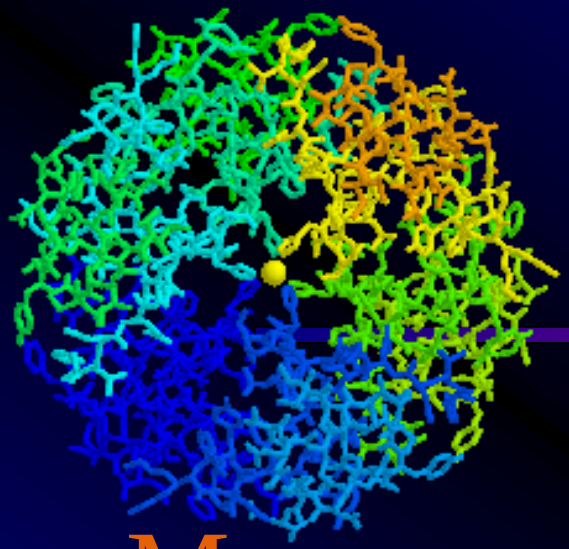
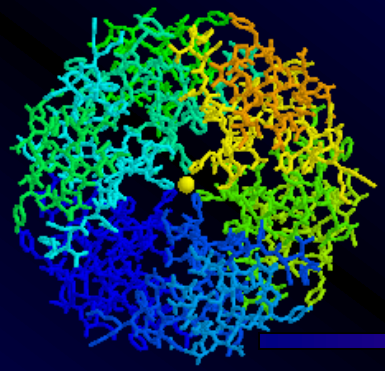


Management of Type 2 Diabetes: 2015

Robert E. Jones, MD, FACP, FACE

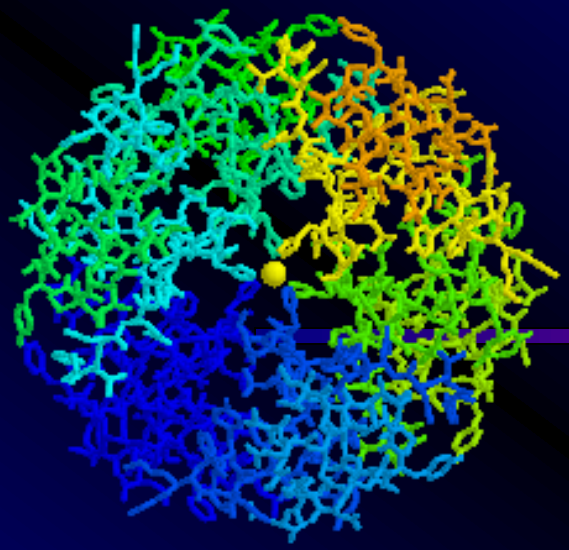
Professor of Medicine

University of Utah School of Medicine

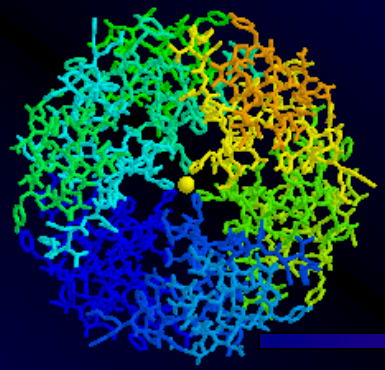


Objectives

1. Review the benefits and limitations of “tight” glycemic control in people with diabetes
2. Discuss newer medications used to treat diabetes
3. Explore the initiation and escalation of insulin management in type 2 diabetes
4. Address the impact of appropriate treatment of diabetes on preventing micro- and macrovascular complications



Glucose Control Targets

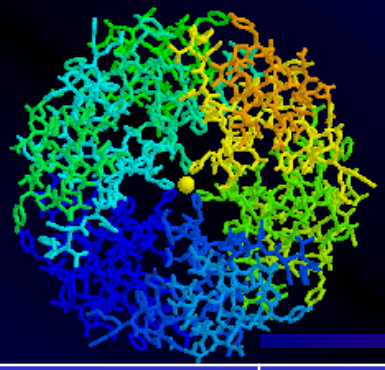


Control: Reduction In Complications

Complications	DCCT[1,2] 9% → 7%	UKPDS[3] 8% → 7%
Retinopathy	63%	17%–21%
Nephropathy	54%	24%–33%
Neuropathy	60%	
Macrovascular disease	41%*	16%*

*Not statistically significant

[1]DCCT Research Group. *N Engl J Med*. 1993;329:977; [2]DCCT Research Group. *Diabetes*. 1995;44:968;
[3]UKPDS Group. *Lancet*. 1998;352:837



Therapy in T2DM

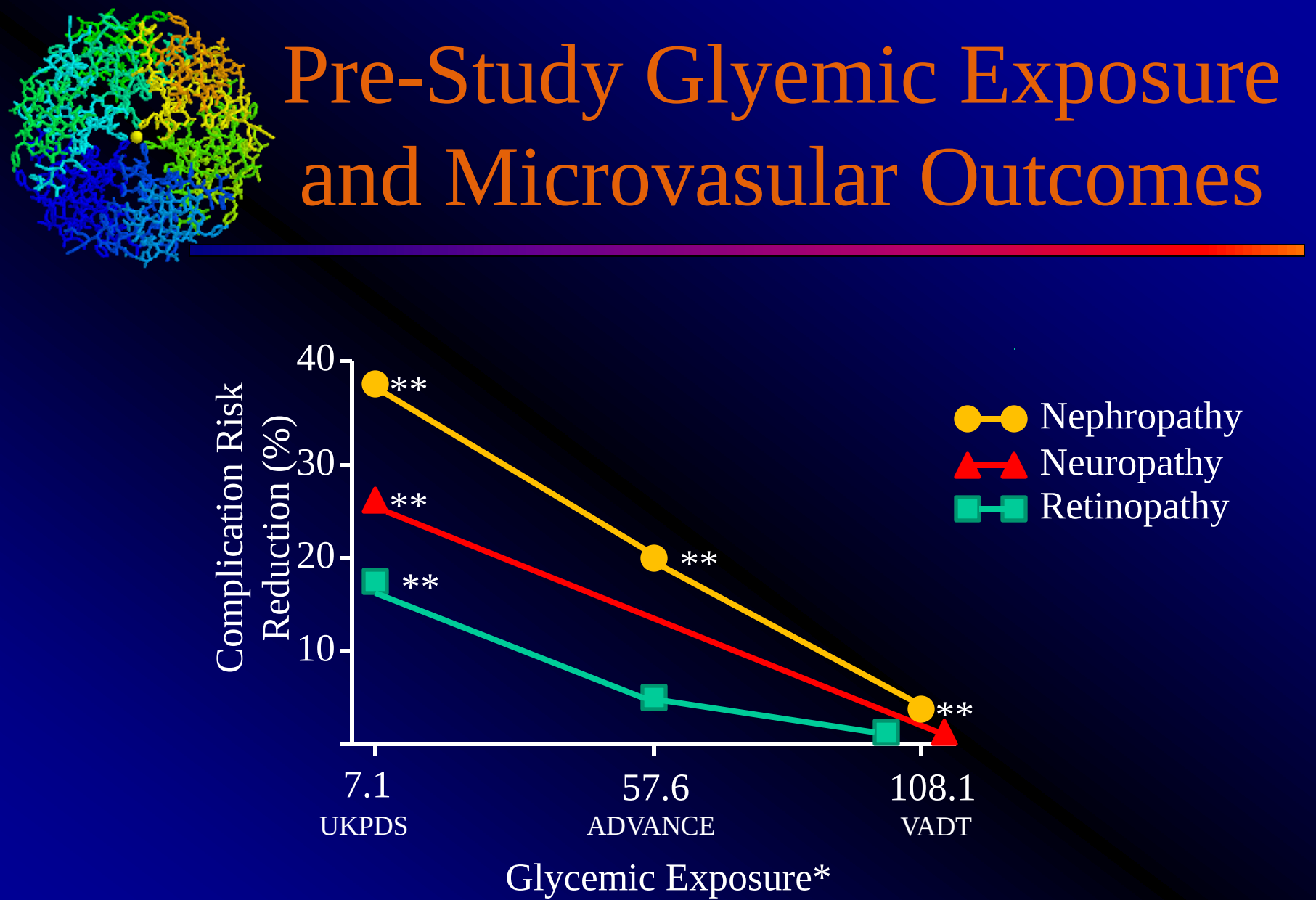
Endpoints: Microvascular Outcomes

	UKPDS (N=3867)		ADVANCE (N=11140)		VADT (N=1791)	
Parameter	Intensive	Standard	Intensive	Standard	Intensive	Standard
Age (yr)	53.3		66		60	
Duration DM	0 years		8 years		11.5 years	
Entry A1C	7.1%		7.2%		9.4%	
Target A1C	Not Specified		<6.5%		Delta 1.5%	
Study Length	“9 years”		5.0 years		5.6 years	
Ending A1C	~7.0%	~7.9%	6.4%	7.0%	6.9%	8.4%
Retinopathy	31.0%	37.5% RR=17%*	6.0%	6.3% RR=5%	42.2%	48.9%
Nephropathy	19.2%	25.4% RR=38%*	4.1%	5.2 % RR=21%*	4.1	6.6*
Neuropathy	23.3%	27.78% RR=26%*	ND	ND	43.5	43.3

*Significant Difference

Wadwekar D, Jones RE. Focus: Diabetes in Women, 2011.

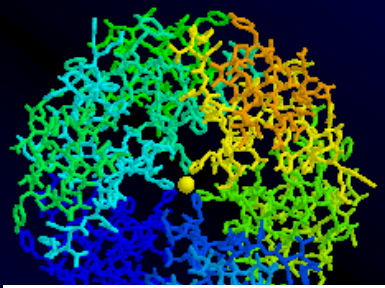
Pre-Study Glyemic Exposure and Microvasular Outcomes



** P < 0.05

*Glycemic Exposure=Duration of Diabetes x Study Entry A1C

Wadwekar D, Jones RE. Focus: Diabetes in Women, 2011.



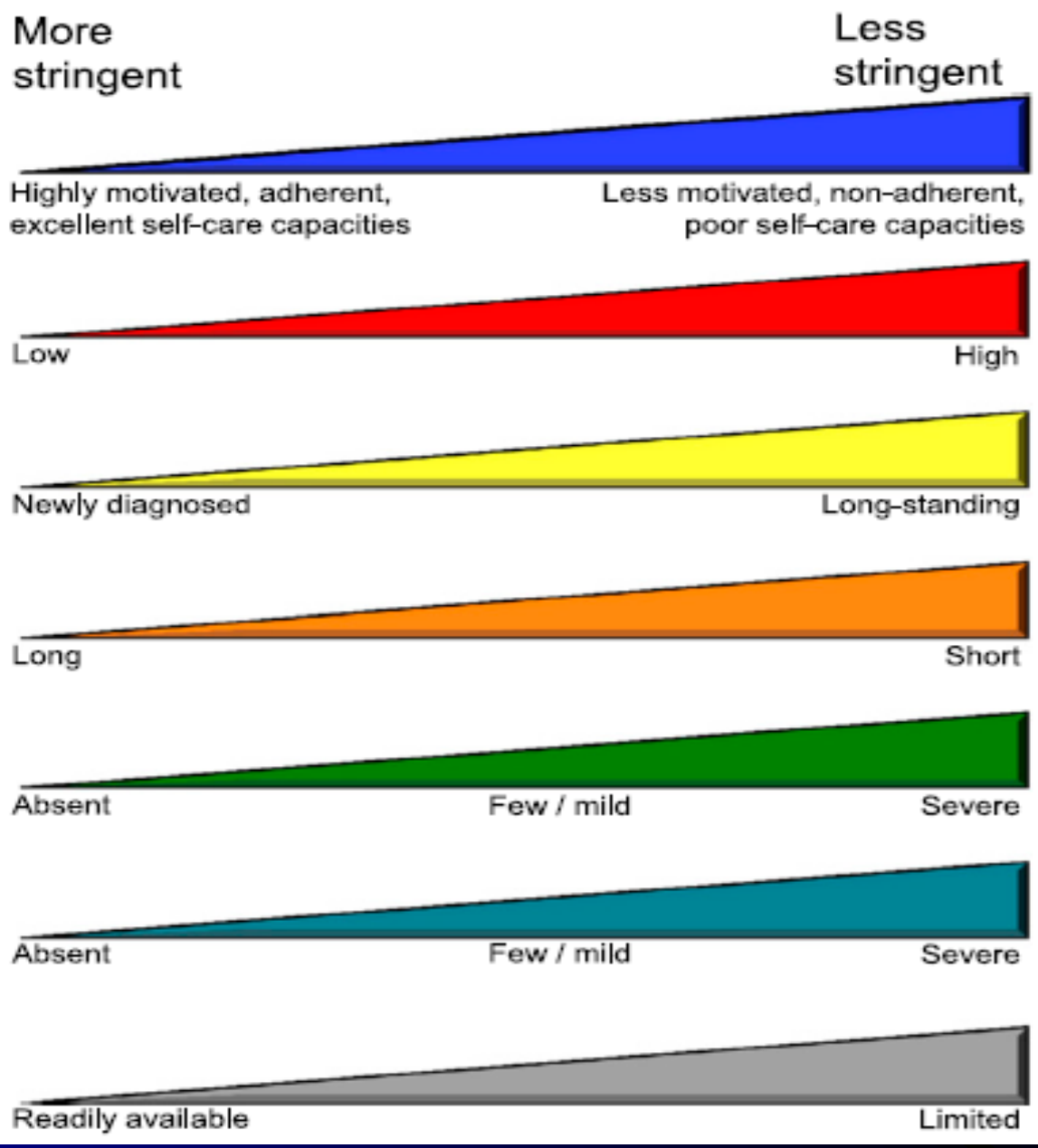
VA/DoD Guidelines

Major Comorbidity [d] or Physiologic Age	Microvascular Complications		
	Absent or Mild [a]	Moderate [b]	Advanced [c]
Absent >10 years of life expectancy	<7%	<8%	8-9% *
Present [e] 5 to 10 years of life expectancy	<8 %	<8%	8-9% *
Marked [f] <5 years of life expectancy	8-9% *	8-9% *	8-9% *

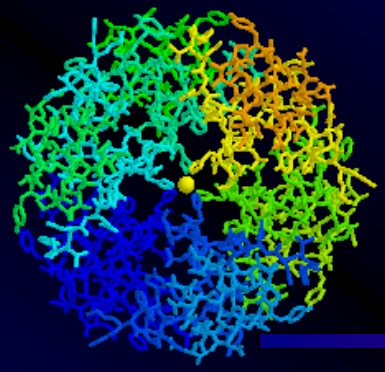
(d) Major comorbidity includes, but is not limited to, any or several of the following active conditions: significant cardiovascular disease, severe chronic kidney disease, severe chronic obstructive pulmonary disease, severe chronic liver disease, recent stroke, and life-threatening malignancy.

http://www.healthquality.va.gov/diabetes/DM2010_SUM-v4.pdf
Accessed Jan 2011

Approach to management of hyperglycemia:



ADA. Diabetes Care 2012;35:1364-1379.

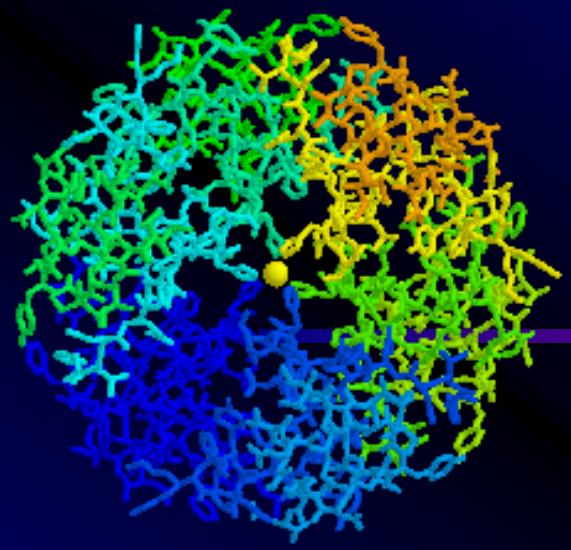


Trials and CV Outcomes in Type 2 Diabetes

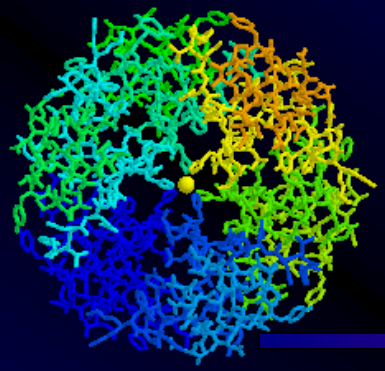
Trial	CV Benefits	Other Findings	Publication Year
DIGAMI 2	None		2004
ADVANCE	None	Glicazide has a neutral CV profile	2008
ACCORD	None	All cause mortality was 22% higher in the intensive treatment group	2008
VADT	None		2009

About ACCORD: "…cases may be suggested where intensive blood pressure treatment or addition of fenofibrate to statin therapy may be warranted, whereas intensive glycemic therapy is rarely, if ever, justified in ACCORD type patients."

Genuth S, Ismail-Beigi F. JCEM 2012; 97:41-48.

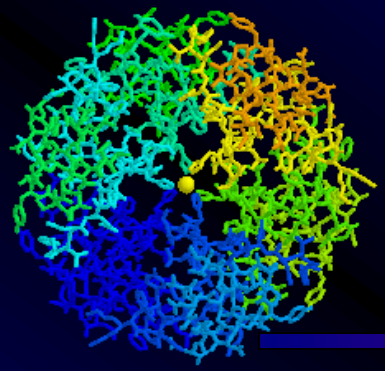


Glucose Lowering Medications



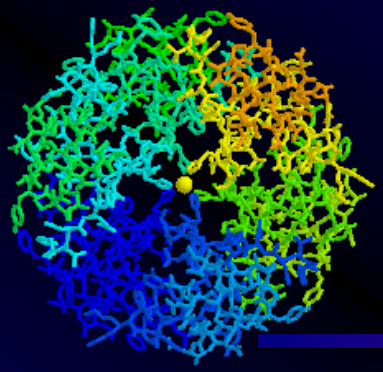
Classes of Agents

Class	Nick Name	Example	Approval
Biguanides		Metformin	1996
Sulfonylureas		Amaryl (glimepiride)	1950’s
Meglitinides	Glitinides	Prandin (repaglinide)	1999
Thiazolidinediones	TZD (Glitazones)	Actos (pioglitazone)	1998
Insulin		Lantus (glargine)	1920’s
GLP-1 R Agonists		Byetta (exenetide)	2004
DPP- IV Inhibitors	Gliptins	Januvia (sitagliptin)	2006
SGLT2 Inhibitors	Gliflozins	Invokana (canagliflozin)	2012

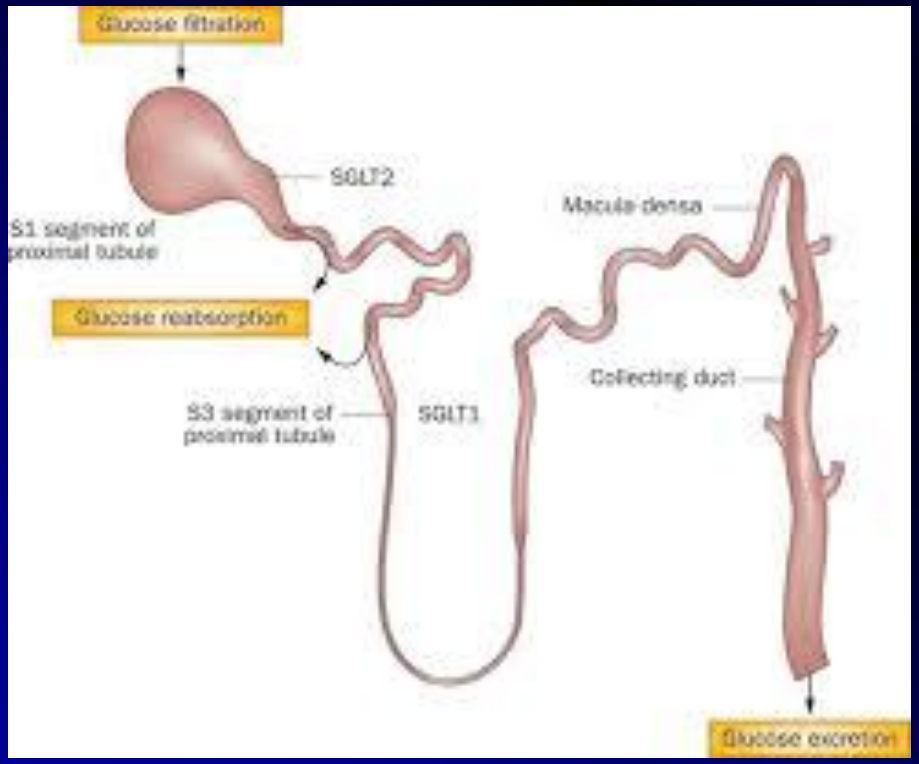


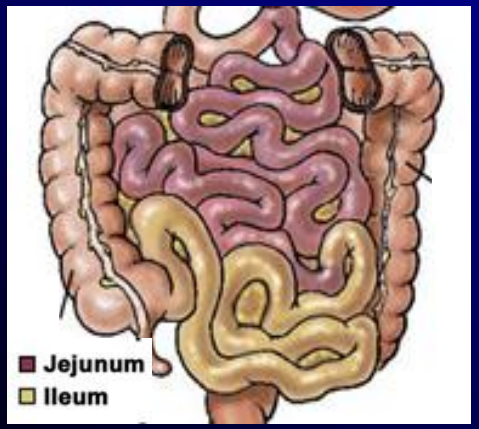
Insulins

Manufacturer	Approved	Product	Characteristics
MannKind	Yes	Alfrezza	Inhaled
Sanofi	No	Truejo (glargine)	U300 Lantus
NovoNordisk	No	Tresiba (degludec)	Very long half life
Lilly	No	Peg Lispro (BIL)	Basal insulin
Lilly	Yes (pending litigation)	Basaglar	Biosimilar glargine

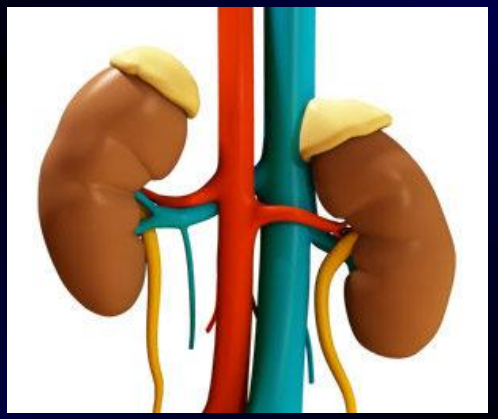


SGLT 2 Inhibition

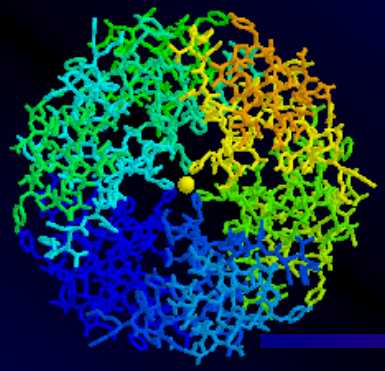




SGLT1 (100%)

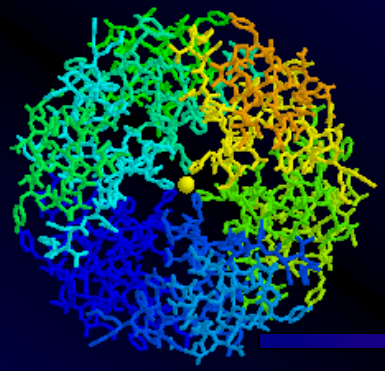


SGLT1 (10%)
SGLT2 (90%)



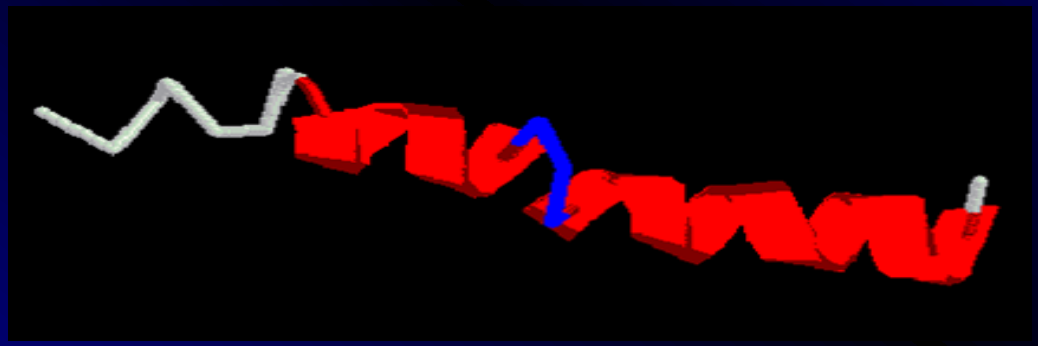
SGLT 2 Inhibitors

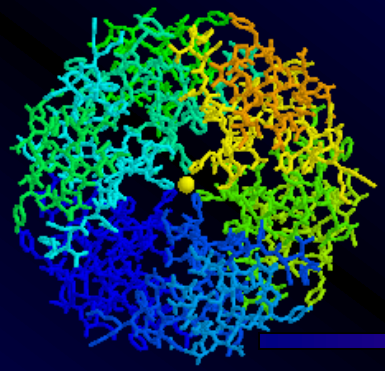
Brand Name	Generic
Invokana	Canagliflozin
Farxiga	Dapagliflozin
Jardiance	Empaglifozin



Biologic Actions of GLP-1

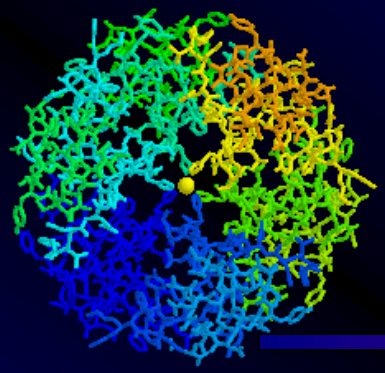
- Islet effects
  - Inhibit glucagon secretion
  - Enhance glucose dependent insulin secretion
  - Upregulation of insulin gene
  - Increase β-cell mass (anti-apoptotic/neogenic)
- Gut effects
  - Inhibit gastric emptying (‘ileal brake’)
- CNS effects
  - Induce satiety
- Peripheral effects
  - Promote glucose uptake
  - Adipogenesis





GLP-1 Receptor Agonists

Brand Name	Generic Name	Dosing
Byetta	Exenetide	BID
Victoza	Liraglutide	QD
Bydureon	Exenetide LAR	Q week
Tanzeum	Albliglutide	Q week
Trulicity	Dulaglitide	Q week



Pharmacologic Approaches to GLP-1

GLP-1 Receptor Agonists

- Exenatide
- Lixenatide
- Albiglutide

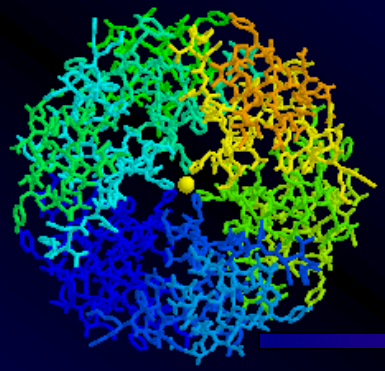
GLP-1 → Receptor

DPP-IV

- Sitagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

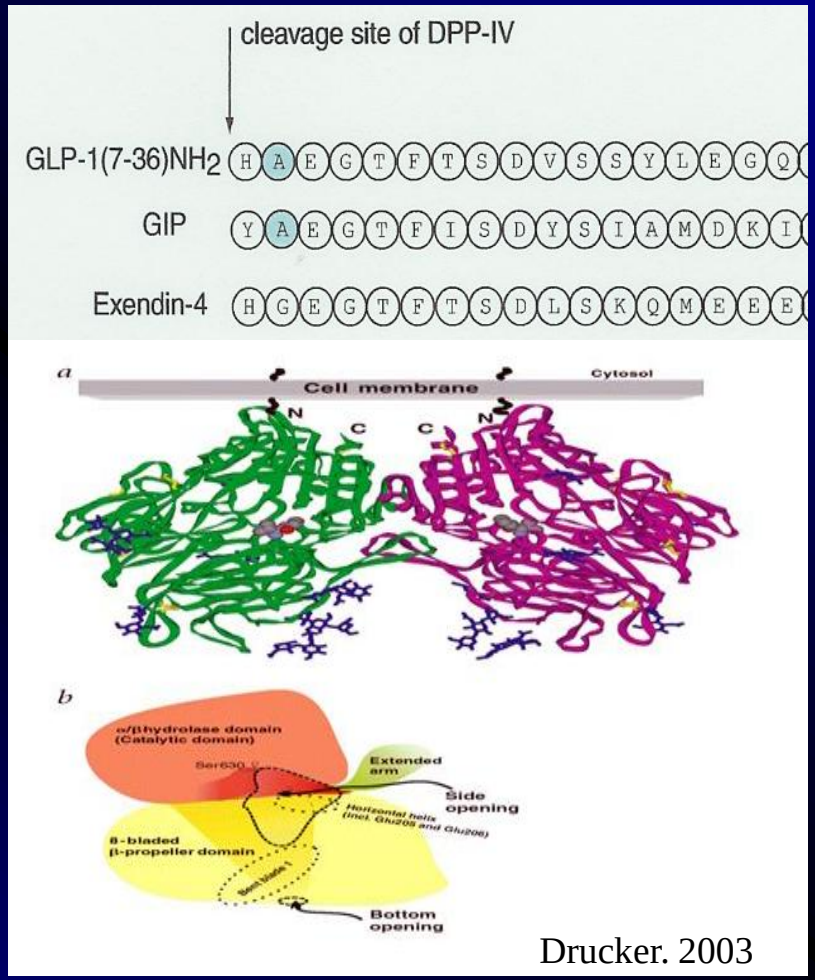
GLP-1 Analogs

- Litaglutide

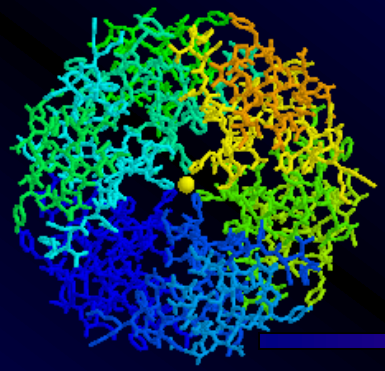


Dipeptylpeptidase-IV

- DPP-IV is also known as CD26, a lymphocyte cell surface protein
- Membrane bound
- Three major activities:
  - Adenosine deamidase binding protein
  - Extracellular matrix binding
  - Proline or alanine peptidase activity
- Ubiquitously expressed
- Modulates inflammation, immune function and endothelial inactivation of peptides
- Substrates:
  - MCPs, IL's, Substance P, GH/IGF, GIP, GLP-1, etc

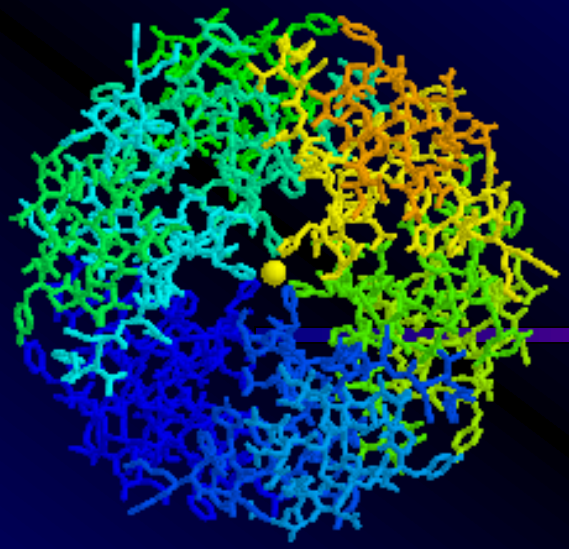


Drucker. 2003

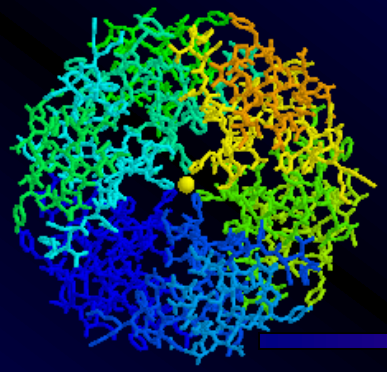


DPP IV Inhibition

Brand Name	Generic	Characteristic
Januvia	Sitagliptin	Renal and liver
Onglyza	Saxagliptin	Renal and liver
Tragenta	Linagliptin	Hepatic clearance only
Nesina	Alogliptin	Renal and liver

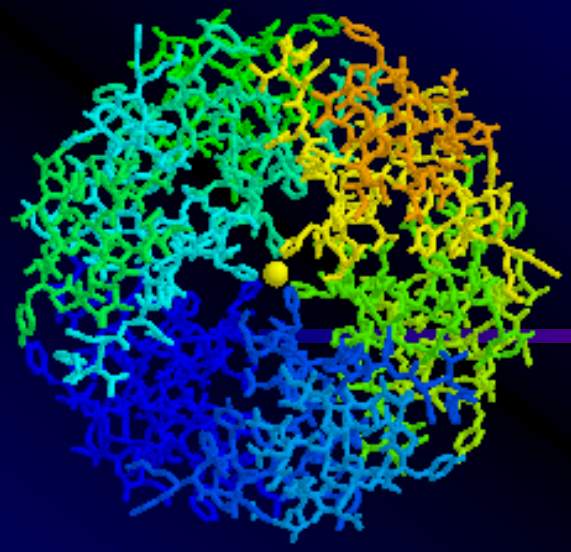


Using Insulin

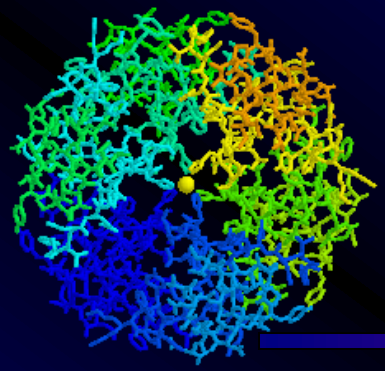


Why Is Insulin So Highly Rated?

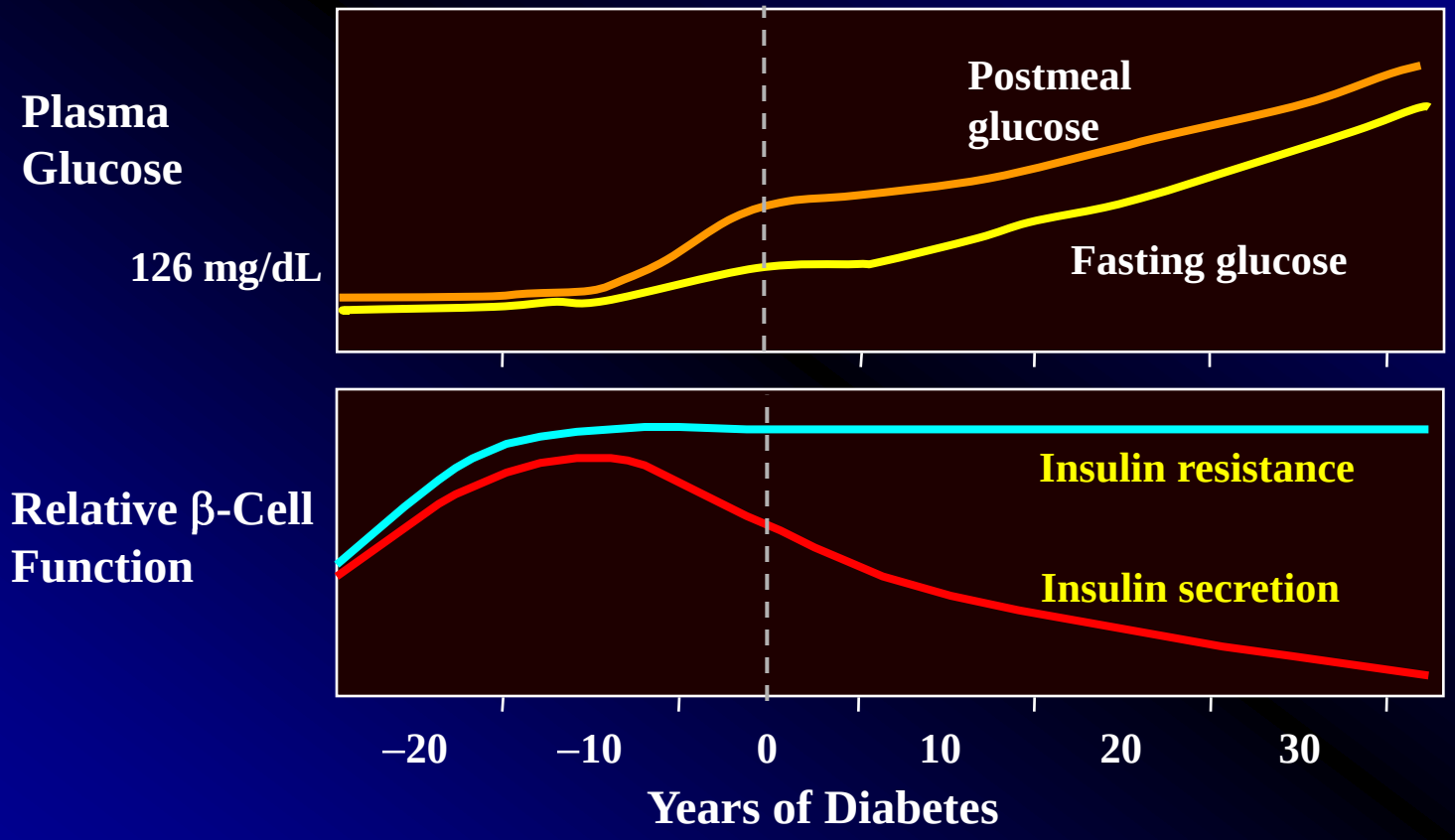
- The natural history of type 2 diabetes suggests the majority of patients will eventually require it as part of their regimen
- Insulin therapy has the greatest relative efficacy and most flexibility of any hypoglycemic agent
- Early, aggressive insulinization has been documented to achieve extended remissions in 40-50% of patients



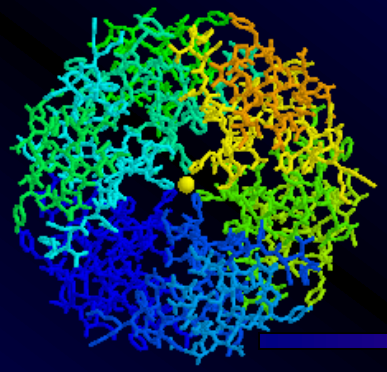
When Should Insulin Be Introduced?



Natural History of Type 2 Diabetes

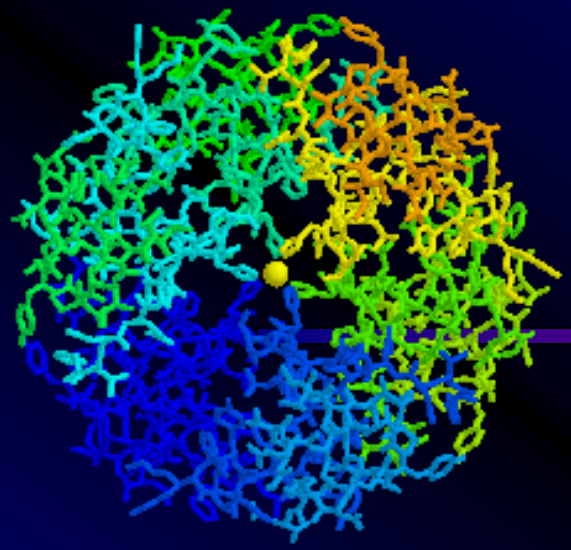


Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.

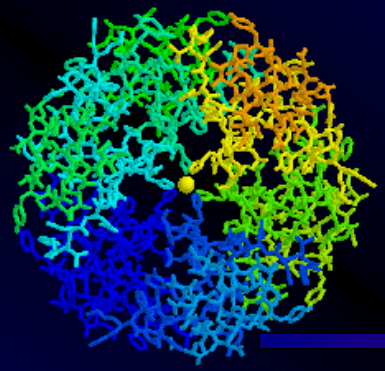


When to Start Insulin?

- ADA/EASD/AACE recommend metformin as initial therapy
- Recommendations for second add-on:
  - Insulin is considered
  - ADA/EASD “insulin is most effective; 70% of patients with type 2 diabetes will eventually require insulin; flexible”
- Based upon A1C or symptomatic hyperglycemia

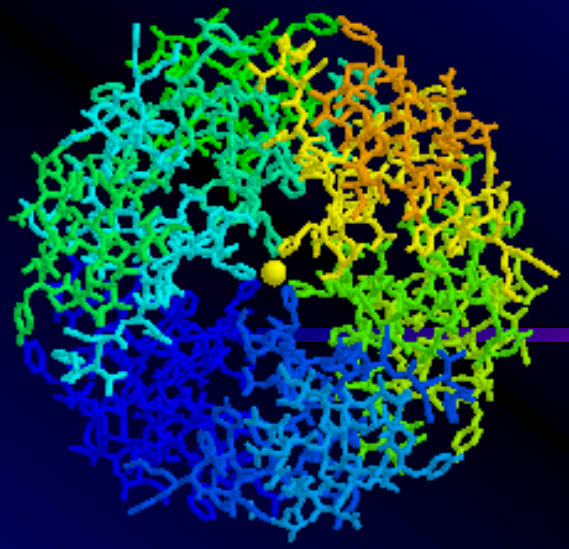


What About Oral Agents?

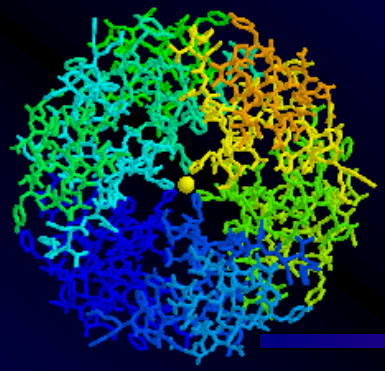


Oral Agents with Insulin

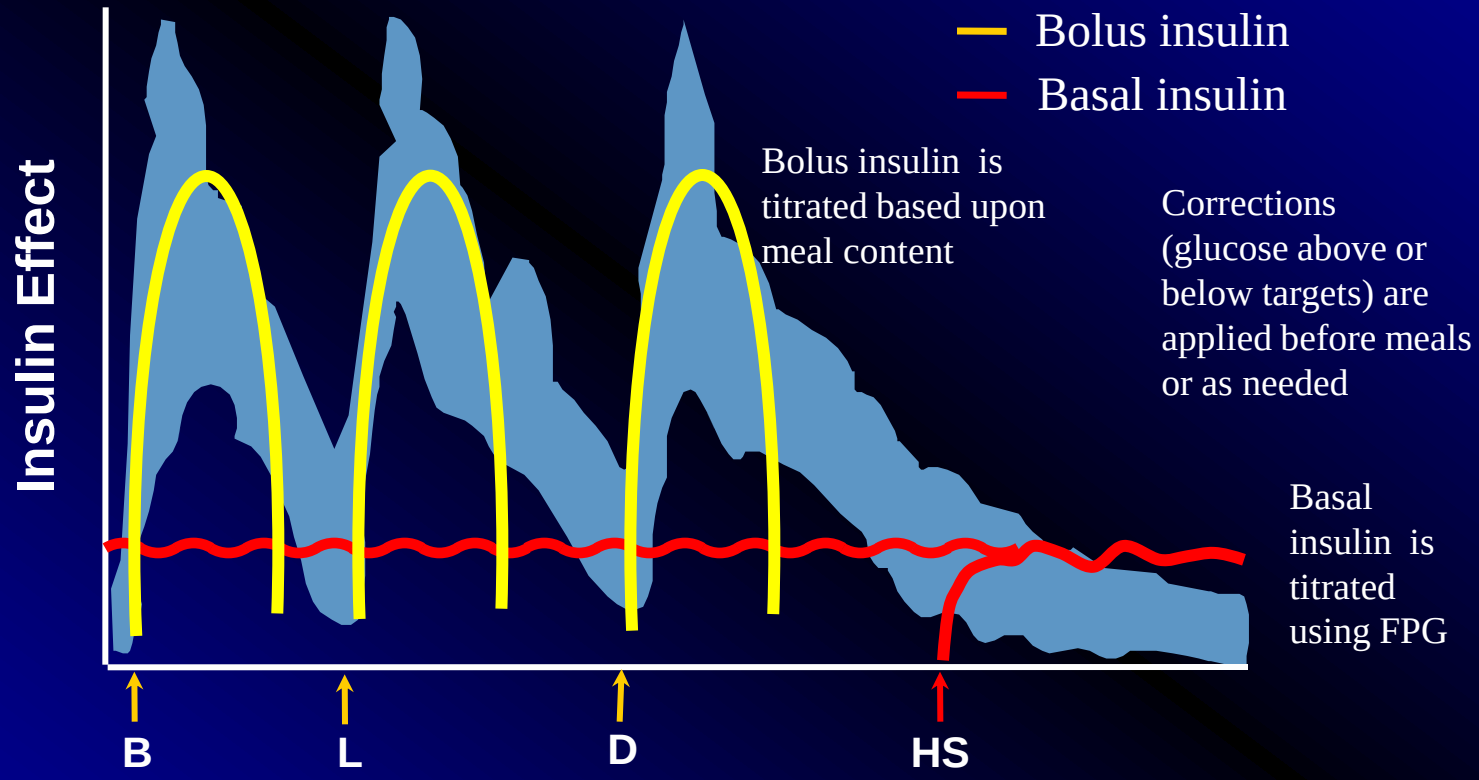
Class of Medication	Benefits	Drawbacks
Biguanides (metformin)	Reduce insulin requirements	Prescribe within guidelines (CHF, CRF)
Sulfonylureas	Augments endogenous prandial ‘bolus’	Requires endogenous insulin secretion
TZDs	Reduce insulin requirements	Edema, weight gain, CHF
SGLT2 Inhibitors	Reduce fasting glucose and prandial excursions; weight loss	Genitourinary infections
DPP IV Inhibitors	Reduce prandial excursions	Requires endogenous insulin secretion



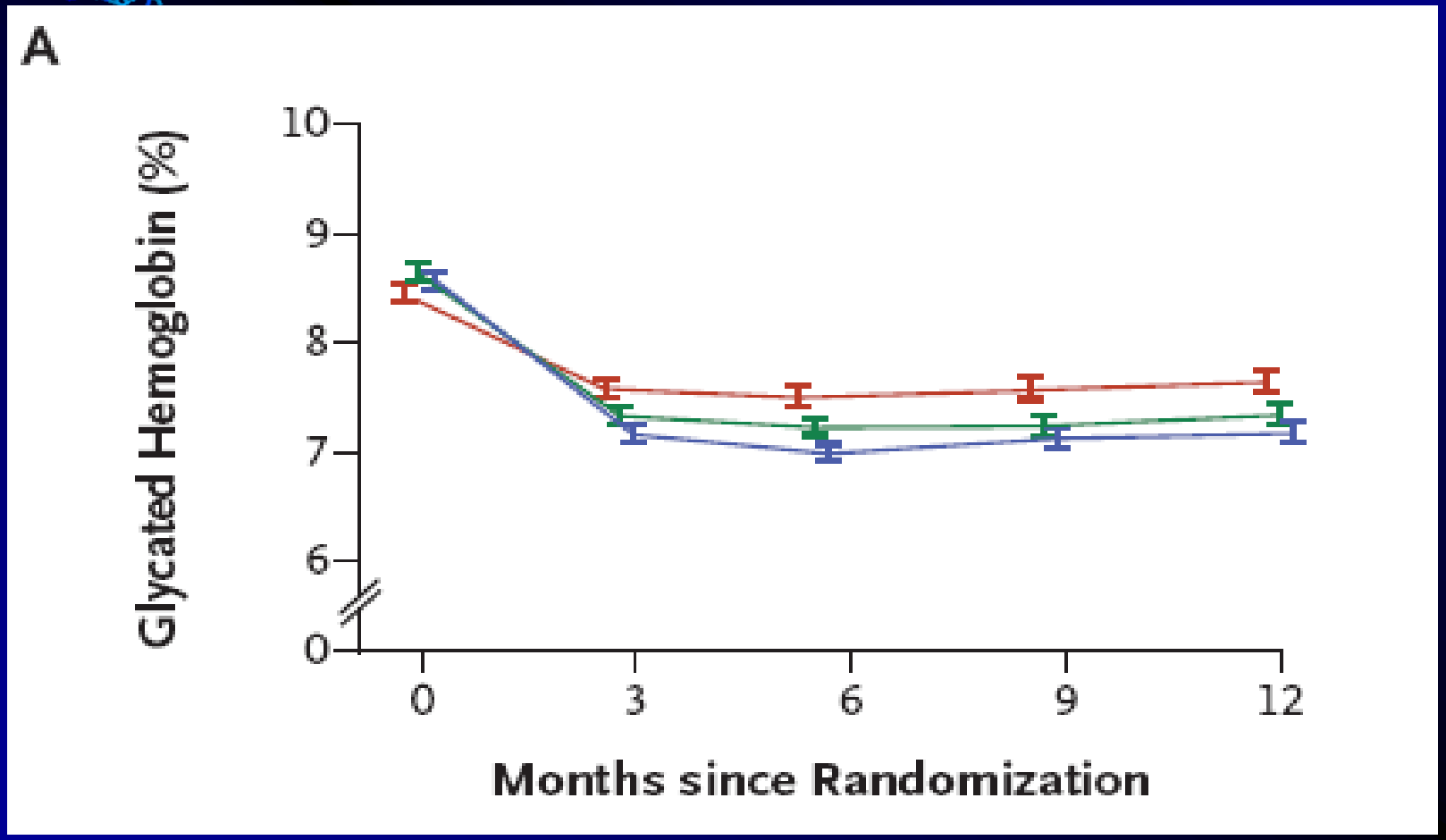
How Should Insulin Be Started?



Physiologic Insulin Therapy



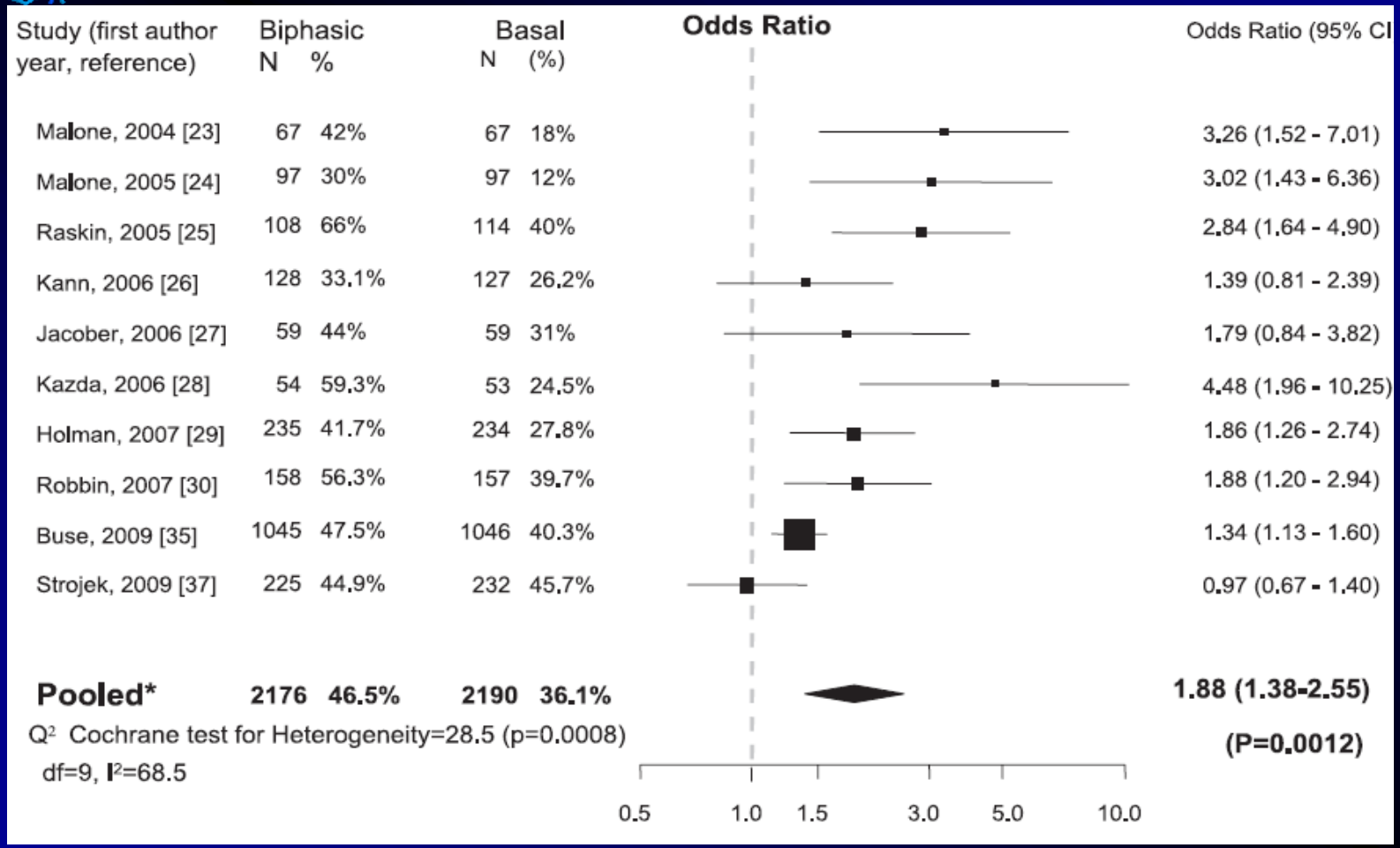
4-T Study: First Year



Holman RR et al. NEJM 2007;357 (epublished)

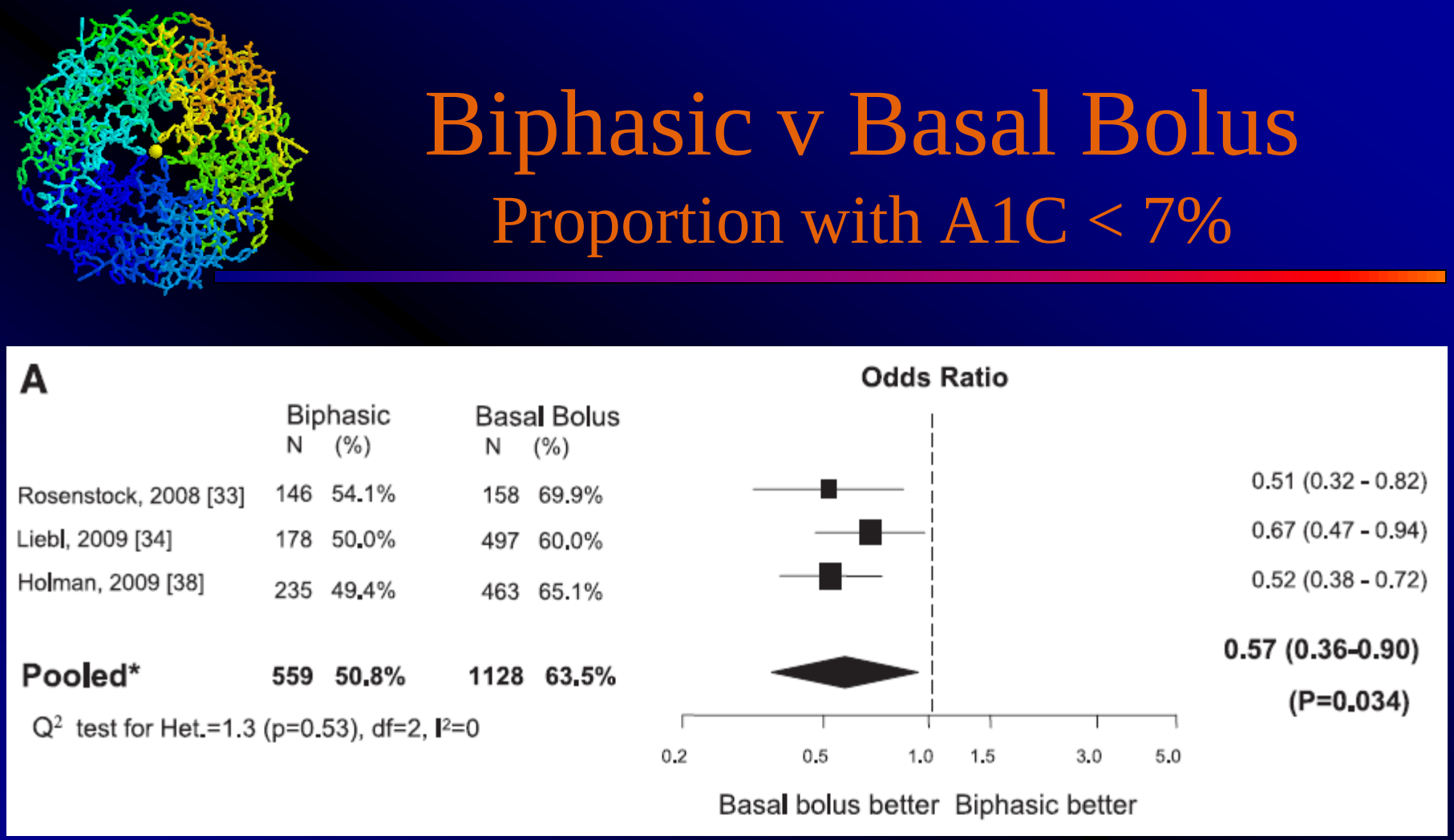
Biphasic v Basal Therapy

Proportion with A1C < 7%



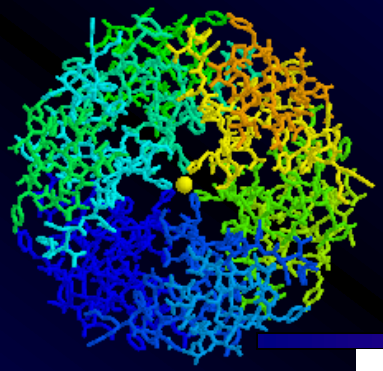
Giugliano G et al. Diabetes Care 2011;34:510

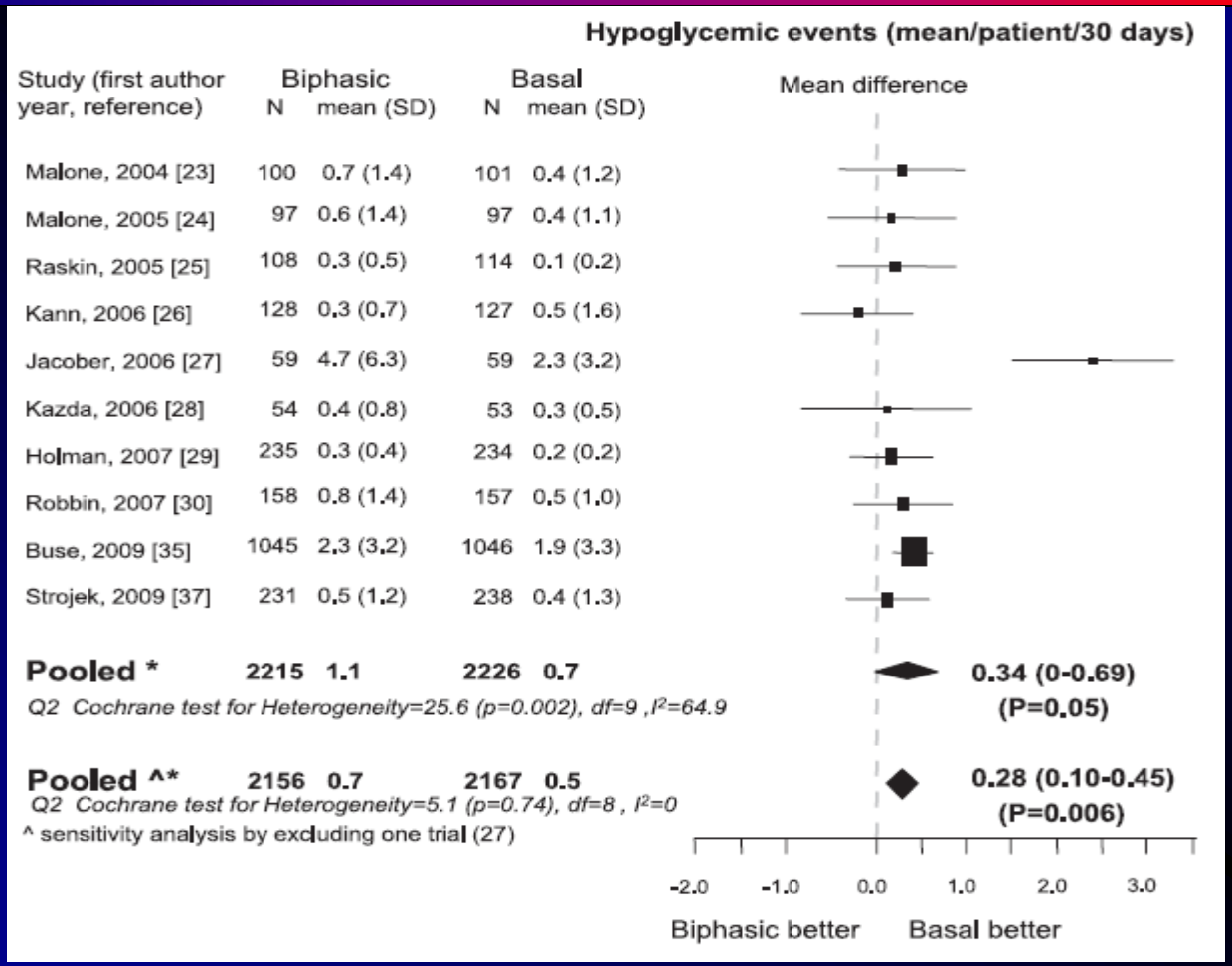
Biphasic v Basal Bolus
Proportion with A1C < 7%



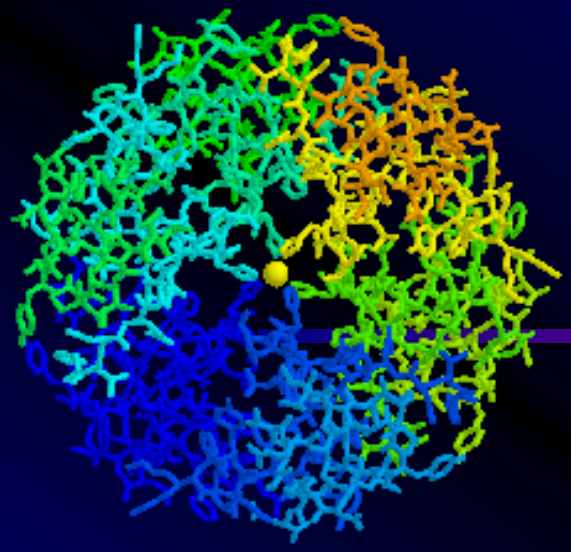
Giugliano G et al. Diabetes Care 2011;34:510

Hypoglycemia Rates



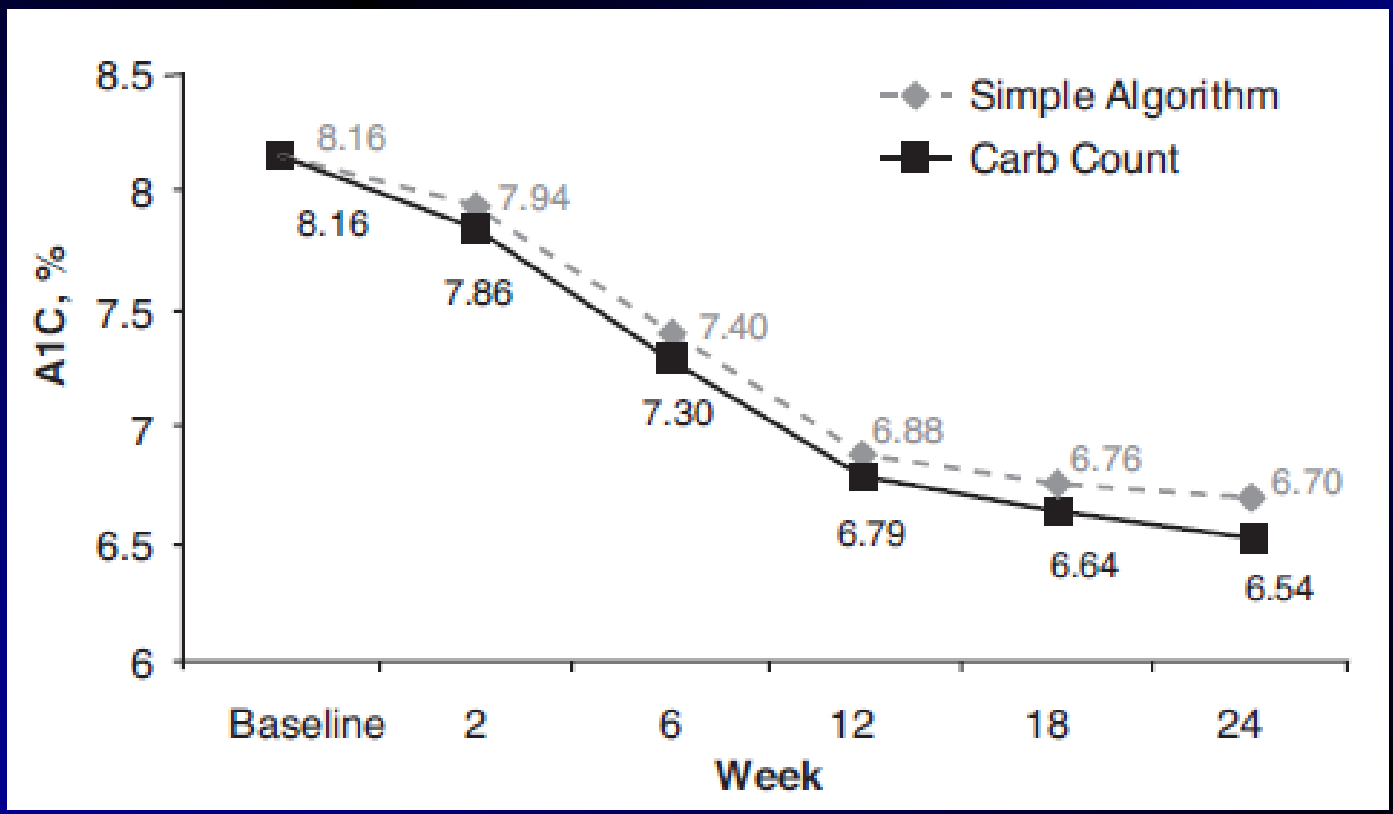


Giugliano G et al. Diabetes Care 2011;34:510



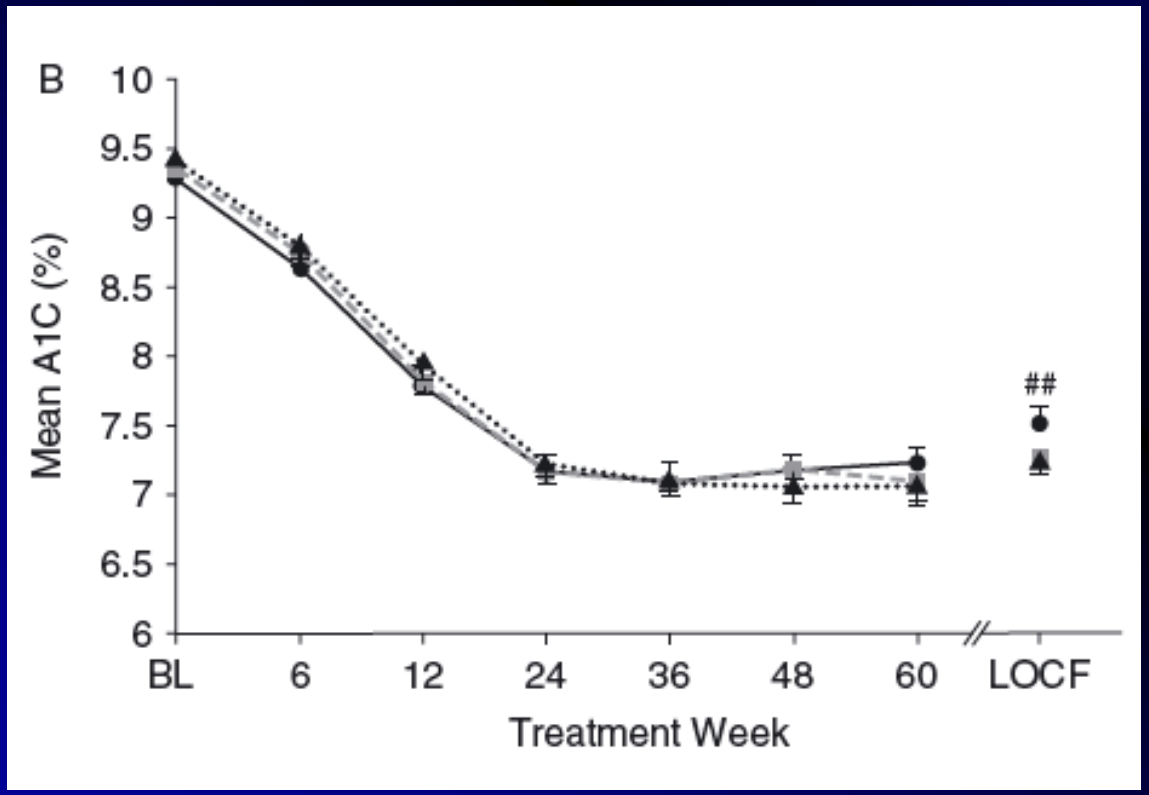
Adding a Prandial Insulin

Carbohydrate Counting



Bergenstal RM et al. Diabetes Care 2008;31:1305-1310.

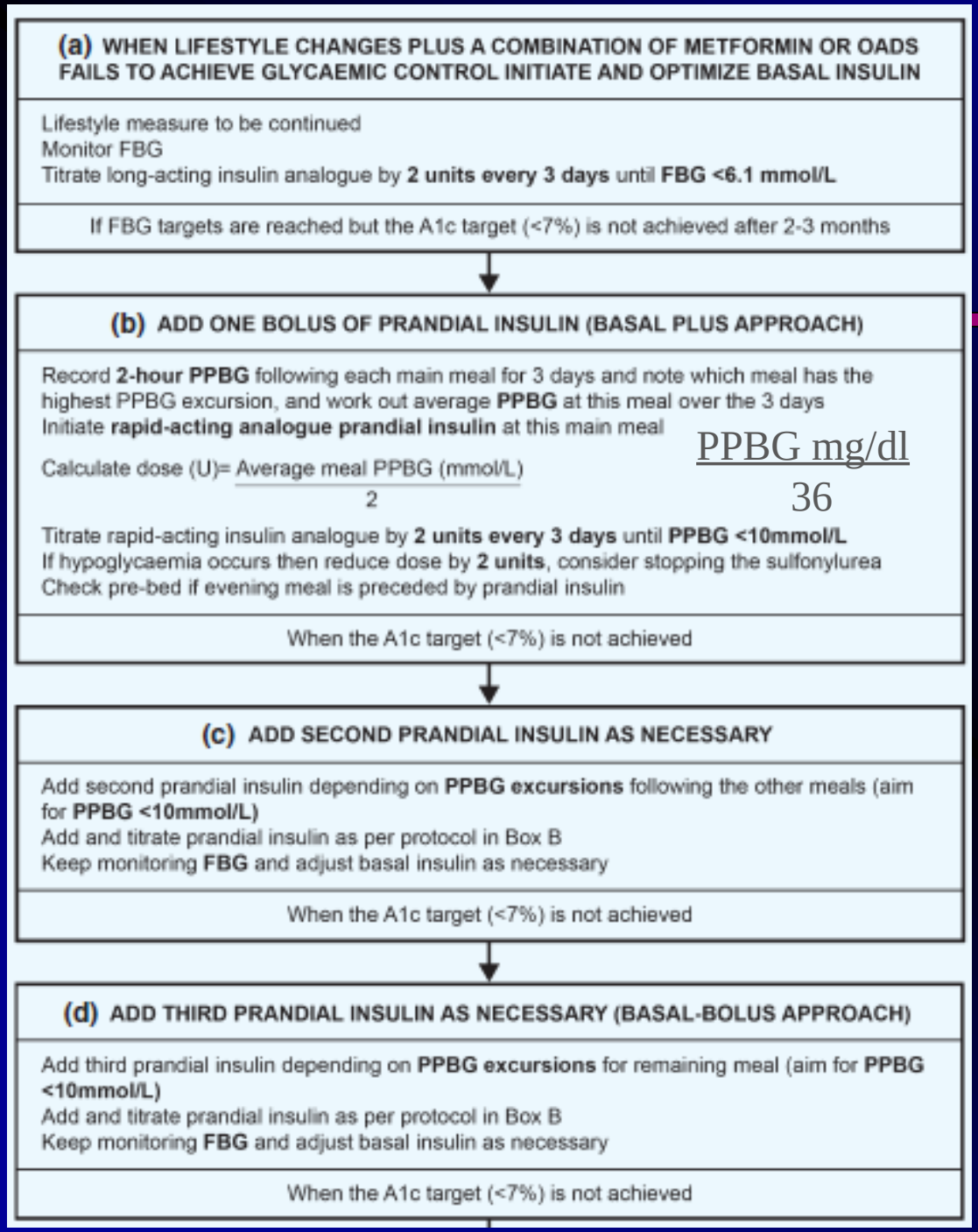
Adding Prandial Insulin



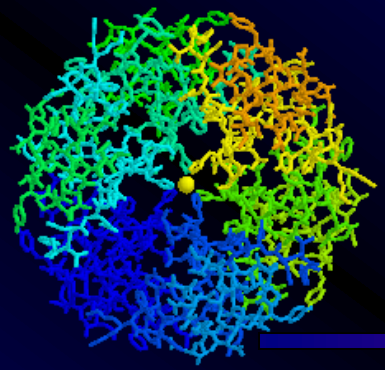
- ● Premix
- ■ Basal Plus 1
  - -25% Basal only
  - -75% Single bolus
- ▲ Basal Plus 3
  - -38% Basal only
  - -23% Single bolus
  - -21% 2 Boluses
  - -18% 3 Boluses

Riddle MC et al. Diabetes Obesity Metab 2014;16:396-402.

Suggested Insulin Algorithm



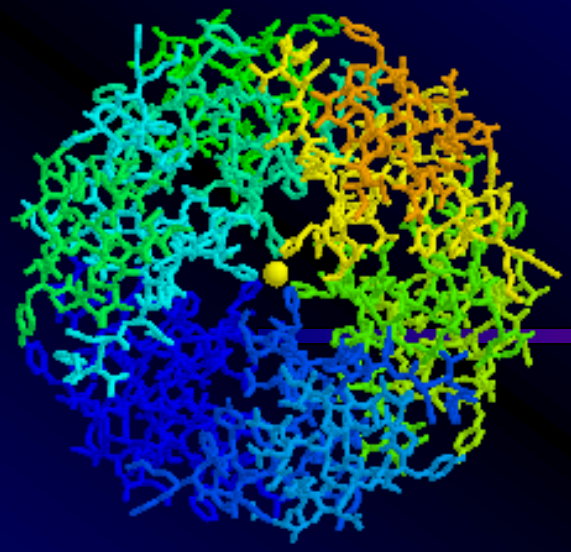
Owen DR. Diabetic Medicine
DOI 10.1111/dme 12019.



Choice of Regimens

- Conclusion:
- “A once-daily basal insulin regimen added to oral medication is an ideal starting point. All next steps, from one to two or even more injections per day should be taken very carefully and in thorough deliberation with the patient, who has to comply with such a regimen for many years.”

van Avendonk M et al. Diabetes Obesity Metab 2009;11:415-432



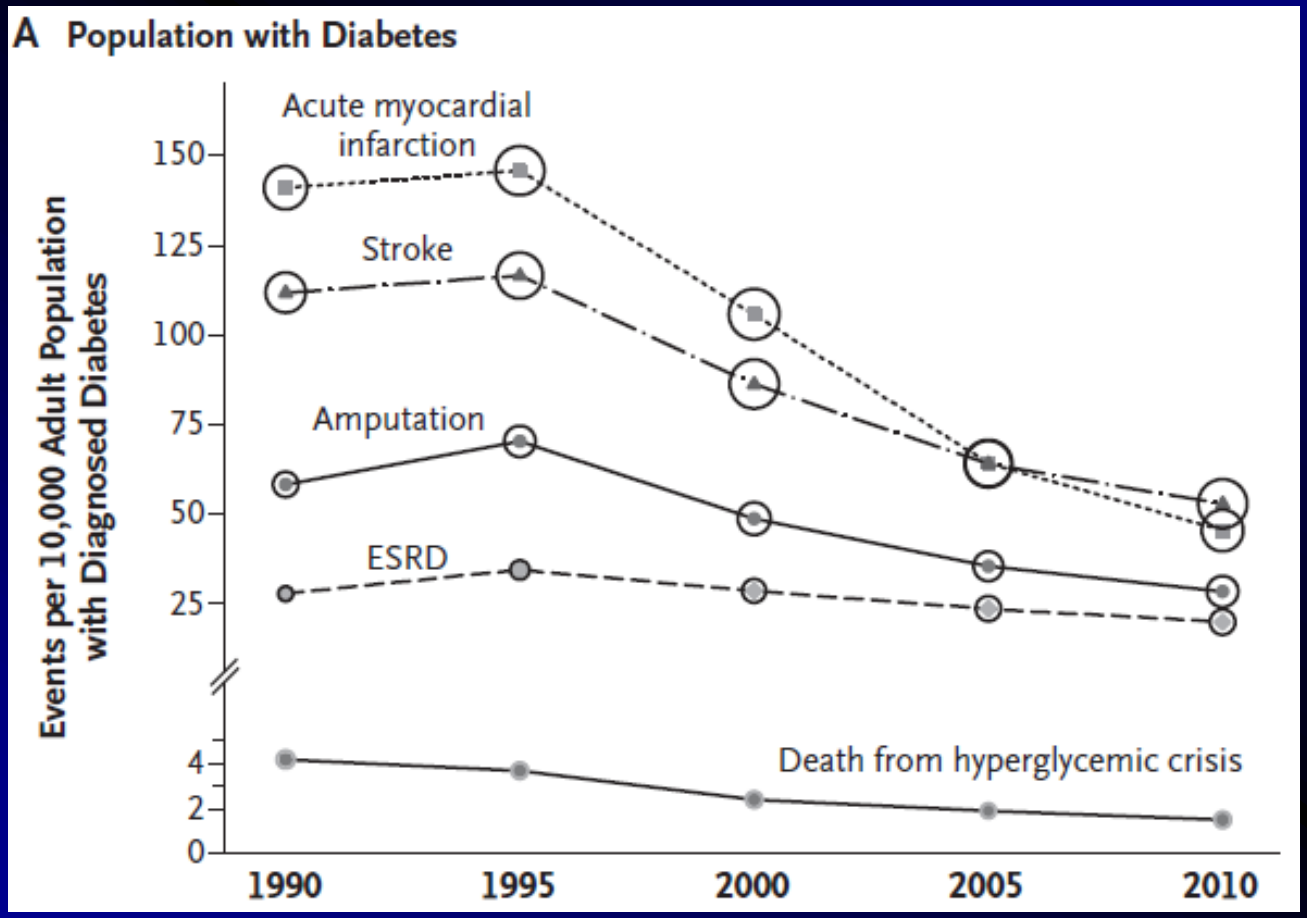
Population Based Assessment in Lowering Complications from Diabetes

Variable	Year			Change (1990-2010)	
	1990	2000	2010	Change	% Change
Adults with Diabetes	6,536,163	11,799,201	20,676,427		
Acute Myocardial Infarction					
No. of Cases	140,122	191,011	135,743		
No./10,000	141.1	105.7	45.5	-95.6	-67.8%*
Stroke					
No. of Cases	127,016	178,755	186,719		
No./10,000	111.8	86.2	52.9	-58.9	-52.7%*
LE Amputation					
No. of Cases	50,364	80,658	73,067		
No./10,000	58.4	48.7	28.4	-30.0	-51.4%*
End-stage Renal Disease					
No. of Cases	17,763	41,477	50,197		
No./10,000	27.9	28.6	20.0	-7.9	-28.3%*

Gregg EW et al. NEJM 2014;370:1514-23.

Trends in Standardized Rates for Complications

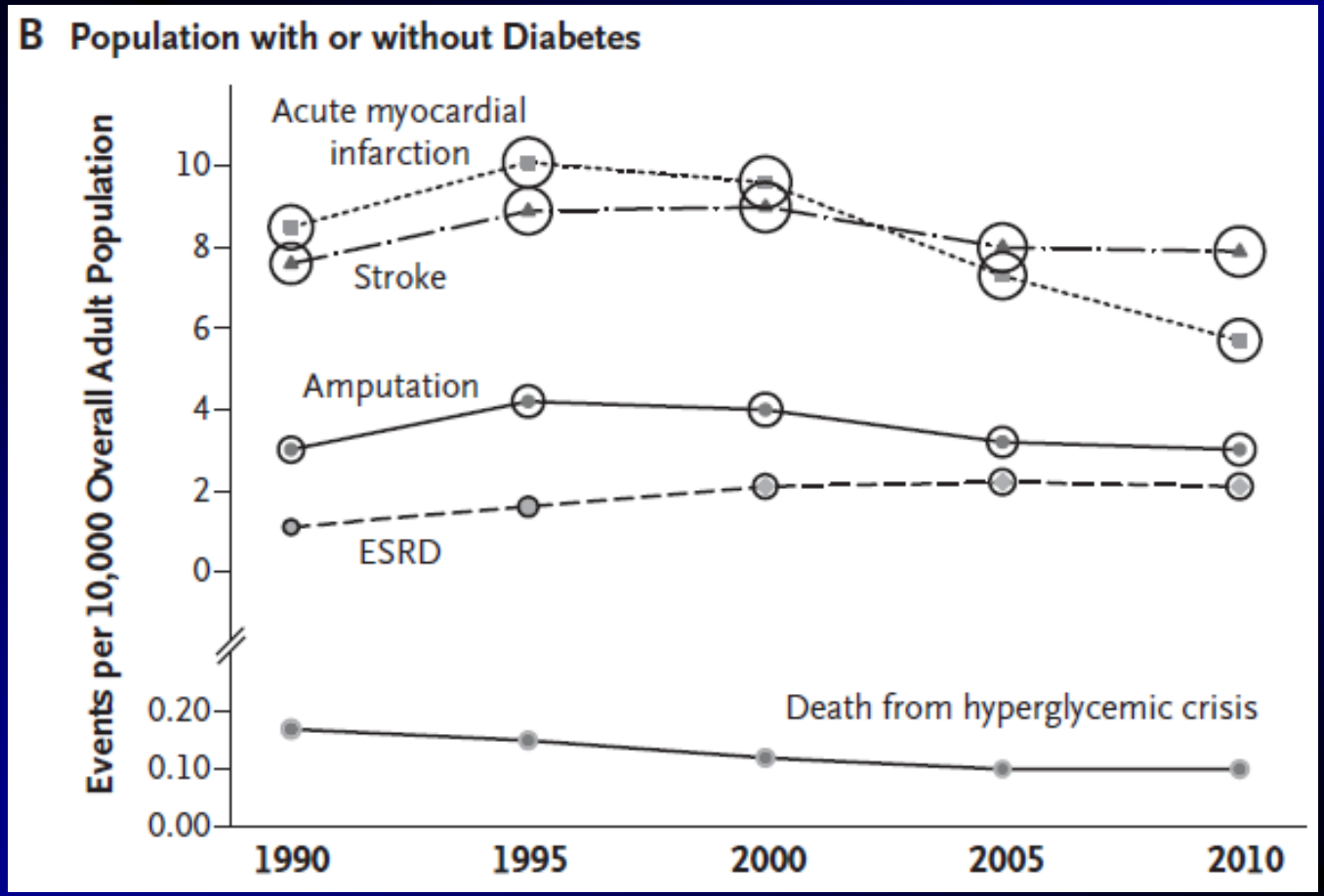
1990-2010



Gregg EW et al. NEJM 2014;370:1514-23.

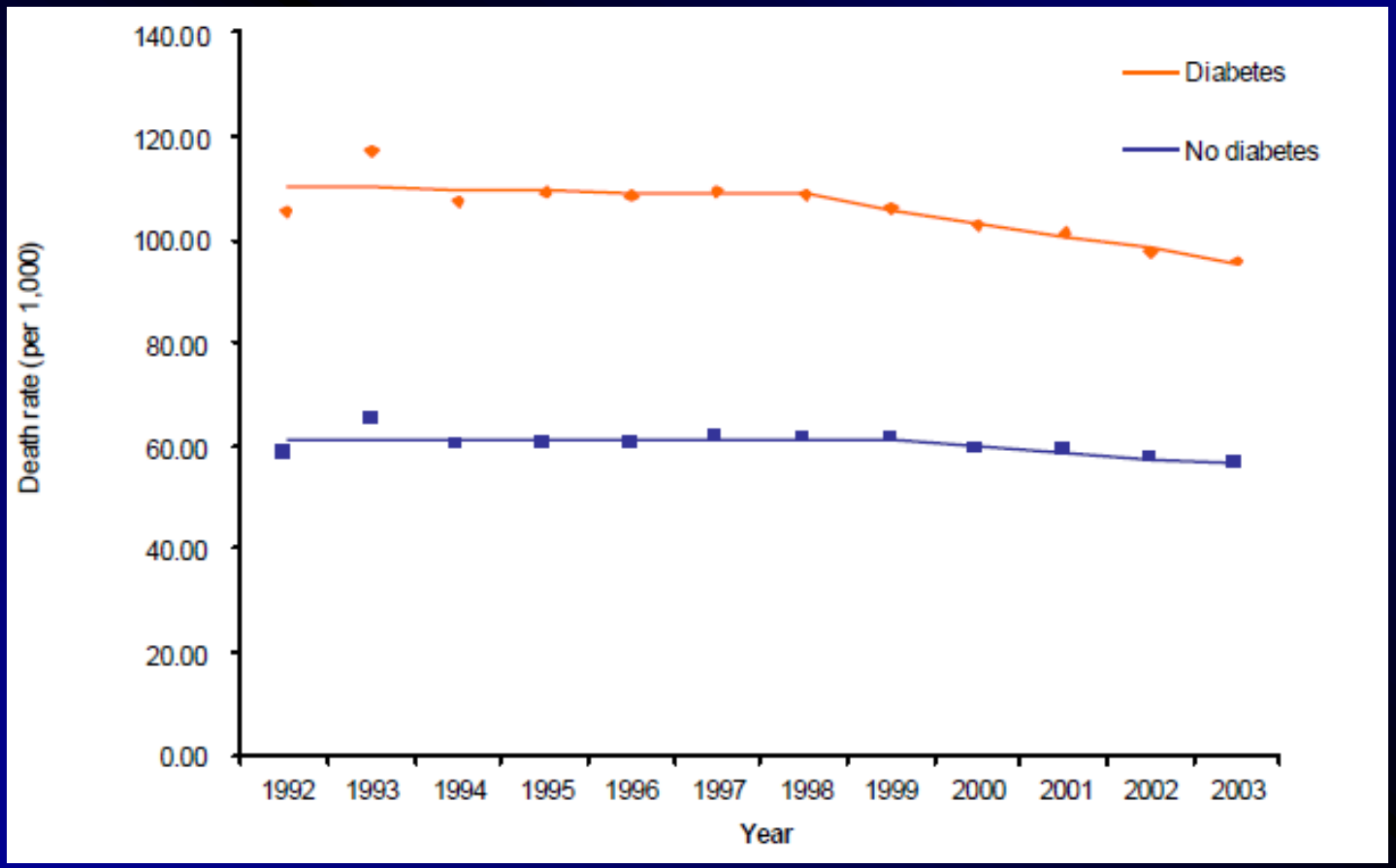
Trends in Standardized Rates for Complications

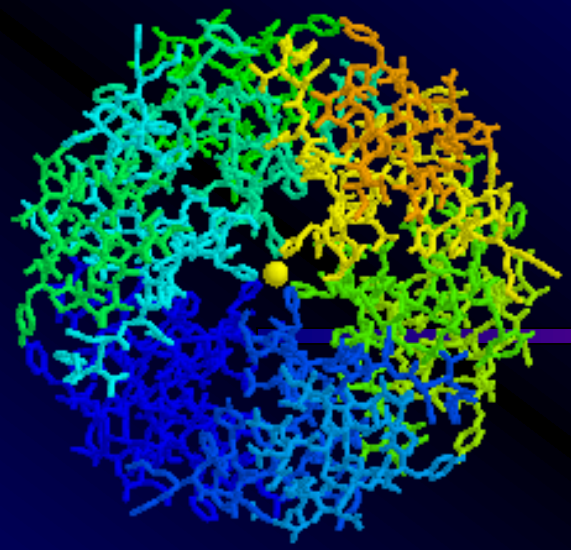
1990-2010



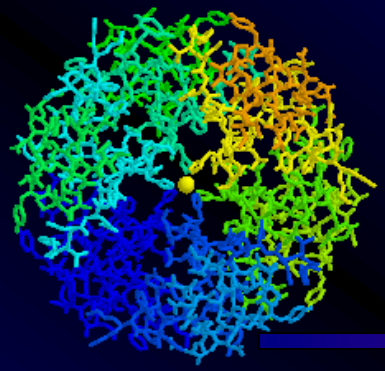
Gregg EW et al. NEJM 2014;370:1514-23.

Medicare Mortality
1992-2003





Adding a Prandial Insulin



GLP-1 Analog v Prandial Insulin

Factor	Prandial Insulin	GLP-1 RA
Endogenous Insulin Production	Not Required	Required
Cost	Less expensive	More expensive
Weight	Gain in weight typical	Neutral to weight loss
Hypoglycemia	Common	Much less common
Complexity	Premeal dosing	BID to weekly injections
Tolerability (Side Effects)	Not usually an issue	Side effects can be limiting