomized, Open-Label, Controlled, Intention to Treat Study

- 10,251 patients with diabetes (mean A1c: 8.1%) received:
  - Intensive Therapy: Target A1c: <6.0% (N=5128)
  - Standard Therapy: Target A1c: 7.0-7.9%(N=5123)

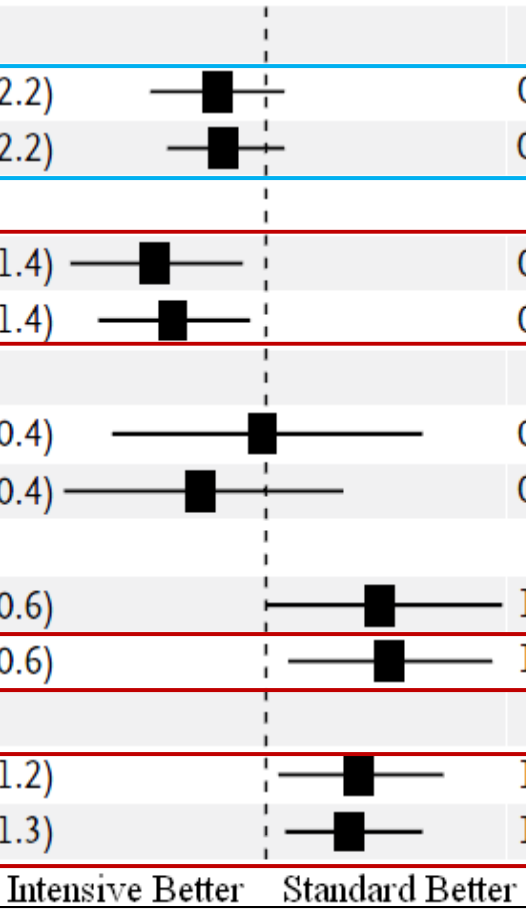
- Outcomes Measured – Five Years
  - Primary: Composite of Nonfatal MI, Nonfatal Stroke, or Death from CV Causes
  - Secondary: All-Cause Mortality

Gerstein HC, et.al. *N Engl J Med* 2011;364:818-28.

Intensive Glucose Lowering-Cardiovascular Outcomes ACCORD Study Update

American College of Clinical Pharmacy

Outcome	Intensive	Standard	Hazard Ratio (95% CI)	P Value
	no. of events (%)			
Primary outcome				
Before transition	380 (2.0)	414 (2.2)	0.90 (0.78–1.03)	0.13
Until end of study	503 (2.1)	543 (2.2)	0.91 (0.81–1.03)	0.12
Nonfatal myocardial infarction				
Before transition	207 (1.1)	257 (1.4)	0.79 (0.66–0.95)	0.01
Until end of study	287 (1.2)	344 (1.4)	0.82 (0.70–0.96)	0.01
Nonfatal stroke				
Before transition	72 (0.4)	72 (0.4)	0.99 (0.72–1.38)	0.98
Until end of study	82 (0.3)	94 (0.4)	0.87 (0.65–1.17)	0.35
Death from cardiovascular causes				
Before transition	140 (0.7)	109 (0.6)	1.27 (0.99–1.63)	0.07
Until end of study	187 (0.7)	144 (0.6)	1.29 (1.04–1.60)	0.02
Death from any cause				
Before transition	283 (1.4)	232 (1.2)	1.21 (1.02–1.44)	0.03
Until end of study	391 (1.5)	327 (1.3)	1.19 (1.03–1.38)	0.02



Gerstein HC, et.al. N Engl J Med. 2011;364:818-28.

Concerns with AACE Treatment Algorithm A1c goal ≤6.5%

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- Insufficient evidence of CV and mortality benefit with intensive glycemic control compared to standard glycemic control.
- Increased risk of hypoglycemia with intensive glycemic lowering compared to standard glycemic lowering.

Severe Hypoglycemia Rates in Recent Trials

American College of Clinical Pharmacy

ACCORD- annual incidence of hypoglycemia:

3.14% intensive treatment group

1.03% standard glycemia group

	ACCORD (%)	ADVANCE	VADT
Intensive glycemic control arm	16.2 %	2.7%	21.2%
Standard glycemic control arm	5.1%	1.5%	9.9%

BMJ 2009;339:b5444doi:10.1136/bmj.b5444; Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes trials. Diabetes Care. 2009;32(1):187-19.

Benefits of Initiating Metformin Early

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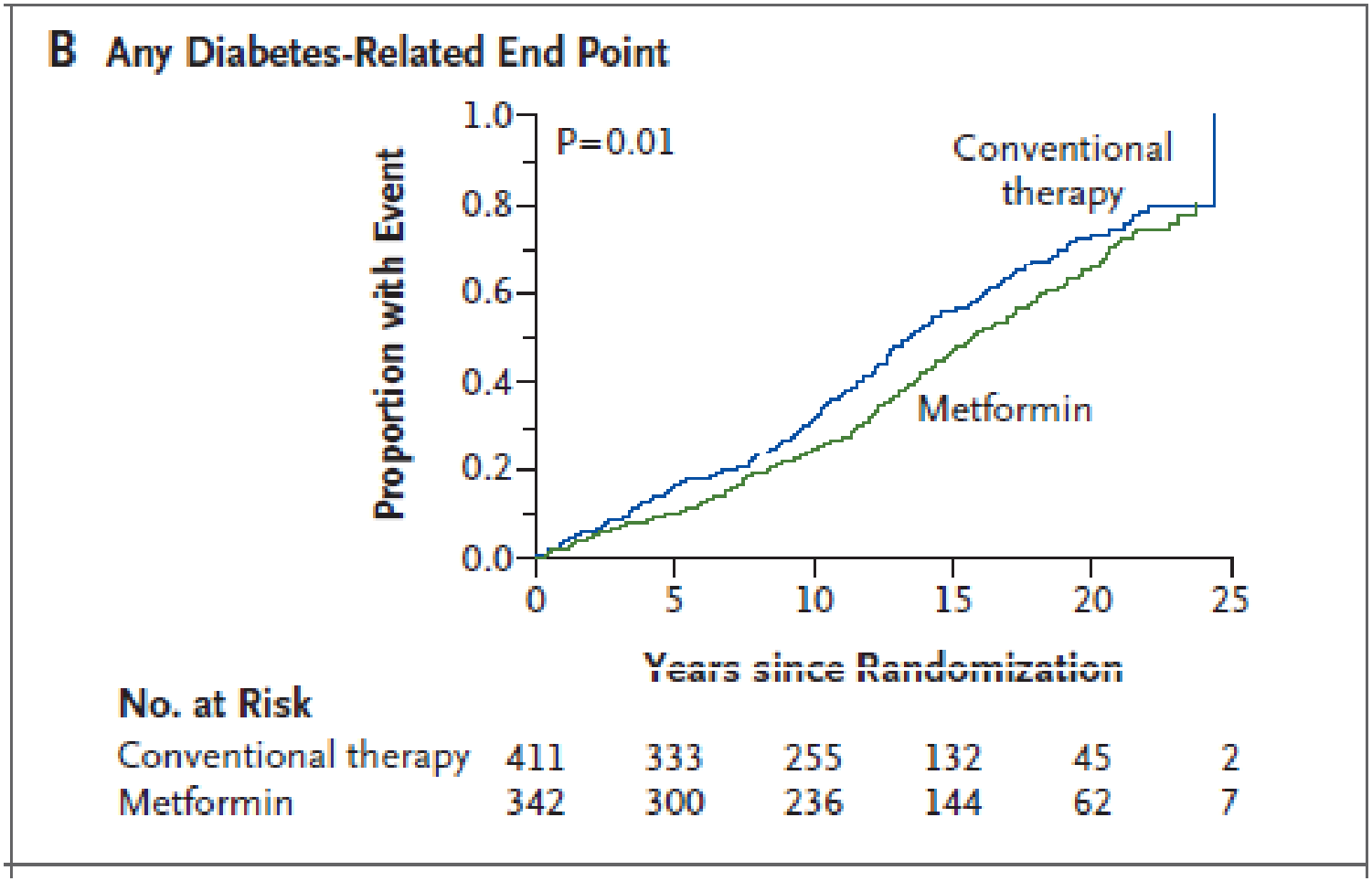
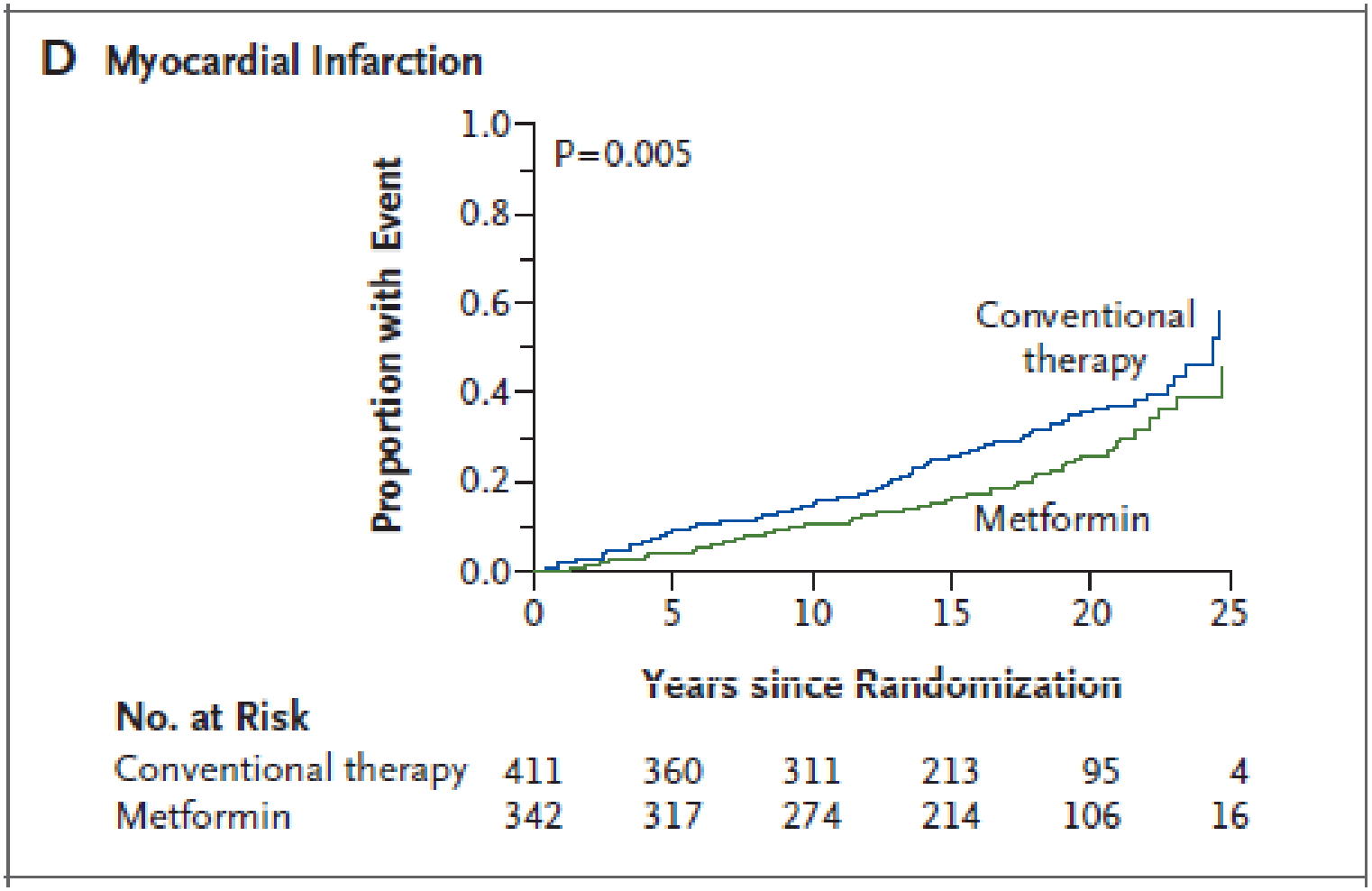
- Treats insulin resistance
- Evidence
  - UKPDS 43
  - 10-year follow-up study (UKPDS 80)
    - Significant risk reduction continued for diabetes-related endpoint (21%), MI (33%), and mortality (27%)
  - REACH
    - Mortality rates: 6.3% metformin vs. 9.3% without metformin
- Tolerable
- Inexpensive

UKPDS 10-yr Follow-up
Any Diabetes-Related End Point



Holman RR, et al. *N Engl J Med* 2008;359:1577-89.

UKPDS 10-yr Follow-up Myocardial Infarction



Holman RR, et al. *N Engl J Med* 2008;359:1577-89.

UKPDS 10-yr follow-up
Death from Any Cause

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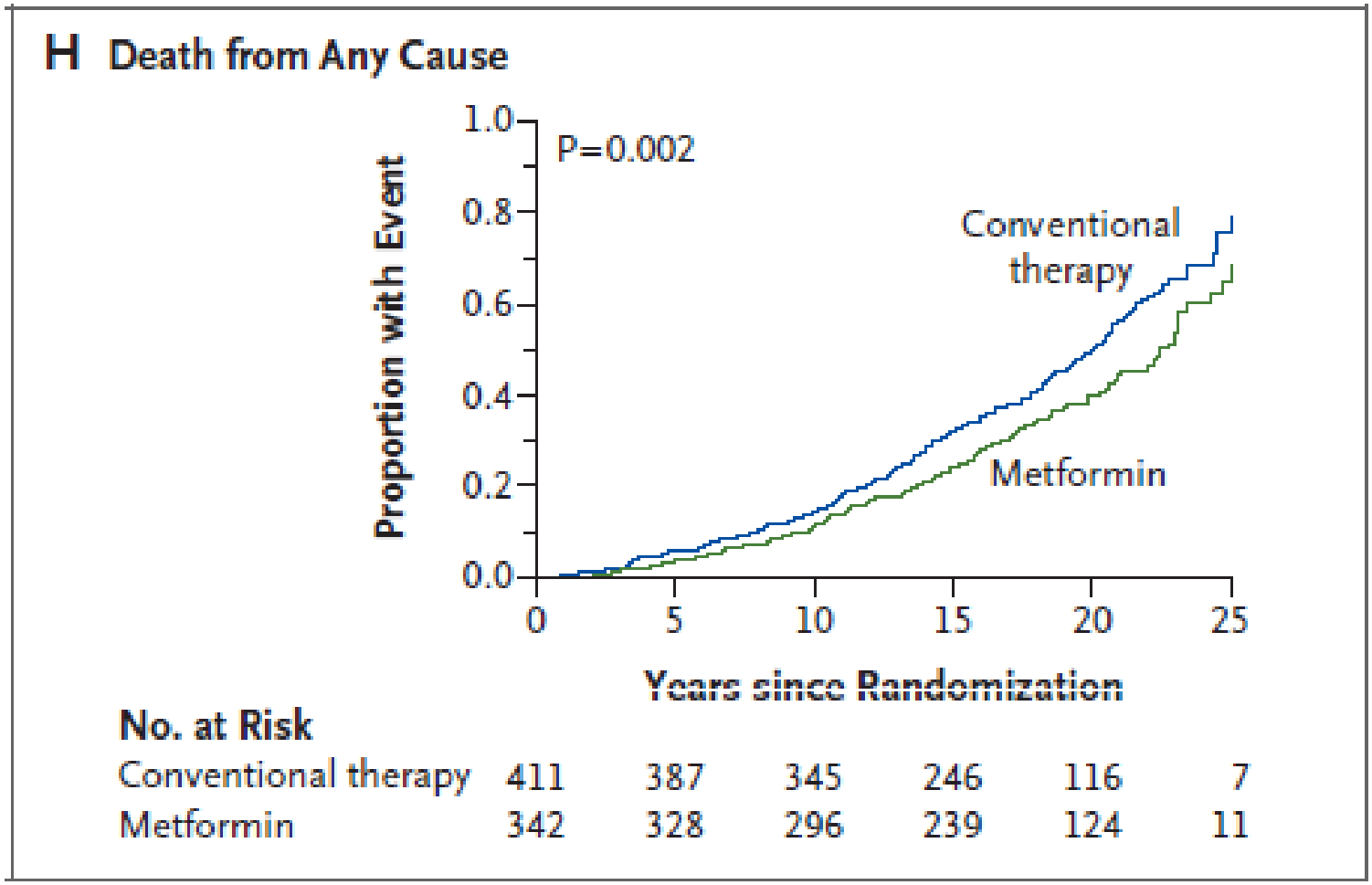
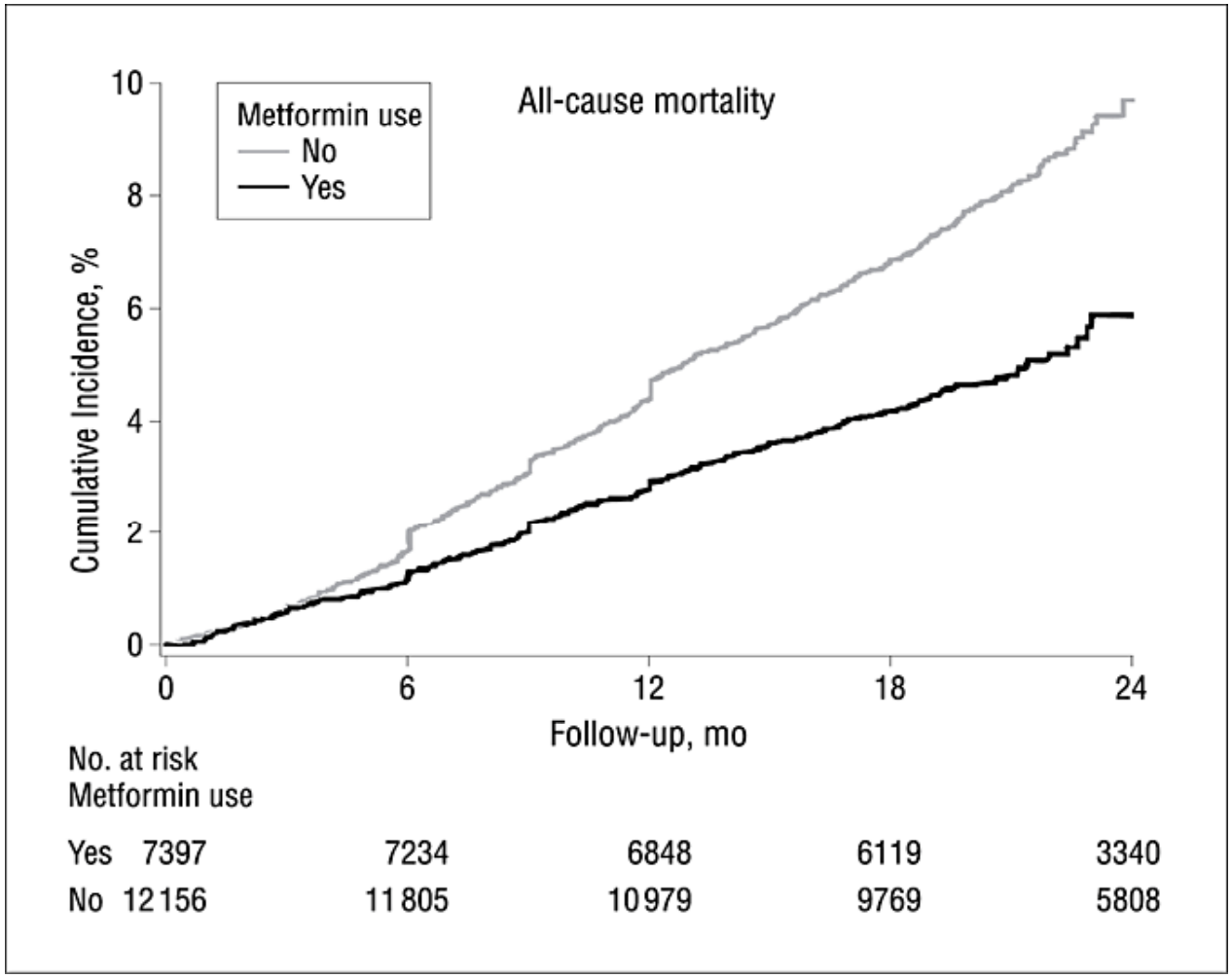


Holman RR, et al. *N Engl J Med* 2008;359:1577-89.

Event Curves for All-cause Mortality From Enrollment to 2 years by Metformin Use as Recorded at Baseline – REACH Study



Roussel, R. et al. *Arch Intern Med* 2010;170:1892-1899.

ADA Treatment Algorithm Pros - Conclusions

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- ADA treatment algorithm is evidence-based and practical.
- A1c goal <7% appropriate in majority of patients based on current evidence.
- Metformin preferred starting therapy for patients –effective, safe and inexpensive compared to other therapies.
- ADA algorithm provides rapid titration and addition of other therapies if needed.

AACE Pro

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Conflict of Interest Disclosure

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- Dr. Logemann has no conflicts of interest to disclose.

Objectives

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- Review the advantages of recommending an A1c goal of ≤6.5% for the management of type 2 diabetes according to the AACE treatment algorithm.
- Identify any concerns with the ADA treatment algorithm glycemic goal of A1c of <7%.
- Discuss the benefits of initiating other medications besides metformin as monotherapy options, such as thiazolidinediones, DPP-4 inhibitors, incretin mimetics or alpha-glucosidase inhibitors.

Background

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Statement by an American Association of Clinical Endocrinologists / American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus:

An Algorithm for Glycemic Control

- Published in Endocrine Practice 2009; Vol 15(6):541-9.
  - 12 Authors (clinicians and clinical investigators, both academicians and practitioners)

Rodbard HW, Jellinger PS, et al. Endocrine Practice 2009; Vol 15(6):541-9.

Things that are in common with the ADA Guidelines

- Lifestyle modification important
- A1c target should be customizable based on other patient factors
- Metformin considered cornerstone of therapy
- Choose agents with different mechanism of action when adding therapy

Things that are different from the ADA Guidelines

- A1c goal (for most patients):
  - AACE < 6.5
  - ADA < 7.0
- Initial therapy:
  - AACE: More choices listed (Metformin, TZD, DPP-4 inhibitors, incretin mimetics & alpha-glucosidase inhibitors)
  - ADA: Metformin listed as primary choice
- A1c stratification:
  - AACE: categorizes treatment choices based on initial A1c (6.5-7.5%, 7.6-9.0%, >9.0%)
  - ADA: No specific breakdown for treatment choices, unless initial A1c>10% (severe hyperglycemia)
- Sulfonylurea use:
  - AACE: Lower priority given to this class when dual or triple therapy warranted
  - ADA: Considered a "well-validated" core therapy as an add-on medication

AACE/ACE Algorithm (Simplified)

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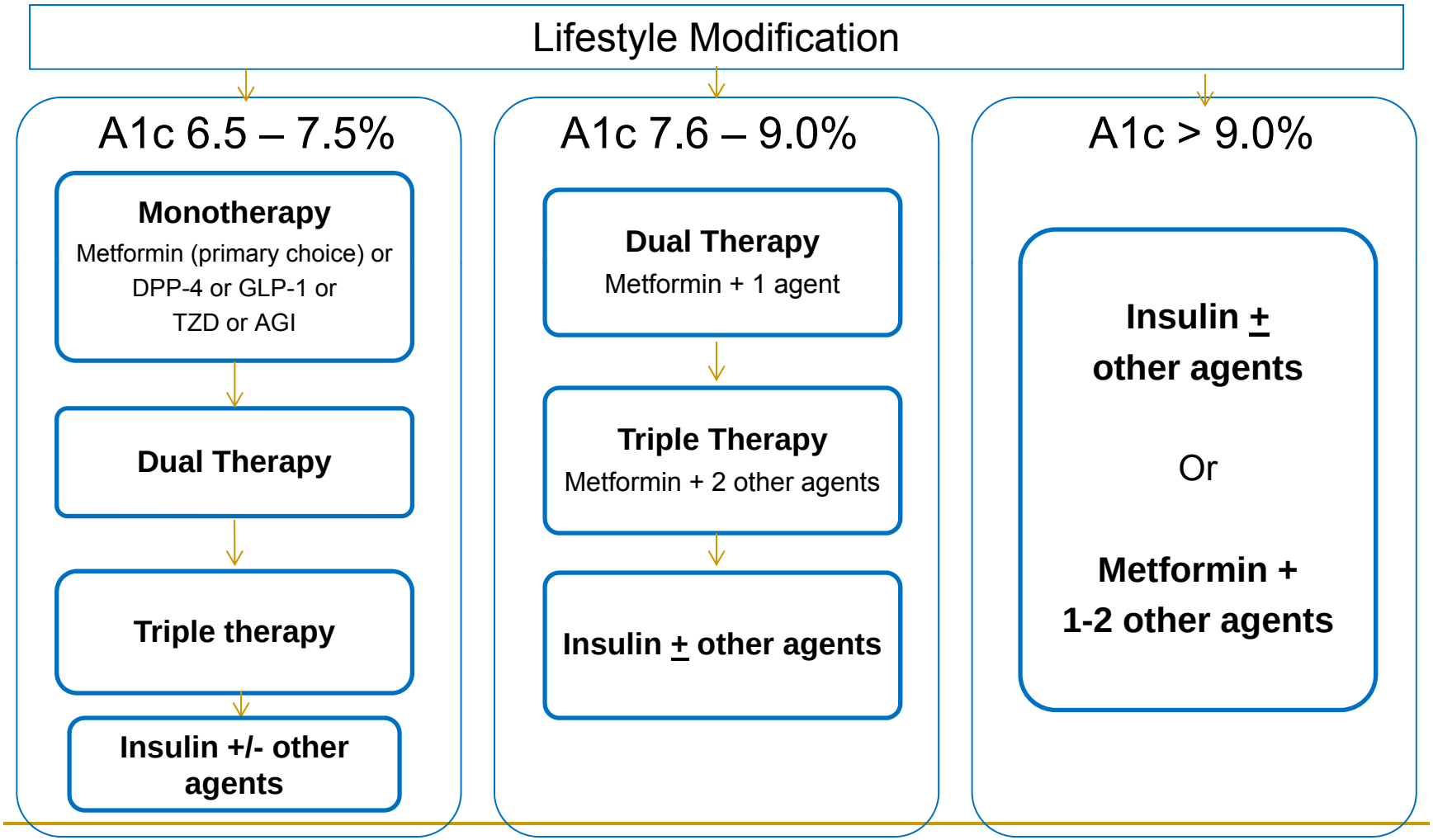
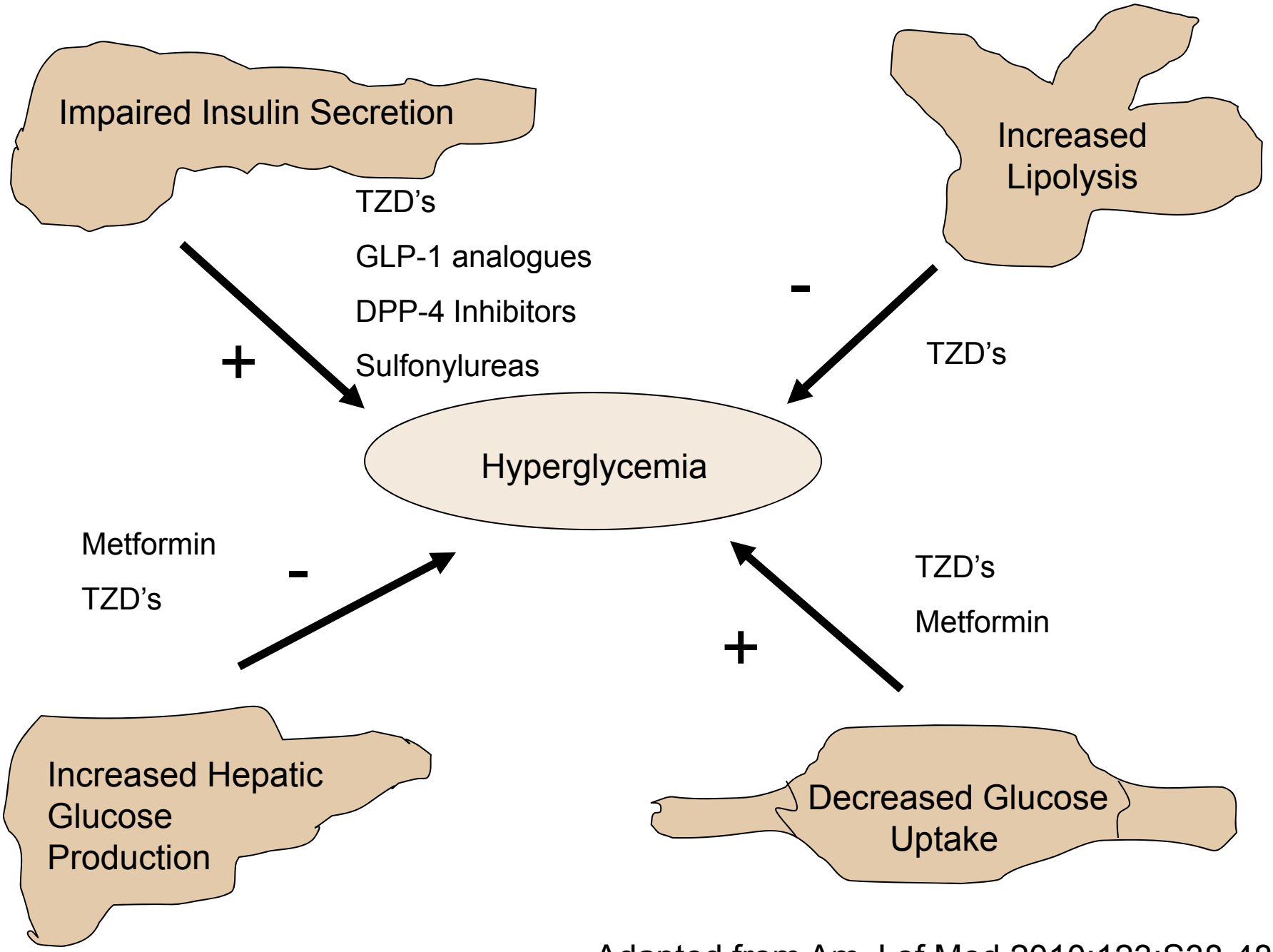


AACE/ACE Algorithm. *Endocrine Practice* 2009;15(6):541-9.

AACE: Why more initial choices for monotherapy?

- Metformin is considered the preferred initial agent by AACE
- Other options listed in the guidelines:
  - DPP-4: if ↑PPG and ↑ FPG
  - GLP-1: if ↑ ↑ PPG
  - TZD: if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
  - AGI: if ↑PPG



Adapted from Am J of Med 2010;123:S38-48.

AACE: Why more initial choices for monotherapy?

- DPP-4 Inhibitors: Good safety profile; low risk of hypoglycemia; no weight gain
- GLP-1 Analogues: Added benefit of wt loss to assist with other metabolic disorders; sustained glycemic control
- TZDs: Low risk of hypoglycemia; sustained glycemic control; efficacy with prediabetes
- α - Glucosidase inhibitors (Acarbose & Miglitol): Decrease post-prandial hyperglycemia

AACE: Why A1c goal < 6.5 for majority of patients ?

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- Meta-Analysis of 5 trials (n=33,040)
  - UKPDS, PROactive, ADVANCE, VADT, ACCORD
    - Intensive Treatment vs. Standard Treatment
      - Mean A1c at follow-up (6.6% vs. 7.5%)
      - 17% reduction in non-fatal MI
        - (odds ratio 0.83, 95% CI 0.75-0.93)
      - 15% reduction in CAD events
        - (odds ratio 0.85, 95% CI 0.77-0.93)
      - No difference in overall mortality
        - (odds ratio 1.02, 95% CI 0.87-1.19)

Lancet 2009;373:1765-73.

AACE: Why A1c goal < = 6.5% for majority of patients ?

- ADVANCE Study (NEJM 2008;358:2560-72)
  - n=11,140; Median duration of 5 yrs. Baseline A1c=7.5%. f/u A1c=6.5% (intensive) and 7.3% (standard)
  - Benefits of intensive treatment
    - delayed onset of microalbuminuria
      [HR=0.91; 95% CI=0.85-0.98; p=0.02]
    - decreased incidence of nephropathy
      [HR=0.79; 95% CI=0.66-0.93; p<0.01]

AACE: Why A1c goal < = 6.5% for majority of patients ?

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- VADT Study (NEJM 2009;360:129-139)
  - N=1791; Mean duration of 5.6 yrs. Mean baseline A1c=9.5%. f/u A1c=6.9% (intensive) and 8.5% (standard)
  - Benefits of intensive treatment:
    - Decrease in incidence of worsening albumin excretion (p=0.01)
    - Decrease in progression to macroalbuminuria (p=0.04)
    - Decrease in # of CV events in patients with T2DM of less than 15 years duration

AACE: Why Sulfonylureas less favored?

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- ADOPT Study (NEJM 2006;355:2427-43)
  - Rosiglitazone vs. Metformin vs. Glyburide Monotherapy.
  - N=4360 Newly Diagnosed Type 2 Diabetics
  - Median Duration of treatment = 4 yrs
  - Failure rate at 5 yrs
    - 15% ROSI vs. 21% METF vs. 34% GLYB
  - Concern: Progressive loss of β cell function with SU's compared to insulin sensitizers

AACE: Why Sulfonylureas less favored?

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- DeFronzo, RA. *Am J Med 2010;123:S38-48.*

"..many of the agents (especially the sulfonylureas and insulin) currently used are associated with hypoglycemia and weight gain. Given our increased knowledge regarding the pathophysiology of type 2 diabetes and the role of β-cell dysfunction, a more targeted approach is warranted."

Rebuttal

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Why ADA DM treatment algorithm preferred?

ADA vs. AACE/ACE DM Treatment Algorithm

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- ADA recommends A1c <7% vs. A1c ≤6.5% (AACE/ACE).
- Clinical trials did not find improved CV mortality and all-cause mortality.
- Increase in hypoglycemia.
- Recent meta-analysis results show minimal benefits of intensive glucose lowering compared to standard glucose lowering on all-cause and CV mortality.

Intensive Glucose Lowering- Vascular Outcomes - ADVANCE

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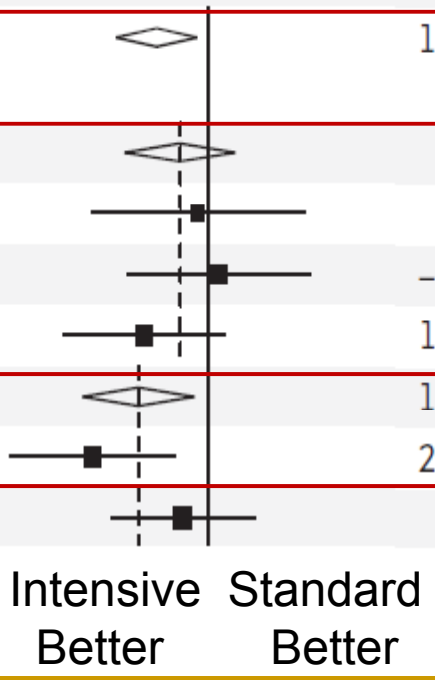
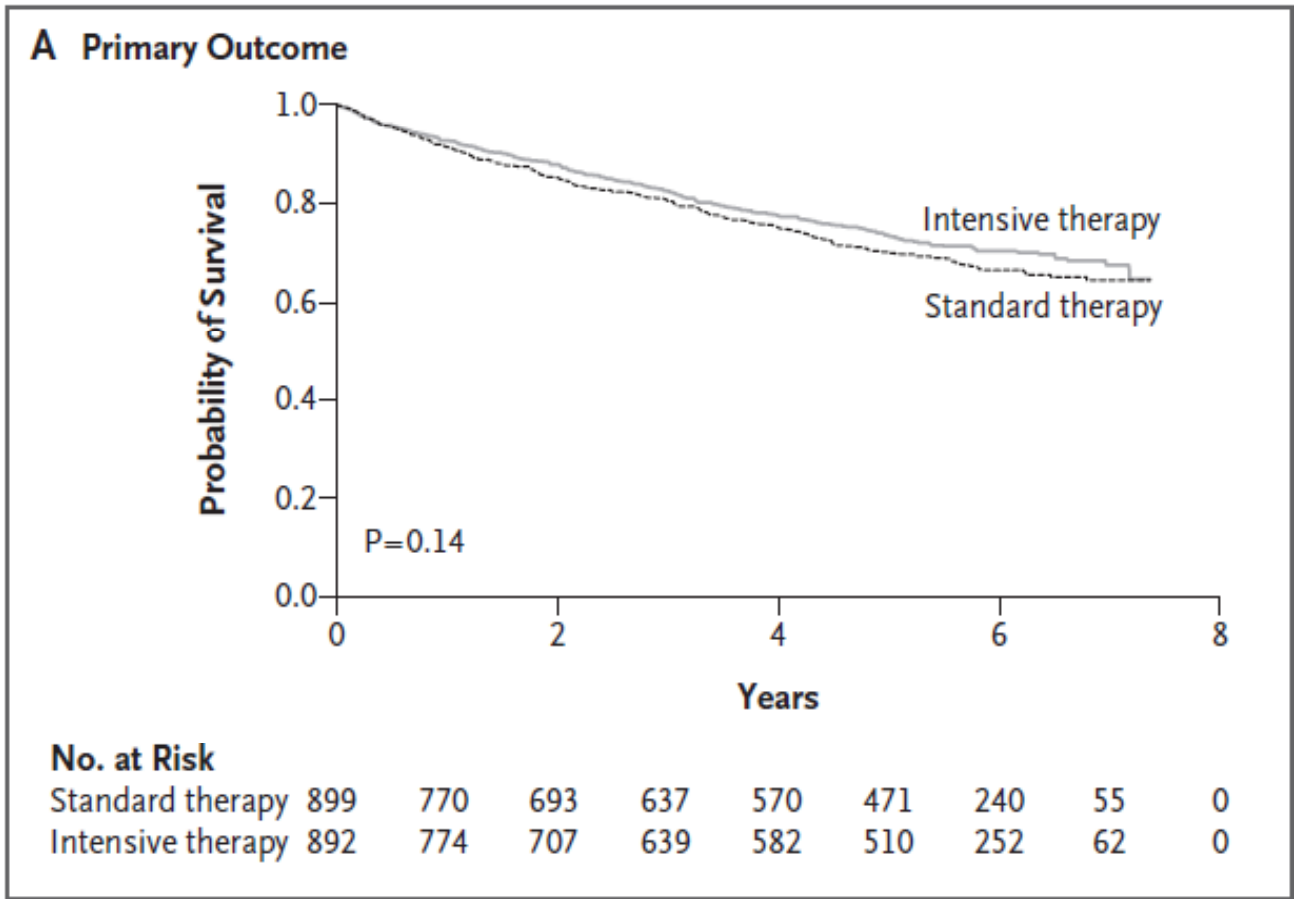
Subgroup	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI)
	number of patients (percent)			*percent*
Primary End Points				
Combined major macrovascular and microvascular events	1009 (18.1)	1116 (20.0)		10 (2 to 18)
Major macrovascular events	557 (10.0)	590 (10.6)		6 (–6 to 16)
Nonfatal MI	153 (2.7)	156 (2.8)		2 (–23 to 22)
Nonfatal stroke	214 (3.8)	209 (3.8)		–2 (–24 to 15)
Death from cardiovascular causes	253 (4.5)	289 (5.2)		12 (–4 to 26)
Major microvascular events	526 (9.4)	605 (10.9)		14 (3 to 23)
New or worsening nephropathy	230 (4.1)	292 (5.2)		21 (7 to 34)
New or worsening retinopathy	332 (6.0)	349 (6.3)		5 (–10 to 18)



Patel A, et.al. *N Engl J Med.* 2008;358:2560-72.

Intensive Glucose Lowering- Vascular Complications - VADT



HR: 0.88, 95% CI (0.74-1.05), p=0.14

Duckworth W, et.al. *N Engl J Med.* 2009;360:129-39.

Meta-analysis of intensive glucose lowering vs. standard glucose lowering

- To determine all-cause mortality and CV mortality related to intensive glucose lowering in patients with Type 2 DM.
- 13 RCT studies (34,533 patients)
- Results:
  - Intensive glucose lowering did not significantly affect all-cause mortality (risk ratio 0.04, CI 0.91-1.19) or CV mortality (risk ratio 1.11, 0.86-1.43).
  - Reductions in non-fatal MI (0.85, 0.74-0.96, P<0.001) and microalbuminuria (0.90, 0.85-0.96, P<0.001)
  - 2-fold increase in severe hypoglycemia (2.33, 21.62-3.36, P<0.001)

Boussageon R, et al. *BMJ* 2011:343:d4169 doi:10.1136/bmj.d4169.

Meta-analysis of intensive glucose lowering vs. standard glucose lowering

- Results continued:
  - Over 5 years,
    - NNT to avoid 1 MI: 117-150
    - NNT to avoid 1 episode of microalbuminuria: 32-142
    - NNH: for every 15-52 patients treated, one severe episode of hypoglycemia would occur
  - Analysis of high-quality studies performed (Jadad score >3)
    - Intensive treatment not associated with significant risk reductions
    - 47% increased risk of CHF

Boussageon R, et al. *BMJ* 2011:343:d4169 doi:10.1136/bmj.d4169.

ADA DM Treatment Algorithm

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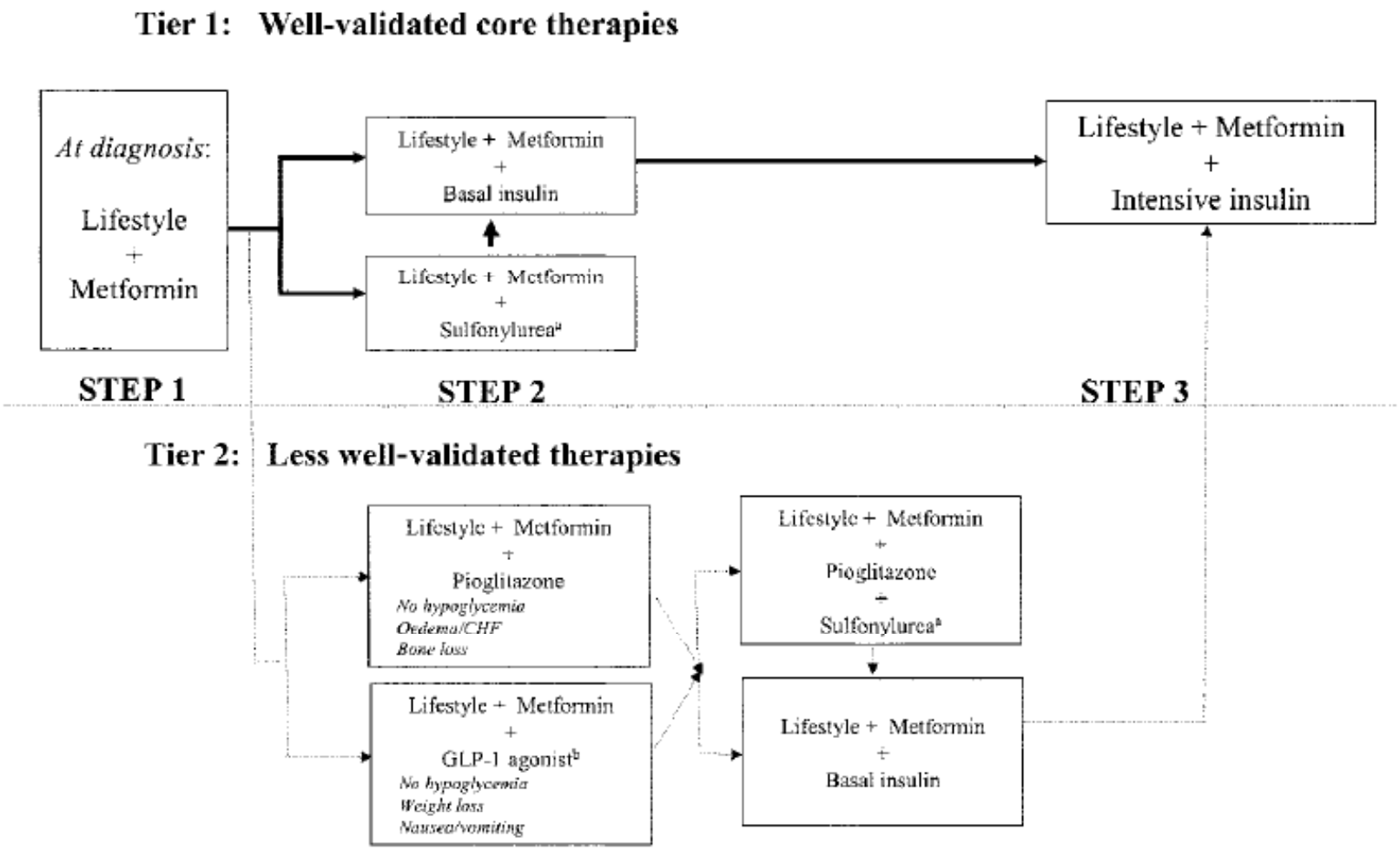
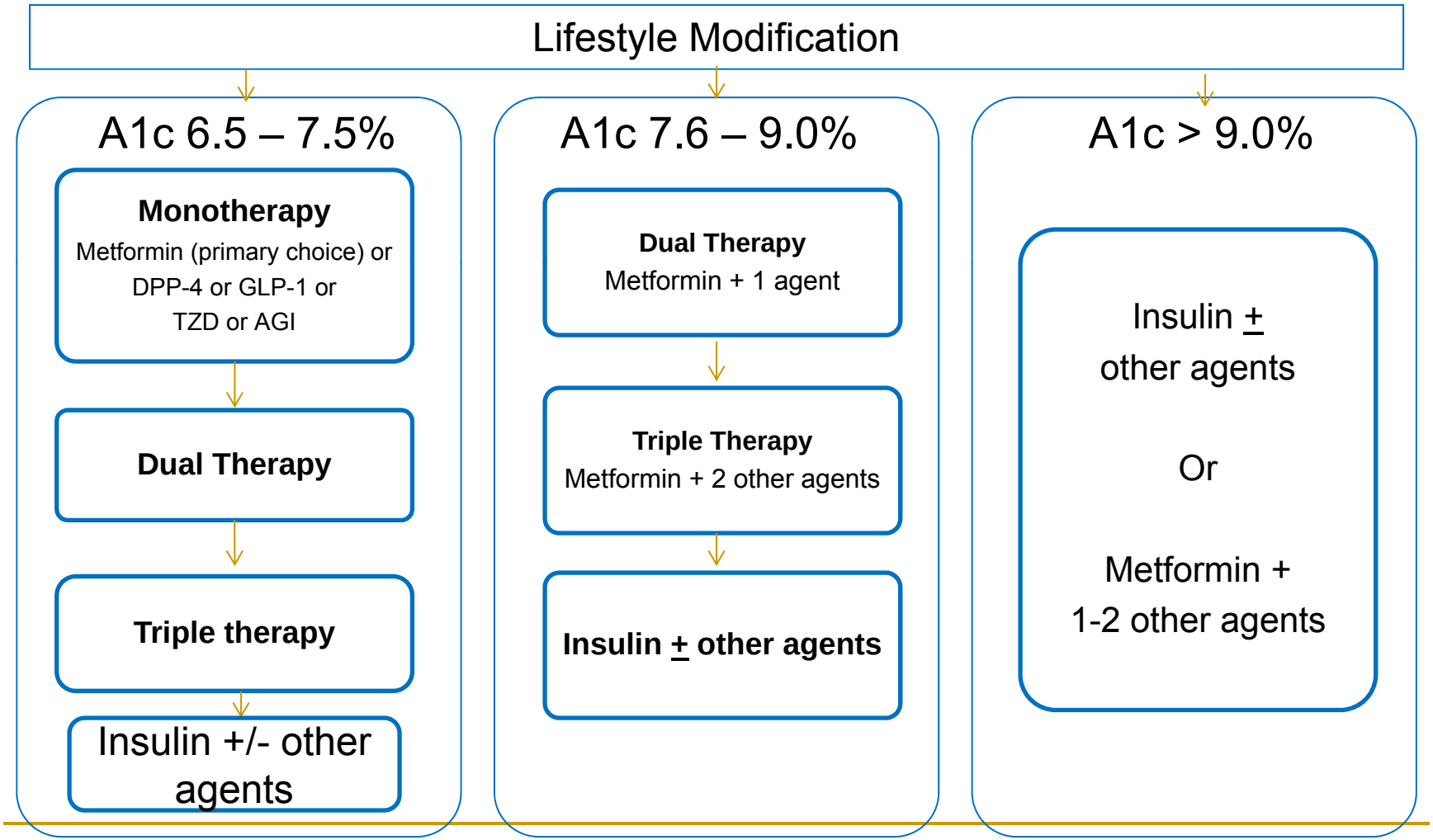


ADA and the EASD. Consensus algorithm on medical management of type 2 diabetes. *Diabetes Care*. 2009;32:193-203.

AACE/ACE Algorithm (Simplified)



AACE/ACE Algorithm. *Endocrine Practice* 2009;15(6):541-9.

Why metformin preferred initial agent compared to other therapies?

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- Metformin preferred first-line treatment
  - Efficacy
  - Safety
  - Cost
- AACE Treatment Algorithm
  - Recommends metformin as preferred agent, but other therapies as well
  - Less evidence/clinical use
  - Branded name medications

ADA's Glycemic Control Recommendations

- **Goal A1C = ≤ 7%**
  - Lower microvascular/neuropathic complications
  - Implement soon after diagnosis for macrovascular benefits
- **Stringent A1C Goal**
  - Benefits: Microvascular benefits
  - Who?:
    - Short duration of diabetes
    - Long life expectancy
    - No significant CVD
    - Low hypoglycemia risk

ADA: Standards of medical care. *Diabetes Care.* 2011;34(1):S11-61.

ADA's Glycemic Control Recommendations

- **Less Stringent A1C Goal**
  - Who?:
    - Severe hypoglycemic episodes
    - Limited life expectancy
    - Advanced microvascular or macrovascular complications
    - Extensive comorbid conditions
    - Having longstanding DM

ADA: Standards of medical care. *Diabetes Care.* 2011;34(1):S11-61.

Cochrane Review: Targeting Intensive Glycemic Control vs. Conventional Glycemic Control for Type 2 DM

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"There is insufficient evidence to demonstrate whether targeting intensive glycemic control influences all-cause or CV mortality. Intensive glycemic control is likely to reduce microvascular disease as a composite outcome and may reduce occurrence of specific patient outcomes such as non-fatal MI and lower extremity amputation. It increases risk of severe adverse events (e.g., hypoglycemia). The A1c must be evaluated individually for different patients and should take both benefits and harms into account."

Hemmingsen B, et al. Targeting intensive glycemic control versus targeting conventional glycemic control for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.:CD008143. DOI: 10.1002/14651858.CD008143.pub2.

Glycemic Control Conclusions

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- Guidelines are guidelines!
  - Guidelines vary
  - Overall goal is to ensure appropriate patient care
- Treat the individual patient!

Rebuttal

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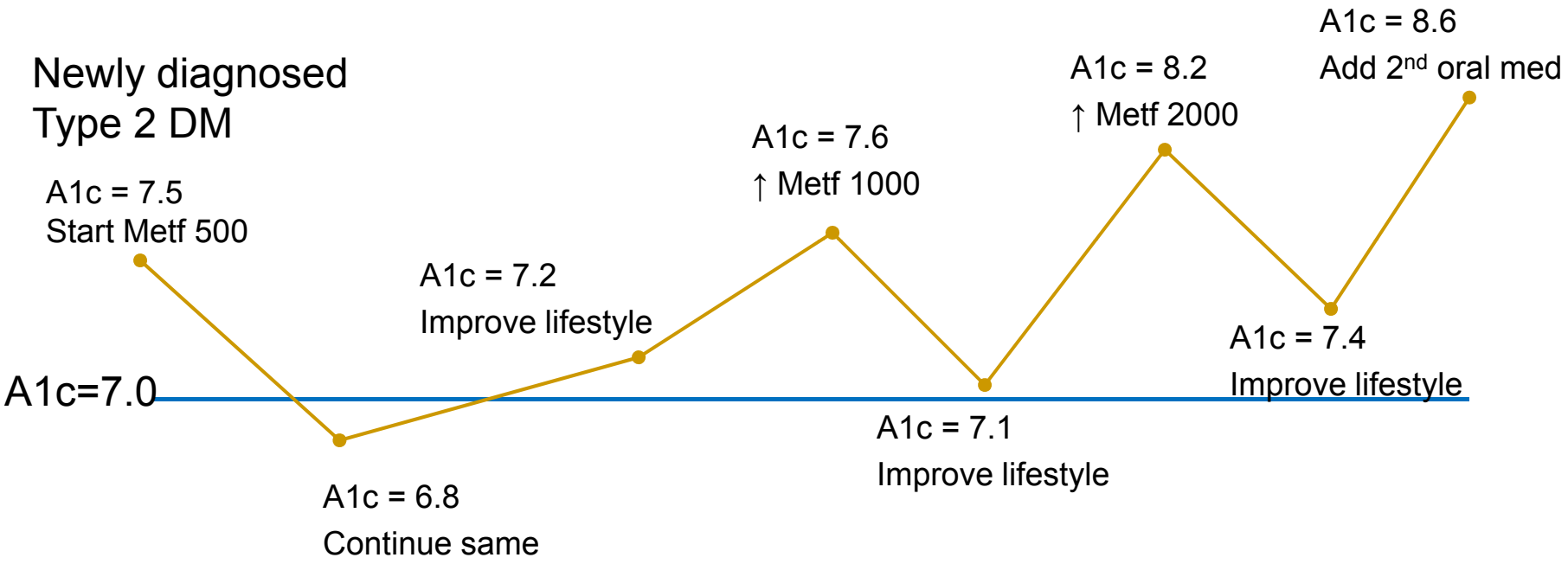
Why AACE algorithm preferred?

Concerns with setting the A1c goal < 7 for majority of patients

- Lack of aggressive treatment during early stages of Type 2 DM
  - Importance of maintaining β-cell function
- Clinical inertia: Delayed response to elevated A1c levels especially during early stages of T2DM
  - Less emphasis in ADA guidelines about dual therapy at time of diagnosis
- Applying findings in the ACCORD study to the universe of T2 DM patients

Clinical inertia



"Clinical inertia may be simply defined as failure to intensify treatment of a patient who is not at their evidence-based HbA1c goal."

Improving Diabetes Care by Combating Clinical Inertia
Patrick J O'Connor. *Health Serv Res. 2005 December; 40(6 Pt 1): 1854–1861.*

AACE: Why A1c stratification important?

- Benefits: Emphasis placed on achieving improved glucose control rapidly to help preserve β-cell function.
  - The higher the baseline A1c, the greater the risk of secondary failure of Metformin monotherapy.

Kaiser Permanente Northwest (KPNW) database

- Observational study n=1799 Type 2 DM patients who lowered their A1c<7.0 using Metformin monotherapy.
  - 42% of 1,799 patients who achieved A1c < 7% with the initiation of metformin monotherapy experienced secondary failure within a 2- to 5-year follow-up

Diabetes Care 2010;33:501-6.

AACE: Why A1c stratification important?

- Secondary Failure of Metformin Monotherapy in Clinical Practice

Baseline A1c	Failure rate per year
< 7%	12.3% (10.5-14.4)
7 - 7.9%	17.8% (15.7-20.1)
8 - 8.9%	19.2% (16.2-22.8)
>=9.0%	19.4% (16.8-22.4)

Diabetes Care 2010;33:501-6.

Final Comments

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- Cochrane Review
  - "Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings."

Hemmingsen B, et al. Targeting intensive glycemic control versus targeting conventional glycemic control for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.:CD008143.

Questions

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