Management of Type 2 Diabetes: 2015

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- 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	$\frac{\text{DCCT}^{1,2}}{9\%} \rightarrow 7\%$	$\begin{array}{c} UKPDS^{3} \\ 8\% \rightarrow 7\% \end{array}$					
Retinopathy	63%	17%-21%					
Nephropathy	54%	24%-33%					
Neuropathy	60%						
Macrovascular disease	41%*	16%*					

*Not statistically significant

¹DCCT Research Group. *N Engl J Med.* 1993;329:977; ²DCCT Research Group. *Diabetes.* 1995;44:968; ³UKPDS 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)	4	53.3		66	60		
Duration DM	0	years	8	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%	6.4% 7.0%		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



*Glycemic Exposure=Duration of Diabetes x Study Entry A1C

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



VA/DoD Guidelines

Major Comorbidity ^(d)	Microvascular Complications							
or	Absent or Mild ^(a)	Moderate ^(b)	Advanced ^(c)					
Physiologic Age								
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	8-9% *	8-9% *	8-9% *					
expectancy								

(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.



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 (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





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

GLP-1(7-36)NH₂ HAEGTFTSDVSSYLEGQ GIP YAEGTFTSDVSTAMDKT Exendin-4 HGEGTFTSDLSKQMEEE





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

Insulin Effect





4-T Study: First Year





Biphasic v Basal Therapy Proportion with A1C < 7%

Study (first author	Biph	nasic	Ba	asal	Odds R	atio				Odds Ratio (95% CI
year, reference)	Ν	%	N	(%)	1					
Ma l one, 2004 [23]	67	42%	67	18%	1				-	3.26 (1.52 - 7.01)
Ma l one, 2005 [24]	97	30%	97	12%						3.02 (1.43 - 6.36)
Raskin, 2005 [25]	108	66%	114	40%			-			2.84 (1.64 - 4.90)
Kann, 2006 [26]	128	33.1%	127	26.2%		-				1.39 (0.81 - 2.39)
Jacober, 2006 [27]	59	44%	59	31%	-					1.79 (0.84 - 3.82)
Kazda, 2006 [28]	54	59.3%	53	24.5%		-		_		4.48 (1.96 - 10.25)
Holman, 2007 [29]	235	41.7%	234	27.8%	1					1.86 (1.26 - 2.74)
Robbin, 2007 [30]	158	56.3%	157	39.7%						1.88 (1.20 - 2.94)
Buse, 2009 [35]	1045	47.5%	1046	40.3%		-				1.34 (1.13 - 1.60)
Strojek, 2009 [37]	225	44.9%	232	45.7%	- ÷					0 . 97 (0.67 - 1.40)
Pooled*	2176	46.5%	2190	36.1%						1.88 (1.38-2.55)
Q ² Cochrane test f	or Het	erogene	ity=28.5 (p	=0.0008)	1					(P=0.0012)
df=9, I ² =68.5				Г	1		1	1		. ,
				0.5	1.0	1.5	3.0	5.0	10.0	

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

Hypoglycemic events (mean/patient/30 days) Study (first author Biphasic Basa Mean difference year, reference) N mean (SD) N mean (SD) Malone, 2004 [23] 100 0.7 (1.4) 101 0.4 (1.2) 97 0.6 (1.4) 97 0.4 (1.1) Malone, 2005 [24] 108 0.3 (0.5) 114 0.1 (0.2) Raskin, 2005 [25] 127 0.5 (1.6) Kann, 2006 [26] 128 0.3 (0.7) Jacober, 2006 [27] 59 4.7 (6.3) 59 2.3 (3.2) Kazda, 2006 [28] 54 0.4 (0.8) 53 0.3 (0.5) 235 0.3 (0.4) 234 0.2 (0.2) Holman, 2007 [29] 158 0.8 (1.4) 157 0.5 (1.0) Robbin, 2007 [30] 1045 2,3 (3,2) Buse, 2009 [35] 1046 1.9 (3.3) Strojek, 2009 [37] 231 0.5 (1.2) 238 0.4 (1.3) Pooled * 2215 1.1 2226 0.7 0.34 (0-0.69) Q2 Cochrane test for Heterogeneity=25.6 (p=0.002), df=9, l2=64.9 (P=0.05) 0.28 (0.10-0.45) Pooled ^* 2156 0.7 2167 0.5 Q2 Cochrane test for Heterogeneity=5.1 (p=0.74), df=8, I²=0 (P=0.006) ^ sensitivity analysis by excluding one trial (27) 2.0 3.0 2.0 -1.0 0.0 1.0 Biphasic better Basal better

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.

(a) WHEN LIFESTYLE CHANGES PLUS A COMBINATION OF METFORMIN OR OADS FAILS TO ACHIEVE GLYCAEMIC CONTROL INITIATE AND OPTIMIZE BASAL INSULIN

Lifestyle measure to be continued Monitor FBG

Titrate long-acting insulin analogue by 2 units every 3 days until FBG <6.1 mmol/L

If FBG targets are reached but the A1c target (<7%) is not achieved after 2-3 months

(b) ADD ONE BOLUS OF PRANDIAL INSULIN (BASAL PLUS APPROACH)

Record 2-hour PPBG following each main meal for 3 days and note which meal has the highest PPBG excursion, and work out average PPBG at this meal over the 3 days Initiate rapid-acting analogue prandial insulin at this main meal PPBG mg/dl

Calculate dose (U)= Average meal PPBG (mmol/L)

2

Titrate rapid-acting insulin analogue by 2 units every 3 days until PPBG <10mmol/L If hypoglycaemia occurs then reduce dose by 2 units, consider stopping the sulfonylurea Check pre-bed if evening meal is preceded by prandial insulin

When the A1c target (<7%) is not achieved

36

(C) ADD SECOND PRANDIAL INSULIN AS NECESSARY

Add second prandial insulin depending on PPBG excursions following the other meals (aim for PPBG <10mmol/L)

Add and titrate prandial insulin as per protocol in Box B

Keep monitoring FBG and adjust basal insulin as necessary

When the A1c target (<7%) is not achieved

(d) ADD THIRD PRANDIAL INSULIN AS NECESSARY (BASAL-BOLUS APPROACH)

Add third prandial insulin depending on PPBG excursions for remaining meal (aim for PPBG <10mmol/L)

Add and titrate prandial insulin as per protocol in Box B Keep monitoring FBG and adjust basal insulin as necessary

When the A1c target (<7%) is not achieved

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."



Population Based Assessment in Lowering Complications from Diabetes

Variable		Year		Change (19	990-2010)				
	1990	2000	2010	Change	% Change				
Adults with Diabetes	6,536,163	11,799,201	20,676,427						
	Acut	e 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 Amputat	ion						
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

A Population with Diabetes



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



Trends in Standardized Rates for Complications 1990-2010

B Population with or without Diabetes



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